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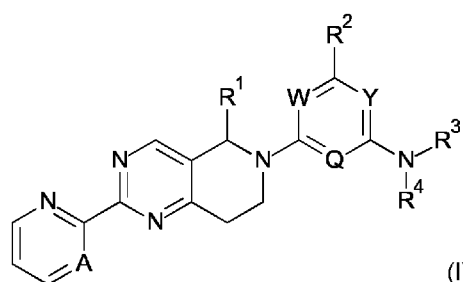
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(54) Title: NOVEL TETRAHYDROPYRIDOPYRIMIDINES FOR THE TREATMENT AND PROPHYLAXIS OF HBV INFECTION



(57) Abstract: The present invention provides novel compounds having general formula (I), wherein R¹ to R⁴, A, W, Q and Y are as described herein, compositions including the compounds and methods of using the compounds.

(I)

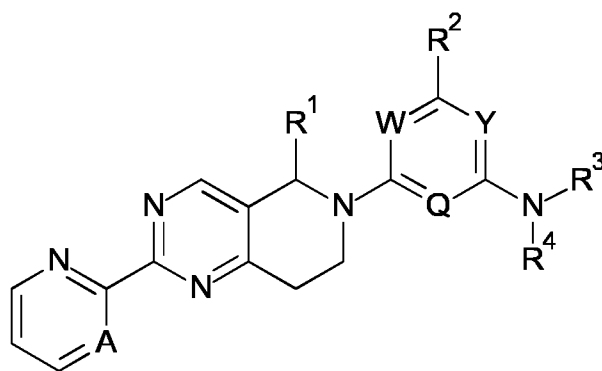
Novel tetrahydropyridopyrimidines for the treatment and prophylaxis of HBV infection

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, and in particular to HBsAg (HBV Surface antigen) inhibitors and HBV DNA production inhibitors useful for treating HBV infection.

FIELD OF THE INVENTION

- 5 The present invention relates to novel tetrahydropyridopyrimidines having pharmaceutical activity, their manufacture, pharmaceutical compositions containing them and their potential use as medicaments.

The present invention relates to compounds of formula I,



(I)

- 10 wherein R¹ to R⁴, A, W, Q and Y are as described below, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

- 15 The hepatitis B virus (HBV) is an enveloped, partially double-stranded DNA virus. The compact 3.2 kb HBV genome consists of four overlapping open reading frames (ORF), which encode for the core, polymerase (Pol), envelope and X-proteins. The Pol ORF is the longest and the envelope ORF is located within it, while the X and core ORFs overlap with the Pol ORF. The lifecycle of HBV has two main events: 1) generation of closed circular DNA (cccDNA) from relaxed circular (RC DNA), and 2) reverse transcription of pregenomic RNA (pgRNA) to produce RC DNA. Prior to the infection of host cells, the HBV genome exists within the virion as RC DNA. It has been determined that HBV virions are able to gain entry into host cells by

non-specifically binding to the negatively charged proteoglycans present on the surface of human hepatocytes (Schulze, A., P. Gripon & S. Urban. *Hepatology*, 46, (2007), 1759-68) and via the specific binding of HBV surface antigens (HBsAg) to the hepatocyte sodium-taurocholate cotransporting polypeptide (NTCP) receptor (Yan, H. et al. *J Virol*, 87, (2013), 7977-91). Once the virion has entered the cell, the viral cores and the encapsidated RC DNA are transported by host factors, via a nuclear localization signal, into the nucleus through the Imp β /Imp α nuclear transport receptors. Inside the nucleus, host DNA repair enzymes convert the RC DNA into cccDNA. cccDNA acts as the template for all viral mRNAs and as such, is responsible for HBV persistence in infected individuals. The transcripts produced from cccDNA are grouped into two categories; Pregenomic RNA (pgRNA) and subgenomic RNA. Subgenomic transcripts encode for the three envelopes (L, M and S) and X proteins, and pgRNA encodes for Pre-Core, Core, and Pol proteins (Quasdorff, M. & U. Protzer. *J Viral Hepat*, 17, (2010), 527-36). Inhibition of HBV gene expression or HBV RNA synthesis leads to the inhibition of HBV viral replication and antigens production (Mao, R. et al. *PLoS Pathog*, 9, (2013), e1003494; Mao, R. et al. *J Virol*, 85, (2011), 1048-57). For instance, IFN- α was shown to inhibit HBV replication and viral HBsAg production by decreasing the transcription of pgRNA and subgenomic RNA from the HBV covalently closed circular DNA (cccDNA) minichromosome. (Belloni, L. et al. *J Clin Invest*, 122, (2012), 529-37; Mao, R. et al. *J Virol*, 85, (2011), 1048-57). All HBV viral mRNAs are capped and polyadenylated, and then exported to the cytoplasm for translation. In the cytoplasm, the assembly of new virions is initiated and nascent pgRNA is packaged with viral Pol so that reverse transcription of pgRNA, via a single stranded DNA intermediate, into RC DNA can commence. The mature nucleocapsids containing RC DNA are enveloped with cellular lipids and viral L, M, and S proteins and then the infectious HBV particles are then released by budding at the intracellular membrane (Locarnini, S. *Semin Liver Dis*, (2005), 25 Suppl 1, 9-19). Interestingly, non-infectious particles are also produced that greatly outnumber the infectious virions. These empty, enveloped particles (L, M and S) are referred to as subviral particles. Importantly, since subviral particles share the same envelope proteins and as infectious particles, it has been surmised that they act as decoys to the host immune system and have been used for HBV vaccines. The S, M, and L envelope proteins are expressed from a single ORF that contains three different start codons. All three proteins share a 226aa sequence, the S-domain, at their C-termini. M and L have additional pre-S domains, Pre-S2 and Pre-S2 and Pre-S1, respectively. However, it is the S-domain that has the HBsAg epitope (Lambert, C. & R. Prange. *Virol J*, (2007), 4, 45).

The control of viral infection needs a tight surveillance of the host innate immune system which could respond within minutes to hours after infection to impact on the initial growth of the virus and limit the development of a chronic and persistent infection. Despite the available current treatments based on IFN and nucleos(t)ide analogues, the Hepatitis B virus (HBV) infection remains a major health problem worldwide which concerns an estimated 350 million chronic carriers who have a higher risk of liver cirrhosis and hepatocellular carcinoma.

The secretion of antiviral cytokines in response to HBV infection by the hepatocytes and/or the intra-hepatic immune cells plays a central role in the viral clearance of infected liver. However, chronically infected patients only display a weak immune response due to various escape strategies adopted by the virus to counteract the host cell recognition systems and the subsequent antiviral responses.

Many observations showed that several HBV viral proteins could counteract the initial host cellular response by interfering with the viral recognition signaling system and subsequently the interferon (IFN) antiviral activity. Among these, the excessive secretion of HBV empty subviral particles (SVPs, HBsAg) may participate to the maintenance of the immunological tolerant state observed in chronically infected patients (CHB). The persistent exposure to HBsAg and other viral antigens can lead to HBV-specific T-cell deletion or to progressive functional impairment (Nayersina et al. *Journal of Immunology* (1993), 150, 4659–4671; Kondo et al. *Journal of Medical Virology* (2004), 74, 425–433; Fiscaro et al. *Gastroenterology*, (2010), 138, 682-93;). Moreover HBsAg has been reported to suppress the function of immune cells such as monocytes, dendritic cells (DCs) and natural killer (NK) cells by direct interaction (Op den Brouw et al. *Immunology*, (2009b), 126, 280-9; Woltman et al. *PLoS One*, (2011), 6, e15324; Shi et al. *J Viral Hepat.* (2012), 19, e26-33; Kondo et al. *ISRN Gastroenterology*, (2013), Article ID 935295).

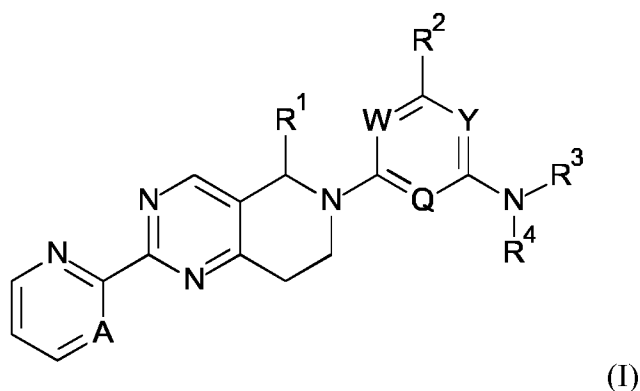
HBsAg quantification is a significant biomarker for prognosis and treatment response in chronic hepatitis B. However the achievement of HBsAg loss and seroconversion is rarely observed in chronically infected patients but remains the ultimate goal of therapy. Current therapy such as Nucleos(t)ide analogues are molecules that inhibit HBV DNA synthesis but are not directed at reducing HBsAg level. Nucleos(t)ide analogs, even with prolonged therapy, have demonstrated rates of HBsAg clearance comparable to those observed naturally (between -1%-2%) (Janssen et al. *Lancet*, (2005), 365, 123-9; Marcellin et al. *N. Engl. J. Med.*, (2004), 351, 1206-17; Buster et al. *Hepatology*, (2007), 46, 388-94). Therefore, there is an unmet medical need to target HBsAg for HBV treatment (Wieland, S. F. & F. V. Chisari. *J Virol*, (2005), 79,

9369-80; Kumar et al. *J Virol*, (2011), 85, 987-95; Woltman et al. *PLoS One*, (2011), 6, e15324; Op den Brouw et al. *Immunology*, (2009b), 126, 280-9).

SUMMARY OF THE INVENTION

Objects of the present invention are novel compounds of formula I, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I as HBV inhibitors and for the treatment or prophylaxis of HBV infection. The compounds of formula I show superior anti-HBV activity.

The present invention relates to a compound of formula I



10 wherein

R^1 is aminoC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, C₁₋₆alkyl, C₃₋₇cycloalkyl, carboxyC₁₋₆alkyl, cyanoC₁₋₆alkyl, haloC₁₋₆alkyl, hydrogen or hydroxyC₁₋₆alkyl;

R^2 is C₁₋₆alkoxy, C₁₋₆alkyl, haloC₁₋₆alkoxy, haloC₁₋₆alkyl, halogen or hydrogen;

One of R^3 and R^4 is C₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkyl or hydrogen; the other one is 1,1-

15 dioxothianyl, aminocarbonylC₁₋₆alkyl, azetidiny, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonylazetidiny, C₁₋₆alkylsufonylpiperidiny, C₁₋₆alkylsufonyl, C₃₋₇cycloalkylcarbonyl, C₃₋₇cycloalkylsufonyl, carboxyC₁₋₆alkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkylcarbonyl, phenylcarbonyl, phenylsufonyl or tetrahydropyrany; or

R^3 and R^4 together with the nitrogen to which they are attached form 1,1-dioxo-thiazolidiny;

20 1,1-dioxo-thiazinany; 2-oxa-6-azaspiro[3.3]heptany; 2-oxa-7-azaspiro[4.4]nonany; 3-oxa-8-azabicyclo[3.2.1]octany; 6-oxo-2-oxa-7-azaspiro[3.4]octany; azetidiny;

oxoimidazolidiny; oxopyrrolidiny; substituted azetidiny; substituted morpholiny;

substituted oxooxazolidiny; substituted oxopiperaziny; substituted oxopyrrolidiny;

substituted piperaziny; substituted piperidiny or substituted pyrrolidiny; wherein said

25 substituted azetidiny, substituted morpholiny, substituted oxooxazolidiny, substituted

oxopiperazinyl, substituted oxopyrrolidinyl, substituted piperazinyl, substituted piperidinyl and substituted pyrrolidinyl are substituted with one, two or three substituents independently selected from aminocarbonyl, aminocarbonylC₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkylsulfonyl, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfonylamino, C₁₋₆alkylsulfonylaminocarbonyl, carboxy, carboxyC₁₋₆alkyl, cyano, halogen, hydroxy and hydroxyC₁₋₆alkyl;

A is N or CH;

One of W, Q and Y is N, the others are CH;

with the proviso that *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]methanesulfonamide and *N*-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]methanesulfonamide are excluded; or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

As used herein, the term “C₁₋₆alkyl” alone or in combination signifies a saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms, for example methyl, ethyl, propyl, isopropyl, 1-butyl, 2-butyl, *tert*-butyl and the like. Particular “C₁₋₆alkyl” groups are methyl, ethyl, isopropyl and *tert*-butyl. More particularly, “C₁₋₆alkyl” group is methyl or ethyl.

The term “C₃₋₇cycloalkyl”, alone or in combination, refers to a saturated carbon ring containing from 3 to 7 carbon atoms, particularly from 3 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Particular “C₃₋₇cycloalkyl” groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. More particularly, “C₃₋₇cycloalkyl” group is cyclopropyl.

The term “C₁₋₆alkoxy” alone or in combination signifies a group C₁₋₆alkyl-O-, wherein the “C₁₋₆alkyl” is as defined above; for example methoxy, ethoxy, propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, 2-butoxy, *tert*-butoxy, pentoxy, hexyloxy and the like. Particular “C₁₋₆alkoxy” groups are methoxy, ethoxy and propoxy. More particularly, “C₁₋₆alkoxy” group is methoxy.

The term “halogen” means fluorine, chlorine, bromine or iodine.

The term “haloC₁₋₆alkyl” denotes a C₁₋₆alkyl group wherein at least one of the hydrogen atoms of the C₁₋₆alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloC₁₋₆alkyl include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 3,3- difluoropropyl, 2-fluoroethyl, 2,2-
5 difluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, difluoromethyl or trifluoromethyl. Particular “haloC₁₋₆alkyl” group is difluoromethyl, 2,2-difluoroethyl or trifluoromethyl. More particularly, “haloC₁₋₆alkyl” group is 2,2-difluoroethyl.

The term “haloC₁₋₆alkoxy” denotes a C₁₋₆alkoxy group wherein at least one of the
10 hydrogen atoms of the C₁₋₆alkoxy group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloC₁₋₆alkoxyl include monofluoro-, difluoro- or trifluoro-methoxy, -ethoxy or -propoxy, for example fluoropropoxy, difluoropropoxy, trifluoropropoxy, fluoroethoxy, difluoroethoxy, trifluoroethoxy, fluoromethoxy, difluoromethoxy or trifluoromethoxy. Particular “haloC₁₋₆alkoxy” group is 3-fluoropropoxy, 3,3
15 -difluoropropoxy, 3,3,3-trifluoropropoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, fluoromethoxy, difluoromethoxy or trifluoromethoxy.

The term “amino” denotes a group of the formula -NR'R'' wherein R' and R'' are independently hydrogen or C₁₋₆alkyl. Alternatively, R' and R'', together with the nitrogen to which they are attached, can form a heteroC₃₋₇cycloalkyl.

20 The term “carbonyl” alone or in combination refers to the group -C(O)-.

The term “cyano” alone or in combination refers to the group -CN.

The term “C₁₋₆alkylsulfonyl” denotes a group -SO₂-C₁₋₆alkyl, wherein C₁₋₆alkyl group is defined above. Examples of C₁₋₆alkylsulfonyl include methylsulfonyl and ethylsulfonyl.

25 The term “enantiomer” denotes two stereoisomers of a compound which are non-superimposable mirror images of one another.

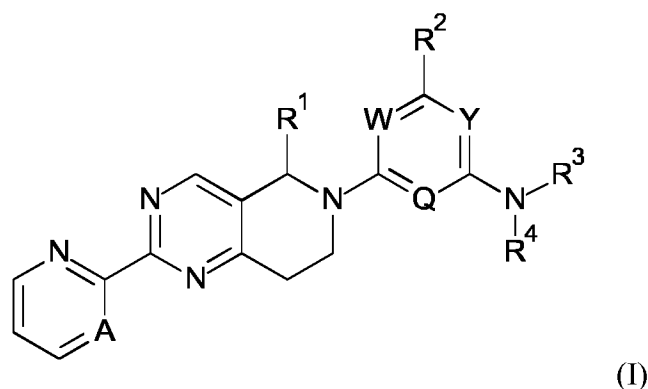
The term “diastereomer” denotes a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities.

The compounds according to the present invention may exist in the form of their pharmaceutically acceptable salts. The term “pharmaceutically acceptable salt” refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as *p*-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethyl ammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Bastin R.J., *et al.*, Organic Process Research & Development 2000, 4, 427-435. Particular are the sodium salts of the compounds of formula I.

Compounds of the general formula I which contain one or several chiral centers can either be present as racemates, diastereomeric mixtures, or optically active single isomers. The racemates can be separated according to known methods into the enantiomers. Particularly, diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by reaction with an optically active acid such as e.g. D- or L-tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid.

INHIBITOR OF HBsAg

The present invention provides (i) a compound having the general formula I:



25 wherein

-8-

R¹ is aminoC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, C₁₋₆alkyl, C₃₋₇cycloalkyl, carboxyC₁₋₆alkyl, cyanoC₁₋₆alkyl, haloC₁₋₆alkyl, hydrogen or hydroxyC₁₋₆alkyl;

R² is C₁₋₆alkoxy, C₁₋₆alkyl, haloC₁₋₆alkoxy, haloC₁₋₆alkyl, halogen or hydrogen;

One of R³ and R⁴ is C₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkyl or hydrogen; the other one is 1,1-

5 dioxothianyl, aminocarbonylC₁₋₆alkyl, azetidiny, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonylazetidiny, C₁₋₆alkylsulfonylpiperidiny, C₁₋₆alkylsulfonyl, C₃₋₇cycloalkylcarbonyl, C₃₋₇cycloalkylsulfonyl, carboxyC₁₋₆alkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkylcarbonyl, phenylcarbonyl, phenylsulfonyl or tetrahydropyrany; or

R³ and R⁴ together with the nitrogen to which they are attached form 1,1-dioxo-thiazolidiny;

10 1,1-dioxo-thiazinany; 2-oxa-6-azaspiro[3.3]heptany; 2-oxa-7-azaspiro[4.4]nonany; 3-oxa-8-azabicyclo[3.2.1]octany; 6-oxo-2-oxa-7-azaspiro[3.4]octany; azetidiny; oxoimidazolidiny; oxopyrrolidiny; substituted azetidiny; substituted morpholiny; substituted oxooxazolidiny; substituted oxopiperaziny; substituted oxopyrrolidiny; substituted piperaziny; substituted piperidiny or substituted pyrrolidiny; wherein said
15 substituted azetidiny, substituted morpholiny, substituted oxooxazolidiny, substituted oxopiperaziny, substituted oxopyrrolidiny, substituted piperaziny, substituted piperidiny and substituted pyrrolidiny are substituted with one, two or three substituents independently selected from aminocarbonyl, aminocarbonylC₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkylsulfonyl, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfonylamino, C₁₋₆alkylsulfonylaminocarbonyl, carboxy, carboxyC₁₋₆alkyl, cyano, halogen, hydroxy and
20 hydroxyC₁₋₆alkyl;

A is N or CH;

One of W, Q and Y is N, the others are CH;

25 with the proviso that *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]methanesulfonamide and *N*-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]methanesulfonamide are excluded; or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

A further embodiment of the present invention is (ii) a compound of formula I, wherein,

30 R¹ is C₁₋₆alkyl;

R² is halogen;

One of R³ and R⁴ is C₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkyl or hydrogen; the other one is 1,1-dioxothianyl, aminocarbonylC₁₋₆alkyl, azetidiny, C₁₋₆alkylcarbonyl, C₁₋

alkylcarbonylazetidiny], C₁₋₆alkylsulfonylpiperidiny], C₁₋₆alkylsulfonyl, C₃₋₇cycloalkylcarbonyl, C₃₋₇cycloalkylsulfonyl, carboxyC₁₋₆alkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkylcarbonyl, phenylcarbonyl, phenylsulfonyl or tetrahydropyrany]; or

R³ and R⁴ together with the nitrogen to which they are attached form 1,1-dioxo-thiazolidiny];

- 5 1,1-dioxo-thiazinany]; 2-oxa-6-azaspiro[3.3]heptany]; 2-oxa-7-azaspiro[4.4]nonany]; 3-oxa-8-azabicyclo[3.2.1]octany]; 6-oxo-2-oxa-7-azaspiro[3.4]octany]; azetidiny]; oxoimidazolidiny]; oxopyrrolidiny]; substituted azetidiny]; substituted morpholiny]; substituted oxooxazolidiny]; substituted oxopiperaziny]; substituted oxopyrrolidiny]; substituted piperaziny]; substituted piperidiny] or substituted pyrrolidiny]; wherein said
- 10 substituted azetidiny], substituted morpholiny], substituted oxooxazolidiny], substituted oxopiperaziny], substituted oxopyrrolidiny], substituted piperaziny], substituted piperidiny] and substituted pyrrolidiny] are substituted with one, two or three substituents independently selected from aminocarbonyl, aminocarbonylC₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkylsulfonyl, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfonylamino, C₁₋₆alkylsulfonylaminocarbonyl, carboxy, carboxyC₁₋₆alkyl, cyano, halogen, hydroxy and hydroxyC₁₋₆alkyl;

A is N or CH;

One of W, Q and Y is N, the others are CH;

- 20 or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

Another embodiment of the present invention is (iii) a compound of formula I, wherein,

R¹ is C₁₋₆alkyl;

R² is halogen;

One of R³ and R⁴ is C₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkyl or hydrogen; the other one is 1,1-

- 25 dioxothianyl, aminocarbonylC₁₋₆alkyl, azetidiny], C₁₋₆alkylcarbonylazetidiny], C₁₋₆alkylsulfonylpiperidiny], carboxyC₁₋₆alkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkylcarbonyl, phenylcarbonyl, phenylsulfonyl or tetrahydropyrany]; or

R³ and R⁴ together with the nitrogen to which they are attached form

- 2-oxa-6-azaspiro[3.3]heptany];
- 30 2-oxa-7-azaspiro[4.4]nonany];
- 3-oxa-8-azabicyclo[3.2.1]octany];
- 6-oxo-2-oxa-7-azaspiro[3.4]octany];

azetidinyl substituted with one or two substituents independently selected from
aminocarbonyl, C₁₋₆alkoxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylsulfonylamino, C₁₋₆alkylsulfonylaminocarbonyl, carboxy, cyano, halogen, hydroxy and hydroxyC₁₋₆alkyl;

5 morpholinyl substituted with one or two substituents independently selected from
aminocarbonyl, C₁₋₆alkoxyC₁₋₆alkylcarboxy, carboxyC₁₋₆alkyl and hydroxyC₁₋₆alkyl;
oxopyrrolidinyl substituted with one or two substituents independently selected from
carboxy and hydroxyC₁₋₆alkyl;

piperazinyl substituted with one, two or three substituents independently selected from

10 aminocarbonylC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkylsulfonyl, carboxy and carboxyC₁₋₆alkyl;
piperidinyl substituted with one or two substituents independently selected from
aminocarbonyl, C₁₋₆alkylsulfonylamino, C₁₋₆alkylsulfonylaminocarbonyl and
carboxy; or

pyrrolidinyl substituted with one, two or three substituents independently selected from

15 aminocarbonyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkylsulfonylaminocarbonyl, C₁₋₆alkyl, carboxy, halogen, hydroxy and hydroxyC₁₋₆alkyl;

A is N or CH;

One of W, Q and Y is N, the others are CH;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

20 A further embodiment of the present invention is (iv) a compound of formula I, wherein

R¹ is C₁₋₆alkyl;

R² is halogen;

One of R³ and R⁴ is C₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkyl or hydrogen; the other one is 1,1-

dioxothianyl, aminocarbonylC₁₋₆alkyl, azetidinyl, C₁₋₆alkylcarbonylazetidinyl, C₁₋

25 ₆alkylsulfonylpiperidinyl, carboxyC₁₋₆alkyl, hydroxyC₁₋₆alkylcarbonyl, phenylcarbonyl;
phenylsulfonyl or tetrahydropyranyl; or

R³ and R⁴ together with the nitrogen to which they are attached form

2-oxa-6-azaspiro[3.3]heptanyl;

2-oxa-7-azaspiro[4.4]nonanyl;

30 3-oxa-8-azabicyclo[3.2.1]octanyl;

6-oxo-2-oxa-7-azaspiro[3.4]octanyl;

azetidinyl substituted with one or two substituents independently selected from

aminocarbonyl, C₁₋₆alkoxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylsulfonylamino, C₁₋

₆alkylsulfonylaminocarbonyl, carboxy, cyano, halogen, hydroxy and hydroxyC₁₋₆alkyl;

morpholinyl substituted with one or two substituents independently selected from

aminocarbonyl, C₁₋₆alkoxyC₁₋₆alkyl, carboxy, carboxyC₁₋₆alkyl and hydroxyC₁₋₆alkyl;

5 oxopyrrolidinyl substituted with one or two substituents independently selected from carboxy and hydroxyC₁₋₆alkyl;

piperazinyl substituted with one, two or three substituents independently selected from

aminocarbonylC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkylsulfonyl, carboxy and carboxyC₁₋₆alkyl;

piperidinyl substituted with one or two substituents independently selected from

10 aminocarbonyl, C₁₋₆alkylsulfonylamino, C₁₋₆alkylsulfonylaminocarbonyl and carboxy; or

pyrrolidinyl substituted with one, two or three substituents independently selected from

aminocarbonyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, carboxy, halogen, hydroxy and hydroxyC₁₋₆alkyl;

15 A is N;

One of W, Q and Y is N, the others are CH;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

Another embodiment of the present invention is (v) a compound of formula I, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R¹ is methyl,

20 and all remaining substituents have the significances given herein before.

A further embodiment of the present invention is (vi) a compound of formula I, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R² is fluoro, and all remaining substituents have the significances given herein before.

A further embodiment of the present invention is (vii) a compound of formula I, or a
 25 pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R³ and R⁴ together with the nitrogen to which they are attached form 2-oxa-6-azaspiro[3.3]heptanyl; 2-oxa-7-azaspiro[4.4]nonanyl; azetidiny substituted with one or two substituents independently selected from C₁₋₆alkoxy, halogen and hydroxyC₁₋₆alkyl; (C₁₋₆alkoxyC₁₋₆alkyl)morpholinyl; (C₁₋₆alkoxyC₁₋₆alkylsulfonyl)piperazinyl; (C₁₋₆alkylsulfonylamino)piperidinyl; or pyrrolidinyl
 30 substituted with one or two substituents independently selected from aminocarbonyl, C₁₋₆alkoxy, halogen, hydroxy and hydroxyC₁₋₆alkyl; and all remaining substituents have the significances given herein before.

A further embodiment of the present invention is (viii) a compound of formula I, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R³ and R⁴ together with the nitrogen to which they are attached form 2-oxa-6-azaspiro[3.3]heptanyl; 2-oxa-7-azaspiro[4.4]nonanyl; azetidinyI substituted with one or two substituents independently selected from fluoro, hydroxymethyl and methoxy; (methoxymethyl)morpholinyl; (methoxyethylsulfonyl)piperazinyl; (methylsulfonylamino)piperidinyl; or pyrrolidinyl substituted with one or two substituents independently selected from aminocarbonyl, fluoro, hydroxy, hydroxymethyl and methoxy; and all remaining substituents have the significances given herein before.

Another embodiment of the present invention is (ix) a compound of formula I, wherein R¹ is C₁₋₆alkyl; R² is halogen; R³ and R⁴ together with the nitrogen to which they are attached form azetidinyI substituted with one or two substituents independently selected from C₁₋₆alkoxy and halogen; (C₁₋₆alkylsulfonylamino)-piperidinyl; or pyrrolidinyl substituted with one or two substituents independently selected from C₁₋₆alkoxy and halogen;

A is N;

One of W, Q and Y is N, the others are CH;
or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

A further embodiment of the present invention is (x) a compound of formula I, wherein, R¹ is methyl; R² is fluoro;

R³ and R⁴ together with the nitrogen to which they are attached form azetidinyI substituted with one or two substituents independently selected from fluoro and methoxy; (methylsulfonylamino)-piperidinyl; or pyrrolidinyl substituted with one or two substituents independently selected from methoxy and fluoro;

A is N;

One of W, Q and Y is N, the others are CH;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

Another embodiment of the present invention is (xi) a compound selected from

6-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]hexanoic acid ;

5 6-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]amino]hexanoic acid;

N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-hydroxy-acetamide;

8-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-oxa-8-azabicyclo[3.2.1]octane;

8-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-3-oxa-8-azabicyclo[3.2.1]octane;

7-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-7-azaspiro[4.4]nonane;

15 7-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-7-azaspiro[4.4]nonane;

4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-(methoxymethyl)morpholine;

4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-(methoxymethyl)morpholine;

6-[6-fluoro-4-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-fluoro-6-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

25 6-[4-(3,3-difluoropyrrolidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-(3,3-difluoropyrrolidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholin-2-yl]methanol;

[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholin-2-yl]methanol;

4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine-2-carboxylic acid;

4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholine-2-carboxylic acid;

5 2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholin-2-yl]acetic acid;

2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholin-2-yl]acetic acid;

10 [1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-2-yl]methanol;

[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidin-2-yl]methanol;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-2-carboxylic acid;

15 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-2-carboxylic acid;

6-[6-fluoro-4-[2-(methoxymethyl)pyrrolidin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

20 6-[4-fluoro-6-[2-(methoxymethyl)pyrrolidin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-3-ol;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidin-3-ol;

25 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-3-carboxylic acid;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-3-carboxylic acid;

30 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-2-carboxamide;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-2-carboxamide;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-3-carboxamide;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-3-carboxamide;

5 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine-2-carboxamide;

4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholine-2-carboxamide;

10 2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-N-tetrahydropyran-4-yl-pyridin-4-amine;

4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-N-tetrahydropyran-4-yl-pyridin-2-amine;

4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazine-2-carboxylic acid;

15 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperidine-4-carboxylic acid;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperidine-4-carboxylic acid;

20 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidine-3-carboxylic acid;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carboxylic acid;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperidine-4-carboxamide;

25 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperidine-4-carboxamide;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-N-methylsulfonyl-azetidine-3-carboxamide;

30 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methylsulfonyl-azetidine-3-carboxamide;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-N-methylsulfonyl-piperidine-4-carboxamide;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methylsulfonyl-piperidine-4-carboxamide;

N-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]benzenesulfonamide;

5 N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]benzenesulfonamide;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidine-3-carboxamide;

10 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carboxamide;

6-[6-fluoro-4-[4-(2-methoxyethylsulfonyl)piperazin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

N-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-piperidyl]methanesulfonamide;

15 N-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-4-piperidyl]methanesulfonamide;

2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]acetic acid;

20 2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]acetic acid;

2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-N-(1-methylsulfonyl-4-piperidyl)pyridin-4-amine;

2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]acetamide;

25 2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]acetamide;

3-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]propanamide;

30 3-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]propanamide;

6-[2-fluoro-6-(3-methoxypyrrolidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-fluoro-6-(3-methoxyazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-fluoro-4-(3-methoxyazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

5 N-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]methanesulfonamide;

N-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]methanesulfonamide;

10 N-(azetidin-3-yl)-4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)pyridin-2-amine;

N-(azetidin-3-yl)-2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)pyridin-4-amine;

6-[4-fluoro-6-(3-fluoroazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

15 6-[6-fluoro-4-(3-fluoroazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-ol;

20 6-[6-(3,3-difluoroazetidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-(3,3-difluoroazetidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-6-azaspiro[3.3]heptane;

25 6-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-6-azaspiro[3.3]heptane;

N-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]acetamide;

30 N-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]acetamide;

[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]methanol;

[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]methanol;

5-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]pentanamide;

5 N-(1,1-dioxothian-4-yl)-2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)pyridin-4-amine;

1-[3-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]amino]azetidin-1-yl]ethanone;

10 1-[3-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]azetidin-1-yl]ethanone;

5-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-methyl-amino]pentanamide;

5-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-methyl-amino]pentanamide;

15 5-[cyclopropylmethyl-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]pentanamide;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carbonitrile;

20 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-5-oxo-pyrrolidine-3-carboxylic acid;

6-[2-fluoro-6-(3-methoxyazetidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[2-(3,3-difluoroazetidin-1-yl)-6-fluoro-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

25 6-[2-fluoro-6-(3-fluoroazetidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

7-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-7-azaspiro[3.4]octan-6-one;

30 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-(hydroxymethyl)pyrrolidin-2-one;

6-[6-fluoro-4-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-6-azaspiro[3.3]heptane;

N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-benzenesulfonamide; and

N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-benzamide;

5 or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

A further embodiment of the present invention is (xii) a compound selected from

6-[6-fluoro-4-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

10 6-[4-(3,3-difluoropyrrolidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-(3,3-difluoropyrrolidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

N-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-piperidyl]methanesulfonamide;

15 6-[2-fluoro-6-(3-methoxypyrrolidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-fluoro-4-(3-methoxyazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

20 6-[6-fluoro-4-(3-fluoroazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine; and

6-[4-(3,3-difluoroazetidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

Another embodiment of the present invention is (xiii) a compound of formula I, wherein

25 R^1 is C_{1-6} alkyl;

R^2 is halogen;

One of R^3 and R^4 is hydrogen; the other one is halo C_{1-6} alkyl; or

R^3 and R^4 together with the nitrogen to which they are attached form aminocarbonylpiperidinyl,

aminocarbonylpyrrolidinyl, C_{1-6} alkylsulfonylaminocarbonylpyrrolidinyl, C_{1-6}

30 ϵ alkoxypyrrolidinyl, carboxypyrrolidinyl or hydroxypyrrolidinyl;

A is CH;

One of W and Q is N, the other one is CH;

Y is CH₃;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

A further embodiment of the present invention is (xiv) a compound of formula I, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R¹ is methyl,
5 and all remaining substituents have the significances given herein before.

Another further embodiment of the present invention is (xv) a compound of formula I, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R² is fluoro, and all remaining substituents have the significances given herein before.

Another embodiment of the present invention is (xvi) a compound of formula I, or a
10 pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R³ and R⁴ together with the nitrogen to which they are attached form aminocarbonylpiperidinyl, hydroxypyrrolidinyl or C₁₋₆alkoxypyrrolidinyl, and all remaining substituents have the significances given herein before.

Another further embodiment of the present invention is (xvii) a compound of formula I, or
15 a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R³ and R⁴ together with the nitrogen to which they are attached form aminocarbonylpiperidinyl, hydroxypyrrolidinyl or methoxypyrrolidinyl, and all remaining substituents have the significances given herein before.

Another embodiment of the present invention is (xviii) a compound selected from
20 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]pyrrolidin-3-ol;

1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidin-3-ol;

1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-
25 pyridyl]pyrrolidine-3-carboxamide;

1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidine-3-carboxamide;

1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]pyrrolidine-3-carboxylic acid;

1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidine-3-carboxylic acid;

1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperidine-4-carboxamide;

5 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperidine-4-carboxamide;

1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperidine-3-carboxamide;

10 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperidine-3-carboxamide;

N-(2,2-difluoroethyl)-2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]pyridin-2-amine;

N-(2,2-difluoroethyl)-4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]pyridin-2-amine;

15 6-[6-fluoro-4-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-fluoro-6-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

20 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]-N-methylsulfonyl-pyrrolidine-3-carboxamide; and

1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]-N-methylsulfonyl-pyrrolidine-3-carboxamide;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

25 A further embodiment of the present invention is (xix) a compound which is 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperidine-4-carboxamide; or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

Another embodiment of the present invention is (xx) a compound of formula I, wherein

R¹ is C₁₋₆alkyl;

R² is halogen;

30 One of R³ and R⁴ is C₁₋₆alkyl; the other one is C₁₋₆alkylcarbonyl, C₁₋₆alkylsulfonyl, C₃₋

7cycloalkylcarbonyl or C₃₋₇cycloalkylsulfonyl; or

R³ and R⁴ together with the nitrogen to which they are attached form

- 1,1-dioxo-thiazolidinyl;
 1,1-dioxo-thiazinanyl;
 azetidiny;
 morpholinyl substituted once or twice by C₁₋₆alkyl;
 5 oxoimidazolidinyl;
 diC₁₋₆alkyl-oxooxazolidinyl;
 oxopiperazinyl substituted with one or two substituents independently selected from C₁₋₆alkyl, C₁₋₆alkylcarbonyl and C₁₋₆alkylsulfonyl;
 oxopyrrolidinyl;
 10 C₁₋₆alkyloxopyrrolidinyl;
 piperazinyl substituted with one, two or three substituents independently selected from C₁₋₆alkyl, C₁₋₆alkylcarbonyl and C₁₋₆alkylsulfonyl; or
 pyrrolidinyl substituted with one, two or three substituents independently selected from C₁₋₆alkyl and carboxy;
 15 A is N or CH;
 One of W, Q and Y is N, the others are CH;
 or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

Another embodiment of the present invention is (xxi) a compound of formula I, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R¹ is methyl,
 20 and all remaining substituents have the significances given herein before.

Another embodiment of the present invention is (xxii) a compound of formula I, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R² is fluoro, and all remaining substituents have the significances given herein before.

Another embodiment of the present invention is (xxiii) a compound of formula I, or a
 25 pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R³ and R⁴ together with the nitrogen to which they are attached form azetidiny; morpholinyl substituted once or twice by C₁₋₆alkyl; C₁₋₆alkyloxopiperazinyl; C₁₋₆alkyloxopyrrolidinyl; piperazinyl substituted with one, two or three substituents independently selected from C₁₋₆alkyl, C₁₋₆alkylcarbonyl and C₁₋₆alkylsulfonyl; or C₁₋₆alkylpyrrolidinyl, and all remaining substituents
 30 have the significances given herein before.

A further embodiment of the present invention is (xxiv) a compound of formula I, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R³ and R⁴ together with the nitrogen to which they are attached form azetidiny; methylmorpholinyl; ethylmorpholinyl; dimethylmorpholinyl; methyloxopiperazinyl; methyloxopyrrolidinyl; piperazinyl substituted with one, two or three substituents independently selected from acetyl, ethylsulfonyl, methyl and methylsulfonyl; or methylpyrrolidinyl, and all remaining substituents have the significances given herein before.

Another embodiment of the present invention is (xxv) a compound of formula I, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein A is N, and all remaining substituents have the significances given herein before.

Another embodiment of the present invention is (xxvi) a compound of formula I, wherein R¹ is C₁₋₆alkyl;
R² is halogen;
R³ and R⁴ together with the nitrogen to which they are attached form

piperazinyl substituted with one, two or three substituents independently selected from C₁₋₆alkyl, C₁₋₆alkylcarbonyl and C₁₋₆alkylsulfonyl;

A is N or CH;

One of W, Q and Y is N, the others are CH;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

A further embodiment of the present invention is (xxvii) a compound of formula I, wherein

R¹ is methyl;

R² is fluoro;

piperazinyl substituted with one, two or three substituents independently selected from acetyl, ethylsulfonyl, methyl and methylsulfonyl;

A is N or CH;

One of W, Q and Y is N, the others are CH;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

Another embodiment of the present invention is (xxviii) a compound selected from 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-methyl-morpholine;

4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-methyl-morpholine;

2-ethyl-4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine;

5 2-ethyl-4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholine;

4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2,2-dimethyl-morpholine;

10 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2,2-dimethyl-morpholine;

1-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]ethanone;

1-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]ethanone;

15 6-[6-fluoro-4-(3-methylpyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-fluoro-6-(3-methylpyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

20 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-methyl-morpholine;

4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-3-methyl-morpholine;

6-[4-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

25 6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

1-[4-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperazin-1-yl]ethanone;

30 1-[4-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperazin-1-yl]ethanone;

6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-(4-ethylsulfonylpiperazin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

5 6-[6-(4-ethylsulfonylpiperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-4,4-dimethyl-pyrrolidine-3-carboxylic acid;

10 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4,4-dimethyl-pyrrolidine-3-carboxylic acid;

(5R)-6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

(5S)-6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

15 6-[6-(3,3-dimethyl-4-methylsulfonyl-piperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-(3,3-dimethyl-4-methylsulfonyl-piperazin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

20 6-[4-fluoro-6-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-fluoro-4-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[2-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

25 6-[6-(azetidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-(azetidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

30 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-2-one;

3-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-5,5-dimethyl-oxazolidin-2-one;

2-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-1,2-thiazolidine 1,1-dioxide;

4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-3-methyl-piperazin-2-one;

5 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-methyl-piperazin-2-one;

4-acetyl-1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-2-one;

10 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-methylsulfonyl-piperazin-2-one;

4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-6-methyl-piperazin-2-one;

4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-6-methyl-piperazin-2-one;

15 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-1,4-thiazinane 1,1-dioxide;

6-[2-(azetidin-1-yl)-6-fluoro-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

20 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-methyl-pyrrolidin-2-one;

N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-acetamide;

N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-propanamide;

25 N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-cyclopropanecarboxamide;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]imidazolidin-2-one;

30 N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-methanesulfonamide;

N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-cyclopropanesulfonamide; and

2-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]thiazinane 1,1-dioxide;
or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

Another embodiment of the present invention is (xxix) a compound selected from

1-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]ethanone;

1-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]ethanone;

6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

1-[4-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperazin-1-yl]ethanone;

1-[4-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperazin-1-yl]ethanone;

6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-(4-ethylsulfonylpiperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

(5R)-6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-fluoro-4-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine; and

6-[2-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

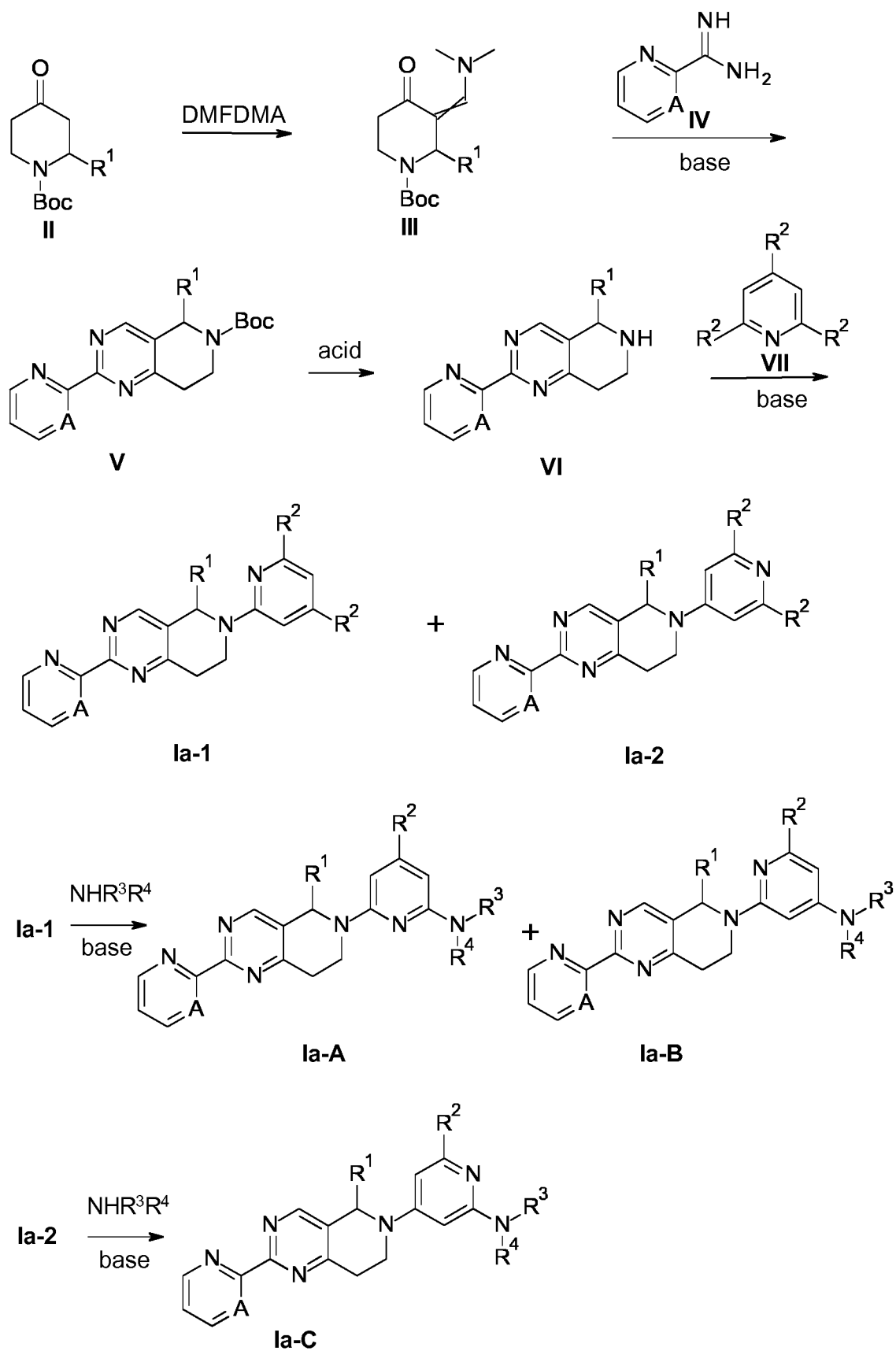
or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

SYNTHESIS

The compounds of the present invention can be prepared by any conventional means. Suitable processes for synthesizing these compounds as well as their starting materials are provided in the schemes below and in the examples. All substituents, in particular, A, W, Q and Y are defined as above unless otherwise indicated. Furthermore, and unless explicitly otherwise stated, all reactions, reaction conditions, abbreviations and symbols have the meanings well known to a person of ordinary skill in organic chemistry.

General synthetic route for Compound **Ia-A**, **Ia-B** and **Ia-C** (Scheme 1)

Scheme 1

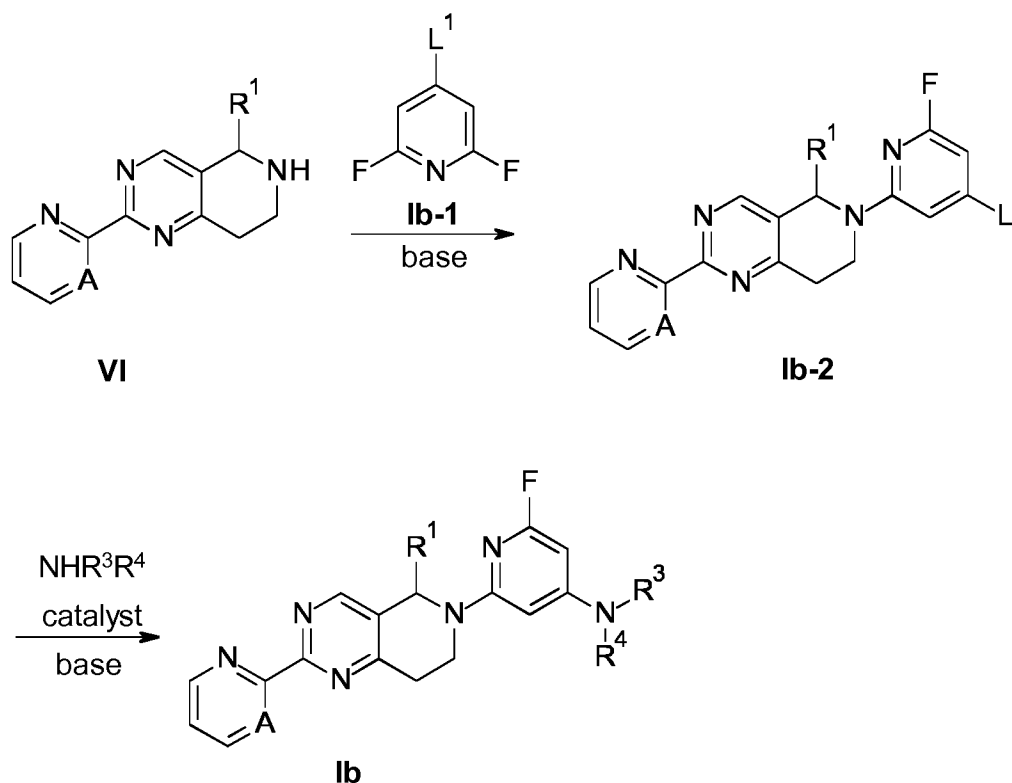


The compound of formula **Ia-A**, **Ia-B** and **Ia-C** can be prepared according to Scheme 1, wherein R^2 is F, Cl or Br.

Treatment of compound **II** with DMFDMA in the presence or absence of a suitable solvent such as DMF and CH_3CN produces intermediate **III**. Cyclization of intermediate **III** with
 5 compound **IV** affords compound **V**. The reaction can be carried out in the presence of a suitable base such as NaOMe, $NaHCO_3$ or K_2CO_3 in a suitable solvent such as MeOH or EtOH. Deprotection of compound **V** with an acid such as HCl or TFA generates intermediate **VI**. Coupling of intermediate **VI** with halopyridine **VII** in the presence of a suitable base such as DIPEA in a suitable solvent such as DMSO or NMP gives compound **Ia-1** and **Ia-2**. Compound
 10 **Ia-A**, **Ia-B** and **Ia-C** can be obtained by reaction of compound **Ia-1** or **Ia-2** with amine NHR^3R^4 in the presence of a suitable base such as K_2CO_3 or DIPEA in a suitable solvent such as NMP or DMSO, respectively.

General synthetic route for Compound **Ib** (Scheme 2)

Scheme 2



The compound of formula **Ib** can be prepared according to Scheme 2, wherein L^1 is Cl, Br or I.

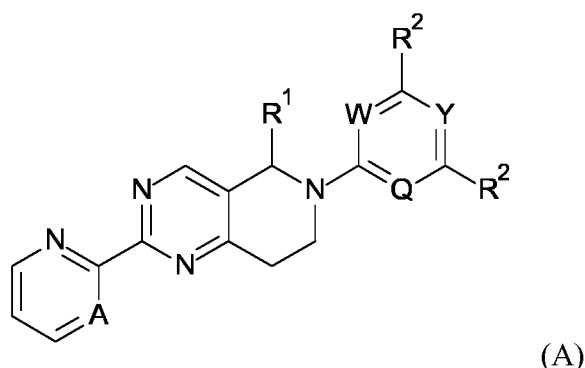
Condensation of intermediate **VI** with fluoropyridine **Ib-1** in the presence of a suitable base such as DIPEA or $NaHCO_3$ in a suitable solvent such as DMSO produces compound **Ib-2**.

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Compound **Ib** can be obtained by coupling of compound **Ib-2** with amine NHR^3R^4 in the presence of a suitable catalyst such as $\text{Pd}(\text{OAc})_2$, a suitable ligand such as Xantphos and a suitable base such as Cs_2CO_3 in a suitable solvent such as dioxane.

This invention also relates to a process for the preparation of a compound of formula I comprising one of the following steps:

(a) coupling of a compound of formula (A)



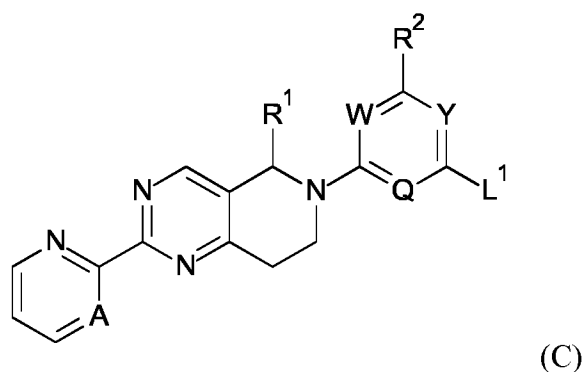
with a compound of formula (B)

NHR^3R^4 (B)

in the presence of a base;

wherein R^1 , R^3 and R^4 , A, U, W, Q and Y are defined as above; R^2 is F, Cl or Br; the base can be for example K_2CO_3 or DIPEA;

(b) coupling of a compound of formula (C)



with a compound of formula (B)

NHR^3R^4 (B)

in the presence of a catalyst, a ligand and a base;

wherein R^1 to R^4 , A, U, W, Q and Y are defined as above; L^1 is Cl, Br or I; the catalyst can be for example $\text{Pd}(\text{OAc})_2$; the ligand can be for example Xantphos; the base can be for example Cs_2CO_3 .

A compound of formula I when manufactured according to the above process is also an object of the invention.

PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

5 The invention also relates to a compound of formula I for use as therapeutically active substance.

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

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being
20 treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The “effective amount” of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit HBsAg. For example, such amount may be below the
25 amount that is toxic to normal cells, or the mammal as a whole.

In one example, the pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.01 to 100 mg/kg, alternatively about 0.01 to 100 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. In another embodiment, oral unit dosage forms, such

as tablets and capsules, preferably contain from about 0.1 to about 1000 mg of the compound of the invention.

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

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art.

The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

An example of a suitable oral dosage form is a tablet containing about 0.1 to 1000 mg of the compound of the invention compounded with about 0 to 2000 mg anhydrous lactose, about 0 to 2000 mg sodium croscarmellose, about 0 to 2000 mg polyvinylpyrrolidone (PVP) K30, and about 0 to 2000 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 0.1 to 1000 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

An embodiment, therefore, includes a pharmaceutical composition comprising a compound of Formula I, or a stereoisomer or pharmaceutically acceptable salt thereof. In a further embodiment includes a pharmaceutical composition comprising a compound of Formula I, or a stereoisomer or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

The following example A and B illustrate typical compositions of the present invention, but serve merely as representative thereof.

Example A

A compound of formula I can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

	<u>Per tablet</u>
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	<u>20 mg</u>
	425 mg

Example B

A compound of formula I can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

	<u>Per capsule</u>
Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	<u>0.5 mg</u>
	220.0 mg

INDICATIONS AND METHODS OF TREATMENT

The compounds of the invention can inhibit HBsAg production or secretion and inhibit HBV gene expression. Accordingly, the compounds of the invention are useful for the treatment or prophylaxis of HBV infection.

The invention relates to the use of a compound of formula I for the inhibition of HBsAg production or secretion.

The invention relates to the use of a compound of formula I for the inhibition of HBV DNA production.

5 The invention relates to the use of a compound of formula I for the inhibition of HBV gene expression.

The invention relates to the use of a compound of formula I for the treatment or prophylaxis of HBV infection.

10 The use of a compound of formula I for the preparation of medicaments useful in the treatment or prophylaxis diseases that are related to HBV infection is an object of the invention.

The invention relates in particular to the use of a compound of formula I for the preparation of a medicament for the treatment or prophylaxis of HBV infection.

15 Another embodiment includes a method for the treatment or prophylaxis of HBV infection, which method comprises administering an effective amount of a compound of Formula I, a stereoisomer, tautomer, prodrug, conjugates or pharmaceutically acceptable salt thereof.

EXAMPLES

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

Abbreviations used herein are as follows:

20	μL :	microliter
	μm :	micrometer
	μM :	micromoles per liter
	(Boc) ₂ O:	di- <i>tert</i> -butyl dicarbonate
	BSA:	bovine serum albumin
25	IC ₅₀ :	the half maximal inhibitory concentration
	LC/MS:	liquid chromatography/mass spectrometry
	M:	molarity
	MHz:	megahertz

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	min:	minute
	hr(s):	hour(s)
	mM:	millimoles per liter
	MS (ESI):	mass spectroscopy (electron spray ionization)
5	nM:	nanomoles per liter
	NMR:	nuclear magnetic resonance
	obsd.	observed
	rt:	room temperature
	Pd/C:	palladium on activated carbon
10	Pd(OAc) ₂	Palladium(II) acetate
	TFA:	trifluoroacetic acid
	δ:	chemical shift
	Xantphos:	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
	DMFDMA:	<i>N,N</i> -dimethylformamide dimethyl acetal
15	DIPEA:	<i>N,N</i> -diisopropylethylamine
	CDI:	1,1'-carbonyldiimidazole
	NMP:	<i>N</i> -methyl-2-pyrrolidone
	DMA:	<i>N,N</i> -dimethylacetamide

20 GENERAL EXPERIMENTAL CONDITIONS

Intermediates and final compounds were purified by flash chromatography using one of the following instruments: i) Biotage SP1 system and the Quad 12/25 Cartridge module. ii) ISCO combi-flash chromatography instrument. Silica gel Brand and pore size: i) KP-SIL 60 Å, particle size: 40-60 µm; ii) CAS registry NO: Silica Gel: 63231-67-4, particle size: 47-60 micron silica gel; iii) ZCX from Qingdao Haiyang Chemical Co., Ltd, pore: 200-300 or 300-400.

Intermediates and final compounds were purified by preparative HPLC on reversed phase column using X BridgeTM Perp C₁₈ (5 µm, OBDTM 30 × 100 mm) column or SunFireTM Perp C₁₈ (5 µm, OBDTM 30 × 100 mm) column.

Chiral Separation was conducted on Thar 350 preparative SFC using ChiralPak AD-10u (200 x 50 mm I.D.) with mobile phase A for CO₂ and B for ethanol.

LC/MS spectra were obtained using an Acquity Ultra Performance LC - 3100 Mass Detector or Acquity Ultra Performance LC - SQ Detector. Standard LC/MS conditions were as follows (running time 3 minutes):

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Acidic condition: A: 0.1% formic acid in H₂O; B: 0.1% formic acid in acetonitrile;

Basic condition: A: 0.05% NH₃·H₂O in H₂O; B: acetonitrile;

Neutral condition: A: H₂O; B: acetonitrile.

Mass spectra (MS): generally only ions which indicate the parent mass are reported, and
5 unless otherwise stated the mass ion quoted is the positive mass ion (M+H)⁺.

The microwave assisted reactions were carried out in a Biotage Initiator Sixty or CEM
Discover.

NMR Spectra were obtained using Bruker Avance 400MHz.

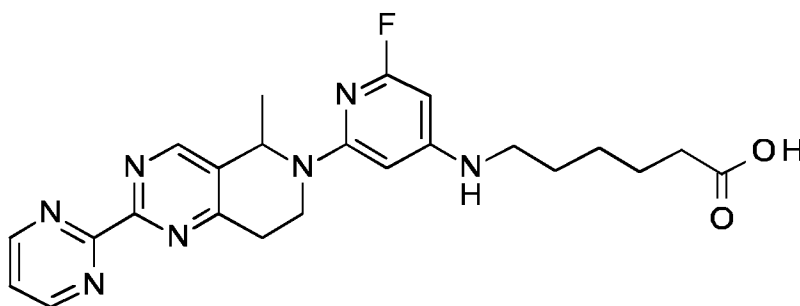
Optical rotation was measured on a AUTOPOL[®] V automatic polarimeter.

10 All reactions involving air-sensitive reagents were performed under an argon atmosphere.
Reagents were used as received from commercial suppliers without further purification unless
otherwise noted.

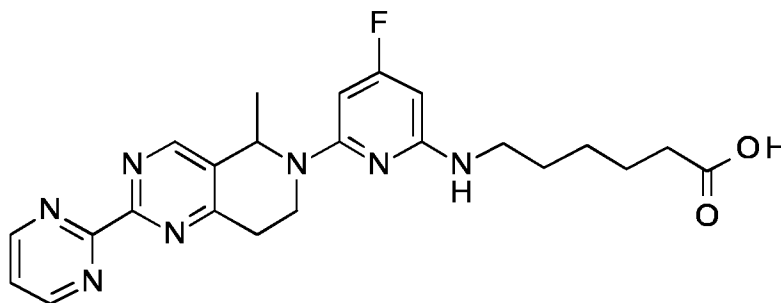
PREPARATIVE EXAMPLES

Example 1 and 2

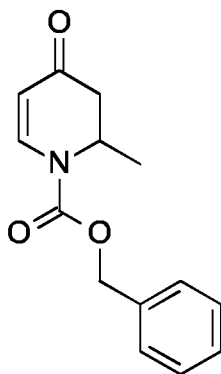
15 6-[[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]hexanoic acid and 6-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]amino]hexanoic acid



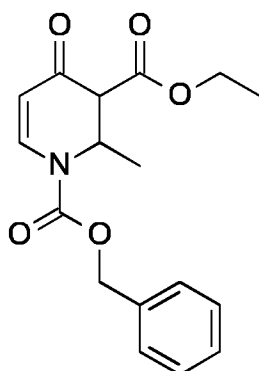
Example 1



Example 2

Step 1: Preparation of benzyl 2-methyl-4-oxo-2,3-dihydropyridine-1-carboxylate

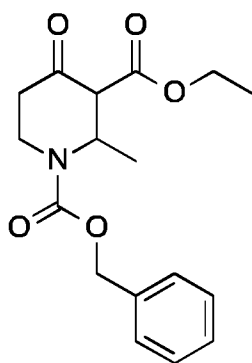
To a stirred solution of 4-methoxypyridine (50.0 g, 458 mmol) in anhydrous THF (500 mL) was added a solution of benzyl chloroformate (50.0 g, 458 mmol) in anhydrous THF (400 mL) at -25 °C. After being stirred for 1 hr at the same temperature, the reaction mixture was cooled to -40 °C. Then to the cooled mixture was added drop-wise methylmagnesium bromide (3.0 M in diethyl ether, 183 mL, 550 mmol). After the addition, the cooling bath was removed. The resulting mixture was stirred at rt for 0.5 hr and then poured into 10 % aqueous HCl (1 L). The resulting mixture was stirred further at rt for 10 mins. The reaction was conducted at the same scale for 4 times. The resulting mixtures from 4 batches were combined, and then extracted with EA (2 L) twice. The organic layers were combined and washed sequentially with saturated aqueous NaHCO₃ (1 L) and brine (1 L), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with PE/EA=3/1, v:v) to give benzyl 2-methyl-4-oxo-2,3-dihydropyridine-1-carboxylate (420.0 g) as a colorless oil.

Step 2: Preparation of O1-benzyl O3-ethyl 2-methyl-4-oxo-2,3-dihydropyridine-1,3-dicarboxylate

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To a solution of benzyl 2-methyl-4-oxo-2,3-dihydropyridine-1-carboxylate (100.0 g, 400 mmol) in THF (1 L) was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 960 mL, 960 mmol) drop-wise at -70 °C. The resulting mixture was stirred at this temperature for 1 hr. Then to the reaction mixture was added ethyl chloroformate (55.4 g, 440 mmol), and the resulting mixture was stirred further at -70 °C for 3 hrs. The reaction was conducted at the same scale for 4 times. The resulting mixtures from 4 batches were combined, diluted with saturated aqueous NH₄Cl (300 mL), and then extracted with EA (3 L). The organic layer was washed sequentially with water (1 L) and brine (1 L), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give O1-benzyl O3-ethyl 2-methyl-4-oxo-2,3-dihydropyridine-1,3-dicarboxylate (440.0 g, crude) as a yellow oil, which was used in the next step without any further purification.

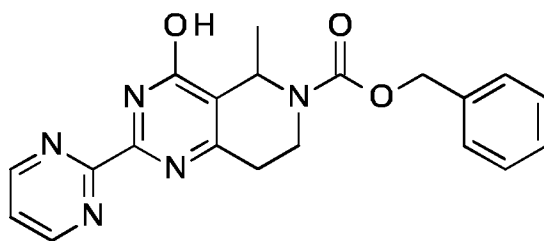
Step 3: Preparation of O1-benzyl O3-ethyl 2-methyl-4-oxo-piperidine-1,3-dicarboxylate



To a solution of O1-benzyl O3-ethyl 2-methyl-4-oxo-2,3-dihydropyridine-1,3-dicarboxylate (110 g, 347 mmol) in acetic acid (1 L) was added Zn (113 g, 1733 mmol, Alfa) portion-wise. The resulting mixture was heated at 75 °C with stirring for 3 hrs. The reaction was conducted at the same scale for 4 times. The resulting mixtures from 4 batches were combined and filtered. The filtrate was concentrated *in vacuo*. The residue was diluted with EA (3 L). The resulting mixture was washed sequentially with water (1 L), aqueous NaHCO₃ (500 mL) and brine (1 L), and then concentrated *in vacuo*. The residue was purified by column chromatography (eluting with PE/EA=20/1, v:v) to give O1-benzyl O3-ethyl 2-methyl-4-oxo-piperidine-1,3-dicarboxylate (210 g) as a yellow oil.

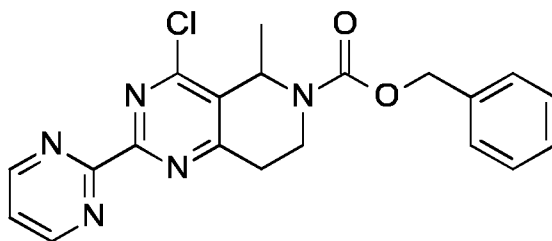
Step 4: Preparation of benzyl 4-hydroxy-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate

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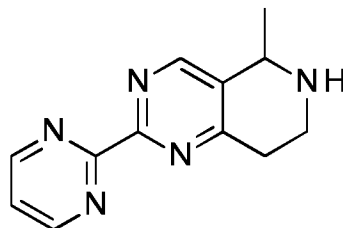
To a solution of O1-benzyl O3-ethyl 2-methyl-4-oxo-piperidine-1,3-dicarboxylate (100.0 g, 313 mmol) in 2,2,2-trifluoroethanol (700 mL) was added K_2CO_3 (129.8 g, 939 mmol) and 2-amidinopyrimidine hydrochloride (54.6 g, 344 mmol). The resulting mixture was heated at 80 °C under N_2 for 20 hrs. The reaction was conducted at the same scale twice. The resulting mixtures from 2 batched were combined and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (eluting with DCM/MeOH=20/1, v:v) to give benzyl 4-hydroxy-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate (170 g) as a yellow oil.

Step 5: Preparation of benzyl 4-chloro-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate



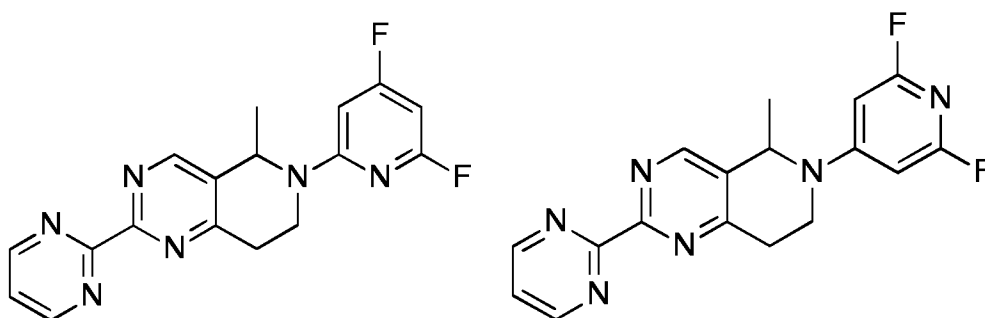
To a solution of benzyl 4-hydroxy-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate (85.0 g, 225 mmol) in MeCN (800 mL) was added $POCl_3$ (172.7 g, 1130 mmol) drop-wise. The mixture was stirred at 60 °C with stirring for 3 hrs. The reaction was conducted at the same scale twice. The resulting mixtures from 2 batched were combined, and poured into ice water (2 L). Then the resulting mixture was stirred for 10 mins and concentrated *in vacuo* to remove MeCN. The resulting aqueous mixture was basified with saturated aqueous $NaHCO_3$ to pH 7-8, and then extracted with EA (1 L) twice. The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with DCM/MeOH=20/1, v:v) to give benzyl 4-chloro-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate (150.0 g) as a green oil.

Step 6: Preparation of 5-methyl-2-pyrimidin-2-yl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



To a solution of benzyl 4-chloro-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate (30.0 g, 75.8 mmol) in EtOH (600 mL) was added NH₄OH (150 mL), H₂O (150 mL) and Pd/C (9.0 g, 10 % wt). The mixture was stirred under H₂ (20 psi) at 15 °C for 12 hrs. The reaction was conducted at the same scale for 5 times. The resulting mixtures from 5 batched were combined, and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH (800 mL), and then to the solution was added K₂CO₃ (83.8 g, 606.6 mmol).
10 The resulting mixture was stirred at 15 °C for 1 hr, and then filtered. The filtrate was concentrate *in vacuo* to give 5-methyl-2-pyrimidin-2-yl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (45.0 g) as a green solid, which was used in the next step without any further purification.

Step 7: Preparation of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-(2,6-difluoro-4-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine

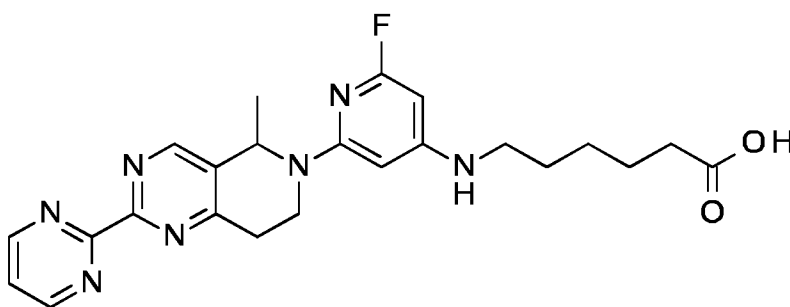


To a mixture of 5-methyl-2-pyrimidin-2-yl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (2.0 g, 8.8 mmol) and 2, 4, 6-trifluoropyridine (1.4 g, 10.6 mmol) in NMP (15 mL) was added DIPEA (3.4 g, 26.4 mmol). Then the reaction vessel was sealed and heated under microwave at
20 150 °C for 1 hr. The reaction was conducted at the same scale for 10 times. The resulting mixtures from 10 batched were combined and diluted with EA (600 mL). The resulting mixture

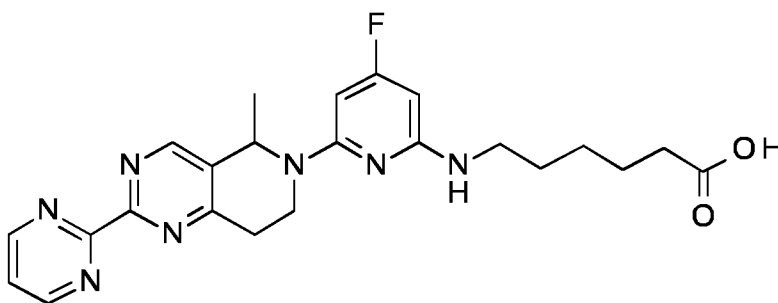
-41-

was washed sequentially with water (200 mL) and brine (200 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with DCM/MeOH=20/1, v:v) and prep-HPLC to give 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (3.5 g) and 6-(2,6-difluoro-4-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (1.0 g).

Step 8: Preparation of 6-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]amino]hexanoic acid and 6-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]amino]hexanoic acid



Example 1



Example 2

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (100 mg, 294 μmol), 6-aminohexanoic acid (57.8 mg, 441 μmol) and potassium carbonate (81.2 mg, 588 μmol) in DMSO (2 mL) was heated at 120 °C in a microwave reactor for 1 hr. The mixture was cooled to rt and purified by prep-HPLC to give 6-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]amino]hexanoic acid (40 mg) and 6-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-

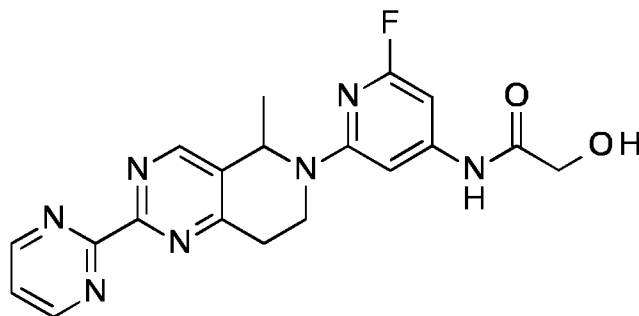
dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]amino]hexanoic acid (10 mg) as light brown solids.

Example 1: 6-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]amino]hexanoic acid, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm:
 5 1.46 (br s, 2 H), 1.55 (d, 3 H), 1.59 - 1.72 (m, 4 H), 2.14 - 2.42 (m, 3 H), 3.07 - 3.31 (m, 3 H), 3.38 - 3.51 (m, 1 H), 4.33 - 4.46 (m, 1 H), 5.53 (d, 1 H), 5.65 - 5.88 (m, 1 H), 7.62 - 7.70 (m, 1 H), 8.20 (s, 1H), 8.85 (s, 1 H), 9.02 (d, 2 H). MS obsd. (ESI⁺) [(M+H)⁺] : 452.

Example 2: 6-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]amino]hexanoic acid, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm:
 10 1.40 - 1.71 (m, 9 H), 2.28 - 2.37 (m, 2 H), 3.05 - 3.24 (m, 4 H), 3.40 - 3.56 (m, 1 H), 4.51 (br dd, 1 H), 5.54 (d, 1 H), 5.68 - 5.90 (m, 1 H), 7.61 - 7.66 (m, 1 H), 8.11 (br s, 1 H), 8.89 (s, 1 H), 9.04 (br d, 2 H). MS obsd. (ESI⁺) [(M+H)⁺] : 452.

Example 3

***N*-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-2-hydroxy-acetamide**
 15

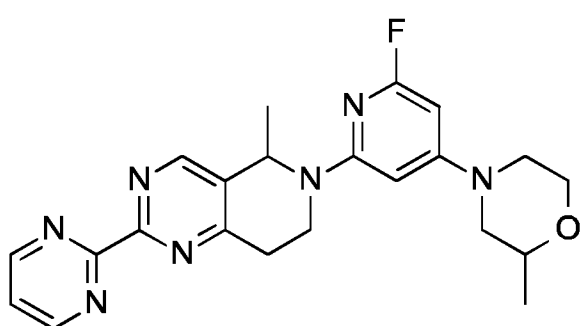


To a stirred solution of 2-hydroxyacetamide (26.5 mg, 0.35 mmol) in DMF (1 mL) was added NaH (28 mg, 0.70 mmol) and 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol)
 20 at 0 °C successively. After being heated at 80 °C for 1 hr, the resulting mixture was partitioned between EA (150 mL) and brine (50 mL). The separated organic layer was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-2-hydroxy-acetamide (24 mg) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm:
 25 10.10 (s, 1 H), 8.99 (d, 2 H), 8.95 (s, 1 H), 7.63 (t, 1 H), 7.17 (s, 1 H), 6.82 (s, 1 H), 5.56 (m, 1

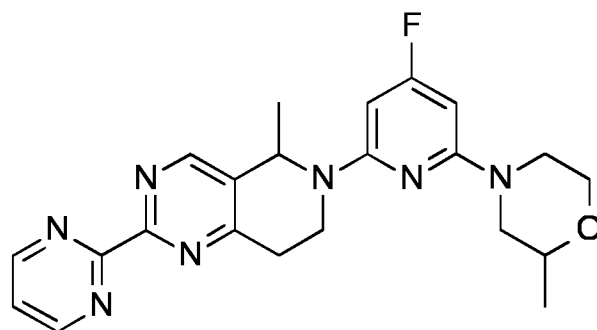
H), 4.32 (d, 1 H), 4.02 (s, 2 H), 3.47 - 3.54 (m, 1 H), 2.97 - 3.11 (m, 2 H), 1.47 - 1.57 (m, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 396.

Example 4 and 5

5 4-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-methyl-morpholine and 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-methyl-morpholine



Example 4



Example 5

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80.0 mg, 0.235 mmol), 2-methylmorpholine (71.3 mg, 0.705 mmol) and K₂CO₃ (97.4 mg, 0.705 mmol) in DMA (3 mL) was heated at 110 °C for 15 hrs. The resulting mixture was poured into brine (4 mL) and then extracted with DCM (3 mL) for 4 times. The combined organic layers were washed sequentially with water and brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-methyl-morpholine (12.7 mg) as a yellow solid and 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-methyl-morpholine (11.0 mg) as a yellow solid.

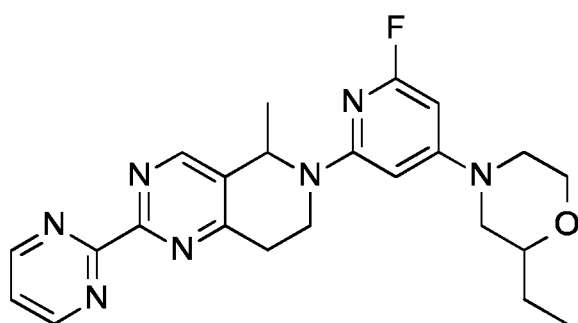
Example 4: 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-methyl-morpholine, ¹H NMR (400 MHz CDCl₃) δ ppm: 8.98 - 9.06 (m, 2 H), 8.81 (s, 1 H), 7.43 (t, 1 H), 5.82 (s, 1 H), 5.63 - 5.74 (m, 2 H), 4.33 - 4.42 (m, 1 H), 3.97 - 4.05 (m, 1 H), 3.72 (br. s., 2 H), 3.42 - 3.59 (m, 3 H), 3.20 - 3.30 (m, 2 H), 2.97 (d, 1 H), 2.63 (d, 1 H), 1.56 (d, 3 H), 1.27 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 422.

Example 5: 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-methyl-morpholine, ¹H NMR (400 MHz CDCl₃) δ ppm: 9.03 (d,

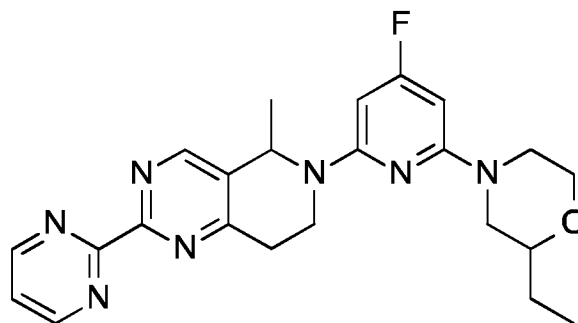
2 H), 8.81 (s, 1 H), 7.44 (t, 1 H), 5.79 - 5.88 (m, 1 H), 5.72 (d, 1 H), 5.56 - 5.65 (m, 1 H), 4.37 - 4.50 (m, 1 H), 4.01 (br. s., 3 H), 3.69 (dd, 2 H), 3.40 - 3.51 (m, 1 H), 3.19 - 3.32 (m, 2 H), 2.95 (s, 1 H), 2.61 (s, 1 H), 1.57 (d, 3 H), 1.28 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 422.

Example 6 and 7

- 5 **2-Ethyl-4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine and 2-ethyl-4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholine**



Example 6



Example 7

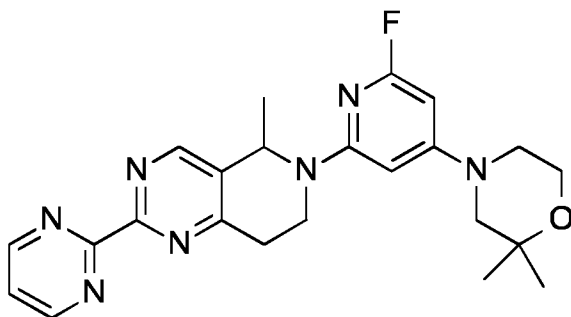
- 10 A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80.0 mg, 0.235 mmol), 2-ethylmorpholine (81.2 mg, 0.705 mmol) and K₂CO₃ (97.4 mg, 0.705 mmol) in DMA (3 mL) was heated at 110 °C for 15 hrs, and then poured into brine (4 mL). The resulting mixture was extracted with DCM (3 mL) for 4 times. The combined organic layers were washed sequentially
- 15 with water then brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by prep-HPLC to afford 2-ethyl-4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine (23.7 mg) as a light yellow solid and 2-ethyl-4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholine (10.6 mg) as a yellow solid.

- 20 **Example 6:** 2-ethyl-4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine, ¹H NMR (400 MHz CDCl₃) δ ppm: 9.02 (d, 2 H), 8.81 (s, 1 H), 7.43 (t, 1 H), 5.82 (s, 1 H), 5.65 - 5.74 (m, 2 H), 4.30 - 4.44 (m, 1 H), 3.98 - 4.08 (m, 1 H), 3.64 - 3.77 (m, 1 H), 3.38 - 3.59 (m, 4 H), 3.17 - 3.35 (m, 2 H), 2.92 - 3.04 (m, 1 H), 2.58 - 2.69 (m, 1 H), 1.56 (m, 5 H), 1.03 (t, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 436.

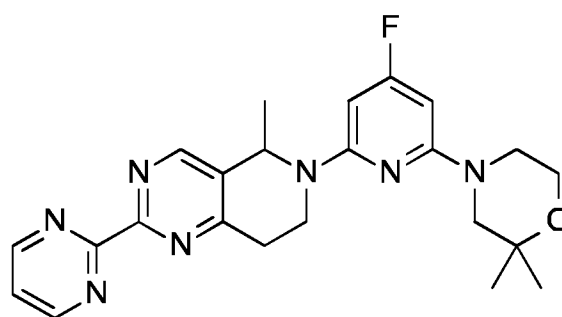
Example 7: 2-ethyl-4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholine, ¹H NMR (400 MHz CDCl₃) δ ppm: 9.04 (d, 2 H), 8.80 (s, 1 H), 7.41 - 7.46 (m, 1 H), 5.80 - 5.87 (m, 1 H), 5.69 - 5.75 (m, 1 H), 5.58 - 5.67 (m, 1 H), 4.36 - 4.47 (m, 1 H), 3.89 - 4.09 (m, 3 H), 3.64 - 3.75 (m, 1 H), 3.39 - 3.52 (m, 2 H), 3.18 - 3.29 (m, 2 H), 2.91 - 3.03 (m, 1 H), 2.58 - 2.68 (m, 1 H), 1.61 - 1.70 (m, 2 H), 1.57 (d, 3 H), 1.04 (t, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 436.

Example 8 and 9

4-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2,2-dimethyl-morpholine and 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2,2-dimethyl-morpholine



Example 8



Example 9

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80.0 mg, 0.235 mmol), 2,2-dimethylmorpholine (81.2 mg, 0.705 mmol) and K₂CO₃ (97.4 mg, 0.705 mmol) in DMA (3 mL) was heated at 110 °C for 15 hrs, and at 130 °C for 15 hrs. The resulting mixture was poured into brine (4 mL), and extracted with DCM (3 mL) for 4 times. The combined organic layers were washed sequentially with water and brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2,2-dimethyl-morpholine (21.5 mg) as a light yellow solid and 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2,2-dimethyl-morpholine (11.2 mg) as a yellow solid.

Example 8: 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2,2-dimethyl-morpholine, ¹H NMR (400 MHz CDCl₃) δ ppm: 9.00 - 9.05 (m, 2 H), 8.81 (s, 1 H), 7.41 - 7.45 (m, 1 H), 5.76 - 5.80 (m, 1 H), 5.68 - 5.73 (m, 1 H),

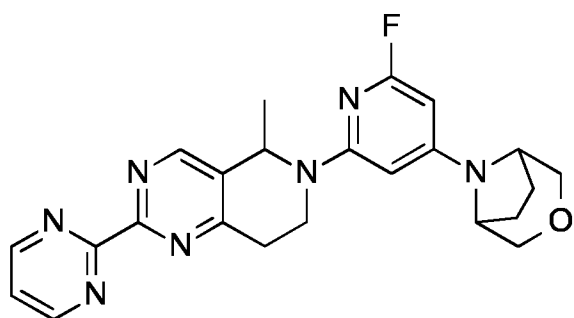
-46-

5.67 (s, 1 H), 4.32 - 4.42 (m, 1 H), 3.81 - 3.90 (m, 2 H), 3.41 - 3.53 (m, 1 H), 3.19 - 3.33 (m, 4 H), 3.11 (s, 2 H), 1.53 - 1.59 (m, 3 H), 1.30 (s, 6 H). MS obsd. (ESI⁺) [(M+H)⁺]: 436.

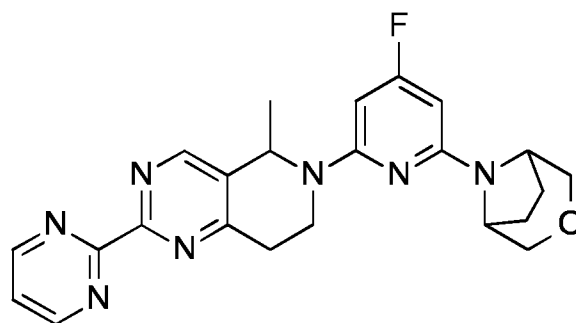
Example 9: 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2,2-dimethyl-morpholine, ¹H NMR (400 MHz CDCl₃) δ ppm: 9.03 (d, 2 H), 8.81 (s, 1 H), 7.41 - 7.46 (m, 1 H), 5.77 - 5.83 (m, 1 H), 5.65 - 5.72 (m, 1 H), 5.56 - 5.64 (m, 1 H), 4.37 - 4.48 (m, 1 H), 3.79 - 3.90 (m, 2 H), 3.39 - 3.61 (m, 3 H), 3.17 - 3.36 (m, 4 H), 1.57 (d, 3 H), 1.30 (s, 6 H). MS obsd. (ESI⁺) [(M+H)⁺]: 436.

Example 10 and 11

8-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-oxa-8-azabicyclo[3.2.1]octane and 8-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-3-oxa-8-azabicyclo[3.2.1]octane



Example 10



Example 11

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.3 mmol), 3-oxa-8-azabicyclo[3.2.1]octane hydrochloride (132 mmol) and K₂CO₃ (122 mg, 0.9 mmol) in DMA (1 mL) was heated at 110 °C with stirring for 12 hrs. The resulting mixture was cooled to rt and concentrated *in vacuo*. The residue was partitioned between DCM (10 mL) and brine (5 mL). The organic layer was concentrated *in vacuo*. The residue was purified by prep-HPLC to give 8-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-oxa-8-azabicyclo[3.2.1]octane (7.8 mg) as a white solid and 8-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-3-oxa-8-azabicyclo[3.2.1]octane (3.1 mg) as a white solid.

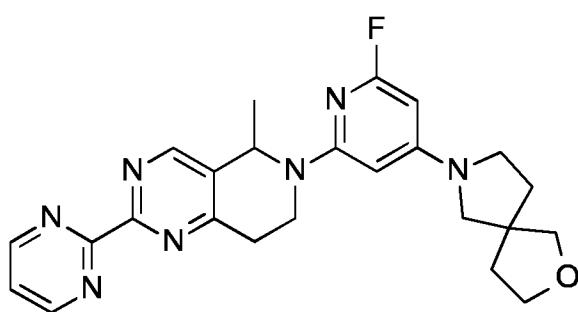
Example 10: 8-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-oxa-8-azabicyclo[3.2.1]octane, ¹H NMR (400 MHz, CDCl₃) δ

ppm: 9.05 (d, 2H), 8.83 (s, 1H), 7.45 (t, 1H), 5.77 - 5.67 (m, 2H), 5.62 (s, 1H), 4.46 - 4.35 (m, 1H), 4.11 (br. s., 2H), 3.87 (d, 2H), 3.58 (d, 2H), 3.54 - 3.43 (m, 1H), 3.37 - 3.19 (m, 2H), 2.19 - 2.03 (m, 4H), 1.60 (br. s., 3H) MS obsd. (ESI⁺) [(M+H)⁺]: 434.

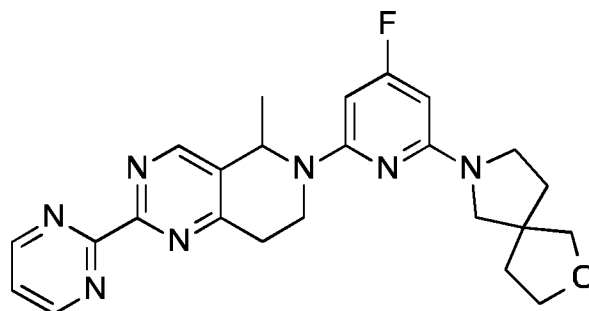
Example 11: 8-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-3-oxa-8-azabicyclo[3.2.1]octane, ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.05 (d, 2H), 8.82 (s, 1H), 7.45 (t, 1H), 5.82 (d, 1H), 5.69 (d, 1H), 5.65 (d, 1H), 4.46 - 4.33 (m, 3H), 3.92 - 3.83 (m, 2H), 3.66 - 3.60 (m, 2H), 3.53 - 3.42 (m, 1H), 3.33 - 3.22 (m, 2H), 2.15 - 1.96 (m, 4H), 1.59 (br. s., 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 434.

Example 12 and 13

10 **7-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-7-azaspiro[4.4]nonane and 7-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-7-azaspiro[4.4]nonane**



Example 12



Example 13

15 A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.3 mmol), 2-oxa-7-azaspiro[4.4]nonane (112 mmol) and K₂CO₃ (122 mg, 0.9 mmol) in DMA (1 mL) was heated at 110 °C with stirring for 12 hrs. The resulting mixture was cooled to rt and concentrated *in vacuo*. The residue was partitioned between DCM (10 mL) and H₂O (5 mL). The organic layer was
20 concentrated *in vacuo*. The residue was purified by prep-HPLC to give 7-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-7-azaspiro[4.4]nonane (31.2 mg) as a white solid and 7-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-7-azaspiro[4.4]nonane (17.9 mg) as a white solid.

Example 12: 7-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-7-azaspiro[4.4]nonane, ¹H NMR(400 MHz, CDCl₃) δ ppm: 9.05 (d, 2H), 8.83 (s, 1H), 7.45 (t, 1H), 5.72 (d, 1H), 5.54 (s, 1H), 5.48 (s, 1H), 4.49 - 4.33 (m, 1H), 3.98 (t, 2H), 3.79 - 3.66 (m, 2H), 3.55 - 3.16 (m, 7H), 2.19 - 1.88 (m, 4H), 1.59 (br. s., 3H).

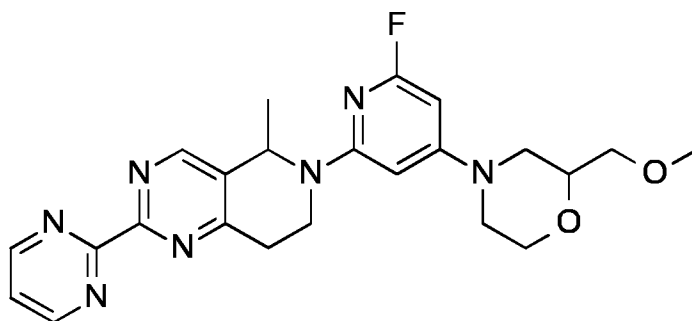
5 MS obsd. (ESI⁺) [(M+H)⁺]: 436.

Example 13: 7-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-7-azaspiro[4.4]nonane, ¹H NMR(400 MHz, CDCl₃) δ ppm: 9.05 (d, 2H), 8.83 (s, 1H), 7.45 (t, 1H), 5.77 (d, 1H), 5.74 - 5.66 (m, 1H), 5.48 (d, 1H), 4.52 - 4.41 (m, 1H), 3.98 (t, 2H), 3.82 - 3.65 (m, 2H), 3.62 - 3.39 (m, 5H), 3.35 - 3.18 (m, 2H), 2.14 -

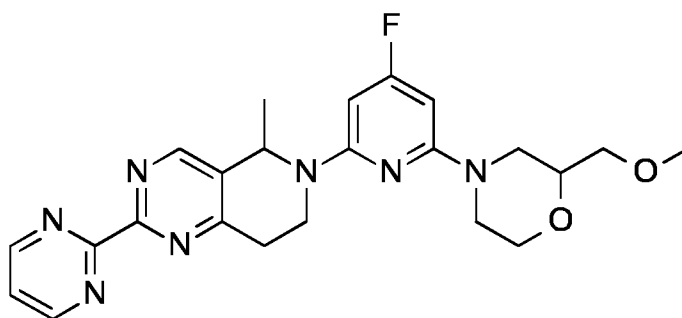
10 1.89 (m, 4H), 1.60 (br. s., 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 436.

Example 14 and 15

4-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-(methoxymethyl)morpholine and 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-(methoxymethyl)morpholine



Example 14



Example 15

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100.0 mg, 0.29 mmol), 2-(methoxymethyl)morpholine hydrochloride (147.5 mg, 0.88 mmol) and K₂CO₃ (121.6 mg, 0.88 mmol) in DMA (3 mL) was heated at 110 °C with stirring for 48 hrs. The resulting mixture was poured into brine (4 mL) and extracted with DCM (3 mL) for 4 times. The combined organic layers were washed sequentially with water and brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-(methoxymethyl)morpholine (29 mg) as a white solid and 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-(methoxymethyl)morpholine (15 mg) as a white solid.

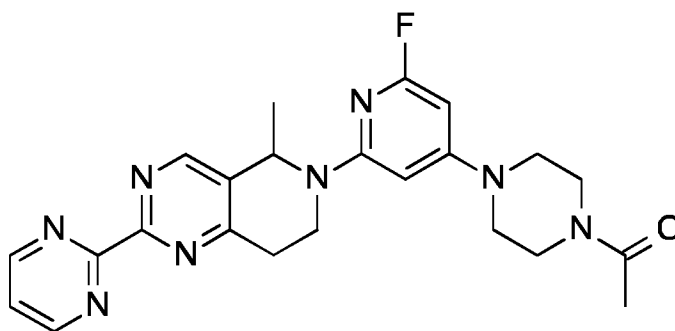
Example 14: 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-(methoxymethyl)morpholine, ¹H NMR (400 MHz CDCl₃) δ ppm: 9.03 (d, 2 H), 8.82 (s, 1 H), 7.43 (s, 1 H), 5.82 - 5.86 (m, 1 H), 5.67 - 5.74 (m, 2 H), 4.33 - 4.44 (m, 1 H), 4.02 - 4.11 (m, 1 H), 3.71 - 3.83 (m, 2 H), 3.58 - 3.66 (m, 1 H), 3.46 - 3.58 (m, 4 H), 3.44 (s, 3 H), 3.20 - 3.34 (m, 2 H), 2.96 - 3.08 (m, 1 H), 2.77 - 2.87 (m, 1 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 452.

Example 15: 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-(methoxymethyl)morpholine, ¹H NMR (400 MHz CDCl₃) δ ppm: 9.02 (d, 2 H), 8.80 (s, 1 H), 7.43 (t, 1 H), 5.81 - 5.87 (m, 1 H), 5.69 - 5.76 (m, 1 H), 5.56 - 5.64 (m, 1 H), 4.35 - 4.48 (m, 1 H), 3.89 - 4.12 (m, 3 H), 3.66 - 3.80 (m, 2 H), 3.48 - 3.58 (m, 2 H), 3.43 (s, 4 H), 3.20 - 3.27 (m, 2 H), 2.93 - 3.03 (m, 1 H), 2.77 (s, 1 H), 1.56 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 452.

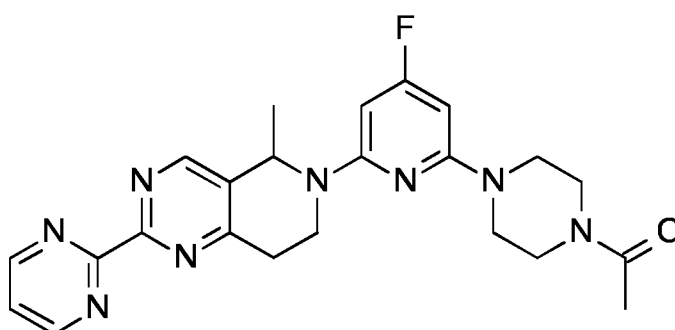
Example 16 and 17

1-[4-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]ethanone and 1-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]ethanone

-50-



Example 16



Example 17

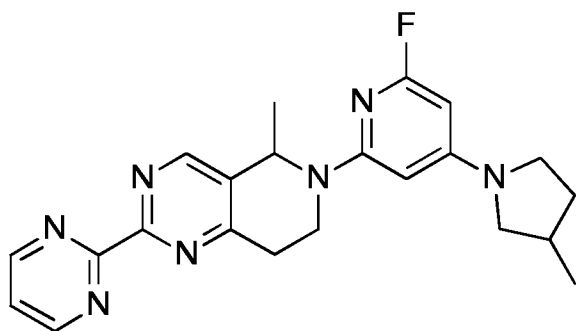
5 A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100.0 mg, 0.29 mmol), 1-(piperazin-1-yl)ethanone (112.7 mg, 0.88 mmol) and K₂CO₃ (121.6 mg, 0.88 mmol) in DMA (3 mL) was heated at 110 °C with stirring for 15 hrs. The resulting mixture was poured into brine (4 mL) and extracted with DCM (3 mL) for 4 times. The combined organic layers were washed
10 sequentially with water and brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 1-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]ethanone (26 mg) as a yellow solid and 1-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]ethanone (12 mg) as a yellow solid.

15 **Example 16:** 1-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]ethanone, ¹H NMR (400 MHz CDCl₃) δ ppm: 9.02 (d, 2 H), 8.81 (s, 1 H), 7.43 (s, 1 H), 5.82 (s, 1 H), 5.65 - 5.74 (m, 2 H), 4.30 - 4.44 (m, 1 H), 3.73 - 3.82 (m, 2 H), 3.62 (d, 2 H), 3.46 - 3.53 (m, 1 H), 3.37 (dt, 4 H), 3.25 (dd, 2 H), 2.15 (s, 3 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 449.

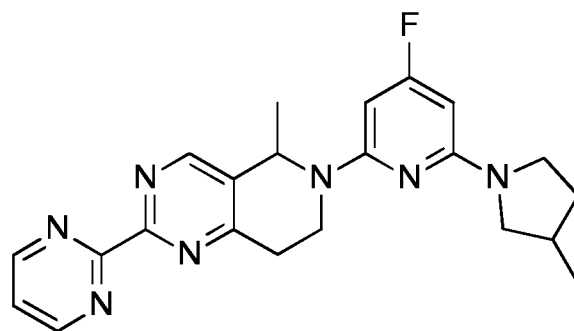
Example 17: 1-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]ethanone, ^1H NMR (400 MHz CDCl_3) δ ppm: 9.02 (d, 2 H), 8.80 (s, 1 H), 7.40 - 7.45 (m, 1 H), 5.81 - 5.89 (m, 1 H), 5.70 - 5.76 (m, 1 H), 5.57 - 5.66 (m, 1 H), 4.35 - 4.47 (m, 1 H), 3.70 - 3.78 (m, 2 H), 3.60 (s, 4 H), 3.49 (d, 3 H), 3.19 - 3.31 (m, 2 H), 2.15 (s, 3 H), 1.57 (d, 3 H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 449.

Example 18 and 19

6-[6-Fluoro-4-(3-methylpyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[4-fluoro-6-(3-methylpyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



Example 18



Example 19

To a solution of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80 mg, 0.23 mmol) and 3-methylpyrrolidine hydrochloride (86 mg, 0.70 mmol) in DMA (1 mL) was added K_2CO_3 (97 mg, 0.70 mmol). The mixture was heated at 110 °C with stirring for 12 hrs and then cooled to rt. The mixture was concentrated *in vacuo* and the residue was partitioned between DCM (10 mL) and H_2O (5 mL). The organic layer was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 6-[6-fluoro-4-(3-methylpyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (18 mg) as a white solid and 6-[4-fluoro-6-(3-methylpyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (9.8 mg) as a white solid.

Example 18: 6-[6-fluoro-4-(3-methylpyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ^1H NMR(400 MHz, CDCl_3) δ ppm: 9.05 (d, 2H), 8.83 (br. s., 1H), 7.45 (t, 1H), 5.73 (d, 1H), 5.53 (s, 1H), 5.47 (s, 1H), 4.42 (d, 1H), 3.56 - 3.16

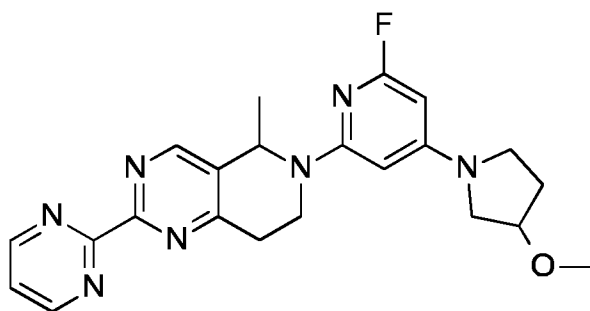
-52-

(m, 8H), 2.92 (t, 1H), 2.43 (dd, 1H), 2.23 - 2.10 (m, 1H), 1.73 - 1.61 (m, 2H), 1.16 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 406.

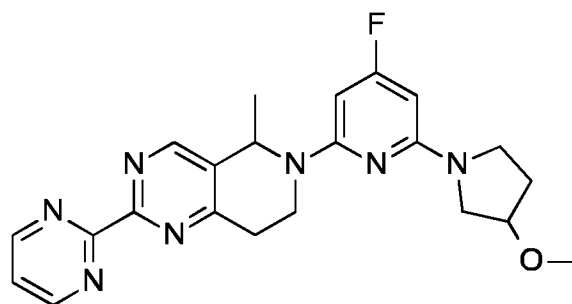
Example 19: 6-[4-fluoro-6-(3-methylpyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR(400 MHz, CDCl₃) δ ppm: 9.05 (d, 1H), 8.82 (s, 1H), 7.44 (t, 1H), 5.73 (d, 2H), 5.47 (d, 1H), 4.47 (d, 1H), 3.72 - 3.16 (m, 7H), 2.99 (t, 1H), 2.49 - 2.31 (m, 1H), 2.20 - 2.07 (m, 1H), 1.68 - 1.62 (m, 1H), 1.58 (s, 2H), 1.16 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 406.

Example 20 and 21

6-[6-Fluoro-4-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[4-fluoro-6-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



Example 20



Example 21

To a solution of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80 mg, 0.23 mmol) and 3-methoxypyrrolidine hydrochloride (96 mg, 0.70 mmol) in DMA (1 mL) was added K₂CO₃ (97 mg, 0.70 mmol). The mixture was heated at 110 °C with stirring for 12 hrs and then cooled to rt. The mixture was concentrated *in vacuo* and the residue was partitioned between DCM (10 mL) and H₂O (5 mL). The organic layer was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 6-[6-fluoro-4-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (34.0 mg) as a white solid and 6-[4-fluoro-6-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (5.4 mg) as a white solid.

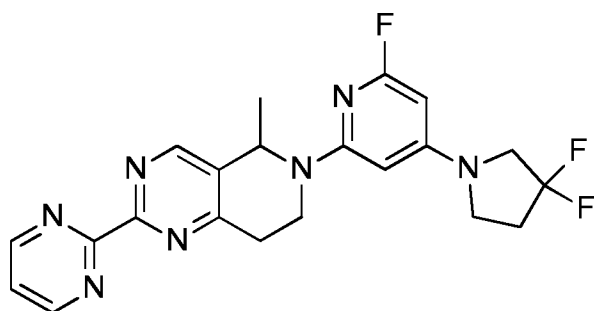
Example 20: 6-[6-fluoro-4-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR(400 MHz, CDCl₃) δ ppm: 9.05 (d, 2H),

8.83 (s, 1H), 7.44 (t, 1H), 5.81 - 5.65 (m, 1H), 5.55 (s, 1H), 5.49 (s, 1H), 4.48 - 4.34 (m, 1H), 4.12 (d, 1H), 3.57 - 3.37 (m, 9H), 3.35 - 3.17 (m, 2H), 2.27 - 2.04 (m, 2H), 1.57 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 422.

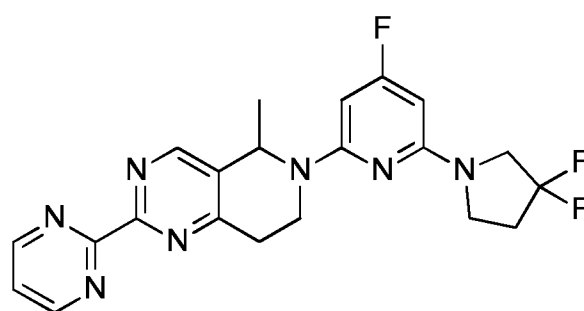
Example 21: 6-[4-fluoro-6-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR(400 MHz, CDCl₃) δ ppm: 8.96 (d, 2H), 8.72 (s, 1H), 7.35 (t, 1H), 5.73 - 5.59 (m, 2H), 5.40 (d, 1H), 4.37 (dd, 1H), 4.07 - 3.94 (m, 1H), 3.57 - 3.35 (m, 5H), 3.34 - 3.28 (m, 3H), 3.24 - 3.09 (m, 2H), 2.16 - 1.91 (m, 2H), 1.49 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 422.

Example 22 and 23

6-[4-(3,3-Difluoropyrrolidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[6-(3,3-difluoropyrrolidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



Example 22



Example 23

To a solution of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80 mg, 0.23 mmol) and 3,3-difluoropyrrolidine hydrochloride (100 mg, 0.70 mmol) in DMA (1 mL) was added K₂CO₃ (97 mg, 0.70 mmol). The mixture was heated at 110 °C with stirring for 12 hrs and then cooled to rt. The mixture was concentrated *in vacuo* and the residue was partitioned between DCM (10 mL) and H₂O (5 mL). The organic layer was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 6-[4-(3,3-difluoropyrrolidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (13.6 mg) as a white solid and 6-[6-(3,3-difluoropyrrolidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (7.2 mg) as a white solid.

Example 22: 6-[4-(3,3-difluoropyrrolidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ^1H NMR(400 MHz, CDCl_3) δ ppm: 8.96 (d, 1H), 8.74 (s, 1H), 7.36 (t, 1H), 5.63 (q, 1H), 5.44 (s, 1H), 5.39 (s, 1H), 4.32 (d, 1H), 3.65 (t, 2H), 3.52 (t, 2H), 3.46 - 3.34 (m, 2H), 3.23 - 3.14 (m, 2H), 2.52 - 2.37 (m, 2H), 1.51 (s, 3H) . MS obsd.

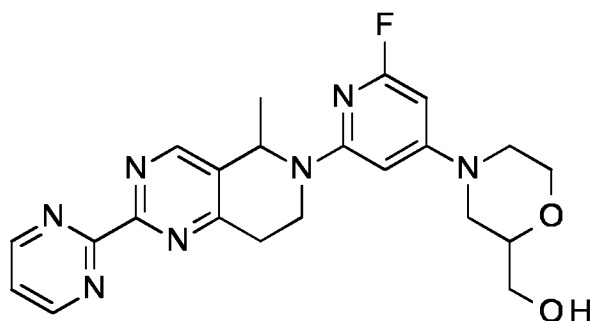
5 (ESI $^+$) [(M+H) $^+$]: 428.

Example 23: 6-[6-(3,3-difluoropyrrolidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ^1H NMR(400 MHz, CDCl_3) δ ppm: 8.96 (d, 2H), 8.74 (s, 1H), 7.36 (t, 1H), 5.75 (d, 1H), 5.60 (q, 1H), 5.41 (d, 1H), 4.42 - 4.29 (m, 1H), 3.78 (t, 2H), 3.58 (t, 2H), 3.44 - 3.31 (m, 1H), 3.22 - 3.12 (m, 2H), 2.41 (tt, 2H), 1.51 (br. s., 3H) . MS

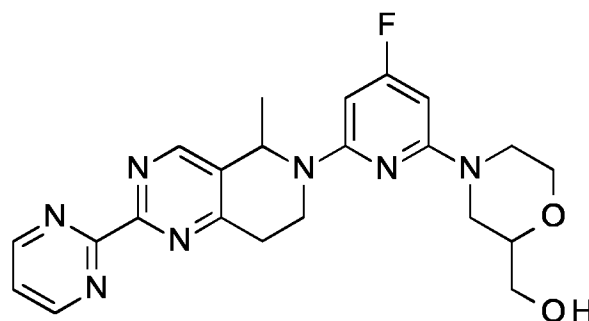
10 obsd. (ESI $^+$) [(M+H) $^+$]: 428.

Example 24 and 25

[4-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholin-2-yl]methanol and [4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholin-2-yl]methanol



Example 24



Example 25

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), morpholin-2-ylmethanol hydrochloride (68 mg, 0.44 mmol) and K_2CO_3 (122 mg, 0.88 mmol) in DMA (2 mL) was heated at 110 $^\circ\text{C}$ with stirring for 12 hrs. Then the mixture was cooled and partitioned between H_2O (5 mL) and EA (20 mL). The aqueous layer was extracted with EA (20 mL) twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-HPLC to give [4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholin-2-yl]methanol (12 mg) as a yellow solid and [4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-

-55-

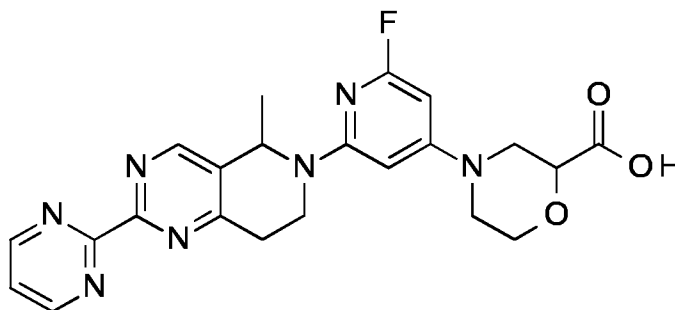
dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]morpholin-2-yl]methanol (10 mg) as a light yellow solid.

Example 24: [4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]morpholin-2-yl]methanol, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm:
 5 9.03 (d, 2 H), 8.87 (s, 1 H), 7.65 (t, 1 H), 6.10 (s, 1 H), 5.84 (s, 1 H), 5.73 (q, 1 H), 4.46 - 4.56 (m, 1 H), 4.02 (dd, 1 H), 3.61 - 3.84 (m, 6 H), 3.43 - 3.56 (m, 1 H), 3.06 - 3.25 (m, 2 H), 2.87 - 3.00 (m, 1 H), 2.64 - 2.76 (m, 1 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 438.

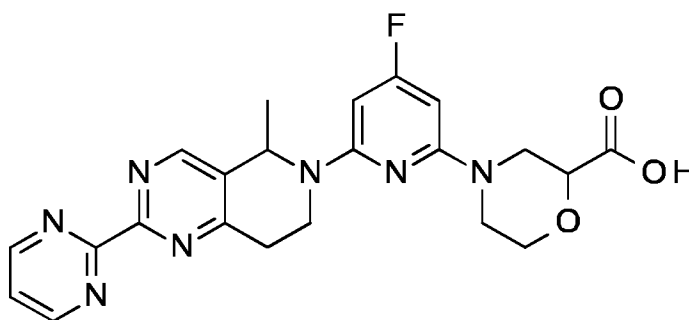
Example 25: [4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]morpholin-2-yl]methanol, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm:
 10 9.03 (d, 2 H), 8.86 - 8.93 (m, 1 H), 7.65 (t, 1 H), 6.03 (d, 1 H), 5.85 (d, 1 H), 5.75 (q, 1 H), 4.52 (d, 1 H), 3.96 - 4.22 (m, 3 H), 3.55 - 3.73 (m, 4 H), 3.43 - 3.53 (m, 1 H), 3.11 - 3.19 (m, 2 H), 2.91 (tt, 1 H), 2.60 - 2.73 (m, 1 H), 1.58 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 438.

Example 26 and 27

15 4-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]morpholine-2-carboxylic acid and 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]morpholine-2-carboxylic acid



Example 26



Example 27

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 200 mg, 0.59 mmol), morpholine-2-carboxylic acid hydrochloride (295 mg, 1.76 mmol) and K₂CO₃ (406 mg, 2.94 mmol) in NMP (5 mL) was heated at 140 °C with stirring for 12 hrs. The mixture was cooled to rt and diluted with H₂O (10 mL). The resulting mixture was extracted with EA (30 mL) for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine-2-carboxylic acid (35 mg) as a yellow solid and 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholine-2-carboxylic acid (22 mg) as a light yellow solid.

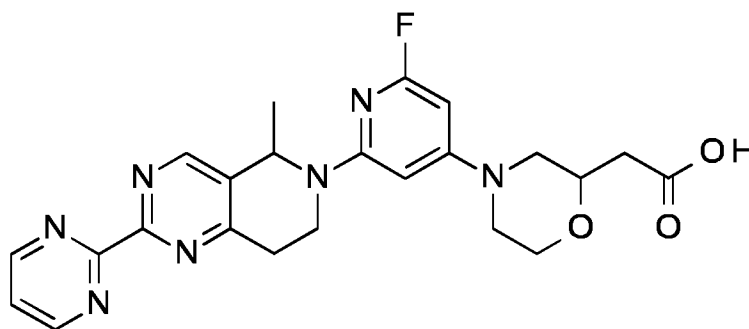
Example 26: 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine-2-carboxylic acid, ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.99 (d, 2 H), 8.91 (s, 1 H), 7.63 (t, 1 H), 6.13 (s, 1 H), 5.89 (s, 1 H), 5.70 (q, 1 H), 4.47 (dd, 1 H), 4.15 (d, 1 H), 3.99 (d, 1 H), 3.54 - 3.77 (m, 4 H), 3.10 - 3.20 (m, 2 H), 2.95 - 3.06 (m, 2 H), 1.48 (d, 3 H).. MS obsd. (ESI⁺) [(M+H)⁺] : 452.

Example 27: 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholine-2-carboxylic acid, ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.99 (s, 1 H), 8.87 (s, 1 H), 7.64 (s, 1 H), 6.15 (d, 1 H), 5.96 (d, 1 H), 5.67 (s, 1 H) 4.50 (m, 1 H), 3.94 - 4.22 (m, 3 H), 3.55 - 3.81 (m, 3 H), 3.01 (m, 4 H), 1.50 (br. s., 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 452.

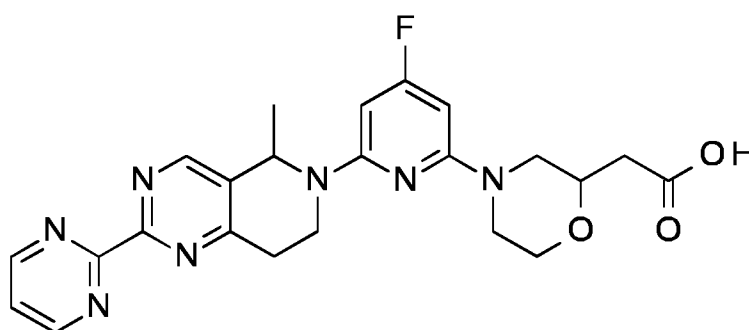
Example 28 and 29

2-[4-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholin-2-yl]acetic acid and 2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholin-2-yl]acetic acid

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Example 28



Example 29

- 5 A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), 2-(morpholin-2-yl)acetic acid hydrochloride (160 mg, 0.88 mmol) and K₂CO₃ (203 mg, 1.47 mmol) in NMP (3 mL) was heated at 140 °C with stirring for 12 hrs. The mixture was cooled to rt and diluted with H₂O (5 mL). The resulting mixture was extracted with EA (20 mL) for three times.
- 10 The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholin-2-yl]acetic acid (31 mg) as a light yellow solid and 2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholin-2-yl]acetic acid (13 mg) as a
- 15 light yellow solid.

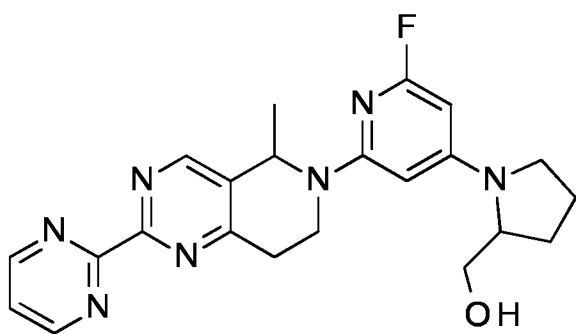
Example 28: 2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholin-2-yl]acetic acid, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 6.10 (s, 1 H), 5.83 (s, 1 H), 5.73 (q, 1 H), 4.44 - 4.56 (m, 1 H), 3.96 (dd, 2 H), 3.85 (d, 1 H), 3.64 - 3.75 (m, 2 H), 3.42 - 3.54 (m, 1 H), 3.07 -

3.25 (m, 2 H), 2.90 - 3.02 (m, 1 H), 2.64 - 2.75 (m, 1 H), 2.47 - 2.61 (m, 2 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 466.

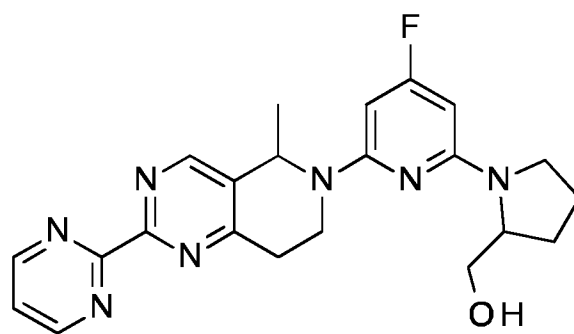
Example 29: 2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholin-2-yl]acetic acid, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.90 (s, 1 H), 7.64 (s, 1 H), 6.03 (d, 1 H), 5.84 (d, 1 H), 5.72 - 5.80 (m, 1 H), 4.47 (t, 1 H), 4.17 - 4.35 (m, 1 H), 3.85 - 4.06 (m, 3 H), 3.60 - 3.72 (m, 1 H), 3.44 - 3.58 (m, 1 H), 3.13 (m, 2 H), 2.93 (t, 1 H), 2.64 (t, 1 H), 2.55 (m, 1 H), 1.58 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 466.

Example 30 and 31

10 [1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-2-yl]methanol and [1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidin-2-yl]methanol



Example 30



Example 31

15 To a solution of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80 mg, 0.23 mmol) and pyrrolidin-2-ylmethanol (90 mg, 0.70 mmol) in DMA (1 mL) was added K₂CO₃ (97 mg, 0.70 mmol). The mixture was heated at 110 °C with stirring for 12 hrs. The resulting mixture was then cooled to rt and concentrated *in vacuo*. The residue was partitioned between DCM (10 mL) and H₂O (5 mL).

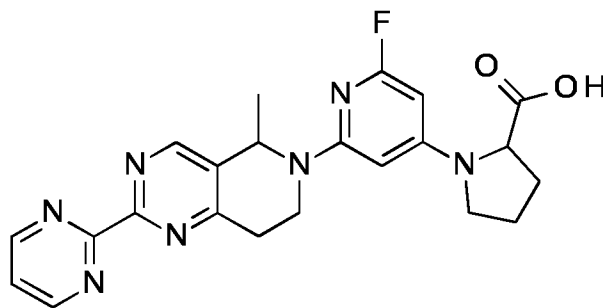
20 The organic layer was concentrated *in vacuo* and the residue was purified by prep-HPLC to give [1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-2-yl]methanol (36.3 mg) as a white solid and [1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidin-2-yl]methanol (3.2 mg) as a white solid.

Example 30: [1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-2-yl]methanol, ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.05 (d, 2H), 8.83 (s, 1H), 7.45 (t, 1H), 5.78 - 5.65 (m, 2H), 5.60 (s, 1H), 4.41 (d, 1H), 3.94 (br. s., 1H), 3.79 - 3.61 (m, 2H), 3.56 - 3.40 (m, 2H), 3.37 - 3.20 (m, 3H), 2.18 - 1.97 (m, 4H), 1.57 (br. s., 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 422.

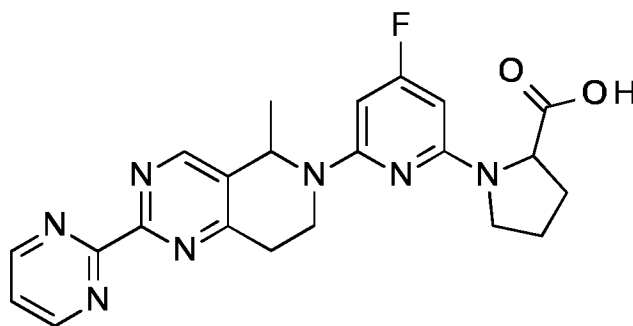
Example 31: [1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidin-2-yl]methanol, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.96 (d, 2H), 8.75 (s, 1H), 7.36 (t, 1H), 5.71 (d, 1H), 5.61 (d, 1H), 5.47 (d, 1H), 4.39 (br. s., 1H), 4.23 (d, 1H), 3.73 (dd, 1H), 3.65 - 3.56 (m, 1H), 3.50 - 3.32 (m, 2H), 3.26 - 3.05 (m, 3H), 2.08 - 1.80 (m, 3H), 1.71 (d, 1H), 1.49 - 1.43 (m, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 422.

Example 32 and 33

1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-2-carboxylic acid and 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-2-carboxylic acid



Example 32



Example 33

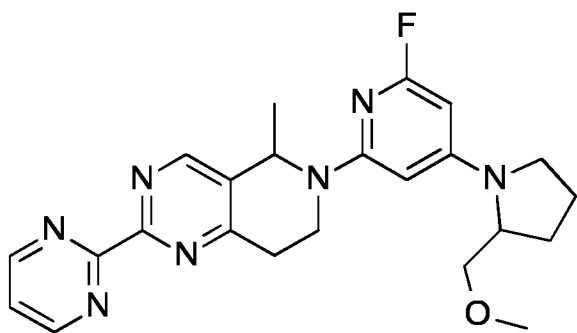
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80 mg, 0.23 mmol), methyl pyrrolidine-2-carboxylate hydrochloride (116 mg, 0.70 mmol) and K₂CO₃ (97 mg, 0.70 mmol) in DMA (1 mL) was heated at 110 °C with stirring for 12 hrs. The mixture was cooled to rt and concentrated *in vacuo*. The residue was partitioned between DCM (10 mL) and H₂O (5 mL). The organic layer was concentrated *in vacuo* and the residue was dissolved in a mixture of H₂O and MeOH (1 mL/1 mL). To the resulting solution was added NaOH (92 mg). The resulting mixture was heated at 50 °C with stirring for 5 hrs. After being cooled to rt, the mixture was concentrated *in vacuo*. The residue was dissolved in H₂O (3 mL) and the resulting solution was acidified to pH= 6 using 1M HCl. The mixture was extracted with DCM (5 mL) for 5 times. The combined organic layers were concentrated *in vacuo* and the residue was purified by prep-HPLC to give 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-2-carboxylic acid (30.4 mg) as a white solid and 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-2-carboxylic acid (12.4 mg) as a white solid.

Example 32: 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-2-carboxylic acid, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.94-8.90 (t, 2H), 8.70 (d, 1H), 7.33 (t, 1H), 5.60 (m, 1H), 5.51 (d, 1H), 5.41 (s, 1H), 4.34 - 4.20 (m, 2H), 3.43 - 3.10 (m, 5H), 1.45 (m, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 436.

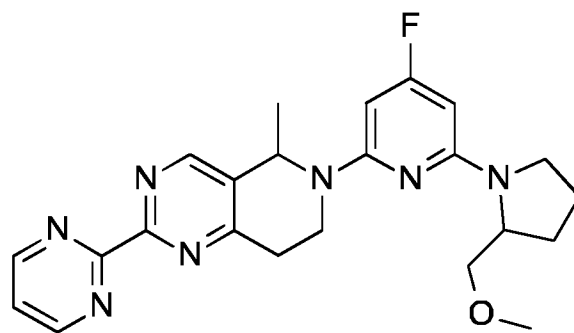
Example 33: 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-2-carboxylic acid, ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.05 (m, 2H), 8.82 (m, 1H), 7.45 (m, 1H), 5.85 (m, 1H), 5.57 - 5.40 (m, 2H), 4.62 (s, 1H), 4.27 (m, 1H), 3.70 - 3.10 (m, 5H), 2.09 (s, 2 H), 1.55 (m, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 436.

Example 34 and 35

6-[6-Fluoro-4-[2-(methoxymethyl)pyrrolidin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[4-fluoro-6-[2-(methoxymethyl)pyrrolidin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



Example 34



Example 35

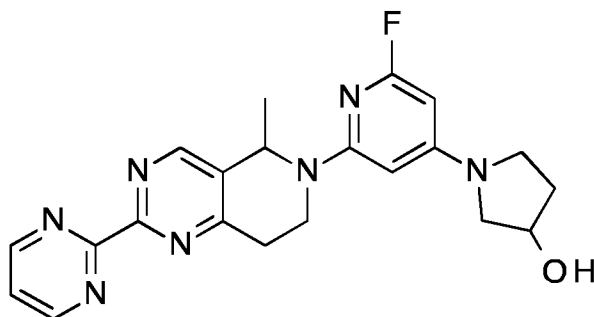
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80 mg, 0.23 mmol), 2-(methoxymethyl)-pyrrolidine (80 mg, 0.70 mmol) and K₂CO₃ (97 mg, 0.70 mmol) in DMA (1 mL) was heated at 120 °C with stirring for 12 hrs. After being cooled to rt, the mixture was concentrated *in vacuo*. The residue was partitioned between DCM (10 mL) and H₂O (5 mL). The organic layer was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 6-[6-fluoro-4-[2-(methoxymethyl)pyrrolidin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (21.7 mg) as a white solid and 6-[4-fluoro-6-[2-(methoxymethyl)pyrrolidin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (12.8 mg) as a white solid.

Example 34: 6-[6-fluoro-4-[2-(methoxymethyl)pyrrolidin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR(400 MHz, CDCl₃) δ ppm: 9.04 (d, 2H), 8.82 (s, 1H), 7.44 (t, 1H), 5.78 - 5.64 (m, 2H), 5.58 (s, 1H), 4.48 - 4.34 (m, 1H), 3.95 (d, 1H), 3.54 - 3.43 (m, 3H), 3.40 (d, 3H), 3.37 - 3.18 (m, 4H), 2.16 - 1.95 (m, 4H), 1.58 (dd, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 436.

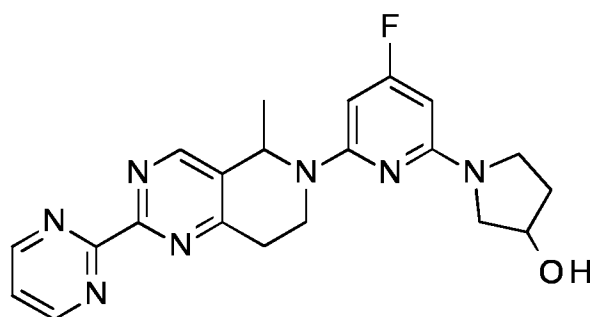
Example 35: 6-[4-fluoro-6-[2-(methoxymethyl)pyrrolidin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR(400 MHz, CDCl₃) δ ppm: 9.05 (d, 2H), 8.80 (d, 1H), 7.48 - 7.42 (m, 1H), 5.83 - 5.69 (m, 2H), 5.54 (d, 1H), 4.49 - 4.36 (m, 1H), 4.28 (br. s., 1H), 3.69 (ddd, 16.3 Hz, 1H), 3.53 - 3.45 (m, 2H), 3.43 (d, 3H), 3.34 - 3.17 (m, 4H), 2.15 - 1.89 (m, 4H), 1.59 (br. s., 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 436.

Example 36 and 37

1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-3-ol and 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidin-3-ol



Example 36



Example 37

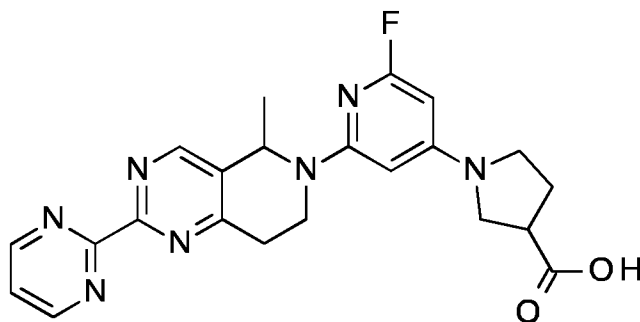
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80 mg, 0.23 mmol), pyrrolidin-3-ol (61 mg, 0.70 mmol) and K₂CO₃ (97 mg, 0.70 mmol) in DMA (1 mL) was heated at 120 °C with stirring for 12 hrs and then cooled to rt. The mixture was concentrated *in vacuo* and the residue was partitioned between DCM (10 mL) and H₂O (5 mL). The organic layer was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-3-ol (23.6 mg) as a white solid and 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidin-3-ol (10.2 mg) as a white solid.

Example 36: 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-3-ol, ¹H NMR(400 MHz, CDCl₃) δ ppm: 9.04 (d, 2H), 8.83 (s, 1H), 7.45 (t, 1H), 5.78 - 5.66 (m, 1H), 5.56 (s, 1H), 5.50 (s, 1H), 4.66 (br. s., 1H), 4.49 - 4.35 (m, 1H), 3.66 - 3.41 (m, 4H), 3.39 - 3.19 (m, 3H), 2.28 - 2.07 (m, 2H), 1.75 (d, 1H), 1.58 (dd, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 408.

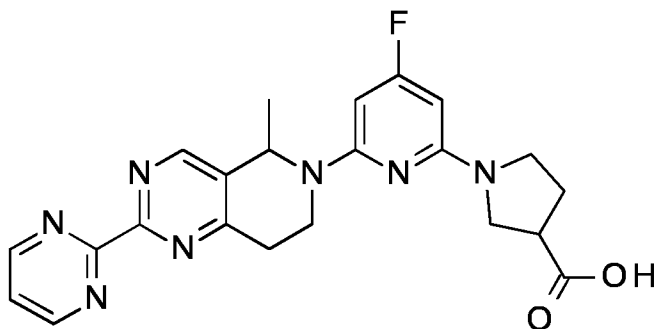
Example 37: 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidin-3-ol, ¹H NMR(400 MHz, CDCl₃) δ ppm: 9.05 (d, 2H), 8.82 (s, 1H), 7.45 (t, 1H), 5.82 - 5.68 (m, 2H), 5.51 (d, 1H), 4.63 (br. s., 1H), 4.46 (d, 1H), 3.72 - 3.39 (m, 5H), 3.33 - 3.18 (m, 2H), 2.25 - 2.01 (m, 2H), 1.65 (d, 1H), 1.58 (br. s., 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 408.

Example 38 and 39

1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-3-carboxylic acid and 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-3-carboxylic acid



Example 38



Example 39

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80 mg, 0.23 mmol), methyl pyrrolidine-3-carboxylate (90 mg, 0.70 mmol) and K₂CO₃ (97 mg, 0.70 mmol) in DMA (1 mL) was heated at 120 °C with stirring for 12 hrs and then cooled to rt. The mixture was concentrated *in vacuo* and the residue was partitioned between DCM (10 mL) and H₂O (5 mL). The organic layer was concentrated to give a solid (100 mg). Then the obtained solid (50 mg) was dissolved in H₂O (1 mL) and MeOH (1 mL), followed by addition of NaOH (22 mg, 0.55 mmol). The resulting mixture was heated at 50 °C with stirring for 12 hrs, and then concentrated *in vacuo*. The residue was dissolved in H₂O (2 mL) and acidified to pH=6 using 1M HCl. The resulting mixture was extracted with DCM (5 mL) for 4 times. The combined organic layers were concentrated *in vacuo* and the residue was purified by prep-HPLC to give 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-3-carboxylic acid (12.8 mg) as a white solid and 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-

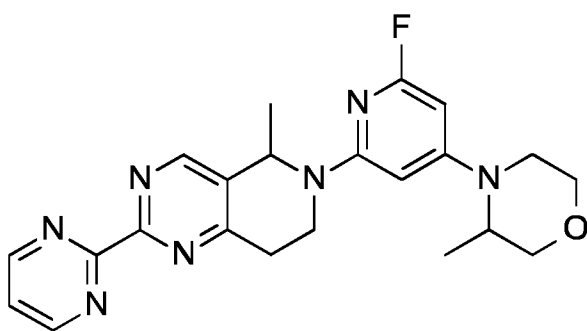
dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-3-carboxylic acid (9.9 mg) as a white solid.

Example 38: 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-3-carboxylic acid, ^1H NMR(400 MHz, CDCl_3) δ ppm: 8.96 (d, 2H), 8.75 (d, 1H), 7.37 (t, 1H), 5.61 (q, 1H), 5.48 (s, 1H), 5.41 (s, 1H), 4.35 (d, 1H), 3.66 - 3.50 (m, 2H), 3.48 - 3.29 (m, 3H), 3.26 - 3.09 (m, 3H), 2.28 (q, 2H), 1.48 (d, 3H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 436.

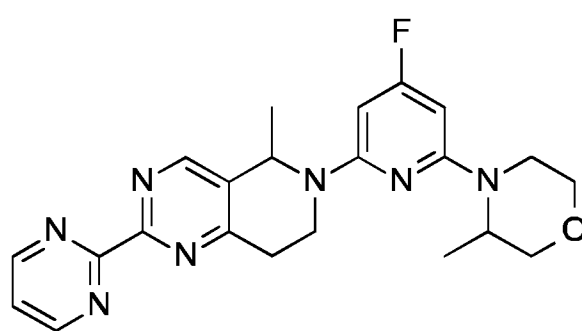
Example 39: 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-3-carboxylic acid, ^1H NMR(400 MHz, CDCl_3) δ ppm: 9.05 (d, 2H), 8.84 (s, 1H), 7.45 (t, 1H), 5.77 (d, 2H), 5.49 (d, 1H), 4.43 (d, 1H), 3.77 (br. s., 2H), 3.60 (br. s., 1H), 3.47 (br. s., 2H), 3.24 (br. s., 3H), 2.32 (br. s., 2H), 1.58 (d, 3H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 436.

Example 40 and 41

4-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-3-methyl-morpholine and 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]-3-methyl-morpholine



Example 40



Example 41

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (one product of step 7 in Example 1, 80.0 mg, 0.235 mmol), 3-methylmorpholine (71.3 mg, 0.705 mmol) and DIPEA (91.1 mg, 0.705 mmol) in NMP (3 mL) was heated at 140 °C for 32 hrs. The mixture was poured into brine (4 mL), and the resulting mixture was extracted with DCM (3 mL) for 4 times. The combined organic layers were washed sequentially with water and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-

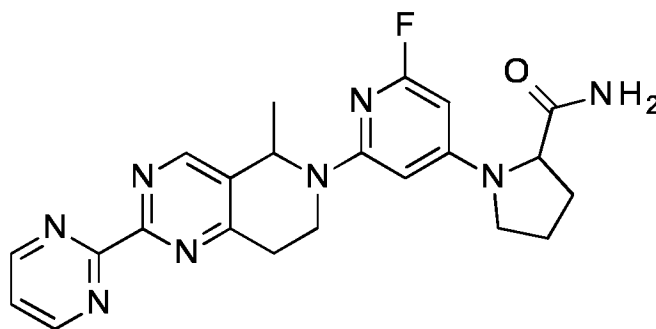
dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-3-methyl-morpholine (12 mg) as a white solid and 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]-3-methyl-morpholine (10 mg) as a yellow solid.

Example 40: 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-3-methyl-morpholine, ¹H NMR (400 MHz CDCl₃) δ ppm: 8.99 - 9.06 (m, 2 H), 8.81 (s, 1 H), 7.40 - 7.46 (m, 1 H), 5.75 - 5.81 (m, 1 H), 5.64 - 5.73 (m, 2 H), 4.33 - 4.44 (m, 1 H), 3.99 - 4.06 (m, 1 H), 3.75 - 3.90 (m, 3 H), 3.59 - 3.70 (m, 1 H), 3.42 - 3.53 (m, 1 H), 3.18 - 3.35 (m, 4 H), 1.55 - 1.59 (m, 3 H), 1.21 - 1.29 (m, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 422.

Example 41: 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]-3-methyl-morpholine, ¹H NMR (400 MHz CDCl₃) δ ppm: 9.03 (d, 2 H), 8.77 - 8.84 (m, 1 H), 7.40 - 7.46 (m, 1 H), 5.79 - 5.85 (m, 1 H), 5.56 - 5.70 (m, 2 H), 4.33 - 4.49 (m, 1 H), 4.13 - 4.33 (m, 1 H), 3.99 - 4.07 (m, 1 H), 3.69 - 3.87 (m, 3 H), 3.57 - 3.66 (m, 1 H), 3.40 - 3.51 (m, 1 H), 3.15 - 3.33 (m, 3 H), 1.55 - 1.59 (m, 3 H), 1.22 - 1.29 (m, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 422.

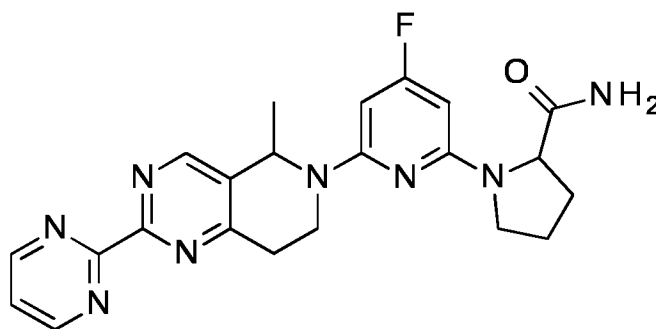
Example 42 and 43

1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-2-carboxamide and 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-2-carboxamide

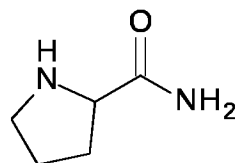


Example 42

-66-

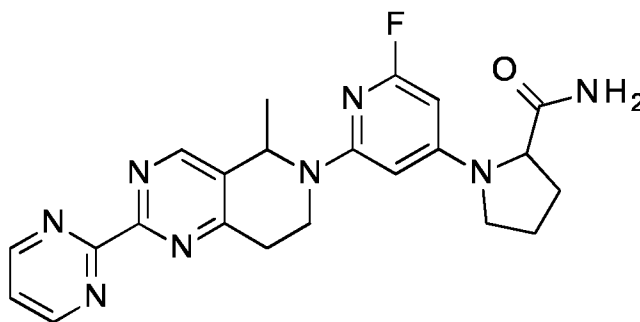


Example 43

Step 1: Preparation of pyrrolidine-2-carboxamide

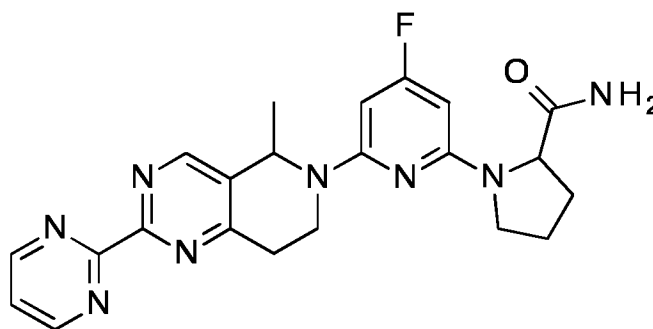
- 5 A mixture of methyl pyrrolidine-2-carboxylate hydrochloride (500 mg, 3.01 mmol) in a solution of NH_3 in THF (10 mL) was heated at 50 °C with stirring for 12 hrs. The mixture was concentrated *in vacuo* to give pyrrolidine-2-carboxamide (450 mg, crude) as a white solid, which was used directly in the next step without any further purification.

- 10 **Step 2: Preparation of 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-2-carboxamide and 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-2-carboxamide**



Example 42

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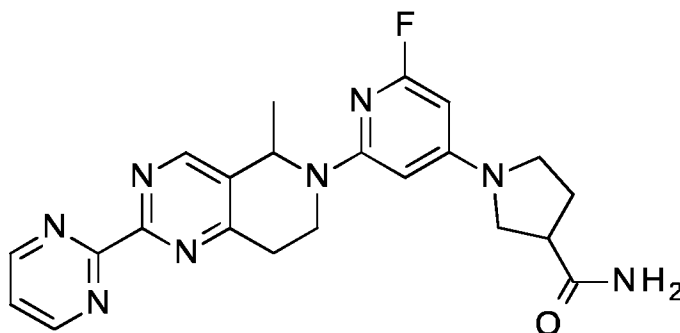
Example 43

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80 mg, 0.23 mmol), pyrrolidine-2-carboxamide (105 mg, 0.70 mmol) and K₂CO₃ (97 mg, 0.70 mmol) in DMA (1 mL) was heated at 120 °C with stirring for 12 hrs. After being cooled to rt, the mixture was concentrated *in vacuo*. The residue was partitioned between DCM (10 mL) and H₂O (5 mL). The organic layer was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-2-carboxamide (11.3 mg) as a brown solid and 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-2-carboxamide (5.7 mg) as a brown solid.

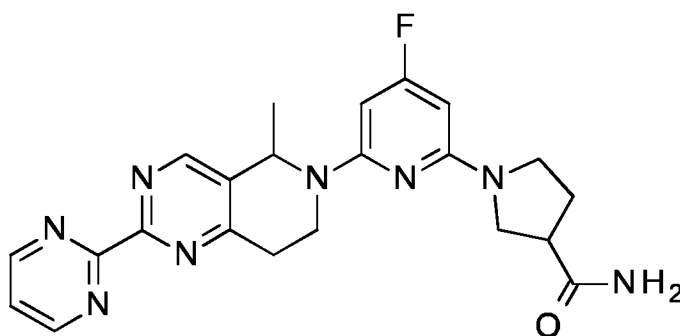
Example 42: 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-2-carboxamide, ¹H NMR(400 MHz, CDCl₃) δ ppm: 9.03 (d, 2 H), 8.82 (s, 1 H), 7.41 - 7.46 (m, 1 H), 6.03 - 6.13 (m, 1 H), 5.63 - 5.73 (m, 1 H), 5.61 (s, 1 H), 5.56 (s, 1 H), 5.35 - 5.46 (m, 1 H), 4.33 - 4.44 (m, 1 H), 4.10 - 4.20 (m, 1 H), 3.61 - 3.72 (m, 1 H), 3.32 - 3.52 (m, 2 H), 3.19 - 3.30 (m, 2 H), 2.26 - 2.41 (m, 2 H), 1.99 - 2.18 (m, 2 H), 1.52 - 1.57 (m, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 435.

Example 43: 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-2-carboxamide, ¹H NMR(400 MHz, CDCl₃) δ ppm: 9.05 (d, 2H), 8.83 (s, 1H), 7.45 (t, 1H), 6.40 - 6.19 (m, 1H), 5.87 (d, 1H), 5.75 - 5.66 (m, 1H), 5.63 (d, 1H), 5.35 - 5.15 (m, 1H), 4.54 (t, 1H), 4.43 - 4.26 (m, 1H), 3.69 - 3.55 (m, 1H), 3.54 - 3.43 (m, 1H), 3.36 (q, 1H), 3.29 - 3.20 (m, 2H), 2.41 - 2.16 (m, 2H), 2.15 - 2.04 (m, 2H), 1.58 (br. s., 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 435.

1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-3-carboxamide and 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-3-carboxamide



Example 44



Example 45

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80.0 mg, 0.235 mmol),
 10 pyrrolidine-3-carboxamide (80.5 mg, 0.705 mmol) and K₂CO₃ (97.5 mg, 0.705 mmol) in DMA (3 mL) was heated at 130 °C with stirring for 24 hrs. The mixture was diluted with brine (4 mL) and extracted with DCM (30 mL) for 4 times. The combined organic layers were washed sequentially with water and brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-3-carboxamide (19.0 mg) as a
 15 yellow solid and 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-3-carboxamide (6.4 mg) as a white solid.

Example 44: 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-3-carboxamide, ¹H NMR (400 MHz, CDCl₃) δ ppm:
 20 9.03 (d, 2 H), 8.81 (s, 1 H), 7.43 (s, 1 H), 5.54 (s, 4 H), 5.47 (s, 1 H), 4.35 - 4.46 (m, 1 H), 3.57 -

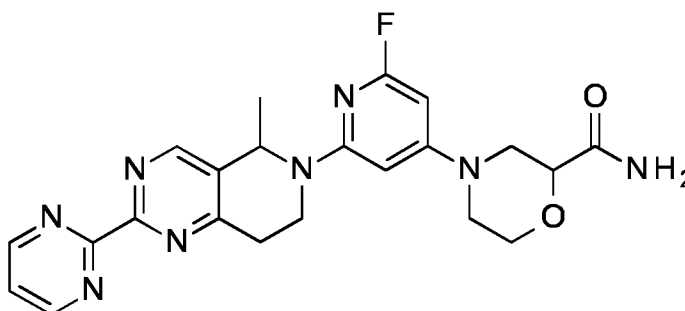
-69-

3.64 (m, 2 H), 3.50 - 3.57 (m, 1 H), 3.35 - 3.49 (m, 2 H), 3.18 - 3.33 (m, 2 H), 3.06 - 3.15 (m, 1 H), 2.25 - 2.37 (m, 2 H), 1.56 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 435.

Example 45: 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-3-carboxamide, ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.03 (d, 2 H), 8.81 (s, 1 H), 7.41 - 7.46 (m, 1 H), 5.74 - 5.80 (m, 1 H), 5.58 - 5.74 (m, 2 H), 5.49 (dd, 2 H), 4.37 - 4.50 (m, 1 H), 3.74 - 3.82 (m, 1 H), 3.61 - 3.73 (m, 2 H), 3.39 - 3.51 (m, 2 H), 3.17 - 3.31 (m, 2 H), 3.03 - 3.13 (m, 1 H), 2.25 - 2.34 (m, 2 H), 1.54 - 1.59 (m, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 435.

Example 46

10 **4-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine-2-carboxamide**

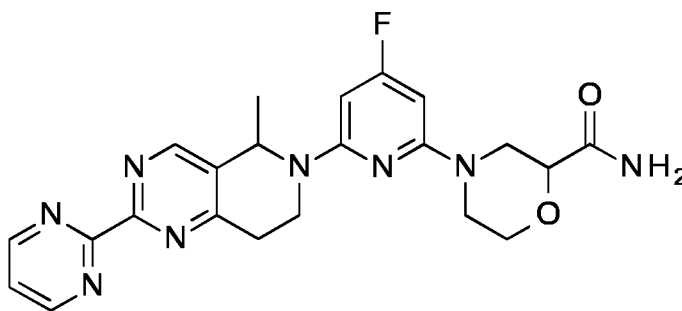


A mixture of 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine-2-carboxylic acid (Example 26, 60 mg, 0.13 mmol), NH₄Cl (71 mg, 1.33 mmol), HATU (252 mg, 0.66 mmol) and DIPEA (86 mg, 0.66 mmol) in DMSO (3 mL) was heated at 90 °C with stirring for 12 hrs. The mixture was cooled to rt and diluted with H₂O (5 mL). The resulting mixture was extracted with EA (10 mL) for three times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine-2-carboxamide (31 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.88 (s, 1 H), 7.64 (t, 1 H), 6.12 (s, 1 H), 5.86 (s, 1 H), 5.74 (q, 1 H), 4.45 - 4.58 (m, 1 H), 4.00 - 4.15 (m, 3 H), 3.67 - 3.84 (m, 2 H), 3.43 - 3.56 (m, 1 H), 3.09 - 3.20 (m, 2 H), 3.01 (td, 1 H), 2.82 - 2.92 (m, 1 H), 1.58 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 451.

Example 47

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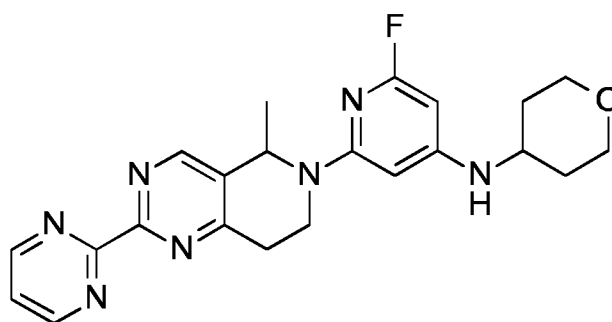
4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholine-2-carboxamide



A mixture of 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-
 5 d]pyrimidin-6-yl)-2-pyridyl]morpholine-2-carboxylic acid (Example 27, 10 mg, 0.02 mmol),
 NH₄Cl (12 mg, 0.22 mmol), HATU (42 mg, 0.11 mmol) and DIPEA (29 mg, 0.22 mmol) in
 DMSO (1 mL) was heated at 90 °C with stirring for 12 hrs. The mixture was then cooled to rt
 and diluted with H₂O (2 mL). The resulting mixture was extracted with EA (5 mL) for three
 times. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and
 10 concentrated *in vacuo*. The residue was purified by prep-HPLC to give 4-[4-fluoro-6-(5-methyl-
 2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholine-2-
 carboxamide (4 mg) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H),
 8.92 (s, 1 H), 7.65 (t, 1 H), 6.06 (d, 1 H), 5.88 (d, 1 H), 5.79 (t, 1 H), 4.43 - 4.58 (m, 2 H), 3.94 -
 4.18 (m, 3 H), 3.73 (td, 1 H), 3.43 - 3.57 (m, 1 H), 3.09 - 3.20 (m, 2 H), 2.98 (td, 1 H), 2.79 (t, 1
 15 H), 1.58 (dd, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 451.

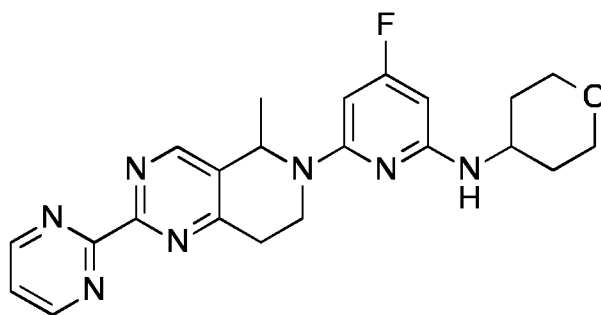
Example 48 and 49

**2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-
 N-tetrahydropyran-4-yl-pyridin-4-amine and 4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-
 dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-N-tetrahydropyran-4-yl-pyridin-2-amine**



Example 48

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Example 49

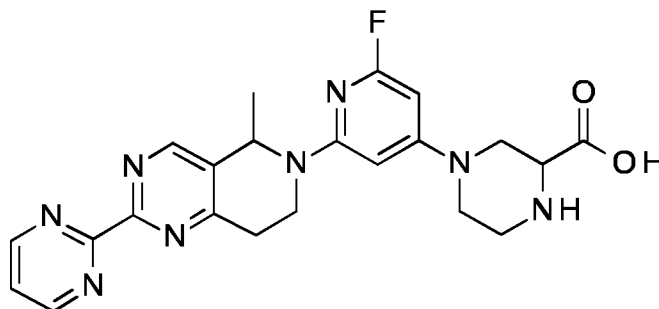
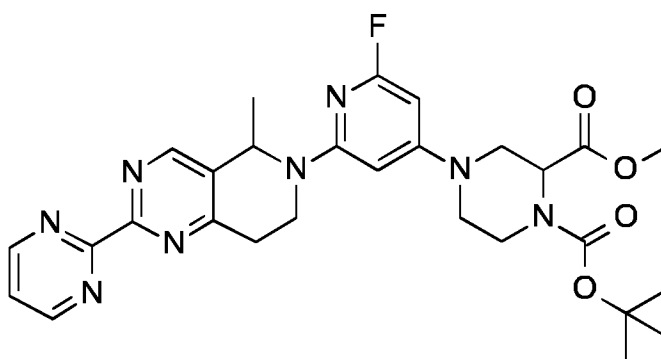
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80.0 mg, 0.235 mmol), tetrahydro-
 5 2H-pyran-4-amine (71.0 mg, 0.702 mmol) and DIPEA (100.0 mg, 0.774 mmol) in NMP (3 mL) was heated at 120 °C with stirring for 48 hrs. The mixture was poured into brine (4 mL) and extracted with DCM (3 mL) for 4 times. The combined organic layers were washed sequentially with water and brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-N-tetrahydropyran-4-yl-pyridin-4-amine (22.1 mg) as a light
 10 yellow solid and 4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-N-tetrahydropyran-4-yl-pyridin-2-amine (6.0 mg) as a light yellow solid.

Example 48: 2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-N-tetrahydropyran-4-yl-pyridin-4-amine, ¹H NMR (400 MHz CDCl₃) δ ppm:
 15 9.03 (d, 2 H), 8.80 (s, 1 H), 7.43 (t, 1 H), 5.59 - 5.73 (m, 2 H), 5.51 (s, 1 H), 4.27 - 4.40 (m, 1 H), 4.10 - 4.20 (m, 1 H), 3.96 - 4.07 (m, 2 H), 3.53 (s, 4 H), 3.23 (br. s., 2 H), 2.03 (d, 2 H), 1.45 - 1.59 (m, 5 H). MS obsd. (ESI⁺) [(M+H)⁺]: 422.

Example 49: 4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-N-tetrahydropyran-4-yl-pyridin-2-amine, ¹H NMR (400 MHz CDCl₃) δ ppm:
 20 9.03 (d, 2 H), 8.79 (s, 1 H), 7.43 (s, 1 H), 5.73 - 5.82 (m, 1 H), 5.59 - 5.70 (m, 1 H), 5.45 - 5.56 (m, 1 H), 4.33 - 4.47 (m, 2 H), 3.94 - 4.08 (m, 2 H), 3.64 - 3.79 (m, 1 H), 3.49 - 3.60 (m, 2 H), 3.37 - 3.47 (m, 1 H), 3.15 - 3.31 (m, 2 H), 1.98 - 2.10 (m, 2 H), 1.56 (d, 5 H). MS obsd. (ESI⁺) [(M+H)⁺]: 422.

Example 50

25 4-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-

yl)-4-pyridyl]piperazine-2-carboxylic acid**Step 1: Preparation of 1-tert-butyl 2-methyl 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazine-1,2-dicarboxylate**

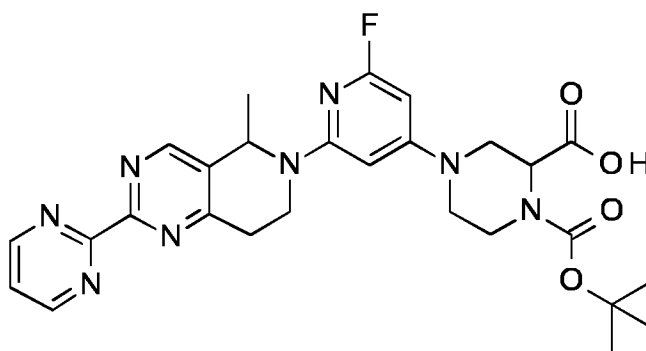
5

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 340 mg, 1 mmol) and potassium carbonate (276 mg, 2 mmol), 1-tert-butyl 2-methyl piperazine-1,2-dicarboxylate (366 mg, 1.5 mmol) in DMSO (15 mL) were heated at 120°C with stirring for 10 hrs. After being cooled to rt, the mixture was diluted with water (50 mL) and extracted with EA (80 mL). The organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (eluting with DCM/MeOH=10/1, v:v) to give 1-tert-butyl 2-methyl 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazine-1,2-dicarboxylate (282 mg) as a red oil.

Step 2: Preparation of 1-tert-butoxycarbonyl-4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazine-2-carboxylic acid

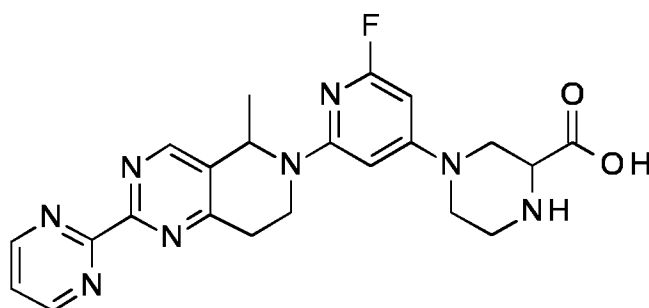
15

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To a solution of 1-*tert*-butyl 2-methyl 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]piperazine-1,2-dicarboxylate (282 mg, 0.5 mol) in methanol (5 mL), THF (2 mL) and water (1 mL) was added LiOH (84 mg, 2 mol). The resulting mixture was stirred overnight at rt and then acidified to pH=6-7 with 2.0 M hydrochloric acid. The mixture was extracted with DCM (50 mL) twice and the combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give crude 1-*tert*-butoxycarbonyl-4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]piperazine-2-carboxylic acid (275 mg) which was directly used in the next step without purification.

Step 3: Preparation of 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]piperazine-2-carboxylic acid



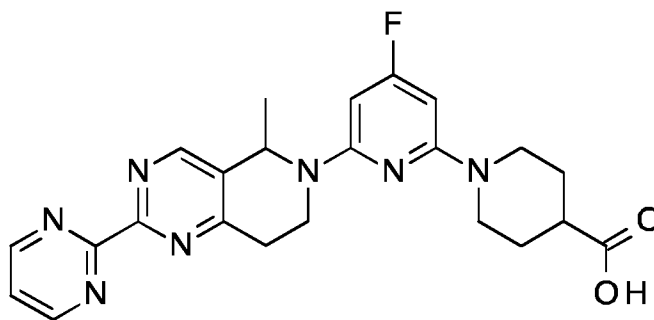
To a solution of 1-*tert*-butoxycarbonyl-4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]piperazine-2-carboxylic acid (275 mg, 0.5 mmol) in DCM (5 mL) was added TFA (1 mL) drop wise at 0 °C and the resulting mixture was stirred for 4 hrs at rt. The resulting reaction mixture was poured into ice water, and then adjusted pH to 8 with NH₄OH. The resulting mixture was extracted with DCM (50 mL) twice and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-

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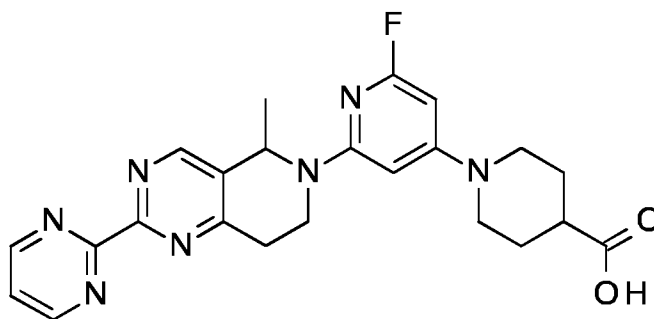
dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]piperazine-2-carboxylic acid (8 mg) as a white powder. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 8.93 (d, 2H), 8.79 (s, 1H), 7.55 (s, 1H), 6.06-6.16 (m, 1H), 5.78-5.87 (m, 1H), 5.60-5.72 (m, 1H), 4.39-4.52 (m, 1H), 4.11-4.23 (m, 1H), 3.79-3.92 (m, 1H), 3.58-3.71 (m, 1H), 3.37-3.48 (m, 1H), 3.27-3.36 (m, 1H), 2.95-3.18 (m, 5H), 1.49 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 451.

Example 51 and 52

1-[4-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]piperidine-4-carboxylic acid and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]piperidine-4-carboxylic acid



Example 51



Example 52

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), isonipecotic acid (114 mg, 0.88 mmol) and K₂CO₃ (122 mg, 0.88 mmol) in NMP (2 mL) was heated at 170 °C in a microwave reactor for 1 hr. The resulting mixture was diluted with H₂O (10 mL) and extracted with DCM (100 mL). The organic layer was washed with H₂O (10 mL). The combined aqueous layer was concentrated *in vacuo* and the residue was purified by prep-HPLC to afford 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-

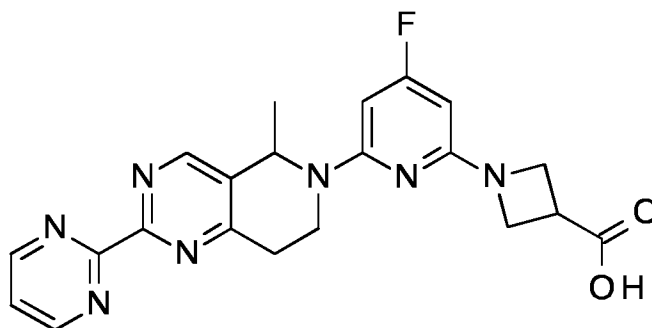
pyridyl]piperidine-4-carboxylic acid (30 mg) as a light yellow solid and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-
methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperidine-4-
carboxylic acid (30 mg) as a light yellow solid.

Example 51: 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-
5 d]pyrimidin-6-yl)-2-pyridyl]piperidine-4-carboxylic acid, ¹H NMR (400 MHz, CDCl₃) δ ppm:
9.05 (d, 2 H), 8.82 (s, 1 H), 7.44 (t, 1 H), 5.78 (m, 2 H), 5.63 (q, 1 H), 4.44 (d, 1 H), 4.20 (d, 2 H),
3.36 - 3.51 (m, 1 H), 3.16 - 3.32 (m, 2 H), 3.01 (t, 2 H), 2.54 - 2.70 (m, 1 H), 2.05 (d, 2 H), 1.77 -
1.85 (m, 2 H), 1.58 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 450.

Example 52: 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-
10 d]pyrimidin-6-yl)-4-pyridyl]piperidine-4-carboxylic acid, ¹H NMR (400 MHz, CDCl₃) δ ppm:
9.04 (d, 2 H), 8.82 (s, 1 H), 7.44 (t, 1 H), 5.85 (s, 1 H), 5.63 - 5.78 (m, 2 H), 4.33 - 4.48 (m, 1 H),
3.80 (d, 2 H), 3.40 - 3.56 (m, 1 H), 3.18 - 3.36 (m, 2 H), 2.96 - 3.11 (m, 2 H), 2.56 - 2.70 (m, 1
H), 2.06 (d, 2 H), 1.80 - 1.91 (m, 2 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 450.

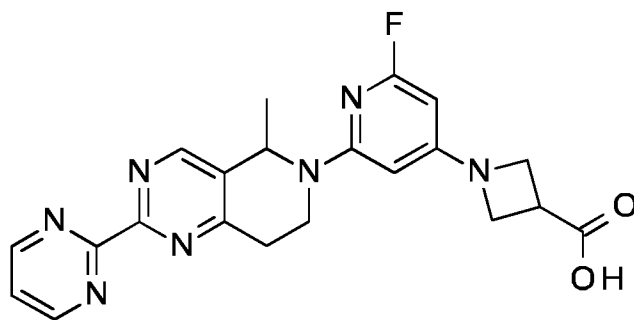
Example 53 and 54

15 **1-[4-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-
yl)-2-pyridyl]azetidine-3-carboxylic acid and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-
dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carboxylic acid**



Example 53

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Example 54

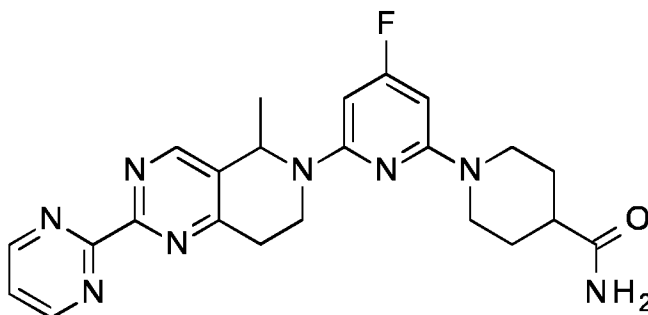
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), azetidine-3-carboxylic acid (89 mg, 0.88 mmol) and K₂CO₃ (122 mg, 0.88 mmol) in NMP (1 mL) was heated at 170 °C in a microwave reactor for 1 hr. The reaction mixture was then diluted with H₂O (10 mL) and extracted with DCM (100 mL). The organic layer was washed with H₂O (10 mL). The combined aqueous layer was concentrated *in vacuo* and the residue was purified by prep-HPLC to afford 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidine-3-carboxylic acid (12.5 mg) as a light yellow solid and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carboxylic acid (33.7 mg) as a light yellow solid.

Example 53: 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidine-3-carboxylic acid, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 5.97 (dd, 1 H), 5.75 (q, 1 H), 5.45 (m, 1 H), 4.48 - 4.60 (m, 1 H), 4.04 - 4.18 (m, 4 H), 3.40 - 3.53 (m, 2 H), 3.05 - 3.23 (m, 2 H), 1.52 - 1.61 (m, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 422.

Example 54: 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carboxylic acid, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 5.69 (q, 1 H), 5.63 (s, 1 H), 5.38 (d, 1 H), 4.41 - 4.52 (m, 1 H), 4.03 - 4.21 (m, 4 H), 3.40 - 3.64 (m, 2 H), 3.05 - 3.23 (m, 2 H), 1.56 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 422.

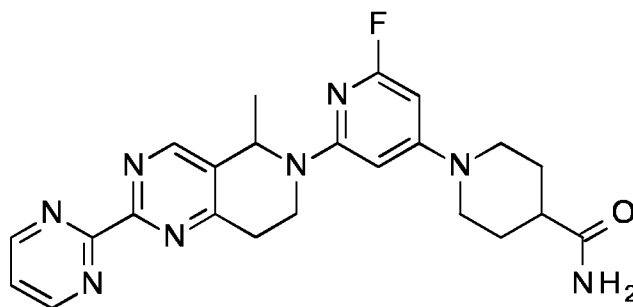
Example 55 and 56

1-[4-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperidine-4-carboxamide and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperidine-4-carboxamide



5

Example 55



Example 56

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80 mg, 0.23 mmol), piperidine-4-carboxamide (90 mg, 0.71 mmol) and K₂CO₃ (98 mg, 0.71 mmol) in NMP (1 mL) was heated at 170 °C in a microwave reactor for 1 hr and then partitioned between DCM (80 mL) and H₂O (20 mL). The organic layer was separated, then washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperidine-4-carboxamide (23 mg) as a light yellow solid and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperidine-4-carboxamide (42 mg) as a light yellow solid.

Example 55: 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperidine-4-carboxamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 2 H), 8.89 (s, 1 H), 7.64 (t, 1 H), 5.96 (d, 1 H), 5.85 (d, 1 H), 5.74 (m, 1 H), 4.46 - 4.56

20

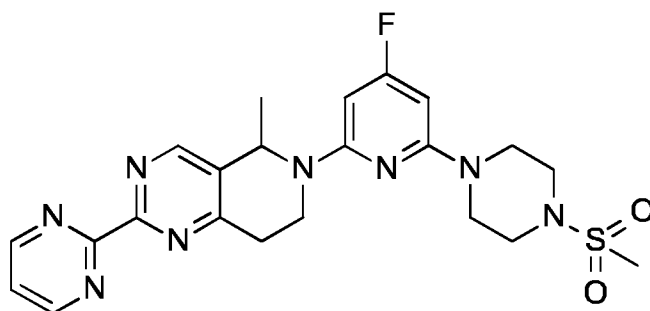
-78-

(m, 1 H), 4.36 (d, 2 H), 3.41 - 3.55 (m, 1 H), 3.07 - 3.19 (m, 2 H), 2.79 - 2.94 (m, 2 H), 2.41 - 2.54 (m, 1 H), 1.86 (d, 2 H), 1.63 - 1.77 (m, 2 H), 1.58 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 449.

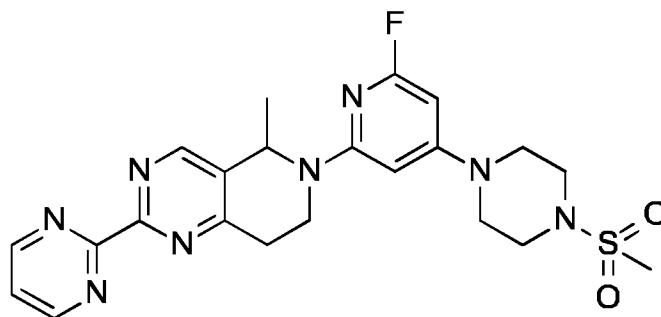
Example 56: 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperidine-4-carboxamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 1 H), 8.85 (s, 1 H), 7.63 (t, 1 H), 6.07 (s, 1 H), 5.81 (s, 1 H), 5.70 (q, 1 H), 4.48 (dd, 1 H), 3.99 (d, 2 H), 3.40 - 3.56 (m, 1 H), 3.05 - 3.24 (m, 2 H), 2.93 (t, 2 H), 2.49 (m, 1 H), 1.87 (d, 2 H), 1.65 - 1.81 (m, 2 H), 1.56 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 449.

Example 57 and 58

6-[4-Fluoro-6-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



Example 57



Example 58

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), 1-(methylsulfonyl) piperazine (145 mg, 0.88 mmol) and K₂CO₃ (122 mg, 0.88 mmol) in NMP (2 mL) was heated at 180 °C in a microwave reactor for 2 hrs. The mixture was diluted with DCM

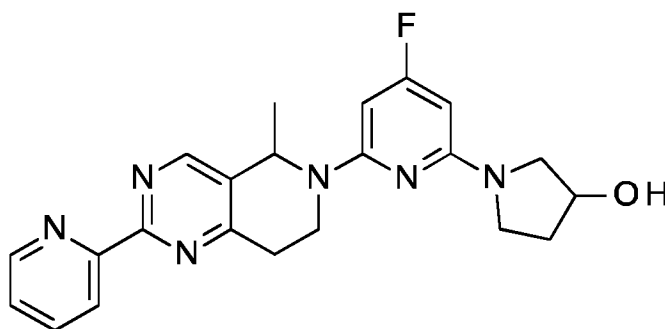
(10 mL) and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 6-[4-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (28 mg) as a light yellow solid and 6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (35 mg) as a light yellow solid.

Example 57: 6-[4-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.90 (s, 1 H), 7.65 (t, 1 H), 6.05 (d, 1 H), 5.91 (d, 1 H), 5.72 - 5.80 (m, 1 H), 4.52 (d, 1 H), 3.64 - 3.71 (m, 4 H), 3.44 - 3.60 (m, 1 H), 3.27 - 3.30 (m, 4 H), 3.11 - 3.20 (m, 2 H), 2.86 (s, 3 H), 1.59 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 485.

Example 58: 6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.65 (t, 1 H), 6.13 (s, 1 H), 5.88 (s, 1 H), 5.74 (q, 1 H), 4.45 - 4.56 (m, 1 H), 3.45 - 3.56 (m, 5 H), 3.34 (m, 4 H), 3.08 - 3.19 (m, 2 H), 2.87 (s, 3 H), 1.58 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 485.

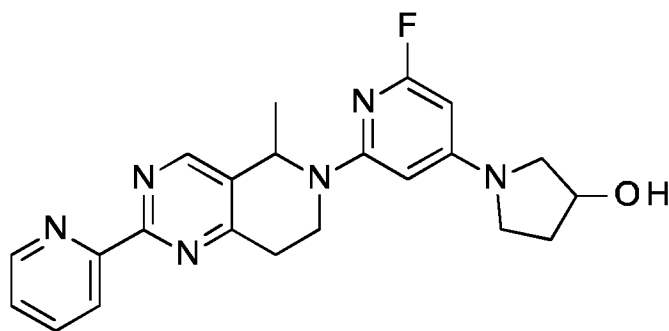
Example 59 and 60

1-[4-Fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl]-2-pyridyl]pyrrolidin-3-ol and 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl]-4-pyridyl]pyrrolidin-3-ol



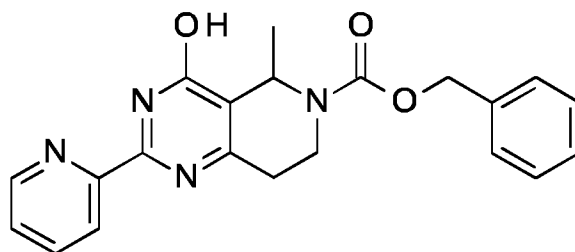
Example 59

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Example 60

Step 1: Preparation of benzyl 4-hydroxy-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate

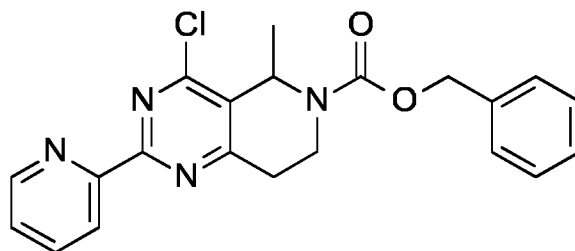


5

To a solution of O1-benzyl O3-ethyl 2-methyl-4-oxo-piperidine-1,3-dicarboxylate (75.0 g, 235 mmol) in 2,2,2-trifluoroethanol (750 mL) was added 2-amidinopyridine hydrochloride (38.9 g, 247 mmol) and K_2CO_3 (97.4 g, 705 mmol). The mixture was heated at 80 °C with stirring for 12 hrs. After being cooled to rt, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified column chromatography (eluting with DCM/MeOH=20/1, v:v) to give benzyl 4-hydroxy-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate (60.0 g) as a yellow solid.

10

Step 2: Preparation of benzyl 4-chloro-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate

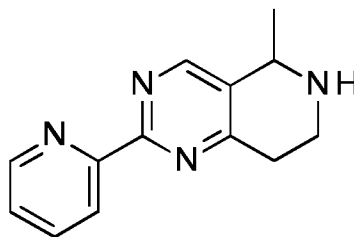


15

-81-

To a solution of benzyl 4-hydroxy-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate (60.0 g, 159 mmol) in MeCN (500 mL) was added POCl₃ (122.2 g, 797 mmol) drop-wise. The mixture was heated at 60 °C with stirring for 3 hrs, and then poured into water and stirred for additional 10 mins. The resulting mixture was concentrated *in vacuo* to remove the organic solvent. The resulting aqueous mixture was adjusted to pH 7-8 with saturated aqueous NaHCO₃, and then extracted with EA (300 mL) twice. The combined organic layer was washed with brine (500 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with DCM/MeOH=20/1, v:v) to give benzyl 4-chloro-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate (60.0 g) as a yellow oil.

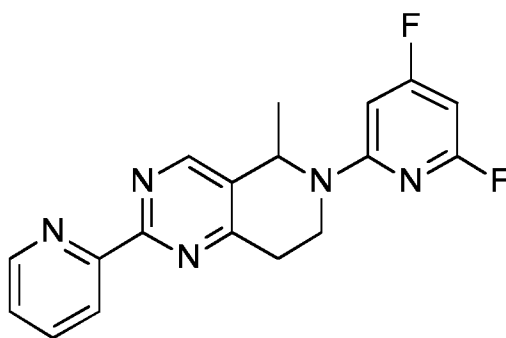
Step 3: Preparation of 5-methyl-2-(2-pyridyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



To a solution of benzyl 4-chloro-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylate (30.0 g, 76.2 mmol) in a mixture of EtOH/NH₄OH/H₂O (600 mL/150 mL/150 mL) was added Pd/C (6.0 g, 10 % wt). The resulting mixture was stirred at rt under H₂ (30 psi) for 12 hrs. The reaction was conducted at the same scale in parallel for four times. The reactions mixtures were filtered, and the combined filtrate were concentrated *in vacuo*. The residue was dissolved in MeOH (200 mL) and DCM (2.0 L), and then treated with K₂CO₃ (210.6 g, 152.4 mmol). The resulting mixture was stirred at rt for 1 hr, and then filtered. The filtrate was concentrated *in vacuo* to give 5-methyl-2-(2-pyridyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (60.0 g, crude) as a yellow oil, which was used in the next step without any further purification.

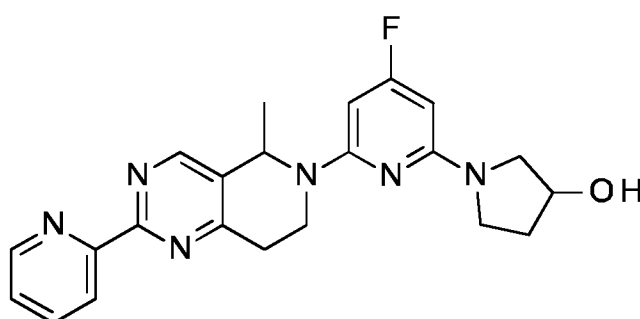
Step 4: Preparation of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine

-82-

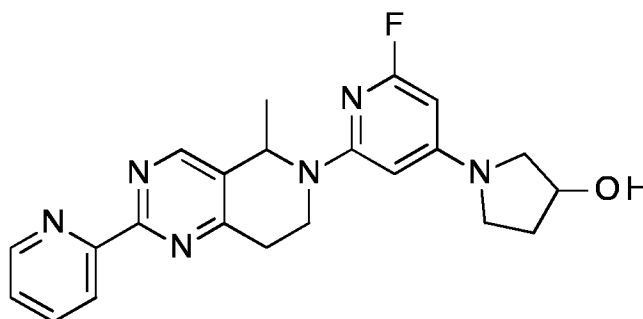


A mixture of 5-methyl-2-(2-pyridyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (1.5 g, 6.6 mmol), 2,4,6-trifluoropyridine (1.1 g, 8.0 mmol) and DIPEA (2.6 g, 19.8 mmol) in NMP (15 mL) was heated at 150 °C in a microwave reactor with stirring for 1 hr. The resulting mixture was
 5 partitioned between H₂O (40 mL) and DCM (40 mL). The aqueous layer was extracted with DCM (100 mL). The combined organic layer was washed with brine (200 mL) and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (400 mg) as a yellow solid.

Step 5: Preparation of 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]pyrrolidin-3-ol and 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidin-3-ol



Example 59



Example 60

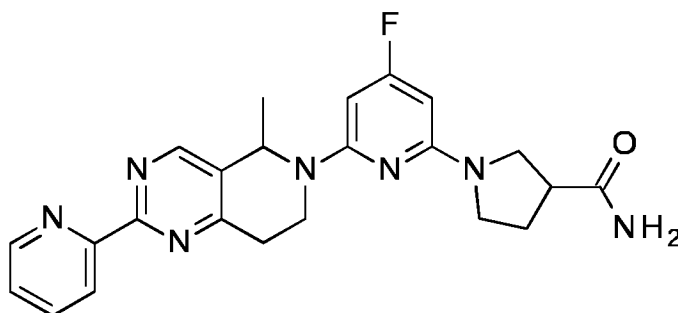
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (100 mg, 0.295 mmol), 3-pyrrolidinol (77 mg, 0.884 mmol) and K₂CO₃ (122 mg, 0.884 mmol) in DMA (2 mL) was heated at 110 °C in a microwave reactor for 1.5 hrs. The mixture was filtered and the filtrate was partitioned between EA (200 mL) and brine (200 mL). The organic layer was washed with brine (200 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]pyrrolidin-3-ol (12 mg) as a yellow solid and 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidin-3-ol (5 mg) as a yellow solid.

Example 59: 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]pyrrolidin-3-ol, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.85 (d, 1 H), 8.71 (s, 1 H), 8.50 (d, 1 H), 7.83 - 7.90 (m, 1 H), 7.36 - 7.43 (m, 1 H), 5.75 (d, 1 H), 5.66 (br d, 1 H), 5.49 (d, 1 H), 4.62 (br s, 1 H), 4.44 (br d, 1 H), 3.52 - 3.70 (m, 4 H), 3.38 - 3.47 (m, 1 H), 3.10 - 3.23 (m, 2 H), 2.03 - 2.22 (m, 2 H), 1.57 (br s, 3 H). MS obsd (ESI) [(M+H)⁺]: 407.

Example 60: 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidin-3-ol, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.85 (d, 1 H), 8.71 (s, 1 H), 8.50 (d, 1 H), 7.87 (t, 1 H), 7.38 - 7.43 (m, 1 H), 5.67 (br d, 1 H), 5.55 (s, 1 H), 5.48 (s, 1 H), 4.65 (br s, 1 H), 4.39 (br d, 1 H), 3.53 - 3.60 (m, 2 H), 3.41 - 3.51 (m, 2 H), 3.33 (br d, 1 H), 3.14 - 3.25 (m, 2 H), 2.07 - 2.21 (m, 2 H), 1.54 - 1.56 (d, 3 H). MS obsd (ESI) [(M+H)⁺]: 407.

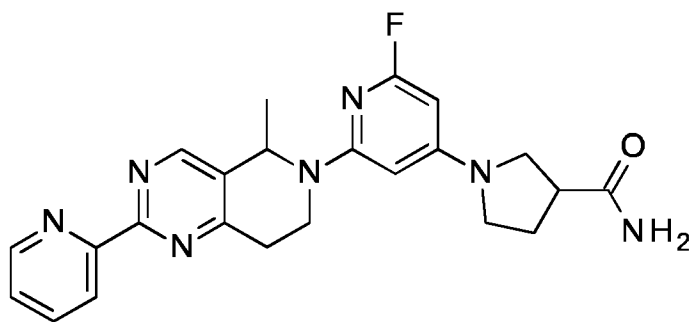
Example 61 and 62

1-[4-Fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]pyrrolidine-3-carboxamide and 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidine-3-carboxamide



Example 61

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Example 62

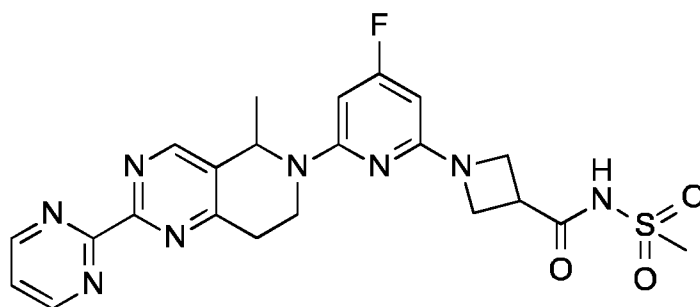
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (product of step 4 in Example 59, 100 mg, 0.295 mmol), pyrrolidine-3-carboxamide hydrochloride (133 mg, 0.884 mmol) and K₂CO₃ (244 mg, 1.768 mmol) in NMP (3 mL) was heated at 130 °C with stirring for 16 hrs. After being cooled to rt, the mixture was filtered and the filtrate was partitioned between EA (200 mL) and brine (200 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]pyrrolidine-3-carboxamide (9 mg) as a white solid and 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidine-3-carboxamide (20 mg) as a white solid.

Example 61: 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]pyrrolidine-3-carboxamide, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.85 (d, 1 H), 8.71 (s, 1 H), 8.50 (d, 1 H), 7.84 - 7.90 (m, 1 H), 7.41 (dd, 1 H), 5.76 (d, 1 H), 5.56 - 5.68 (m, 2 H), 5.49 (br d, 2 H), 4.45 (br d, 1 H), 3.74 - 3.82 (m, 1 H), 3.60 - 3.73 (m, 2 H), 3.38 - 3.51 (m, 2 H), 3.03 - 3.22 (m, 3 H), 2.26 - 2.34 (m, 2 H), 1.55 (d, 3 H). MS obsd (ESI) [(M+H)⁺]: 434.

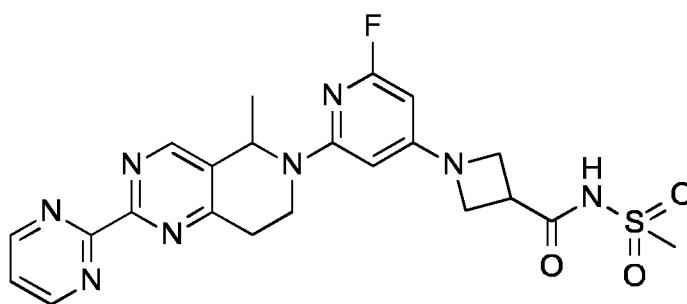
Example 62: 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidine-3-carboxamide, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.85 (d, 1 H), 8.71 (s, 1 H), 8.50 (d, 1 H), 7.87 (td, 1 H), 7.37 - 7.44 (m, 1 H), 5.65 (br d, 1 H), 5.46 - 5.59 (m, 4 H), 4.40 (br d, 1 H), 3.59 - 3.65 (m, 2 H), 3.52 - 3.58 (m, 1 H), 3.38 - 3.49 (m, 2 H), 3.09 - 3.29 (m, 3 H), 2.29 - 2.37 (m, 2 H), 1.53 - 1.56 (d, 3 H). MS obsd (ESI) [(M+H)⁺]: 434.

Example 63 and 64

1-[4-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]-*N*-methylsulfonyl-azetidine-3-carboxamide and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methylsulfonyl-azetidine-3-carboxamide

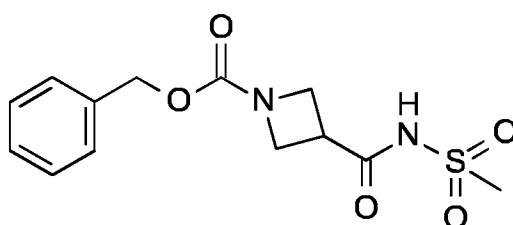


Example 63



Example 64

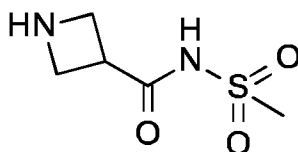
Step 1: Preparation of benzyl 3-(methylsulfonylcarbamoyl)azetidine-1-carboxylate



A mixture of 1-benzyloxycarbonylazetidine-3-carboxylic acid (500 mg, 2.13 mmol) and CDI (414 mg, 2.55 mmol) in DMF (5 mL) was heated at 65 °C with stirring for 1 hr. The resulting mixture was cooled to 0 °C, then to the cooled mixture was added a mixture of NaH (510 mg, 12.7 mmol) and methanesulfonamide (607 mg, 6.38 mmol) in DMF (5 mL). The resulting mixture was warmed to rt and stirred for 1 hr, then neutralized with formic acid and extracted with EA (200 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to afford benzyl 3-(methylsulfonylcarbamoyl)azetidine-1-

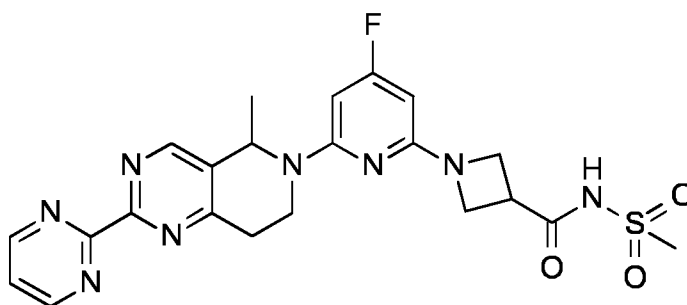
carboxylate (900 mg, crude) as a colorless oil, which was used in the next step without any further purification.

Step 2: Preparation of *N*-methylsulfonylazetidine-3-carboxamide

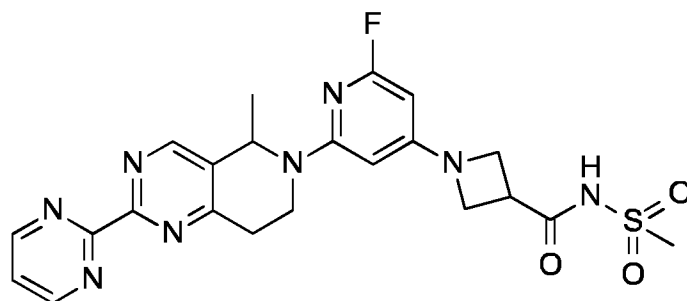


5 To a solution of benzyl 3-(methylsulfonylcarbamoyl)azetidine-1-carboxylate (900 mg, crude) in MeOH (15 mL) was added Pd/C (100 mg, 10 % wt). The resulting mixture was stirred under H₂ atmosphere (H₂ balloon) at rt for 12 hrs, and then filtered. The filter cake was washed sequentially with MeOH (20 mL) and H₂O (30 mL). The filtrate was concentrated *in vacuo* to give *N*-methylsulfonylazetidine-3-carboxamide (200 mg) as a white solid, which was used in the
10 next step without any further purification.

Step 3: Preparation of 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]-*N*-methylsulfonyl-azetidine-3-carboxamide and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methylsulfonyl-azetidine-3-carboxamide



Example 63



Example 64

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), K₂CO₃ (122 mg, 0.88 mmol) and *N*-methylsulfonylazetidine-3-carboxamide (63 mg, 0.35 mmol) in NMP (1 mL) was heated at 150 °C in a microwave reactor for 1 hr. The resulting mixture was diluted
5 with H₂O (20 mL) and extracted with EA (80 mL). The organic layer was washed with H₂O (20 mL) and the combined aqueous layer was concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-*N*-methylsulfonyl-azetidine-3-carboxamide (17.2 mg) as a purple solid and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-*N*-methylsulfonyl-azetidine-3-carboxamide (56.7 mg) as a light yellow solid.
10

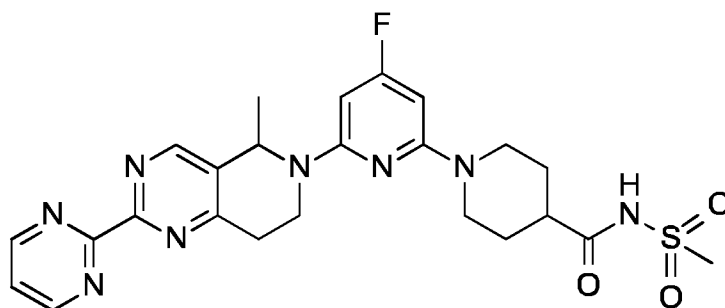
Example 63: 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-*N*-methylsulfonyl-azetidine-3-carboxamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 1 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 5.99 (m, 1 H), 5.75 (q, 1 H), 5.48 (m, 1 H), 4.50 - 4.63 (m, 1 H), 4.05 - 4.17 (m, 4 H), 3.39 - 3.58 (m, 2 H), 3.20 (s, 3 H), 3.06 -
15 3.17 (m, 2 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 499.

Example 64: 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-*N*-methylsulfonyl-azetidine-3-carboxamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 2 H), 8.86 (s, 1 H), 7.64 (t, 1 H), 5.69 (q, 1 H), 5.63 (s, 1 H), 5.38 (d, 1 H), 4.46 (dd, 1 H), 4.04 - 4.20 (m, 4 H), 3.54 - 3.66 (m, 1 H), 3.39 - 3.51 (m, 1 H), 3.27 (s,
20 3 H), 3.05 - 3.22 (m, 2 H), 1.56 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 499.

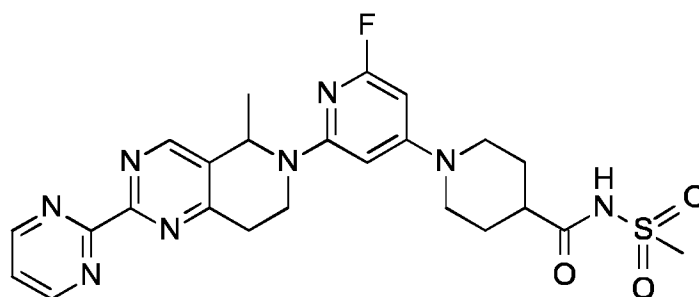
Example 65 and 66

1-[4-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-*N*-methylsulfonyl-piperidine-4-carboxamide and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-*N*-methylsulfonyl-piperidine-4-carboxamide
25

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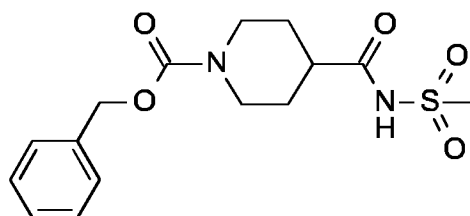


Example 65



Example 66

5 **Step 1: Preparation of benzyl 4-(methanesulfonylcarbamoyl)piperidine-1-carboxylate**



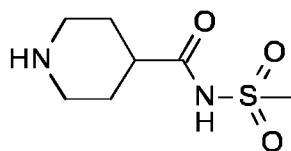
To a solution of 1-benzyloxycarbonylpiperidine-4-carboxylic acid (5.0 g, 19.0 mmol) in DMF (30 mL) was added CDI (9.24 g, 57.0 mmol). The resulting mixture was heated at 65 °C with stirring for 1 hr and then cooled to 0 °C. To the cooled mixture was added a mixture of

10 NaH (3.8 g, 95.0 mmol) and methanesulfonamide (10.8 g, 114.0 mmol) in DMF (30 mL) slowly. The resulting mixture was stirred at rt for 12 hrs, and then partitioned between EA (500 mL) and H₂O (100 mL). The separated organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with DCM/MeOH=20/1, v:v) to give benzyl 4-

15 (methanesulfonylcarbamoyl)piperidine-1-carboxylate (6.0 g) as a yellow solid.

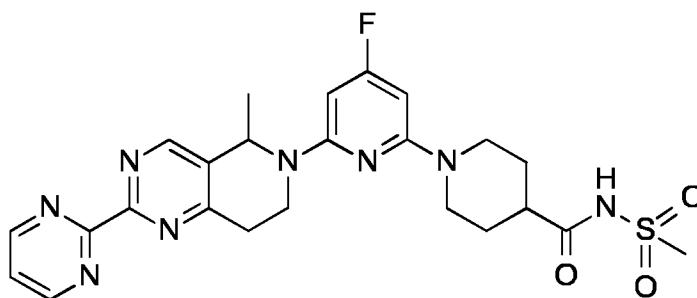
Step 2: Preparation of N-methanesulfonylpiperidine-4-carboxamide

-89-

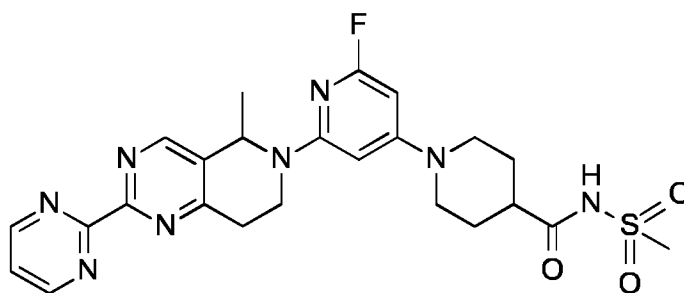


To a solution of benzyl 4-(methylsulfonylcarbamoyl)piperidine-1-carboxylate (1.0 g, 2.94 mmol) in MeOH (15 mL) was added Pd/C (100 mg, 10 % wt). The mixture was stirred at rt under H₂ (H₂ balloon) for 12 hrs, and then filtered. The filter cake was washed sequentially with MeOH (20 mL) and H₂O (30 mL). The aqueous solution was concentrated *in vacuo* to give *N*-methylsulfonylpiperidine-4-carboxamide (400 mg) as a white solid, which was used in the next step without any further purification.

Step 3: Preparation of 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]-*N*-methylsulfonyl-piperidine-4-carboxamide and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methylsulfonyl-piperidine-4-carboxamide



Example 65



Example 66

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.059 mmol), K₂CO₃ (122 mg, 0.88 mmol) and *N*-methylsulfonylpiperidine-4-carboxamide (73 mg, 0.35 mmol) in NMP

-90-

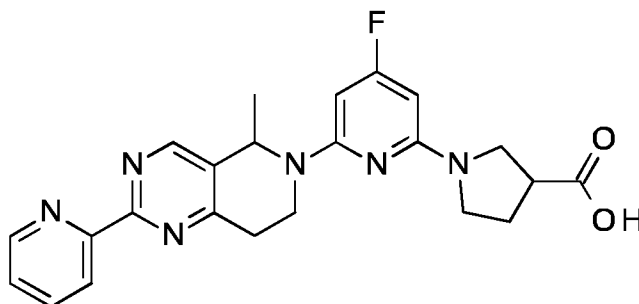
(0.5 mL) was heated at 150 °C in a microwave reactor for 1 hr. The resulting mixture was partitioned between EA (80 mL) and H₂O (20 mL). The separated organic layer was washed with H₂O (20 mL). The combined aqueous layers were concentrated *in vacuo* and the residue was purified by prep-HPLC to afford 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-N-methylsulfonyl-piperidine-4-carboxamide (12 mg) as a light yellow solid and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methylsulfonyl-piperidine-4-carboxamide (42 mg) as a light yellow solid.

Example 65: 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-N-methylsulfonyl-piperidine-4-carboxamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 1 H), 8.88 (s, 1 H), 7.64 (t, 1 H), 5.97 (d, 1 H), 5.85 (d, 1 H), 5.74 (d, 1 H), 4.50 (d, 1 H), 4.33 (d, 2 H), 3.42 - 3.54 (m, 1 H), 3.21 (s, 3 H), 3.07 - 3.18 (m, 1 H), 2.81 - 2.96 (m, 1 H), 2.52 (t, 1 H), 1.83 - 1.94 (m, 2 H), 1.69 (m, 2 H), 1.58 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 527.

Example 66: 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methylsulfonyl-piperidine-4-carboxamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.05 (d, 2 H), 8.89 (s, 1 H), 7.66 (t, 1 H), 6.10 (s, 1 H), 5.84 (s, 1 H), 5.74 (q, 1 H), 4.44 - 4.57 (m, 1 H), 3.99 (d, 2 H), 3.43 - 3.58 (m, 1 H), 3.24 (s, 3 H), 3.09 - 3.21 (m, 2 H), 2.92 - 3.04 (m, 2 H), 2.55 (m, 1 H), 1.93 (d, 2 H), 1.69 - 1.85 (m, 2 H), 1.59 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 527.

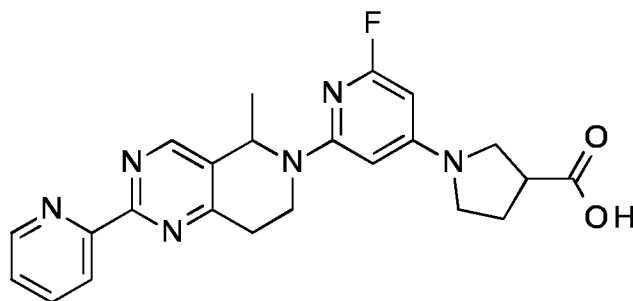
Example 67 and 68

1-[4-Fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]pyrrolidine-3-carboxylic acid and 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidine-3-carboxylic acid



Example 67

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Example 68

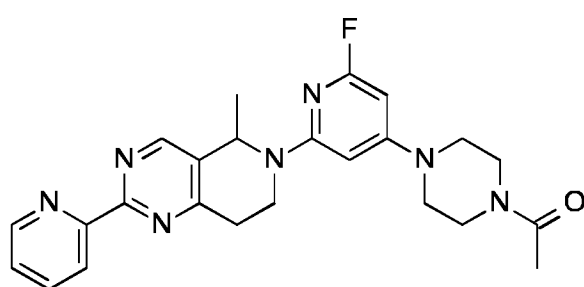
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 4 in Example 59, 100 mg, 0.3 mmol), methyl pyrrolidine-3-carboxylate (116 mg, 0.9 mmol) and K₂CO₃ (124 mg, 0.9 mmol) in NMP (1 mL) was heated at 120 °C with stirring for 12 hrs. After being cooled to rt, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH (1 mL), and then stirred with a solution of NaOH (63 mg, 1.56 mmol) in H₂O (1 mL) at 30 °C for 12 hrs. After being acidified to pH=7 with 1 M aqueous HCl, the resulting mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]pyrrolidine-3-carboxylic acid (10 mg) as a white solid and 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidine-3-carboxylic acid (11 mg) as a white solid.

Example 67: 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]pyrrolidine-3-carboxylic acid, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 8.71 - 8.81 (m, 2 H) 8.52 (br d, 1 H) 8.00 (br t, 1 H) 7.49 - 7.60 (m, 1 H) 7.49 - 7.60 (m, 1 H) 5.85 - 6.06 (m, 1 H) 5.78 (br dd, 1 H) 5.57 (br dd, 1 H) 4.24 - 4.75 (m, 2 H) 3.38 - 3.60 (m, 3 H) 2.96 - 3.22 (m, 2 H) 2.22 - 2.40 (m, 1 H) 2.02 - 2.17 (m, 3 H) 1.49 - 1.62 (m, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 435.

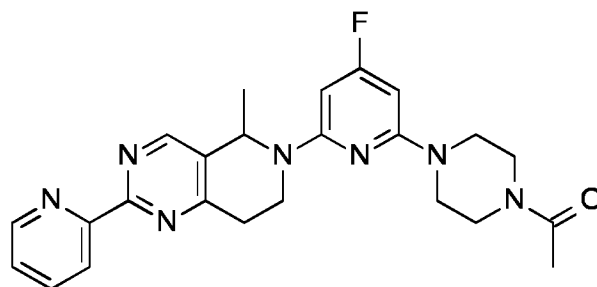
Example 68: 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidine-3-carboxylic acid, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 8.79 (s, 1 H) 8.73 (br d, 1 H) 8.52 (d, 1 H) 8.00 (t, 1 H) 7.54 (dd, 1 H) 5.72 (s, 1 H) 5.54 - 5.66 (m, 1 H) 5.50 (br s, 1 H) 4.43 (br dd, 1 H) 4.09 - 4.21 (m, 1 H) 3.59 (br s, 1 H) 3.35 - 3.52 (m, 2 H) 3.01 - 3.17 (m, 2 H) 2.26 - 2.43 (m, 1 H) 2.08 - 2.22 (m, 2 H) 2.01 - 2.07 (m, 1 H) 1.55 (dd, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 435.

Example 69 and 70

1-[4-[2-Fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperazin-1-yl]ethanone and 1-[4-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperazin-1-yl]ethanone



Example 69



Example 70

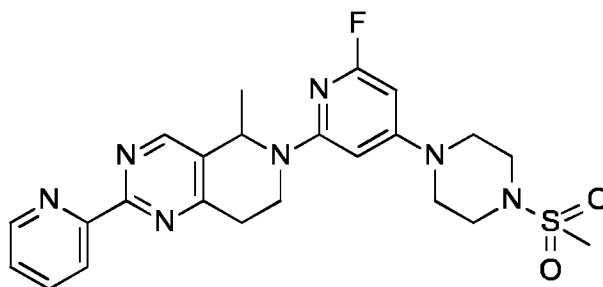
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 4 in Example 59, 136 mg, 0.4 mmol), 1-(piperazin-1-yl)ethanone (154 mg, 1.2 mmol) and K₂CO₃ (166 mg, 1.2 mmol) in DMA (1 mL) was heated at 110 °C with stirring for 20 hrs. After being cooled to rt, the reaction mixture was filtered and the filtrate was purified by prep-HPLC to afford 1-[4-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperazin-1-yl]ethanone (60 mg) as a yellow powder and 1-[4-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperazin-1-yl]ethanone (17 mg) as a yellow powder.

Example 69: 1-[4-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperazin-1-yl]ethanone, ¹H NMR (400MHz, CDCl₃) δ ppm: 8.83 (dd, 1H), 8.70 (s, 1H), 8.49 (d, 1H), 7.85 (dt, 1H), 7.39 (ddd, 1H), 5.82 (s, 1H), 5.69 (d, 1H), 5.63 (q, 1H), 4.42 - 4.32 (m, 1H), 3.81 - 3.71 (m, 2H), 3.67 - 3.58 (m, 2H), 3.53 - 3.31 (m, 5H), 3.28 - 3.11 (m, 2H), 2.14 (s, 3H), 1.55 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 448.

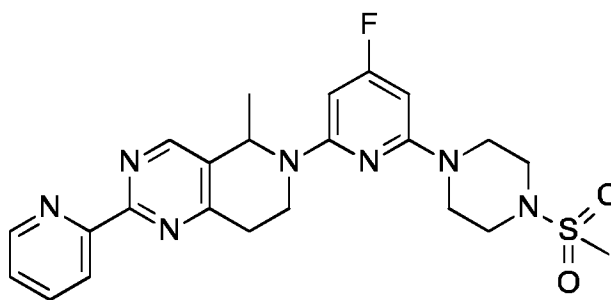
Example 70: 1-[4-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperazin-1-yl]ethanone, ¹H NMR (400MHz, CDCl₃) δ ppm: 8.85 (dd, 1H), 8.72 (s, 1H), 8.51 (d, 1H), 7.87 (dt, 1H), 7.41 (ddd, 1H), 5.86 (dd, 1H), 5.74 (dd, 1H), 5.57 (q, 1H), 4.47 - 4.37 (m, 1H), 3.76 (dd, 2H), 3.67 - 3.57 (m, 4H), 3.53 - 3.41 (m, 3H), 3.23 - 3.16 (m, 2H), 2.17 (s, 3H), 1.57 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 448.

Example 71 and 72

6-[6-Fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[4-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



Example 71



Example 72

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 4 in Example 59, 136 mg, 0.4 mmol), 1-(methylsulfonyl)piperazine (197 mg, 1.2 mmol) and K₂CO₃ (166 mg, 1.2 mmol) in DMA (1 mL) was heated at 110 °C with stirring for 20 hrs. After being cooled to rt, the reaction mixture was filtered and the filtrate was purified by prep-HPLC to afford 6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (65 mg) as a yellow powder and 6-[4-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (13 mg) as a yellow powder.

Example 71: 6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR (400MHz, CDCl₃) δ ppm: 8.88 - 8.82 (m, 1H), 8.72 (s, 1H), 8.50 (d, 1H), 7.87 (dt, 1H), 7.41 (ddd, 1H), 5.85 (s, 1H), 5.73 (d, 1H),

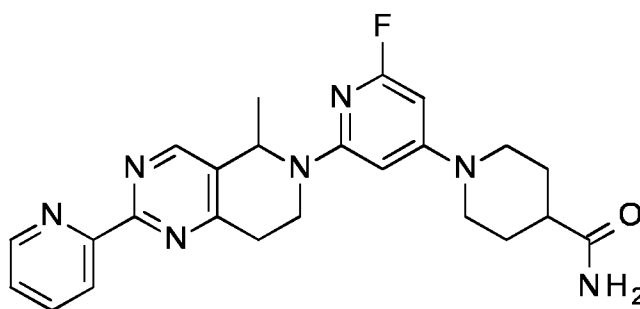
-94-

5.65 (q, 1H), 4.42 - 4.33 (m, 1H), 3.54 - 3.44 (m, 5H), 3.40 - 3.34 (m, 4H), 3.24 - 3.17 (m, 2H), 2.84 (s, 3H), 1.57 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 484.

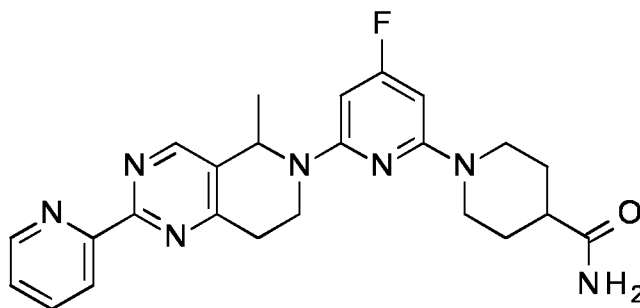
Example 72: 6-[4-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR (400MHz, CDCl₃) δ ppm: 8.86 (dd, 1H), 8.73 (s, 1H), 8.52 (d, 1H), 7.88 (dt, 1H), 7.42 (ddd, 1H), 5.88 (dd, 1H), 5.76 (dd, 1H), 5.56 (q, 1H), 4.48 - 4.38 (m, 1H), 3.72 - 3.64 (m, 4H), 3.52 - 3.42 (m, 1H), 3.35 (t, 4H), 3.24 - 3.17 (m, 2H), 2.83 (s, 3H), 1.58 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 484.

Example 73 and 74

1-[2-Fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperidine-4-carboxamide and 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperidine-4-carboxamide



Example 73



Example 74

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 4 in Example 59, 136 mg, 0.4 mmol), piperidine-4-carboxamide (154 mg, 1.2 mmol) and K₂CO₃ (166 mg, 1.2 mmol) in DMA (1 mL) was heated at 110 °C with stirring for 20 hrs. After being cooled to rt, the reaction mixture was filtered and the

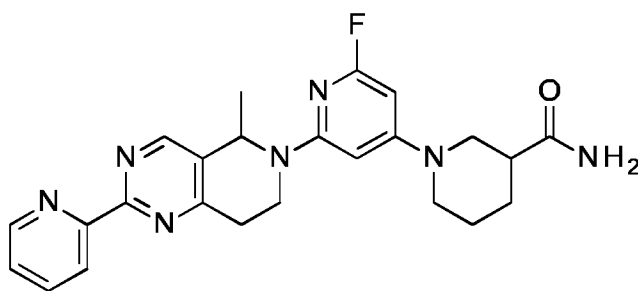
filtrate was purified by prep-HPLC to afford 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperidine-4-carboxamide (65 mg) as a yellow powder and 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperidine-4-carboxamide (25 mg) as a yellow powder.

5 **Example 73:** 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperidine-4-carboxamide, ^1H NMR (400MHz, CDCl_3) δ ppm: 8.86 - 8.82 (m, 1H), 8.72 (s, 1H), 8.50 (d, 1H), 7.86 (dt, 1H), 7.40 (ddd, 1H), 5.87 (s, 1H), 5.81 (br s, 1H), 5.74 (s, 1H), 5.70 - 5.60 (m, 2H), 4.44 - 4.33 (m, 1H), 3.85 (dd, 1H), 3.68 (br d, 1H), 3.52 - 3.40 (m, 1H), 3.28 - 3.12 (m, 3H), 3.08 - 2.98 (m, 1H), 2.57 - 2.43 (m, 1H), 2.09 - 1.99 (m, 1H),
10 1.90 - 1.61 (m, 3H), 1.55 (d, 3H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 448.

Example 74: 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperidine-4-carboxamide, ^1H NMR (400MHz, CDCl_3) δ ppm: 8.89 - 8.83 (m, 1H), 8.72 (s, 1H), 8.51 (d, 1H), 7.87 (dt, 1H), 7.41 (ddd, 1H), 5.78 (ddd, 2H), 5.62 - 5.38 (m, 3H), 4.48 - 4.38 (m, 1H), 4.32 (br d, 2H), 3.49 - 3.41 (m, 1H), 3.28 - 3.11 (m, 2H), 2.98
15 - 2.87 (m, 2H), 2.43 (tt, 1H), 1.98 (br d, 2H), 1.78 (dq, 2H), 1.57 (d, 3H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 448.

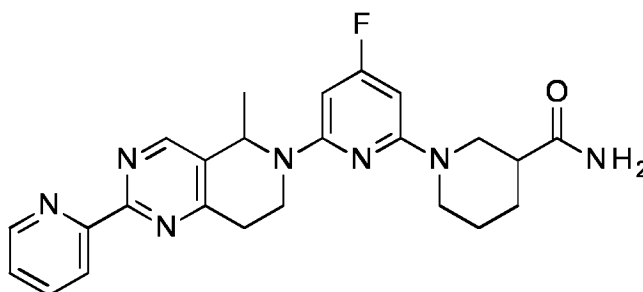
Example 75 and 76

1-[2-Fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperidine-3-carboxamide and 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperidine-3-carboxamide
20



Example 75

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Example 76

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 4 in Example 59, 136 mg, 0.4 mmol), piperidine-3-carboxamide (154 mg, 1.2 mmol) and K₂CO₃ (166 mg, 1.2 mmol) in DMA (1 mL) was heated at 110 °C for 20 hrs. After being cooled to rt, the reaction mixture was filtered and the filtrate was purified by prep-HPLC to afford 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperidine-3-carboxamide (57 mg) as a yellow powder and 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperidine-3-carboxamide (18 mg) as a yellow powder.

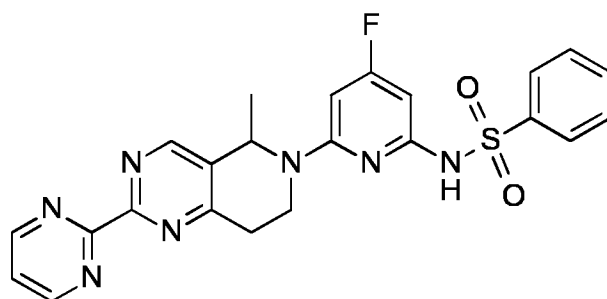
Example 75: 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperidine-3-carboxamide, ¹H NMR (400MHz, CDCl₃) δ ppm: 8.84 (d, 1H), 8.71 (s, 1H), 8.50 (d, 1H), 7.87 (dt, 1H), 7.44 - 7.37 (m, 1H), 5.84 (s, 1H), 5.72 (s, 1H), 5.68 - 5.56 (m, 3H), 4.44 - 4.30 (m, 1H), 3.88 (br d, 2H), 3.53 - 3.41 (m, 1H), 3.29 - 3.11 (m, 2H), 3.02 - 2.89 (m, 2H), 2.42 (tt, 1H), 1.98 (br d, 2H), 1.89 - 1.73 (m, 2H), 1.55 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 448.

Example 76: 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperidine-3-carboxamide, ¹H NMR (400MHz, CDCl₃) δ ppm: 8.90 - 8.81 (m, 1H), 8.72 (s, 1H), 8.51 (dd, 1H), 7.88 (dt, 1H), 7.41 (ddd, 1H), 6.33 - 6.14 (m, 1H), 5.87 - 5.74 (m, 2H), 5.64 - 5.39 (m, 2H), 4.47 - 4.35 (m, 1H), 3.98 - 3.86 (m, 1H), 3.82 - 3.61 (m, 2H), 3.54 - 3.41 (m, 1H), 3.33 - 3.12 (m, 3H), 2.55 (br dd, 1H), 2.10 - 1.88 (m, 2H), 1.82 - 1.63 (m, 2H), 1.57 (dd, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 448.

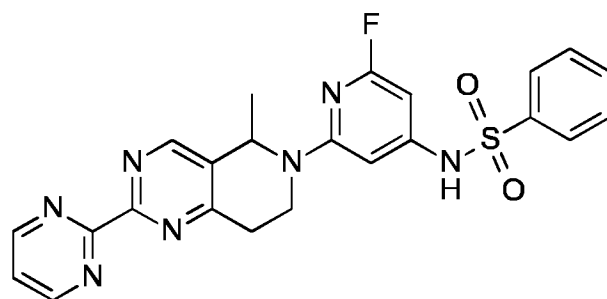
Example 77 and 78

N-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]benzenesulfonamide and *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]benzenesulfonamide

-97-



Example 77



Example 78

- 5 To a solution of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 200 mg, 588 μ mol) in NMP (4 mL) was added benzenesulfonamide (102 mg, 646 μ mol) and potassium carbonate (162 mg, 1.18 mmol). The reaction mixture was heated at 150 °C in a microwave reactor for 4 hrs. The reaction mixture was filtered and the filtrate was purified by prep-HPLC to give *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]benzenesulfonamide (102 mg) as a light yellow solid and *N*-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]benzenesulfonamide (10 mg) as a light yellow solid.
- 10

Example 77: *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]benzenesulfonamide, ^1H NMR (400 MHz, DMSO- d_6) δ ppm: 8.99 (d, 2H), 8.78 (s, 1H), 8.00 - 7.90 (m, 2H), 7.69 - 7.60 (m, 4H), 6.37-6.30 (m, 1H), 6.01 - 5.92 (m, 1H), 5.37 - 5.24 (m, 1H), 4.35 - 4.21 (m, 1H), 3.32-3.23 (m, 1H), 2.92 - 2.76 (m, 2H), 1.35 (d, 3H). $[(\text{M}+\text{H})^+]$: 478.

15

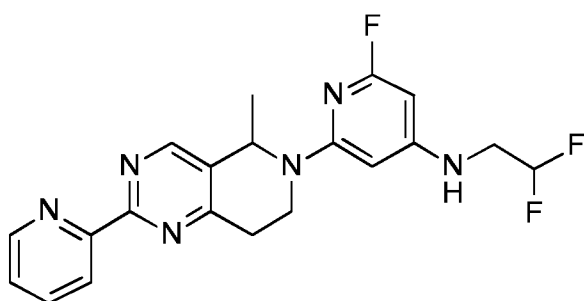
Example 78: *N*-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]benzenesulfonamide, ^1H NMR (400 MHz, DMSO- d_6) δ ppm: 8.99 (d, 2H), 8.96 (s, 1H), 7.95 - 7.90 (m, 2H), 7.71 - 7.56 (m, 4H), 6.37 (s, 1H), 6.00 (s, 1H), 5.50 - 5.39

20

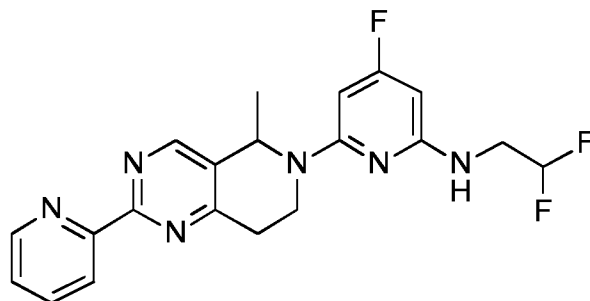
(m, 1H), 4.27 - 4.17 (m, 1H), 3.49 - 3.37 (m, 1H), 3.02 - 2.95 (m, 2H), 1.45 (d, 3H). $[(M+H)^+]$: 478.

Example 79 and 80

N-(2,2-difluoroethyl)-2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl]pyridin-2-amine and *N*-(2,2-difluoroethyl)-4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl]pyridin-2-amine



Example 79



Example 80

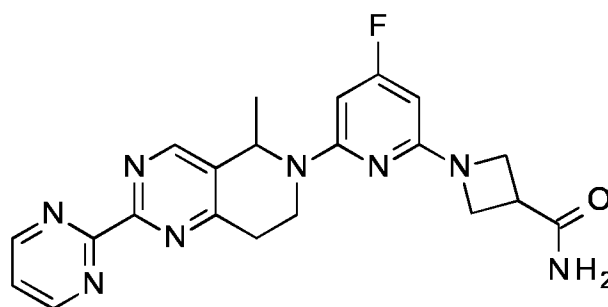
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-(2-pyridyl)-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidine (the product of step 4 in Example 59, 130 mg, 383 μ mol), 2,2-difluoroethanamine (93.2 mg, 1.15 mmol) and K_2CO_3 (159 mg, 1.15 mmol) in NMP (5 mL) was heated at 100 °C with stirring overnight. The resulting mixture was filtered and the filtrate was purified by prep-HPLC to give *N*-(2,2-difluoroethyl)-2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl]pyridin-2-amine (10 mg) as a light yellow solid and *N*-(2,2-difluoroethyl)-4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl]pyridin-2-amine (10 mg) as a light yellow solid.

Example 79: *N*-(2,2-difluoroethyl)-2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl]pyridin-2-amine, ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.55 (d, 3 H), 3.09 - 3.27 (m, 2 H), 3.40 - 3.50 (m, 1 H), 3.52 - 3.65 (m, 2 H), 4.29 - 4.38 (m, 1 H), 4.46 (br s, 1 H), 5.55 (d, 1 H), 5.61 (q, 1 H), 5.70 (s, 1 H), 5.76 - 6.08 (m, 1 H), 7.42 (dd, 1 H), 7.88 (td, 1 H), 8.49 (d, 1 H), 8.70 (s, 1 H), 8.80 - 8.87 (m, 1 H). MS obsd. (ESI $^+$) $[(M+H)^+]$: 401.

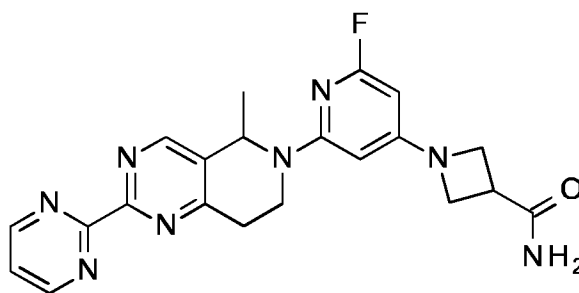
Example 80: *N*-(2,2-difluoroethyl)-4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl]pyridin-2-amine, ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.55 (d, 3 H), 3.11 - 3.25 (m, 2 H), 3.37 - 3.49 (m, 1 H), 3.69 - 3.83 (m, 2 H), 4.32 - 4.44 (m, 1 H), 4.51 - 4.64 (m, 1 H), 5.50 - 5.62 (m, 2 H), 5.76 - 6.13 (m, 2 H), 7.36 - 7.45 (m, 1 H), 7.82 - 7.92 (m, 1 H), 8.46 - 8.54 (m, 1 H), 8.70 (s, 1 H), 8.80 - 8.88 (m, 1 H). MS obsd. (ESI $^+$) $[(M+H)^+]$: 401.

Example 81 and 82

1-[4-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidine-3-carboxamide and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carboxamide

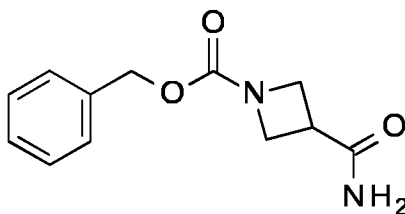


Example 81



Example 82

Step 1: Preparation of benzyl 3-carbamoylazetidine-1-carboxylate

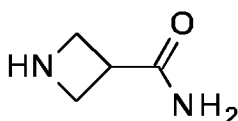


To a solution of 1-benzyloxycarbonylazetidine-3-carboxylic acid (1.5 g, 6.38 mmol) in DMF (20 mL) was added NH₄Cl (3.41g, 63.8 mmol), DIPEA (4.12 g, 31.9 mmol) and HATU (3.64 g, 9.56 mmol). The mixture was stirred at rt for 12 hrs and diluted with H₂O (20 mL). The resulting mixture was extracted with EA (80 mL) twice. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was suspended

-100-

in MeOH (30 mL) and filtered. The filtrate was concentrated *in vacuo* to afford benzyl 3-carbamoylazetidine-1-carboxylate (700 mg, crude) as a yellow solid, which was used in the next step without any further purification.

Step 2: Preparation of azetidine-3-carboxamide

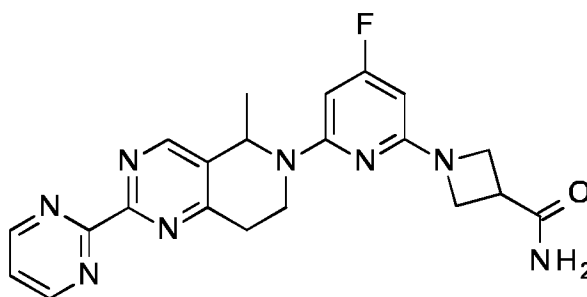


5

To a solution of benzyl 3-carbamoylazetidine-1-carboxylate (500 mg, 2.13 mmol) in MeOH (10 mL) was added Pd/C (100 mg, 10% wt). The mixture was stirred at rt under H₂ atmosphere (H₂ balloon) for 12 hrs, and then filtered. The filtrate was concentrated *in vacuo* to afford azetidine-3-carboxamide (150 mg, crude) as a yellow oil, which was used in the next step without any further purification.

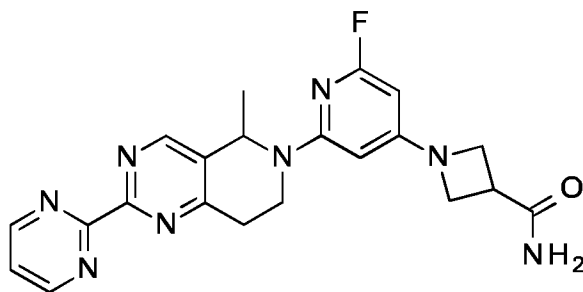
10

Step 3: Preparation of 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidine-3-carboxamide and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carboxamide



15

Example 81



Example 82

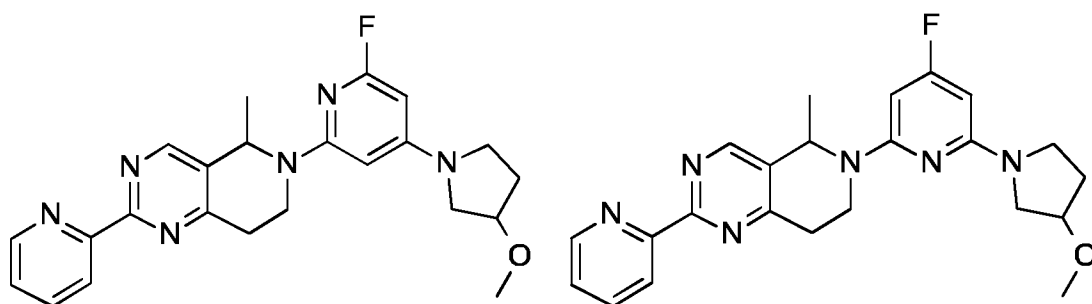
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 80 mg, 0.23 mmol), K₂CO₃ (98 mg, 0.71 mmol) and azetidine-3-carboxamide (35 mg, 0.35 mmol) in NMP (1 mL) was heated at 150 °C in a microwave reactor for 1 hr. The resulting mixture was partitioned between EA (10 mL) and H₂O (5 mL). The separated organic layer was concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidine-3-carboxamide (15 mg) as an orange solid and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carboxamide (43 mg) as an orange solid.

Example 81: 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidine-3-carboxamide, ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.99 (d, 2 H), 8.88 (s, 1 H), 7.64 (t, 1 H), 7.47 (br. s., 1 H), 6.95 - 7.08 (br. s., 1 H), 6.07 (d, 1 H), 5.61 - 5.75 (m, 1 H), 5.51 (d, 1 H), 4.52 (d, 1 H), 4.02 (t, 2 H), 3.88 - 3.96 (m, 2 H), 3.31 - 3.41 (m, 2 H), 2.95 - 3.11 (m, 2 H), 1.49 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 421.

Example 82: 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carboxamide, ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.99 (d, 1 H), 8.91 (s, 1 H), 7.64 (t, 1 H), 7.51 (br. s., 1 H), 7.06 (br. s., 1 H), 5.57 - 5.73 (m, 2 H), 5.40 (s, 1 H), 4.40 (dd, 1 H), 4.03 (m, 2 H), 3.87 - 3.97 (m, 2 H), 3.33 - 3.46 (m, 2 H), 2.92 - 3.12 (m, 2 H), 1.47 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 421.

Example 83 and 84

6-[6-Fluoro-4-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[4-fluoro-6-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



Example 83

Example 84

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 4 in Example 59, 170 mg, 0.5 mmol), K₂CO₃ (207 mg, 1.5 mmol) and 3-methoxypyrrolidine hydrochloride (137 mg, 1.0 mmol) in NMP (5 mL) was heated at 110 °C with stirring for 15 hrs. The resulting mixture was poured into water (20 mL) and extracted with DCM (50 mL) twice. The organic layers were combined and washed with brine, then dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 6-[6-fluoro-4-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (23 mg) as yellow powder and 6-[4-fluoro-6-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (10 mg) as yellow powder.

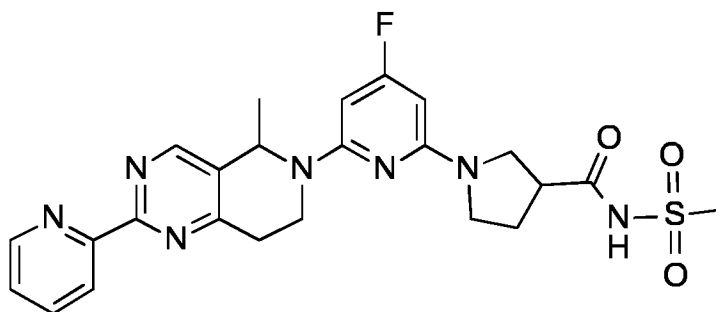
Example 83: 6-[6-fluoro-4-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.81-8.91 (m, 1H), 8.67-8.75 (m, 1H), 8.43-8.54 (m, 1H), 7.80-7.96 (m, 1H), 7.38-7.47 (m, 1H), 5.61-5.73 (m, 1H), 5.51-5.57 (m, 1H), 5.43-5.50 (m, 1H), 4.35-4.46 (m, 1H), 4.08-4.16 (m, 1H), 3.41-3.53 (m, 5H), 3.39 (d, 3H), 3.10-3.30 (m, 2H), 2.17-2.26 (m, 1H), 2.02-2.14 (m, 1H), 1.47-1.59 (m, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 421.

Example 84: 6-[4-fluoro-6-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.71-8.82 (m, 1H), 8.62 (s, 1H), 8.37-8.46 (m, 1H), 7.73-7.84 (m, 1H), 7.28-7.36 (m, 1H), 5.62-5.70 (m, 1H), 5.53-5.61 (m, 1H), 5.36-5.44 (m, 1H), 4.31-4.41 (m, 1H), 3.97-4.05 (m, 1H), 3.51 (d, 2H), 3.40-3.47 (m, 2H), 3.33-3.39 (m, 1H), 3.31 (d, 3H), 3.00-3.18 (m, 2H), 1.96-2.12 (m, 2H), 1.47 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 421.

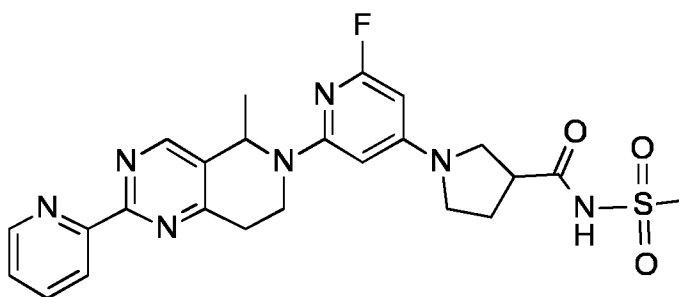
Example 85 and 86

1-[4-Fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]-N-methylsulfonyl-pyrrolidine-3-carboxamide and 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]-N-methylsulfonyl-pyrrolidine-3-carboxamide

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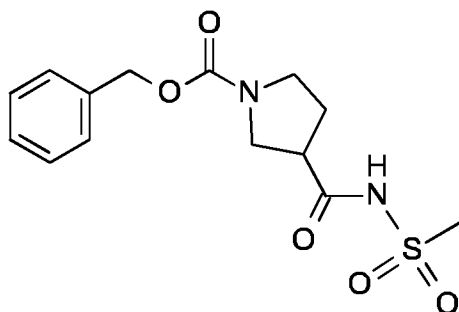


Example 85



Example 86

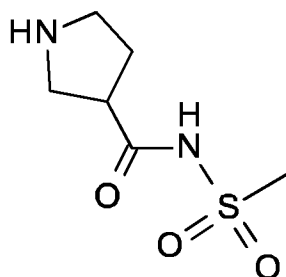
5 **Step 1: Preparation of benzyl 3-(methanesulfonylcarbamoyl)pyrrolidine-1-carboxylate**



To a solution of 1-benzyloxycarbonylpyrrolidine-3-carboxylic acid (2.0 g, 8.02 mmol) in DCM (20 mL) was added a solution of *N,N'*-dicyclohexylcarbodiimide (2.48 g, 12.03 mmol) in DCM (5 mL), followed by addition of methanesulfonamide (763 mg, 8.02 mmol) and 4-
 10 dimethylaminopyridine (980 mg, 8.02 mmol). The mixture was stirred at rt for 16 hrs, and then filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (eluting with DCM/MeOH=40/1, v:v) to give benzyl 3-(methanesulfonylcarbamoyl)pyrrolidine-1-carboxylate (2.2 g) as a white solid.

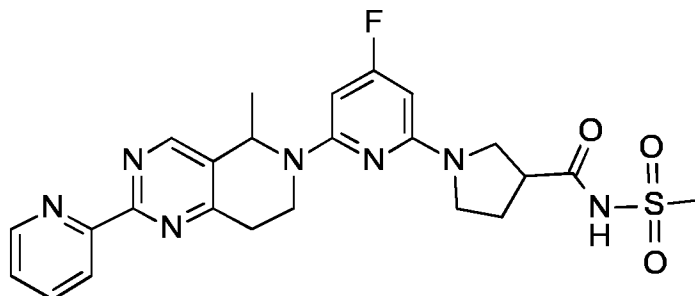
Step 2: Preparation of *N*-methanesulfonylpyrrolidine-3-carboxamide

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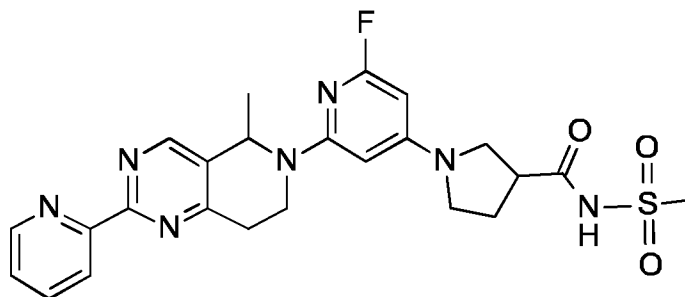


To a solution of benzyl 3-(methylsulfonylcarbamoyl)pyrrolidine-1-carboxylate (2.2 g, 6.74 mmol) in MeOH (20 mL) was added Pd/C (400 mg, 10 % wt). The mixture was stirred under H₂ atmosphere (H₂ balloon) at rt for 16 hrs. The mixture was then filtered and the filtrate was concentrated *in vacuo* to give *N*-methylsulfonylpyrrolidine-3-carboxamide (1.3 g, crude) as a white solid.

Step 3: Preparation of 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]-*N*-methylsulfonyl-pyrrolidine-3-carboxamide and 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]-*N*-methylsulfonyl-pyrrolidine-3-carboxamide



Example 85



Example 86

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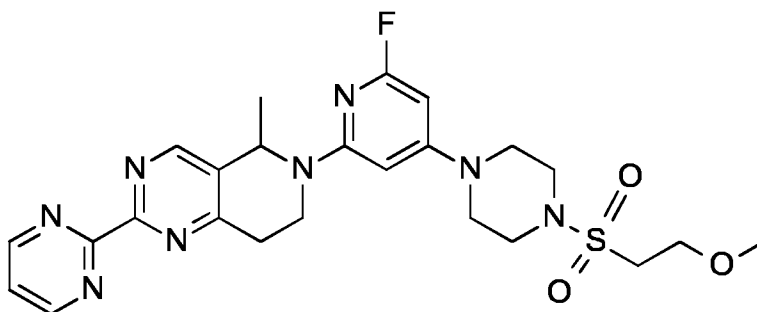
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 4 in Example 59, 100 mg, 0.295 mmol), K₂CO₃ (122 mg, 0.884 mmol) and *N*-methylsulfonylpyrrolidine-3-carboxamide (170 mg, 0.884 mmol) in NMP (3 mL) was heated at 150 °C in a microwave reactor for 1 hr. The resulting mixture was
 5 filtered and the filtrate was partitioned between EA (200 mL) and brine (100 mL). The separated organic layer was dried over with anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]-*N*-methylsulfonyl-pyrrolidine-3-carboxamide (3 mg) as a white solid and 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-
 10 6-yl]-4-pyridyl]-*N*-methylsulfonyl-pyrrolidine-3-carboxamide (8 mg) as a white solid.

Example 85: 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]-*N*-methylsulfonyl-pyrrolidine-3-carboxamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 8.80 (s, 1 H), 8.72 (br d, 1 H), 8.51 (d, 1 H), 7.99 (td, 1 H), 7.50 - 7.55 (m, 1 H), 5.88 (d, 1 H), 5.73 (q, 1 H), 5.49 (d, 1 H), 4.64 (s, 1 H), 4.53 (br d, 1 H), 3.70 (br s, 1 H),
 15 3.53 - 3.64 (m, 2 H), 3.37 - 3.49 (m, 2 H), 3.04 - 3.15 (m, 5 H), 2.22 (q, 2 H), 1.56 (d, 3 H). MS obsd (ESI) [(M+H)⁺]: 512.

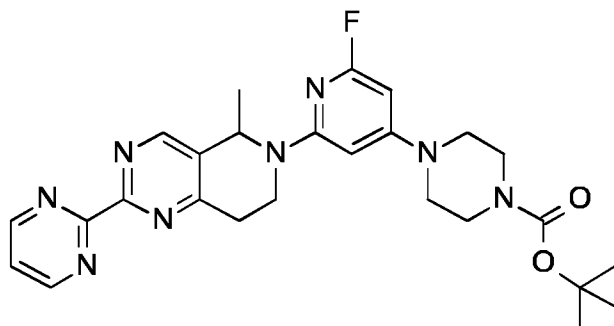
Example 86: 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]-*N*-methylsulfonyl-pyrrolidine-3-carboxamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 8.81 (s, 1 H), 8.72 (d, 1 H), 8.52 (d, 1 H), 7.99 (td, 1 H), 7.50 - 7.56 (m, 1
 20 H), 5.72 (s, 1 H), 5.63 (br d, 1 H), 5.51 (s, 1 H), 4.64 (s, 1 H), 4.40 - 4.51 (m, 1 H), 3.33 - 3.59 (m, 5 H), 3.04 - 3.22 (m, 5 H), 2.25 (q, 2 H), 1.55 (d, 3 H). MS obsd (ESI) [(M+H)⁺]: 512.

Example 87

6-[6-fluoro-4-[4-(2-methoxyethylsulfonyl)piperazin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine

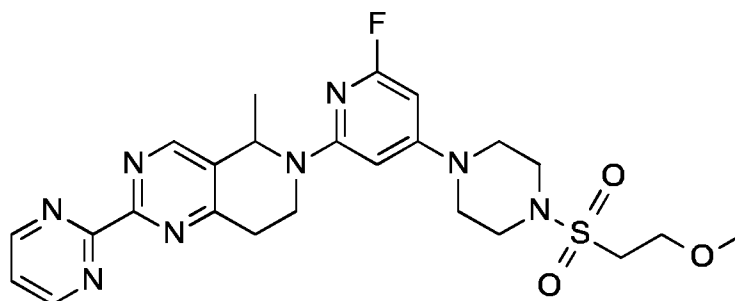


Step 1: Preparation of *tert*-butyl 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]piperazine-1-carboxylate



A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (one product of step 7 in Example 1, 300mg, 881 μ mol) and *tert*-butyl piperazine-1-carboxylate (330 mg, 1.76 mmol) in DMSO (3mL) and DIPEA (3 mL) was heated at 130 °C with stirring for 20 hrs. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with DCM/MeOH=20/1, v:v) to give *tert*-butyl 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]piperazine-1-carboxylate (0.4 g) as a yellow solid.

Step 2: Preparation of 6-[6-fluoro-4-[4-(2-methoxyethylsulfonyl)piperazin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine



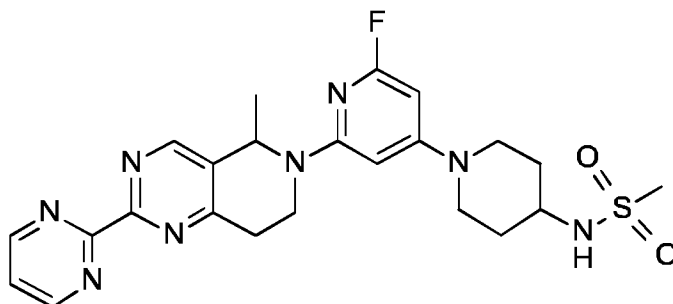
To a solution of *tert*-butyl 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]piperazine-1-carboxylate (0.4 g) in MeOH (5 mL) was added a solution of HCl in MeOH (10%) (5 mL). The reaction was stirred for 18 hrs at rt and concentrated *in vacuo*. The residue was dissolved in DCM (10 mL) and cooled to 0 °C. To the solution was added triethylamine (0.55 mL) and 2-methoxyethanesulfonyl chloride (162.8 mg) successively. The resulting mixture was slowly warmed to rt and stirred for 2 hours at rt. The reaction mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC to give

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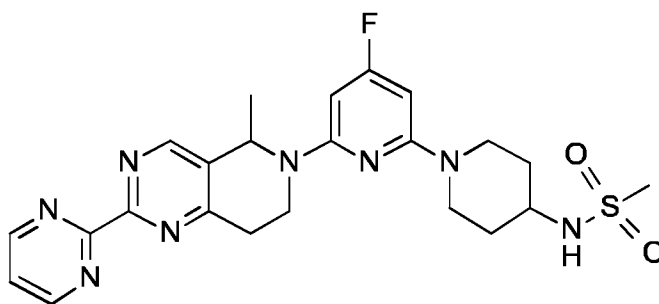
6-[6-fluoro-4-[4-(2-methoxyethylsulfonyl)piperazin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (31 mg) as light yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm: 8.99 (d, 2H), 8.90 (s, 1H), 7.63 (t, 1H), 6.16 (s, 1H), 5.93 (s, 1H), 5.75-5.66 (m, 1H), 4.52 - 4.43 (m, 1H), 3.66 (t, 2H), 3.51 - 3.44 (m, 4H), 3.46 - 3.40 (m, 1H), 3.37 (t, 2H),
 5 3.29 - 3.20 (m, 7H), 3.12 - 2.94 (m, 2H), 1.49 (d, 3H). MS obsd (ESI) [(M+H)⁺]: 529.

Example 88 and 89

N-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-4-piperidyl]methanesulfonamide and *N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]-4-piperidyl]methanesulfonamide
 10 piperidyl]methanesulfonamide



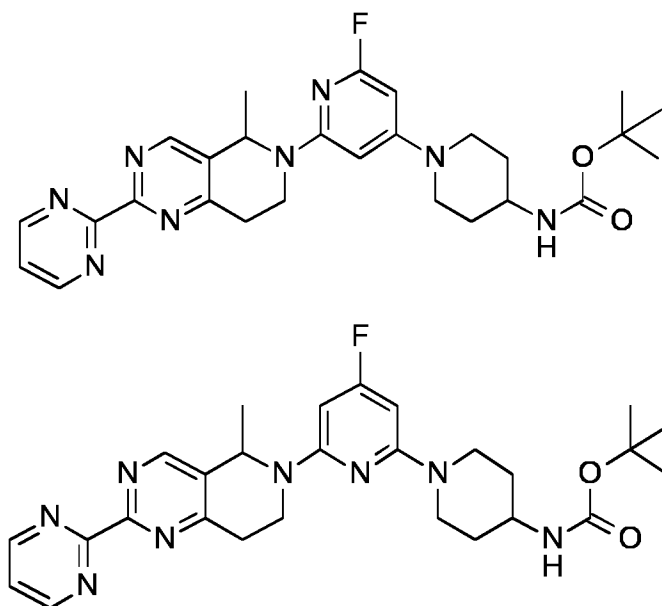
Example 88



Example 89

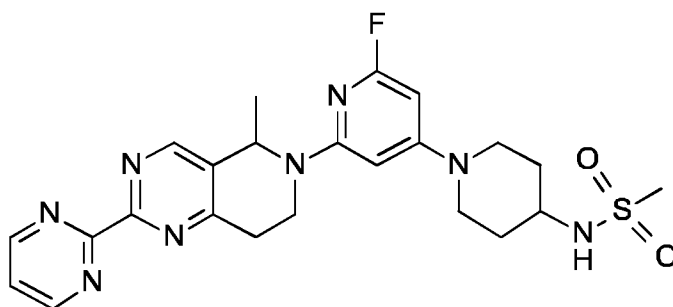
15 **Step 1: Preparation of *tert*-butyl *N*-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-4-piperidyl]carbamate and *tert*-butyl *N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]-4-piperidyl]carbamate**

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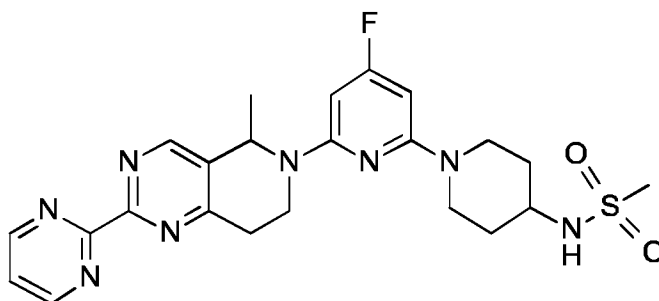
To a solution of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 300mg, 881 μ mol) in DMSO
 5 (3mL) and DIPEA (3 mL) was added *tert*-butyl piperidin-4-ylcarbamate (353 mg, 1.76 mmol) and the resulting mixture was heated at 130 °C with stirring for 20 hrs. The resulting mixture was cooled to rt and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with DCM/MeOH=20/1, v:v) to give a mixture of *tert*-butyl *N*-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-piperidyl]carbamate
 10 and *tert*-butyl *N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-4-piperidyl]carbamate (0.42g) as a yellow solid.

Step 2: Preparation of *N*-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-piperidyl]methanesulfonamide and *N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-4-piperidyl]methanesulfonamide
 15



Example 88

-109-



Example 89

To a solution *tert*-butyl *N*-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-
 5 d]pyrimidin-6-yl)-4-pyridyl]-4-piperidyl]carbamate and *tert*-butyl *N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-
 d]pyrimidin-6-yl)-2-pyridyl]-4-piperidyl]carbamate (0.42 g) in DCM (5 mL) was added TFA (5 mL). The reaction was stirred for 18 hrs at rt and concentrated *in vacuo*. The residue was dissolved in DCM (10 mL) and cooled to 0 °C. To the cooled solution was added triethylamine (0.56 mL) and methanesulfonic anhydride (140.4 mg) successively. After being slowly warmed to rt and stirred for 2 hrs, the
 10 resulting reaction mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC to give *N*-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-
 d]pyrimidin-6-yl)-4-pyridyl]-4-piperidyl]methanesulfonamide (64 mg) as a light yellow solid and *N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-
 d]pyrimidin-6-yl)-2-pyridyl]-4-piperidyl]methanesulfonamide (14 mg) as a light yellow solid.

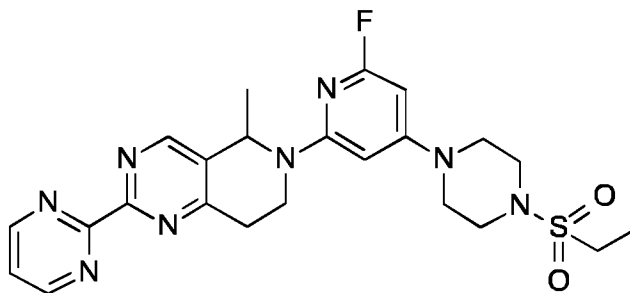
15 **Example 88:** *N*-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-
 d]pyrimidin-6-yl)-4-pyridyl]-4-piperidyl]methanesulfonamide, ¹H NMR (400MHz, DMSO-*d*₆) δ ppm: 8.99 (d, 2H), 8.90 (s, 1H), 7.64 (t, 1H), 7.11 (d, 1H), 6.10 (s, 1H), 5.88 (s, 1H), 5.75-5.66 (m, 1H), 4.54-4.42 (m, 1H), 3.89-3.83 (m, 2H), 3.48 - 3.36 (m, 2H), 3.09 - 2.97 (m, 3H), 2.95 (s, 3H), 1.91 - 1.83 (m, 2H), 1.48 (d, 3H), 1.46 - 1.37 (m, 2H). MS obsd (ESI) [(M+H)⁺]: 499.

20 **Example 89:** *N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-
 d]pyrimidin-6-yl)-2-pyridyl]-4-piperidyl]methanesulfonamide, ¹H NMR (400MHz, DMSO-*d*₆) δ ppm: 8.99 (d, 2H), 8.90 (s, 1H), 7.63 (t, 1H), 7.08 (d, 1H), 6.10 - 6.02 (m, 1H), 6.00-5.93 (m, 1H), 5.73 - 5.63 (m, 1H), 4.51-4.40 (m, 1H), 4.23-4.10 (m, 2H), 3.47 - 3.38 (m, 2H), 3.07 - 2.97 (m, 3H), 2.94 (s, 3H), 1.93 - 1.83 (m, 2H), 1.50 (d, 3H), 1.47 - 1.38 (m, 2H). MS obsd (ESI)
 25 [(M+H)⁺]: 499.

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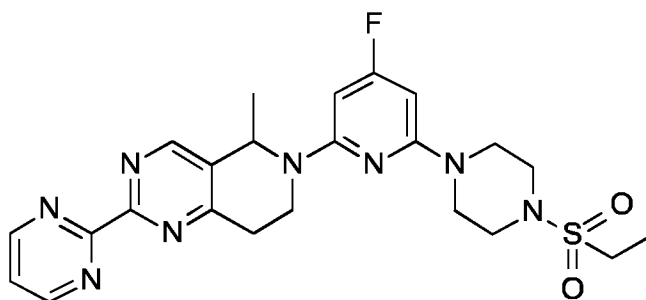
Example 90 and 91

6-[4-(4-Ethylsulfonylpiperazin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[6-(4-ethylsulfonylpiperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine

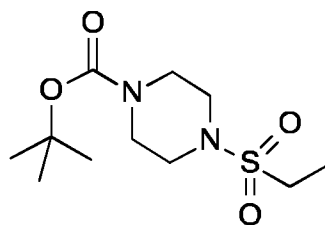


5

Example 90



Example 91

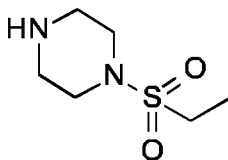
Step 1: Preparation of *tert*-butyl 4-ethylsulfonylpiperazine-1-carboxylate

10

To a solution of *tert*-butyl piperazine-1-carboxylate (1.5 g, 8.05 mmol) and triethylamine (2.18 g, 3 mL, 21.5 mmol) in DCM (10 mL) at 0 °C was added ethanesulfonyl chloride (1.04 g, 8.05 mmol). After being warmed to rt and stirred for 2 hrs, the resulting reaction mixture was diluted with H₂O (40 mL) and extracted with EA (50 mL) for three times. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give crude *tert*-butyl 4-(ethylsulfonyl)piperazine-1-carboxylate (2.3 g) as a brown oil, which was used in the next step directly without any further purification.

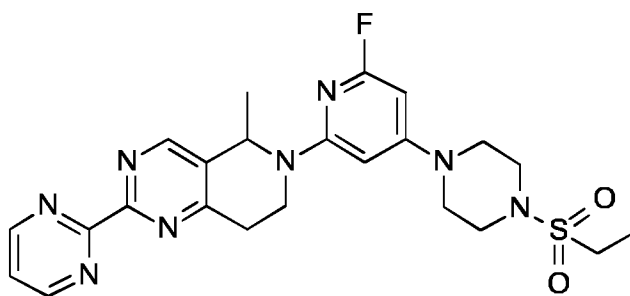
15

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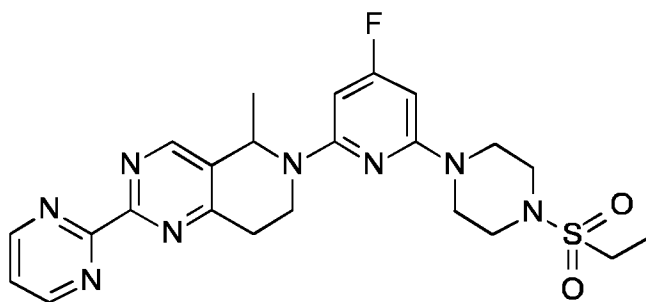
Step 2: Preparation of 1-ethylsulfonylpiperazine

To a solution of crude *tert*-butyl 4-(ethylsulfonyl)piperazine-1-carboxylate (2.3 g, 8.26 mmol) in DCM (10 mL) was added TFA (5 mL) and the mixture was stirred at rt for 2 hrs. The resulting mixture was then concentrated *in vacuo* to give crude 1-(ethylsulfonyl)-piperazine (1.5 g) as a brown oil, which was used in the next step directly without any further purification.

Step 3: Preparation of 6-[4-(4-ethylsulfonylpiperazin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[6-(4-ethylsulfonylpiperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



Example 90



Example 91

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 150 mg, 441 μ mol) and 1-(ethylsulfonyl)piperazine (236 mg, 1.32 mmol) in DMSO (3 mL) and DIPEA (5 mL) was heated at 150 °C with stirring overnight. The resulting mixture was diluted with H₂O (40 mL) and

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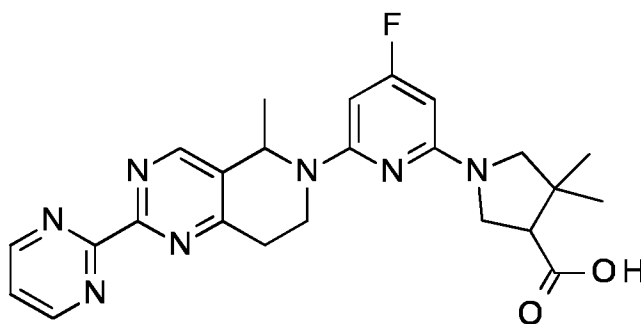
extracted with EA (50 mL) for three times. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 6-[4-(4-ethylsulfonylpiperazin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (30 mg) as a light yellow solid and 6-[6-(4-ethylsulfonylpiperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (10 mg) as a light yellow solid.

Example 90: 6-[4-(4-ethylsulfonylpiperazin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ^1H NMR (400 MHz, CDCl_3) δ ppm: 1.40 (t, 3 H), 1.57 (d, 3 H), 2.91 - 3.08 (m, 2 H), 3.22 - 3.29 (m, 2 H), 3.38 - 3.53 (m, 9 H), 4.31 - 4.47 (m, 1 H), 5.65 - 5.77 (m, 2 H), 5.85 (s, 1 H), 7.45 (t, 1 H), 8.82 (s, 1 H), 9.03 (d, 2 H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 499.

Example 91: 6-[6-(4-ethylsulfonylpiperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ^1H NMR (400 MHz, CDCl_3) δ ppm: 1.40 (t, 3 H), 1.58 (d, 3 H), 2.99 (q, 2 H), 3.15 - 3.36 (m, 2 H), 3.36 - 3.50 (m, 5 H), 3.54 - 3.72 (m, 4 H), 4.41 (dt, 1 H), 5.60 (q, 1 H), 5.75 (d, 1 H), 5.86 (d, 1 H), 7.44 (t, 1 H), 8.82 (s, 1 H), 9.03 (d, 2 H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 499.

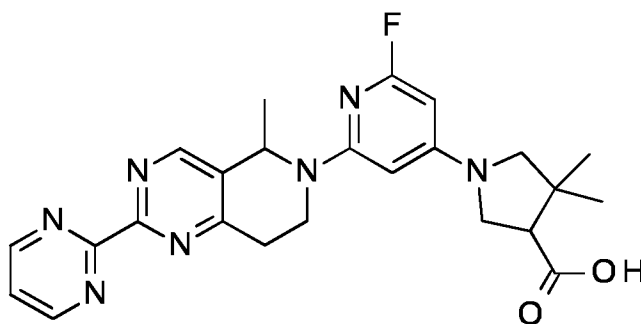
Example 92 and 93

1-[4-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-4,4-dimethyl-pyrrolidine-3-carboxylic acid and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4,4-dimethyl-pyrrolidine-3-carboxylic acid



Example 92

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Example 93

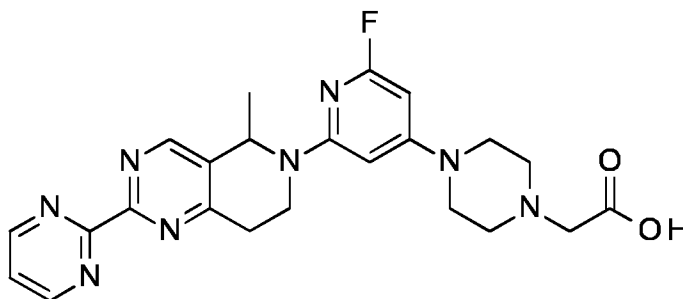
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), K₂CO₃ (122 mg, 0.88 mmol) and 4,4-dimethylpyrrolidine-3-carboxylic acid hydrochloride (158 mg, 0.88 mmol) in NMP (1 mL) was heated at 190 °C in a microwave reactor for 1.5 hrs. The resulting mixture was partitioned between DCM (10 mL) and H₂O (5 mL). The separated aqueous layer was acidified with 1 M HCl and then purified by prep-HPLC to afford 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-4,4-dimethylpyrrolidine-3-carboxylic acid (5.4 mg) as a yellow solid and 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4,4-dimethylpyrrolidine-3-carboxylic acid (17.6 mg) as a yellow solid.

Example 92: 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-4,4-dimethylpyrrolidine-3-carboxylic acid, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.89 (s, 1 H), 7.64 (t, 1 H), 5.88 (d, 1 H), 5.80 (m, 1 H), 5.53 - 5.53 (m, 1 H), 4.60 (s, 1 H), 4.55 (m, 1 H), 3.62 - 3.83 (m, 2 H), 3.40 - 3.53 (m, 2 H), 3.23 (m, 1 H), 3.09 - 3.15 (m, 1 H), 2.81 (m, 1 H), 1.54 - 1.65 (m, 3 H), 1.30 (s, 3 H), 1.10 (s, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 464.

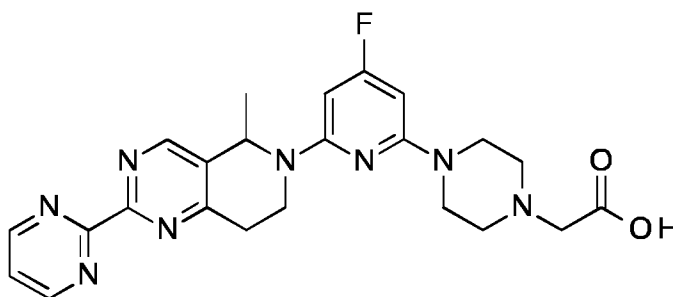
Example 93: 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4,4-dimethylpyrrolidine-3-carboxylic acid, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.88 (s, 1 H), 7.65 (t, 1 H), 5.64 - 5.77 (m, 2 H), 5.51 (s, 1 H), 4.48 (m, 1 H), 3.66 - 3.78 (m, 1 H), 3.60 (br t, 1 H), 3.43 - 3.54 (m, 1 H), 3.46 (s, 1 H), 3.18 - 3.26 (m, 2 H), 3.16 - 3.16 (m, 1 H), 3.04 - 3.18 (m, 1 H), 2.86 - 2.99 (m, 1 H), 1.58 (dd, 3 H), 1.32 (d, 3 H), 1.11 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 464.

Example 94 and 95

2-[4-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-
d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]acetic acid and 2-[4-[4-fluoro-6-(5-methyl-2-
pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-
5 yl]acetic acid

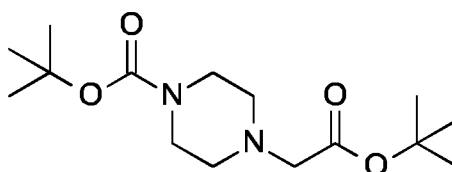


Example 94



Example 95

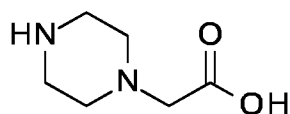
10 **Step 1: Preparation of *tert*-butyl 4-(2-*tert*-butoxy-2-oxo-ethyl)piperazine-1-carboxylate**



To a solution of *tert*-butyl piperazine-1-carboxylate (2.0 g, 10.74 mmol) in THF (20 mL) was added Et₃N (2.17 g, 21.48 mmol) and *tert*-butyl bromoacetate (2.09 g, 10.74 mmol). The
15 resulting mixture was stirred at rt for 12 hrs, and then partitioned between EA (200 mL) and water (100 mL). The organic layer was separated and washed with brine (100 mL), then dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column

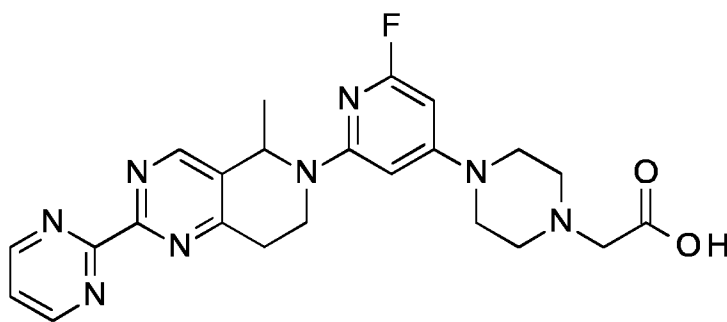
chromatography (eluting with PE/EA=5/1, v:v) to give *tert*-butyl 4-(2-*tert*-butoxy-2-oxo-ethyl)piperazine-1-carboxylate (2.5 g) as a white solid.

Step 2: Preparation of 2-piperazin-1-ylacetic acid



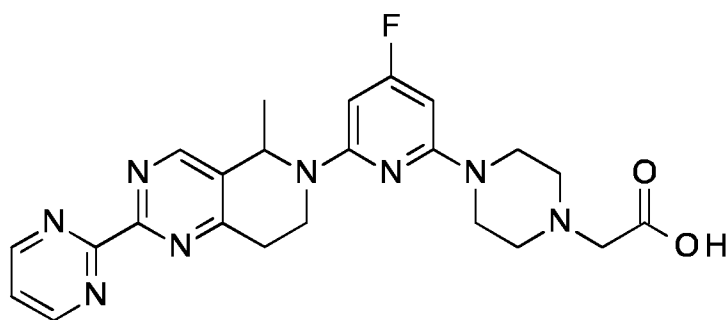
5 A mixture of *tert*-butyl 4-(2-*tert*-butoxy-2-oxo-ethyl)piperazine-1-carboxylate (1.0 g, 3.3 mmol) and a solution of HCl in MeOH (1.0 M, 15 mL) was stirred at rt for 12 hrs. The resulting mixture was concentrated *in vacuo*. The residue was dissolved in MeOH (10 mL), then treated with base resin and filtered. The filtrate was concentrated *in vacuo* to give 2-piperazin-1-ylacetic acid (350 mg) as a white solid.

10 **Step 3: Preparation of 2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]acetic acid and 2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]acetic acid**



15

Example 94



Example 95

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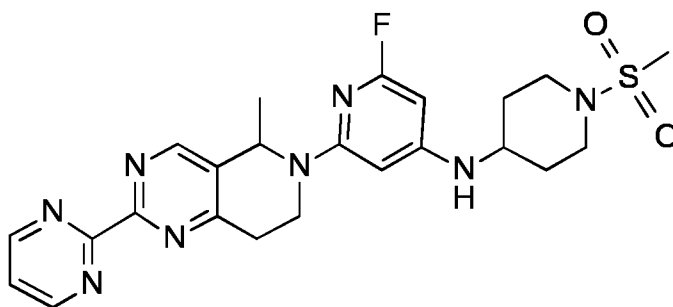
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.294 mmol), 2-piperazin-1-ylacetic acid (51 mg, 0.353 mmol) and K₂CO₃ (122 mg, 0.881 mmol) in NMP (3 mL) was heated at 180 °C in a microwave reactor for 1 hr, and then partitioned between EA (100 mL) and water (20 mL). The separated organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]acetic acid (13 mg) as a yellow solid and 2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]acetic acid (3 mg) as a yellow solid.

Example 94: 2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]acetic acid, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.88 (s, 1 H), 7.64 (t, 1 H), 6.08 (s, 1 H), 5.82 (s, 1 H), 5.68 - 5.76 (m, 1 H), 4.51 (br d, 1 H), 3.40 - 3.47 (m, 5 H), 3.09 - 3.26 (m, 2 H), 3.03 (s, 2 H), 2.62 - 2.71 (m, 4 H), 1.57 (d, 3 H). MS obsd (ESI) [(M+H)⁺]: 465.

Example 95: 2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]acetic acid, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 2 H), 8.90 (s, 1 H), 7.64 (t, 1 H), 5.98 (d, 1 H), 5.68 - 5.87 (m, 2 H), 4.50 (br d, 1 H), 3.37 - 3.58 (m, 5 H), 3.09 - 3.20 (m, 2 H), 3.04 (s, 2 H), 2.59 - 2.70 (m, 4 H), 1.54 - 1.60 (m, 3 H). MS obsd (ESI) [(M+H)⁺]: 465.

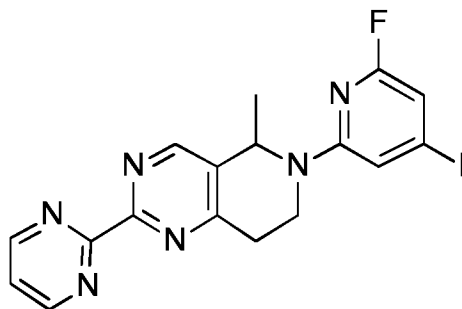
Example 96

2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-N-(1-methylsulfonyl-4-piperidyl)pyridin-4-amine



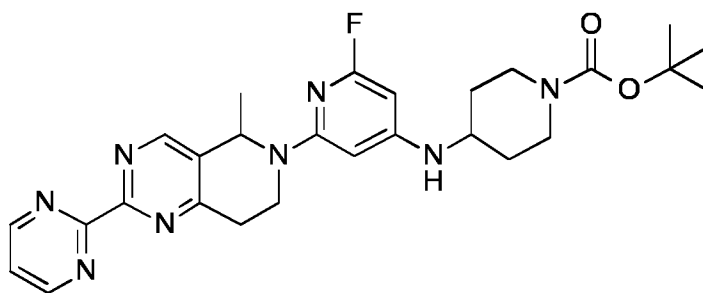
-117-

Step 1: Preparation of 6-(6-fluoro-4-iodo-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



To a solution of 5-methyl-2-(pyrimidin-2-yl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine hydrochloride (the product of step 6 in Example 1, 2.5 g, 9.48 mmol) in DMSO (30 mL) was added 2,6-difluoro-4-iodopyridine (2.74 g, 11.4 mmol) and sodium bicarbonate (3.98 g, 47.4 mmol). The resulting mixture was heated at 80 °C with stirring for 18 hrs. The resulting reaction mixture was diluted with H₂O (20 mL) and extracted with DCM (50 mL) twice. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with DCM/MeOH=20/1, v:v) to give 6-(6-fluoro-4-iodo-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (1.9 g) as a brown solid.

Step 2: Preparation of *tert*-butyl 4-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]piperidine-1-carboxylate



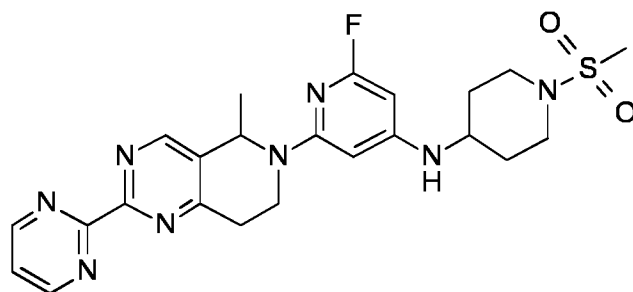
15

To a solution of 6-(6-fluoro-4-iodo-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (130 mg, 290 μmol), *tert*-butyl 4-aminopiperidine-1-carboxylate (69.7 mg, 348 μmol) and cesium carbonate (189 mg, 580 μmol) in dioxane (5 mL) was added Xantphos (33.6 mg, 58 μmol) and Pd(OAc)₂ (6.51 mg, 29 μmol). The resulting mixture was heated at 100 °C with stirring for 20 hrs under Ar. The resulting reaction mixture was filtered

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and the filtrate was concentrated *in vacuo* to give crude *tert*-butyl 4-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]amino]piperidine-1-carboxylate (0.2 g) which was directly used in the next step without further purification.

Step 3: Preparation of 2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-*N*-(1-methylsulfonyl-4-piperidyl)pyridin-4-amine

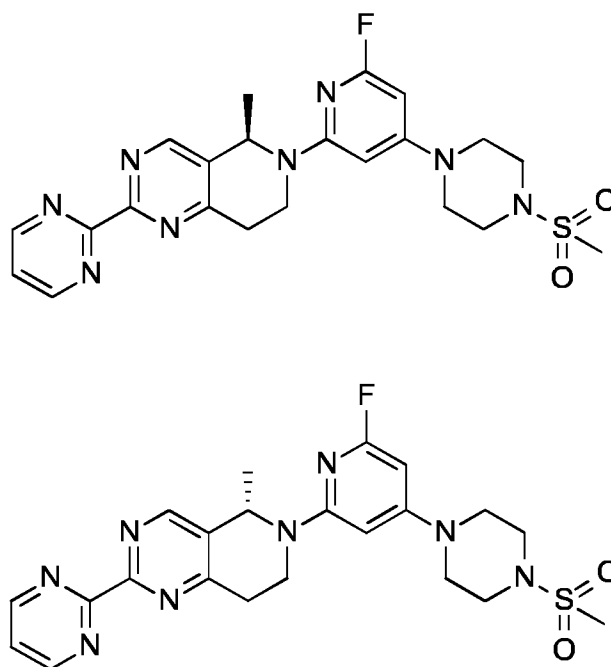


To a solution of crude *tert*-butyl 4-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]amino]piperidine-1-carboxylate (200 mg) in DCM (5 mL) was added TFA (5 mL) and the reaction was stirred for 18 hrs at rt. The resulting reaction mixture was concentrated *in vacuo* and the residue was dissolved in DCM (10 mL). The resulting solution was cooled to 0 °C and to the cooled solution were added triethylamine (146 mg, 201 µL, 1.44 mmol) and methanesulfonyl anhydride (50.2 mg, 288 µmol) successively. The resulting mixture was slowly warmed to rt and stirred for 2 hrs. The resulting reaction mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-*N*-(1-methylsulfonyl-4-piperidyl)pyridin-4-amine (11 mg) as a light yellow solid. ¹H NMR (400MHz, CDCl₃) δ ppm: 9.03 (d, 2H), 8.79 (s, 1H), 7.43 (t, 1H), 5.63 (s, 1H), 5.49 (s, 1H), 4.34-4.28 (m, 1H), 4.16-4.10 (m, 1H), 3.85-3.76 (m, 2H), 3.52 - 3.41 (m, 2H), 3.31 - 3.18 (m, 2H), 2.97-2.87 (m, 2H), 2.83 (s, 3H), 2.20-2.12 (m, 2H), 1.56 (d, 3H), 1.36 - 1.23 (m, 2H). MS obsd (ESI) [(M+H)⁺]: 499.

Example 97 and 98

(-)-6-[6-Fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine and (+)-6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine

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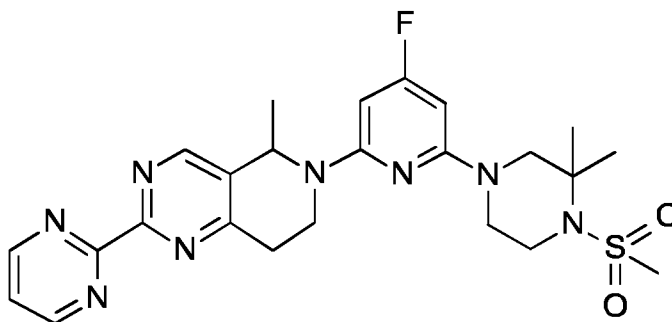
Separation of 6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (Example 58, 700 mg) by chiral preparative HPLC affords (-)-6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (330 mg) as a white solid and (+)-6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (254 mg) as a white solid.

Example 97: (-)-6-[6-Fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 8.91-8.98 (m, 2H), 8.75-8.80 (m, 1H), 7.52-7.58 (m, 1H), 6.01-6.07 (m, 1H), 5.76-5.81 (m, 1H), 5.61-5.69 (m, 1H), 4.37-4.46 (m, 1H), 3.36-3.48 (m, 5H), 3.28-3.21 (m, 4H), 2.98-3.15 (m, 2H), 2.79 (s, 3H), 1.49 (d, 3H). MS obsd (ESI) [(M+H)⁺]: 485. [α]_D²⁰ = -102.2° (0.05 g/100 mL, methanol).

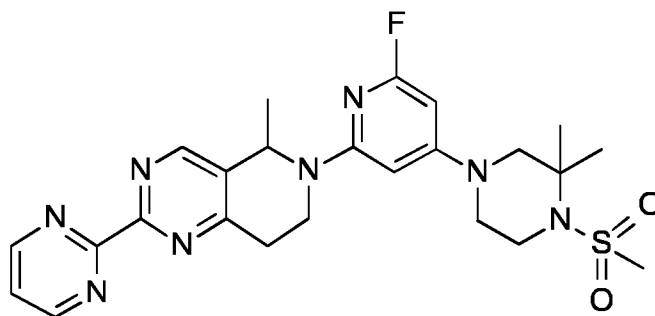
Example 98: (+)-6-[6-Fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 8.91-8.98 (m, 2H), 8.75-8.80 (m, 1H), 7.52-7.58 (m, 1H), 6.01-6.07 (m, 1H), 5.76-5.81 (m, 1H), 5.61-5.69 (m, 1H), 4.37-4.46 (m, 1H), 3.36-3.48 (m, 5H), 3.28-3.21 (m, 4H), 2.98-3.15 (m, 2H), 2.79 (s, 3H), 1.49 (d, 3H). MS obsd (ESI) [(M+H)⁺]: 485.

Example 99 and 100

6-[6-(3,3-Dimethyl-4-methylsulfonyl-piperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[4-(3,3-dimethyl-4-methylsulfonyl-piperazin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine

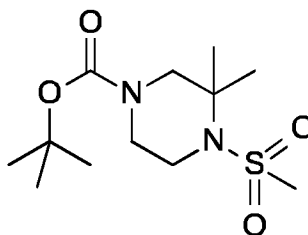


Example 99



Example 100

Step 1: Preparation of *tert*-butyl 3,3-dimethyl-4-methylsulfonyl-piperazine-1-carboxylate

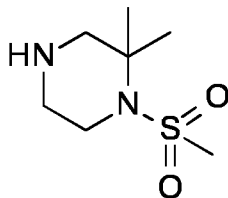


To a stirring solution of *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate (300 mg, 1.4 mmol) in DCM (3 mL) was added MsCl (321 mg, 2.8 mmol) and K₂CO₃ (425 mg, 4.2 mmol).

After being stirred at 20 °C for 4 hrs, the resulting mixture was diluted with DCM (80 mL), then

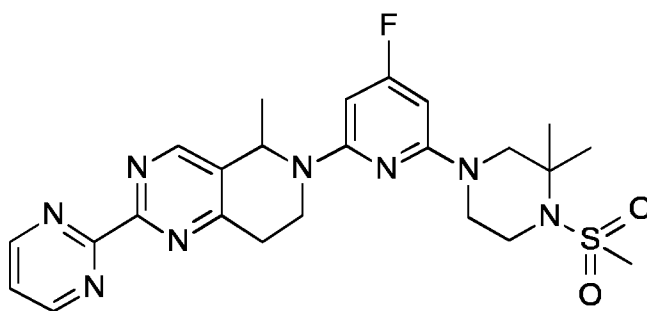
washed with water (30 mL) and brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (eluting with PE/EA=5/1, v:v) to give *tert*-butyl 3,3-dimethyl-4-methylsulfonyl-piperazine-1-carboxylate (270 mg) as a colorless oil.

5 **Step 2: Preparation of 2,2-dimethyl-1-methylsulfonyl-piperazine**



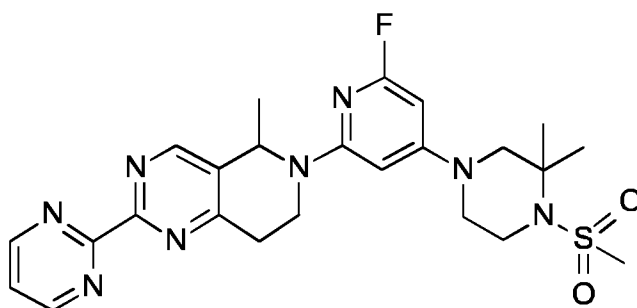
A mixture of *tert*-butyl 3,3-dimethyl-4-methylsulfonyl-piperazine-1-carboxylate (270 mg, 0.92 mmol) and a solution of HCl in MeOH (1.0 M, 3 mL) was stirred at rt for 4 hrs. The resulting reaction mixture was concentrated *in vacuo* to give 2,2-dimethyl-1-methylsulfonyl-piperazine (180 mg) as a white solid, which was used in the next step directly without any purification.

15 **Step 3: Preparation of 6-[6-(3,3-dimethyl-4-methylsulfonyl-piperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[4-(3,3-dimethyl-4-methylsulfonyl-piperazin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine**



Example 99

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Example 100

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), K₂CO₃ (122 mg, 0.88 mmol) and 2,2-dimethyl-1-methylsulfonyl-piperazine (134 mg, 0.59 mmol) in NMP (1 mL) was heated at 190 °C with stirring in a microwave reactor for 1.5 hrs. The resulting reaction mixture was then diluted with DCM (10 mL) and washed with H₂O (5 mL). The separated organic layer was concentrated *in vacuo* and the residue was purified by prep-HPLC to afford 6-[6-(3,3-dimethyl-4-methylsulfonyl-piperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (9 mg) as a yellow solid and 6-[4-(3,3-dimethyl-4-methylsulfonyl-piperazin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (17 mg) as a white solid.

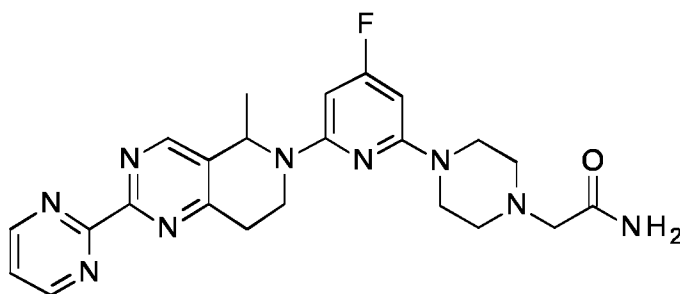
Example 99: 6-[6-(3,3-dimethyl-4-methylsulfonyl-piperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.91 (s, 1 H), 7.65 (t, 1 H), 5.99 (dd, 1 H), 5.70 - 5.79 (m, 2 H), 4.46 - 4.57 (m, 1 H), 3.56 - 3.78 (m, 6 H), 3.42 - 3.54 (m, 1 H), 3.11 - 3.19 (m, 2 H), 2.98 (s, 3 H), 1.59 (d, 3 H), 1.50 (d, 6 H). MS obsd. (ESI⁺) [(M+H)⁺]: 513.

Example 100: 6-[4-(3,3-dimethyl-4-methylsulfonyl-piperazin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.04 (d, 2 H), 8.88 (s, 1 H), 7.66 (t, 1 H), 5.98 (s, 1 H), 5.78 (s, 1 H), 5.71 - 5.77 (m, 1 H), 4.52 (m, 1 H), 3.65 - 3.75 (m, 2 H), 3.52 - 3.59 (m, 2 H), 3.44 - 3.52 (m, 2 H), 3.06 - 3.25 (m, 2 H), 2.99 (s, 3 H), 1.58 (d, 3 H), 1.52 (d, 6 H). MS obsd. (ESI⁺) [(M+H)⁺]: 513.

Example 101 and 102

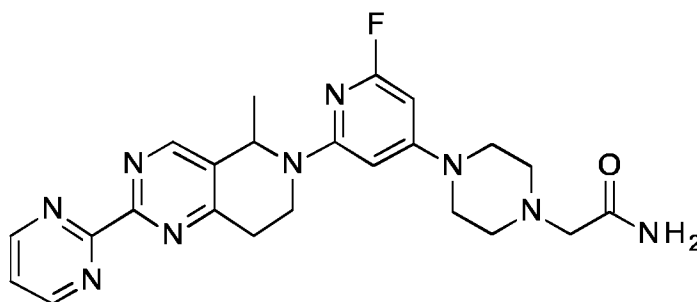
-123-

2-[4-[4-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]acetamide and 2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]acetamide



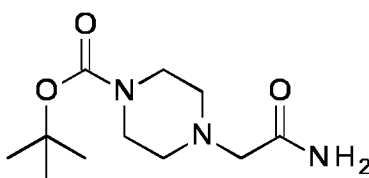
5

Example 101



Example 102

Step 1: Preparation of *tert*-butyl 4-(2-amino-2-oxo-ethyl)piperazine-1-carboxylate



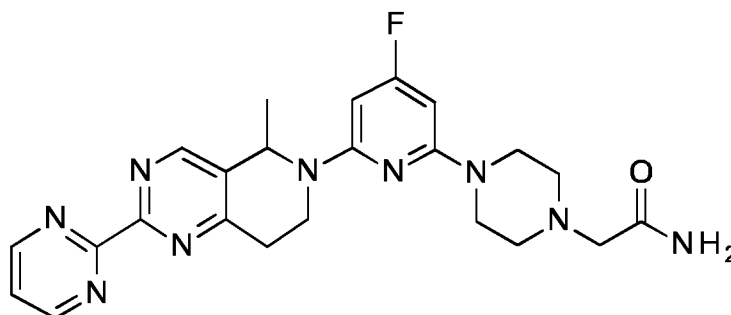
10 To a stirred solution of 1-Boc-piperazine (1.0 g, 5.37 mmol) in THF (15 mL) was added 2-bromoacetamide (889 mg, 6.44 mmol) and Et₃N (1.63 g, 16.1 mmol). After being stirred at rt for 12 hrs and diluted with EA (200 mL), the resulting mixture was washed with water (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column (eluting with PE/EA=1/1, v:v) to give *tert*-butyl 4-(2-amino-2-oxo-ethyl)piperazine-1-carboxylate (1.0 g) as a white solid.

15

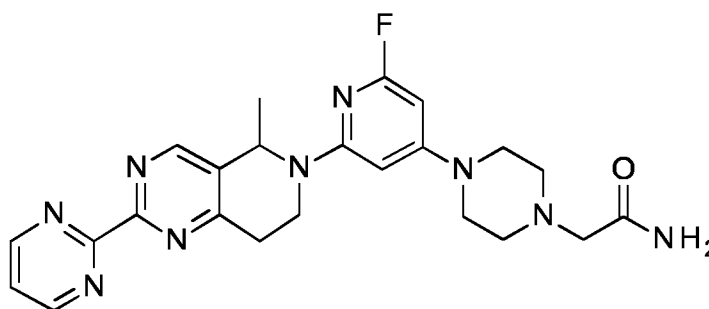
Step 2: Preparation of 2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]acetamide and 2-[4-[2-fluoro-6-(5-

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methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]acetamide



Example 101



Example 102

5

A mixture of *tert*-butyl 4-(2-amino-2-oxo-ethyl)piperazine-1-carboxylate (400 mg, 1.64 mmol) and a solution of HCl in MeOH (5 mL) was stirred at rt for 4 hrs. The resulting mixture was concentrated *in vacuo* and the residue was dissolved in NMP (2 mL). To the resulting solution were added 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 150 mg, 0.44 mmol) and K₂CO₃ (183 mg, 1.32 mmol). The resulting mixture was heated at 170 °C with stirring in a microwave reactor for 2 hrs, then cooled to rt, diluted with DCM (10 mL) and washed with H₂O (5 mL). The organic layer was concentrated *in vacuo* and the residue was purified by prep-HPLC to afford 2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]acetamide (33 mg) as a yellow solid and 2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]acetamide (38 mg) as a yellow solid.

Example 101: 2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]acetamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm:

20

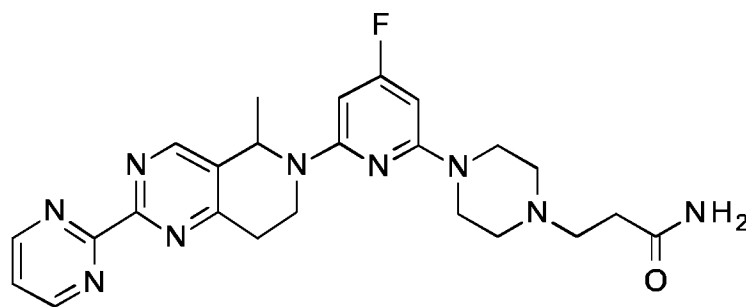
-125-

9.03 (d, 2 H), 8.89 (s, 1 H), 7.65 (t, 1 H), 6.02 (d, 1 H), 5.86 (d, 1 H), 5.75 (q, 1 H), 4.51 (m, 1 H), 3.54 - 3.69 (m, 4 H), 3.48 (m, 1 H), 3.03 - 3.26 (m, 4 H), 2.62 - 2.79 (m, 4 H), 1.58 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 464.

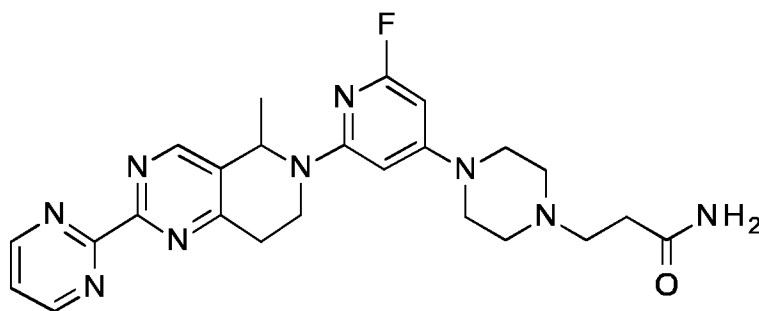
Example 102: 2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]acetamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 6.09 (s, 1 H), 5.83 (s, 1 H), 5.72 (q, 1 H), 4.44 - 4.56 (m, 1 H), 3.47 - 3.55 (m, 1 H), 3.41 - 3.47 (m, 4 H), 3.12 - 3.22 (m, 2 H), 3.10 (s, 2 H), 2.62 - 2.75 (m, 4 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 464.

Example 103 and 104

10 **3-[4-[4-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]propanamide and 3-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]propanamide**



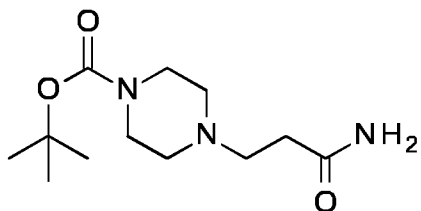
Example 103



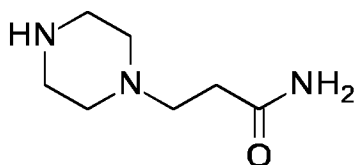
Example 104

15

-126-

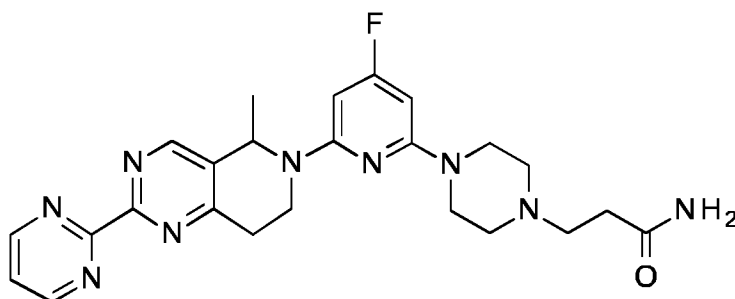
Step 1: Preparation of *tert*-butyl 4-(3-amino-3-oxo-propyl)piperazine-1-carboxylate

A mixture of 1-Boc-piperazine (500 mg, 2.68 mmol), acrylamide (210 mg, 2.95 mmol) and AcOH (16 mg, 0.27 mmol) was heated at 70 °C with stirring for 12 hrs. The resulting reaction mixture was diluted with DCM (100 mL), then washed with saturated aqueous solution of NaHCO₃ (30 mL), water (30 mL) and brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give crude *tert*-butyl 4-(3-amino-3-oxo-propyl)piperazine-1-carboxylate (300 mg) as a white solid, which was used in the next step without any purification.

Step 2: Preparation of 3-piperazin-1-ylpropanamide

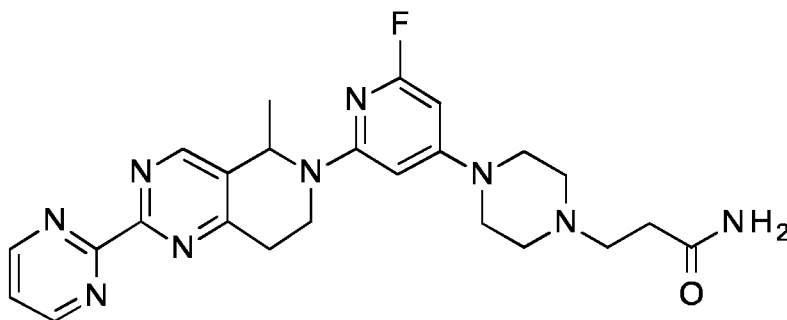
A mixture of *tert*-butyl 4-(3-amino-3-oxo-propyl)piperazine-1-carboxylate (300 mg, 1.17 mmol) and a solution of HCl in MeOH (5 mL, 1 M) was stirred at rt for 2 hrs. The resulting reaction mixture was concentrated *in vacuo* to give 3-piperazin-1-ylpropanamide (250 mg) as a white solid, which was used in the next step without any purification.

Step 3: Preparation of 3-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]propanamide and 3-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]propanamide



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Example 103



Example 104

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (150 mg, 0.44 mmol), K₂CO₃ (183 mg, 1.32 mmol) and 3-piperazin-1-ylpropanamide (one product of step 7 in Example 1, 171 mg, 0.88 mmol) in NMP (2 mL) was heated at 170 °C with stirring in a microwave reactor for 2 hrs. The resulting reaction mixture was diluted with DCM (10 mL) and washed with H₂O (5 mL). The organic layer was concentrated *in vacuo* and the residue was purified by prep-HPLC to afford 3-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]propanamide (5 mg) as a yellow solid and 3-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]propanamide (26 mg) as a white solid.

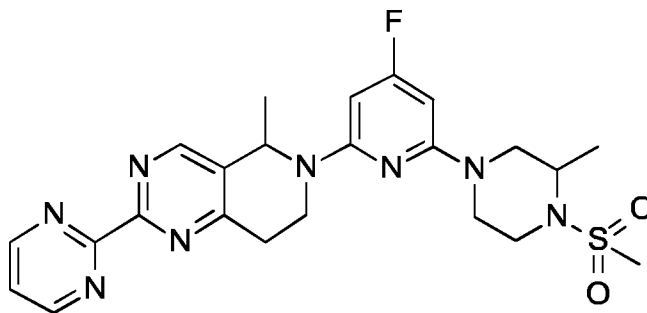
Example 103: 3-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]propanamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 2 H), 8.88 (s, 1 H), 7.63 (t, 1 H), 6.00 (d, 1 H), 5.83 (d, 1 H), 5.73 (q, 1 H), 4.50 (m, 1 H), 3.51 - 3.61 (m, 4 H), 3.42 - 3.51 (m, 1 H), 3.02 - 3.23 (m, 2 H), 2.66 - 2.79 (m, 2 H), 2.60 (m, 4 H), 2.46 (t, 2 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 478.

Example 104: 3-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]propanamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 2 H), 8.86 (s, 1 H), 7.63 (t, 1 H), 6.07 (s, 1 H), 5.82 (s, 1 H), 5.71 (q, 1 H), 4.48 (m, 1 H), 3.43 - 3.54 (m, 1 H), 3.35 - 3.43 (m, 4 H), 3.04 - 3.24 (m, 2 H), 2.69 - 2.79 (m, 2 H), 2.54 - 2.67 (m, 4 H), 2.45 (t, 2 H), 1.56 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 478.

Example 105 and 106

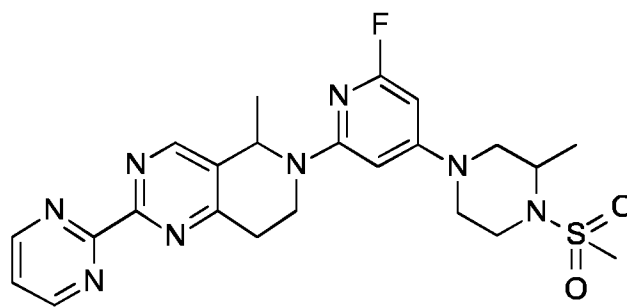
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6-[4-Fluoro-6-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[6-fluoro-4-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



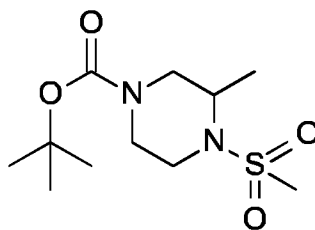
5

Example 105



Example 106

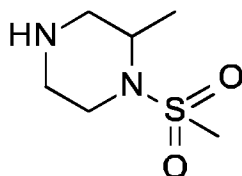
Step 1: Preparation of *tert*-butyl 3-methyl-4-methylsulfonyl-piperazine-1-carboxylate



10

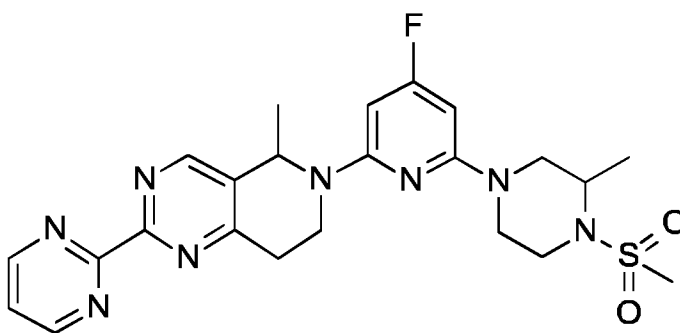
To a stirring solution of *tert*-butyl 3-methylpiperazine-1-carboxylate (400 mg, 2.0 mmol) in DCM (5 mL) was added Et₃N (606 mg, 5.99 mmol) and MsCl (686 mg, 5.99 mmol). The resulting mixture was stirred at rt for 12 hrs and diluted with EA (100 mL). The resulting mixture was washed with water (30 mL) and brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column (eluting with PE/EA=5/1, v:v) to give *tert*-butyl 3-methyl-4-methylsulfonyl-piperazine-1-carboxylate (400 mg) as a white solid.

15

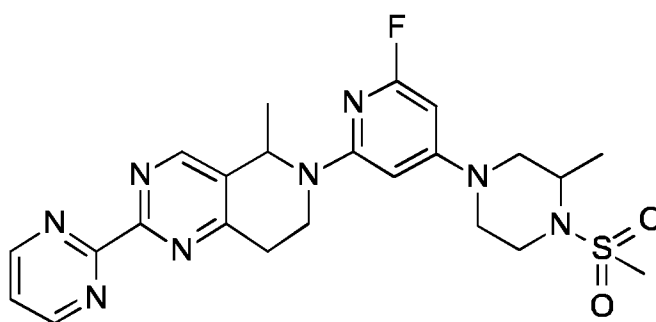
Step 2: Preparation of 2-methyl-1-methylsulfonyl-piperazine

A mixture of *tert*-butyl 3-methyl-4-methylsulfonyl-piperazine-1-carboxylate (400 mg, 1.44 mmol) and a solution of HCl in MeOH (1.0 M, 5 mL) was stirred at rt for 2 hrs. The resulting mixture was concentrated *in vacuo* and the residue was dissolved in MeOH (5 mL). The solution was stirred with basic resin (200 mg) at rt for 2 hrs and then filtered. The filtrate was concentrated *in vacuo* to give crude 2-methyl-1-methylsulfonyl-piperazine (250 mg) as a colorless oil which was used directly in the next step without any purification.

Step 3: Preparation of 6-[4-fluoro-6-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine and 6-[6-fluoro-4-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine



Example 105



Example 106

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), K₂CO₃ (122 mg, 0.88 mmol) and 2-methyl-1-methylsulfonyl-piperazine (157 mg, 0.88 mmol) in NMP (1 mL) was heated at 180 °C with stirring for 2 hrs in a microwave reactor. After being cooled to rt, the resulting mixture was filtered and the filtrate was purified by prep-HPLC to afford 6-[4-fluoro-6-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (20.3 mg) as a yellow solid and 6-[6-fluoro-4-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (31 mg) as a yellow solid.

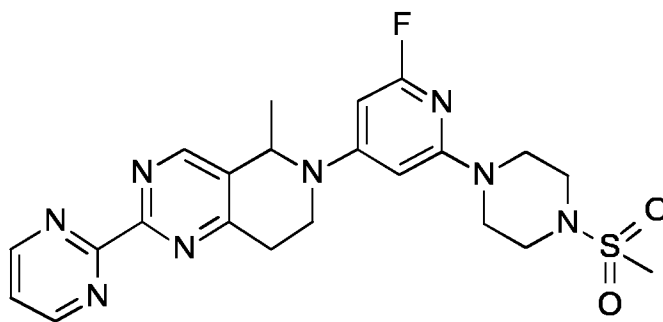
Example 105: 6-[4-fluoro-6-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.04 (d, 2 H), 8.91 (s, 1 H), 7.65 (t, 1 H), 6.01 (m, 1 H), 5.87 (d, 1 H), 5.76 (t, 1 H), 4.53 (br s, 1 H), 4.25 (m, 1 H), 4.22 - 4.31 (m, 1 H), 4.17 (m, 1 H), 4.05 - 4.34 (m, 1 H), 3.64 (m, 1 H), 3.43 - 3.57 (m, 1 H), 3.34 - 3.41 (m, 1 H), 3.13 - 3.14 (m, 1 H), 3.12 - 3.23 (m, 2 H), 3.06 (s, 1 H), 2.96 (s, 3 H), 1.55 - 1.66 (m, 3 H), 1.22 - 1.38 (m, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 499.

Example 106: 6-[6-fluoro-4-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 6.07 (s, 1 H), 5.83 (s, 1 H), 5.73 (q, 1 H), 4.45 - 4.55 (m, 1 H), 4.06 - 4.20 (m, 1 H), 3.87 (m, 1 H), 3.71 - 3.83 (m, 1 H), 3.64 (m, 1 H), 3.35 - 3.54 (m, 2 H), 3.22 - 3.29 (m, 1 H), 3.04 - 3.20 (m, 3 H), 2.95 (s, 3 H), 1.57 (d, 3 H), 1.33 (dd, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 499.

Example 107

6-[2-Fluoro-6-(4-methylsulfonylpiperazin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine

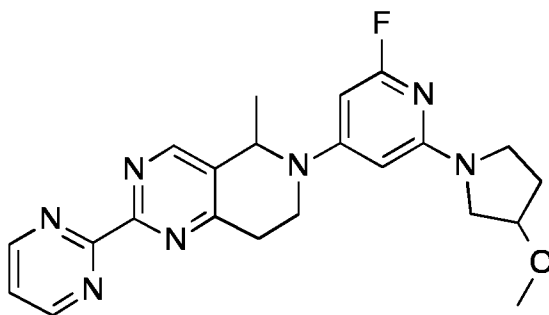
-131-



A mixture of 6-(2,6-difluoro-4-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 204 mg, 0.6 mmol), 1-(methylsulfonyl)piperazine (123 mg, 0.75 mmol) and K₂CO₃ (165 mg, 1.2 mmol) in NMP (5 mL) was heated at 180°C with stirring for 2 hrs in a microwave reactor. The resulting mixture was poured into water (20 mL) and extracted with DCM (50 mL) twice. The combined organic layer was washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 6-[2-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (18 mg) as a light yellow powder. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02-9.09 (m, 2H), 8.88-8.92 (m, 1H), 7.59-7.71 (m, 1H), 6.09-6.17 (m, 1H), 5.99-6.06 (m, 1H), 5.37-5.46 (m, 1H), 4.13-4.23 (m, 1H), 3.37-3.71 (m, 5H), 3.15-3.32 (m, 6H), 2.88 (s, 3H), 1.62 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 485.

Example 108

6-[2-Fluoro-6-(3-methoxypyrrolidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



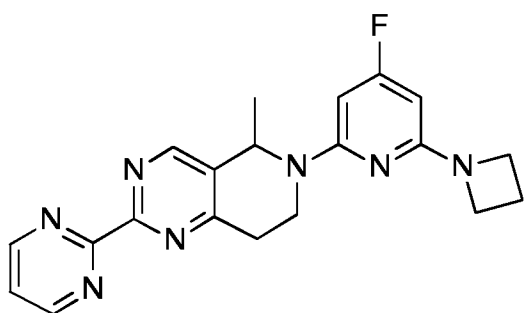
A mixture of 6-(2,6-difluoro-4-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 170 mg, 0.5 mmol), K₂CO₃ (207 mg, 1.5 mmol) and 3-methoxypyrrolidine hydrochloride (137 mg, 1.0 mmol) in NMP (5 mL) was heated at 110°C with stirring for 15 hrs. The resulting mixture was poured into water (20

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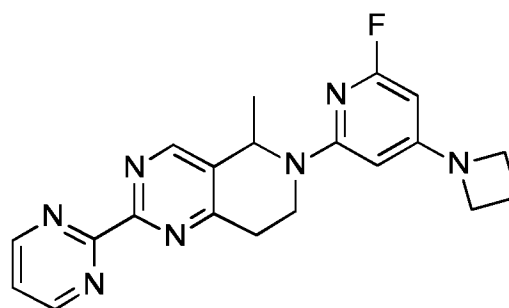
mL) and extracted with DCM (50 mL) twice. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 6-[2-fluoro-6-(3-methoxypyrrolidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (30 mg) as a white powder. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.05 (d, 2H), 8.90 (s, 1H), 7.62-7.70 (m, 1H), 5.89-5.97 (m, 1H), 5.67-5.75 (m, 1H), 5.33-5.43 (m, 1H), 4.12 (m, 2H), 3.42-3.64 (m, 5H), 3.39 (d, 3H), 3.14-3.28 (m, 2H), 2.04-2.21 (m, 2H), 1.61 (dd, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 422.

Example 109 and 110

6-[6-(Azetidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine and 6-[4-(azetidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine



Example 109



Example 110

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), azetidine (50.3 mg, 0.88 mmol) and K₂CO₃ (122 mg, 0.88 mmol) in NMP (1 mL) was heated at 130 °C with stirring for 2 hrs in a microwave reactor. The resulting reaction mixture was diluted with DCM (5 mL) and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 6-[6-(azetidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (5.4 mg) as a red solid and 6-[4-(azetidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (18.2 mg) as a yellow solid.

Example 109: 6-[6-(azetidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 2 H), 8.86 (s, 1 H), 7.64 (t, 1 H), 5.93 (dd, 1 H), 5.74 (q, 1 H), 5.40 (dd, 1 H), 4.48 - 4.59 (m, 1 H),

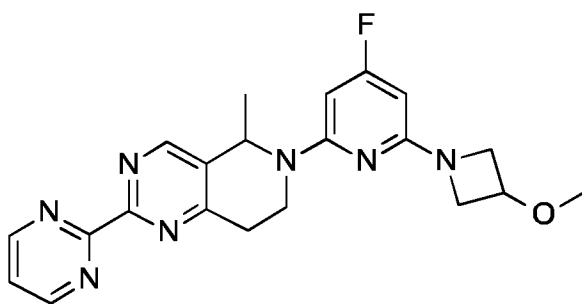
-133-

3.97 (t, 4 H), 3.38 - 3.50 (m, 1 H), 3.03 - 3.20 (m, 2 H), 2.35 (m, 2 H), 1.56 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 378.

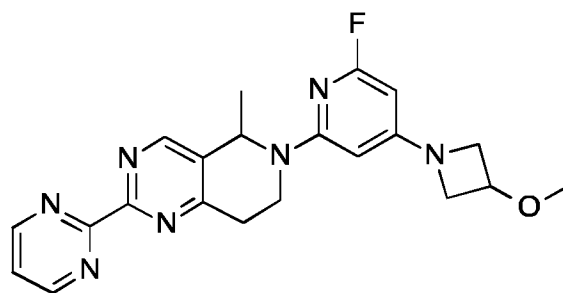
Example 110: 6-[4-(azetidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 2 H), 8.85 (s, 1 H), 7.63 (t, 1 H), 5.66 (q, 1 H), 5.56 (s, 1 H), 5.31 (d, 1 H), 4.37 - 4.49 (m, 1 H), 3.97 (t, 4 H), 3.39 - 3.52 (m, 1 H), 3.04 - 3.22 (m, 2 H), 2.41 (m, 2 H), 1.55 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 378.

Example 111 and 112

6-[4-Fluoro-6-(3-methoxyazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[6-fluoro-4-(3-methoxyazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



Example 111



Example 112

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), 3-methoxyazetidine (76.8 mg, 0.88 mmol) and K₂CO₃ (121.8 mg, 0.88 mmol) in NMP (1 mL) was heated at 130 °C with stirring for 2 hrs in a microwave reactor. The resulting reaction mixture was then diluted with DCM (5 mL) and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 6-[4-fluoro-6-(3-methoxyazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (8.4 mg) as a pink solid and 6-[6-fluoro-4-(3-methoxyazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (32.6 mg) as a yellow solid.

Example 111: 6-[4-fluoro-6-(3-methoxyazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 5.96 (dd, 1 H), 5.74 (q, 1 H), 5.46 (dd, 1 H), 4.49 - 4.60 (m, 1

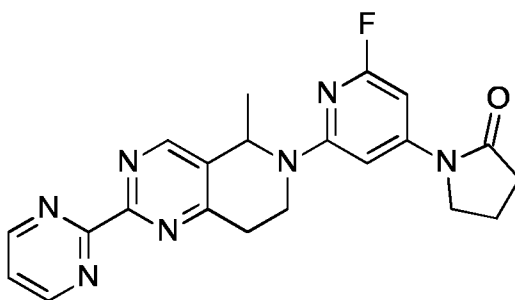
-134-

H), 4.28 - 4.37 (m, 1 H), 4.10 - 4.20 (m, 2 H), 3.78 (m, 2 H), 3.39 - 3.51 (m, 1 H), 3.33 (s, 3 H), 3.05 - 3.21 (m, 2 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 408.

Example 112: 6-[6-fluoro-4-(3-methoxyazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 2 H), 8.85 (s, 1 H), 7.63 (t, 1 H), 5.68 (q, 1 H), 5.61 (s, 1 H), 5.36 (d, 1 H), 4.44 (m, 1 H) 4.40 - 4.50 (m, 1 H), 4.30 - 4.40 (m, 1 H), 4.15 (t, 2 H), 3.77 (dd, 2 H), 3.40 - 3.52 (m, 1 H), 3.34 (s, 3 H), 3.02 - 3.23 (m, 2 H), 1.55 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 408.

Example 113

1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-2-one

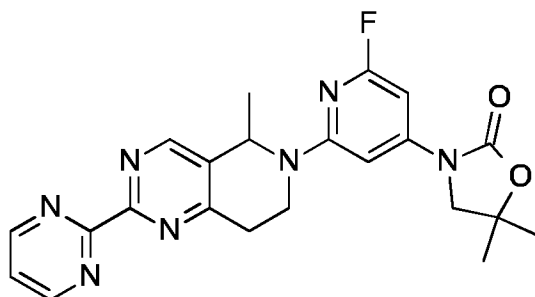


To a solution of 6-(6-fluoro-4-iodo-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 1 in Example 96, 100 mg, 223 μmol) in dioxane (3mL) was added pyrrolidin-2-one (38 mg, 446 μmol), cesium carbonate (145 mg, 446 μmol), Xantphos (25.8 mg, 44.6 μmol) and Pd(OAc)₂ (5.01 mg, 22.3 μmol). The resulting mixture was heated at 100 °C with stirring for 20 hrs under Ar. The resulting reaction mixture was then filtered and the filtrate was concentrated *in vacuo*. The residue was purified by prep-HPLC to give 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-2-one (8 mg) as a light yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm: 8.99 (d, 2H), 8.95 (s, 1H), 7.64 (t, 1H), 6.91 (s, 1H), 6.84 (s, 1H), 5.72-5.61 (m, 1H), 4.51 - 4.37 (m, 1H), 3.93 - 3.84 (m, 2H), 3.54 - 3.44 (m, 1H), 3.11 - 2.98 (m, 2H), 2.58-2.53 (m, 2H), 2.13 - 2.01 (m, 2H), 1.52 (d, 3H). MS obsd (ESI) [(M+H)⁺]: 406.

Example 114

3-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-5,5-dimethyl-oxazolidin-2-one

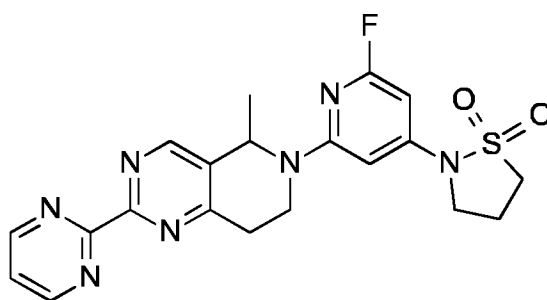
-135-



To a solution of 6-(6-fluoro-4-iodo-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 1 in Example 96, 100 mg, 223 μmol) in dioxane (3mL) was added 5,5-dimethyloxazolidin-2-one (51.4 mg, 446 μmol), cesium carbonate (145 mg, 446 μmol), Xantphos (25.8 mg, 44.6 μmol) and $\text{Pd}(\text{OAc})_2$ (5.01 mg, 22.3 μmol). The reaction mixture was heated at 100 $^{\circ}\text{C}$ with stirring for 20 hrs under Ar. After being cooled to rt, the resulting mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by prep-HPLC to give 3-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-5,5-dimethyl-oxazolidin-2-one (8 mg) as a light yellow solid. ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ ppm: 8.99 (d, 2H), 8.95 (s, 1H), 7.64 (t, 1H), 6.72 (s, 1H), 6.70 (s, 1H), 5.71-5.66 (m, 1H), 4.51 - 4.40 (m, 1H), 3.93 (s, 2H), 3.56 - 3.44 (m, 1H), 3.12 - 2.97 (m, 2H), 1.53 (d, 3H), 1.49 (d, 6H). MS obsd (ESI) $[(\text{M}+\text{H})^+]$: 436.

Example 115

2-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-1,2-thiazolidine 1,1-dioxide



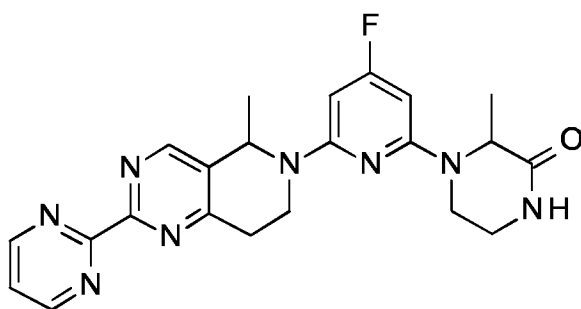
To a solution of 6-(6-fluoro-4-iodo-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 1 in Example 96, 100 mg, 223 μmol) in dioxane (3mL) was added isothiazolidine 1,1-dioxide (54.1 mg, 446 μmol), cesium carbonate (145 mg,

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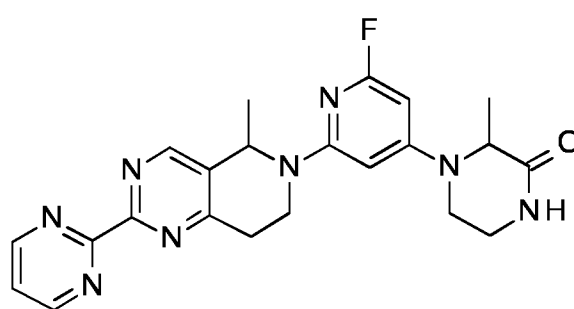
446 μmol), Xantphos (25.8 mg, 44.6 μmol) and $\text{Pd}(\text{OAc})_2$ (5.01 mg, 22.3 μmol). After being heated at 100 $^\circ\text{C}$ with stirring for 20 hrs under argon, the resulting reaction mixture was then filtered and the filtrate was concentrated *in vacuo*. The residue was purified by prep-HPLC to give 2-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-1,2-thiazolidine 1,1-dioxide (8 mg) as a light yellow solid. ^1H NMR (400MHz, $\text{DMSO-}d_6$) δ ppm: 8.99 (d, 2H), 8.95 (s, 1H), 7.64 (t, 1H), 6.32 (s, 1H), 6.15 (s, 1H), 5.69-5.64 (m, 1H), 4.47-4.36 (m, 1H), 3.89 - 3.79 (m, 2H), 3.68-3.59(m, 2H), 3.54 - 3.43 (m, 1H), 3.14 - 2.98 (m, 2H), 2.42-2.37 (m, 2H), 1.52 (d, 3H). MS obsd (ESI) $[(\text{M}+\text{H})^+]$: 442.

Example 116 and 117

10 4-[4-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-3-methyl-piperazin-2-one and 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-methyl-piperazin-2-one



Example 116



Example 117

15 A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), 3-methylpiperazin-2-one (101 mg, 0.88 mmol) and DIPEA (0.15 mL, 0.88 mmol) in NMP (0.5 mL) was heated at 200 $^\circ\text{C}$ with stirring for 2 hrs in a microwave reactor. The resulting reaction mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-3-methyl-piperazin-2-one (4.5 mg) as a yellow solid and 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-methyl-piperazin-2-one (7.5 mg) as a light yellow solid.

20 **Example 116:** 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-3-methyl-piperazin-2-one, ^1H NMR (400 MHz, Methanol- d_4) δ

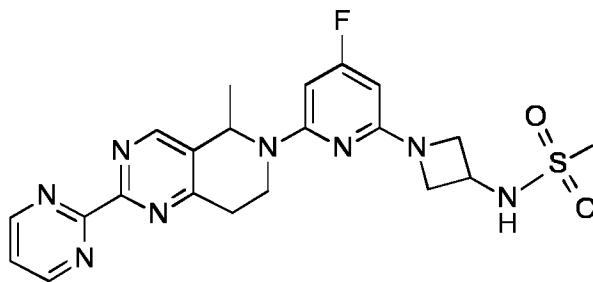
-137-

ppm: 9.03 (d, 2 H), 8.91 (s, 1 H), 7.66 (d, 1 H), 6.03 (d, 1 H), 5.85 (d, 1 H), 5.68 - 5.79 (m, 1 H), 4.44 - 4.67 (m, 2 H), 4.07 - 4.25 (m, 1 H), 3.37 - 3.61 (m, 4 H), 3.16 (s, 2 H), 1.60 (d, 3 H), 1.47 (dd, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 435.

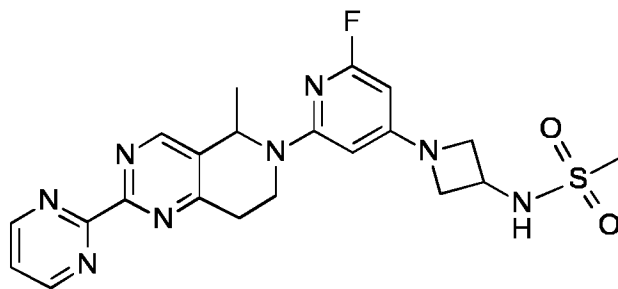
Example 117: 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-methyl-piperazin-2-one, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.88 (s, 1 H), 7.65 (t, 1 H), 6.01 (d, 1 H), 5.80 (s, 1 H), 5.68 - 5.77 (m, 1 H), 4.37 - 4.57 (m, 2 H), 3.79 - 3.92 (m, 1 H), 3.36 - 3.54 (m, 4 H), 3.08 - 3.24 (m, 2 H), 1.58 (dd, 3 H), 1.47 (t, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 435.

Example 118 and 119

***N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]methanesulfonamide and *N*-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]methanesulfonamide**



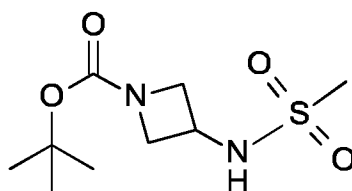
Example 118



Example 119

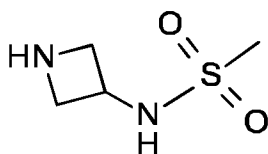
Step 1: Preparation of *tert*-butyl 3-(methanesulfonamido)azetidine-1-carboxylate

-138-



To a solution of 1-Boc-3-(amino)azetidine (1.0 g, 5.81 mmol) in DCM (10 mL) was added triethylamine (2.43 mL, 17.42 mmol) and methanesulfonyl chloride (0.67 mL, 8.71 mmol) at 0 °C. After being warmed to rt and stirred at rt for 12 hrs, the resulting reaction mixture was diluted with DCM (80 mL) and washed with water (20 mL) twice and brine (20 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was then purified by column chromatography (eluting with PE/EA=5/1, v:v) to give *tert*-butyl 3-(methanesulfonamido)azetidine-1-carboxylate (1.2 g) as a yellow solid.

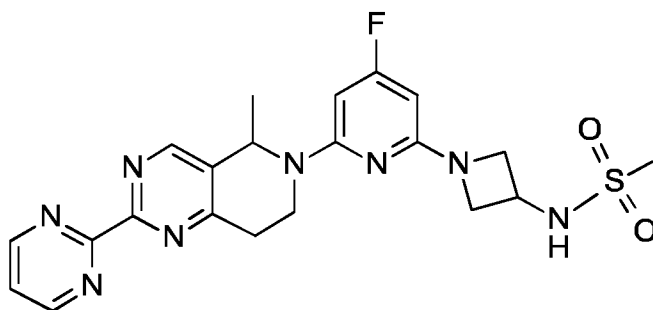
Step 2: Preparation of *N*-(azetidin-3-yl)methanesulfonamide



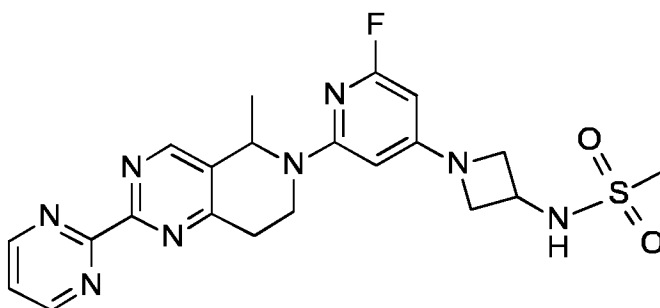
To a solution of *tert*-butyl 3-(methanesulfonamido)azetidine-1-carboxylate (300 mg, 1.2 mmol) in DCM (3 mL) was added TFA (1.0 mL) at 0 °C. After being warmed to rt and stirred for 12 hrs, the resulting mixture was concentrated *in vacuo* to give crude *N*-(azetidin-3-yl)methanesulfonamide (160 mg) as a yellow oil which was used directly in the next step without any purification.

Step 3: Preparation of *N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]methanesulfonamide and *N*-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]methanesulfonamide

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Example 118



Example 119

- 5 A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), *N*-(azetidin-3-yl)methanesulfonamide (132 mg, 0.88 mmol) and potassium carbonate (122 mg, 0.88 mmol) in NMP (1 mL) was heated at 140 °C with stirring for 2 hrs in a microwave reactor. The resulting reaction mixture was then diluted with DCM (5 mL), filtered and concentrated *in vacuo*. The
- 10 residue was purified by prep-HPLC to give *N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]methanesulfonamide (25 mg) as a yellow solid and *N*-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]methanesulfonamide (27 mg) as a yellow solid.

Example 118: *N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]methanesulfonamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 6.00 (dd, 1 H), 5.75 (q, 1 H), 5.48 (dd, 1 H), 4.50 - 4.59 (m, 1 H), 4.35 - 4.43 (m, 1 H), 4.30 (m, 2 H), 3.84 (m, 2 H), 3.40 - 3.51 (m, 1 H), 3.08 - 3.21 (m, 2 H), 2.97 (s, 3 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 471.

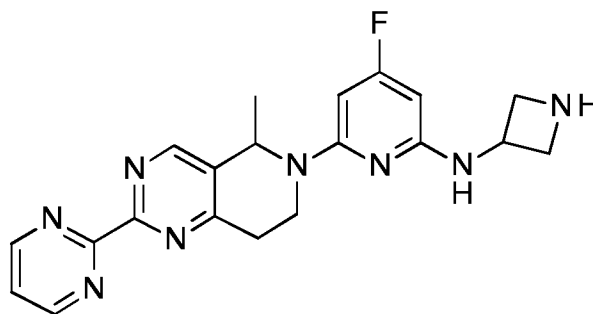
Example 119: *N*-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]methanesulfonamide, ¹H NMR (400 MHz, Methanol-

-140-

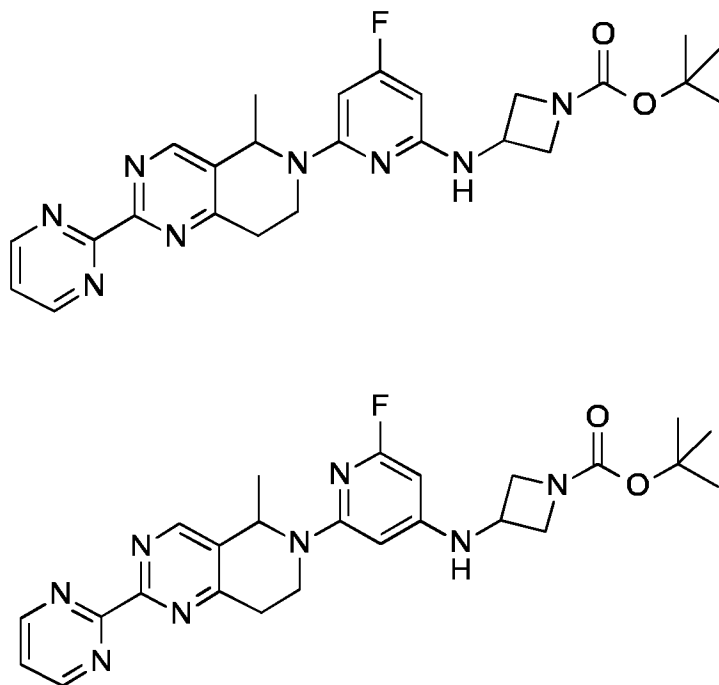
d_4) δ ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 5.69 (q, 1 H), 5.64 (s, 1 H), 5.39 (d, 1 H), 4.40 - 4.53 (m, 2 H), 4.32 (m, 2 H), 3.83 (m, 2 H), 3.42 - 3.55 (m, 1 H), 3.09 - 3.19 (m, 2 H), 2.97 (s, 3 H), 1.56 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 471.

Example 120

5 ***N*-(azetidin-3-yl)-4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)pyridin-2-amine**



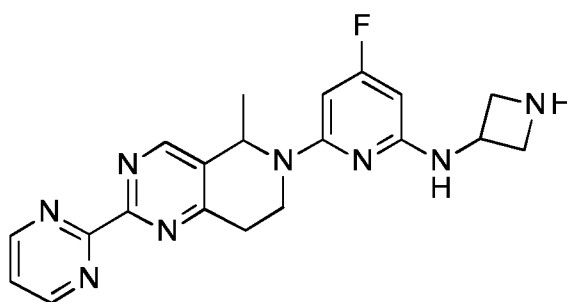
Step 1: Preparation of *tert*-butyl 3-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]amino]azetidine-1-carboxylate and *tert*-
 10 butyl 3-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]azetidine-1-carboxylate



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A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (100 mg, 0.29 mmol), 1-Boc-3-(amino)azetidine (one product of step 7 in Example 1, 152 mg, 0.88 mmol) and potassium carbonate (122 mg, 0.88 mmol) in NMP (0.5 mL) was heated at 170 °C with stirring for 2 hrs in a microwave reactor. The resulting reaction mixture was then diluted with MeOH (3 mL), filtered and purified by prep-HPLC to afford *tert*-butyl 3-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]amino]azetidine-1-carboxylate (25 mg) and *tert*-butyl 3-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]azetidine-1-carboxylate (25 mg).

Step 2: Preparation of *N*-(azetidin-3-yl)-4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)pyridin-2-amine

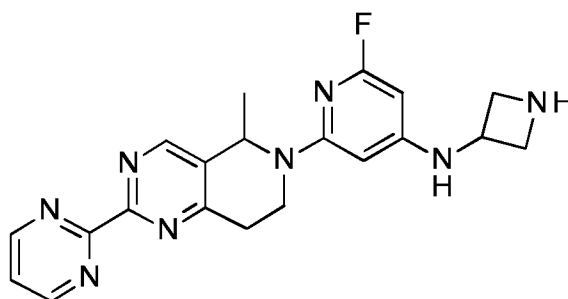


To a stirring solution of *tert*-butyl 3-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]amino]azetidine-1-carboxylate (25 mg, 0.05 mmol) in DCM (0.5 mL) was added trifluoroacetic acid (0.25 mL). The resulting mixture was stirred at rt for 12 hrs and then concentrated *in vacuo*. The residue was purified by prep-HPLC to give *N*-(azetidin-3-yl)-4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)pyridin-2-amine (5 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.04 (d, 2 H), 8.87 (s, 1 H), 7.66 (t, 1 H), 5.99 (m, 1 H), 5.67 - 5.74 (m, 1 H), 5.65 (m, 1 H), 4.59 (br s, 1 H), 4.47 - 4.56 (m, 1 H), 4.30 - 4.45 (m, 2 H), 4.03 (m, 2 H), 3.42 - 3.54 (m, 1 H), 3.10 - 3.18 (m, 2 H), 1.58 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 393.

Example 121

***N*-(azetidin-3-yl)-2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)pyridin-4-amine**

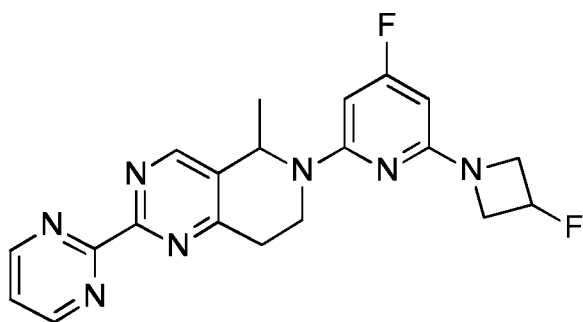
-142-



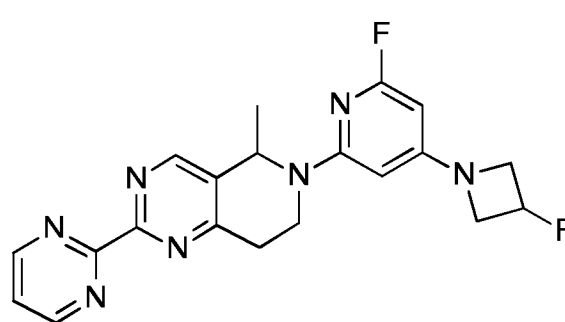
To a stirred solution of *tert*-butyl 3-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]azetidine-1-carboxylate (25 mg, 0.05 mmol) in DCM (0.5 mL) was added trifluoroacetic acid (0.25 mL). The resulting mixture was stirred at 20 °C for 12 hrs and then concentrated *in vacuo*. The residue was purified by prep-HPLC to give *N*-(azetidin-3-yl)-2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)pyridin-4-amine (14.4 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.65 (t, 1 H), 5.80 (s, 1 H), 5.69 (q, 1 H), 5.54 (d, 1 H), 4.58 - 4.67 (m, 1 H), 4.37 - 4.48 (m, 3 H), 3.96 - 4.05 (m, 2 H), 3.45 - 3.55 (m, 1 H), 3.11 - 3.18 (m, 2 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 393.

Example 122 and 123

6-[4-Fluoro-6-(3-fluoroazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[6-fluoro-4-(3-fluoroazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



Example 122



Example 123

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), 3-fluoroazetidine (88.24 mg, 1.18 mmol) and potassium carbonate (162.4 mg, 1.18 mmol) in NMP (1 mL) was heated at 130 °C with stirring for 2 hrs in a microwave reactor. The resulting reaction

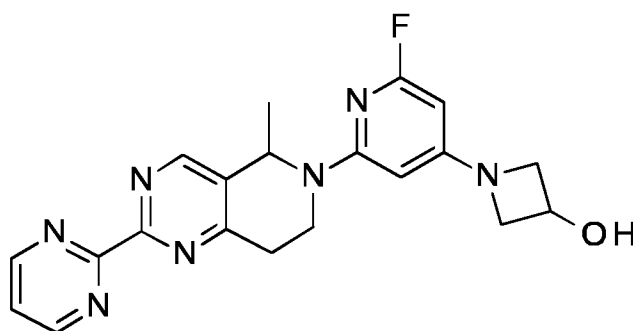
mixture was then diluted with DCM (5 mL), filtered and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 6-[4-fluoro-6-(3-fluoroazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (6.2 mg) as a yellow solid and 6-[6-fluoro-4-(3-fluoroazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (6 mg) as a light yellow solid.

Example 122: 6-[4-fluoro-6-(3-fluoroazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.05 (d, 2 H), 8.90 (s, 1 H), 7.67 (t, 1 H), 6.03 (dd, 1 H), 5.78 (q, 1 H), 5.52 - 5.56 (m, 1 H), 5.48 - 5.52 (m, 0.5 H), 5.31 - 5.40 (m, 0.5 H), 4.58 (br d, 1 H), 4.21 - 4.38 (m, 2 H), 3.94 - 4.10 (m, 2 H), 3.43 - 3.55 (m, 1 H), 3.09 - 3.21 (m, 2 H), 1.60 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 396.

Example 123: 6-[6-fluoro-4-(3-fluoroazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.65 (t, 1 H), 5.70 (q, 1 H), 5.66 (s, 1 H), 5.51 - 5.55 (m, 0.5 H), 5.41 (d, 1 H), 5.35 - 5.40 (m, 0.5 H), 4.40 - 4.54 (m, 1 H), 4.20 - 4.35 (m, 2 H), 3.94 - 4.11 (m, 2 H), 3.40 - 3.56 (m, 1 H), 3.07 - 3.20 (m, 2 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 396.

Example 124

1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]azetidin-3-ol



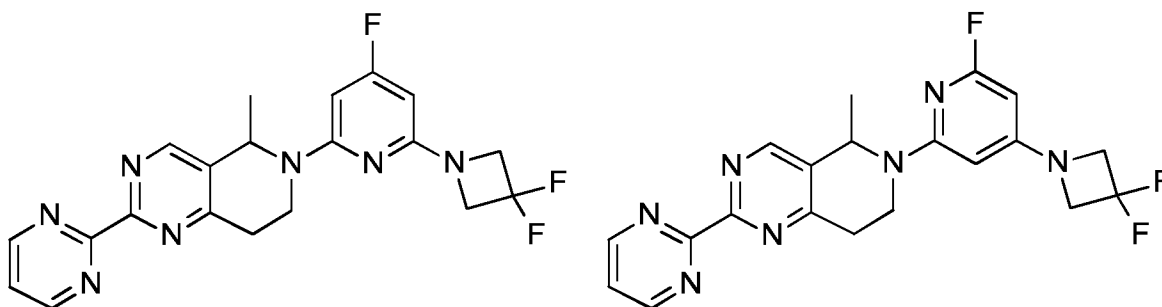
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), azetidin-3-ol hydrochloride (86 mg, 1.18 mmol) and potassium carbonate (162 mg, 1.18 mmol) in NMP (1 mL) was heated at 130 °C with stirring for 2 hrs in a microwave reactor. The resulting reaction mixture was then diluted with DCM (5 mL), filtered and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-

pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-ol (6.8 mg) as a yellow solid. ^1H NMR (400 MHz, Methanol- d_4) δ ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 5.64 - 5.74 (m, 1 H), 5.62 (s, 1 H), 5.37 (s, 1 H), 4.70 (m, 1 H), 4.46 (d, 1 H), 4.21 (t, 2 H), 3.74 (dd, 2 H), 3.39 - 3.54 (m, 1 H), 3.05 - 3.24 (m, 2 H), 1.56 (d, 3 H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 394.

5

Example 125 and 126

6-[6-(3,3-Difluoroazetidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine and 6-[4-(3,3-difluoroazetidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



10

Example 125

Example 126

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), 3,3-difluoroazetidine hydrochloride (114 mg, 0.88 mmol) and DIPEA (0.15 mL, 0.88 mmol) in NMP (2 mL) was heated at 160 °C with stirring in a microwave reactor for 2 hrs. The resulting reaction mixture was cooled to rt, concentrated *in vacuo* and purified by prep-HPLC to afford 6-[6-(3,3-difluoroazetidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (10 mg) as a brown solid and 6-[4-(3,3-difluoroazetidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (15 mg) as a brown solid.

20

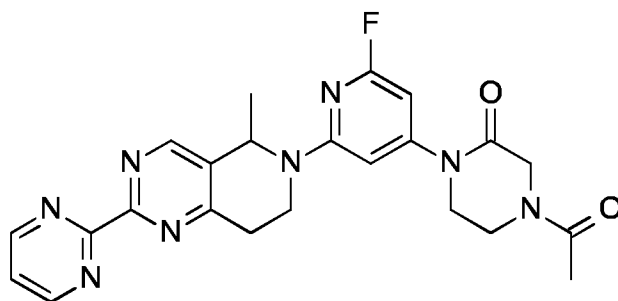
Example 125: 6-[6-(3,3-difluoroazetidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine, ^1H NMR (400 MHz, Methanol- d_4) δ ppm: 9.03 (d, 2 H), 8.88 (s, 1 H), 7.64 (t, 1 H), 6.10 (d, 1 H), 5.70 - 5.83 (m, 1 H), 5.62 (d, 1 H), 4.54 (m, 1 H), 4.32 (t, 4 H), 3.42 - 3.54 (m, 1 H), 3.06 - 3.23 (m, 2 H), 1.58 (d, 3 H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 414.

Example 126: 6-[4-(3,3-difluoroazetidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 5.76 (s, 1 H), 5.69 - 5.75 (m, 1 H), 5.50 (s, 1 H), 4.44 - 4.54 (m, 1 H), 4.34 (t, 4 H), 3.43 - 3.56 (m, 1 H), 3.05 - 3.25 (m, 2 H), 1.58 (d, 3 H). MS obsd. (ESI⁺)

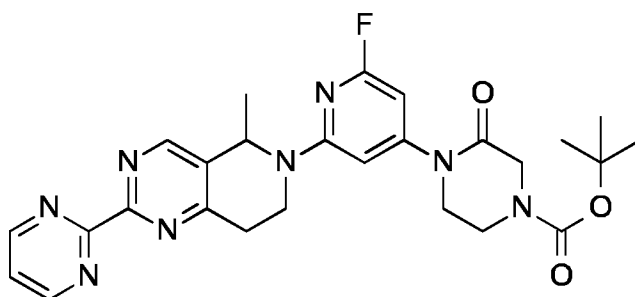
5 [(M+H)⁺]: 414.

Example 127

4-Acetyl-1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]piperazin-2-one



10 **Step 1: Preparation of *tert*-butyl 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-3-oxo-piperazine-1-carboxylate**

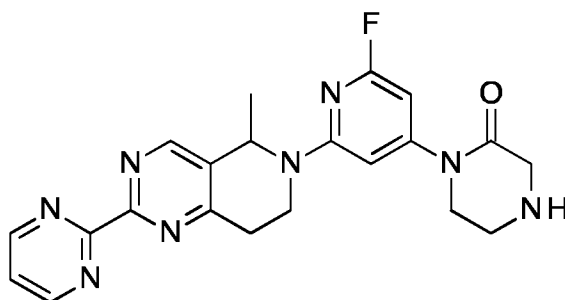


To a solution of 6-(6-fluoro-4-iodo-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (one product of step 7 in Example 1, 300 mg, 669 μmol) in dioxane
 15 (3mL) was added *tert*-butyl 3-oxopiperazine-1-carboxylate (134 mg, 669 μmol), cesium carbonate (436 mg, 1.34 mmol), Xantphos (77.5 mg, 134 μmol) and Pd(OAc)₂ (15 mg, 66.9 μmol). After being heated at 100 °C with stirring for 20 hrs under argon, the resulting reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (eluting with DCM/MeOH=20/1, v:v) to give *tert*-butyl 4-[2-fluoro-6-

-146-

(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-oxo-piperazine-1-carboxylate (256 mg) as a yellow solid.

Step 2: Preparation of 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-2-one

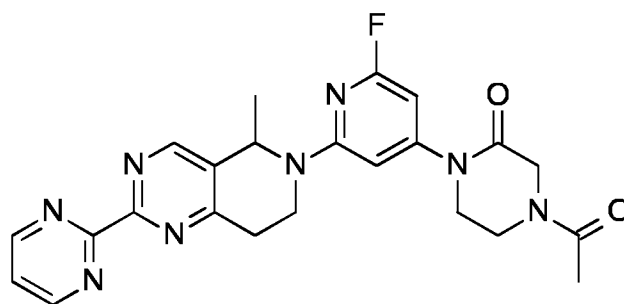


5

To a solution of *tert*-butyl 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-oxo-piperazine-1-carboxylate (256 mg) in DCM (5 mL) was TFA (5 mL) and the resulting mixture was stirred for 16 hrs at rt. The resulting reaction mixture was concentrated *in vacuo* to give the crude 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-2-one (300 mg) which was directly used in the next step without further purification.

10

Step 3: Preparation of 4-acetyl-1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-2-one



15

To a solution of crude 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-2-one (150 mg) in DCM (3 mL) was added triethylamine (68.2 mg, 674 μ mol) and acetic anhydride (34.4 mg, 337 μ mol) successively at 0 °C. After being slowly warmed to rt and stirred for 2 hrs, the resulting mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 4-acetyl-1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-2-one (12 mg)

20

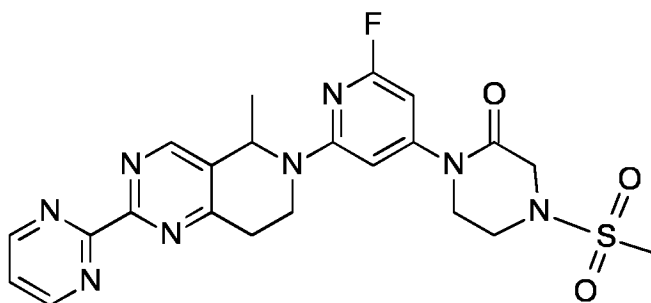
-147-

as a light yellow solid. ^1H NMR (400MHz, DMSO- d_6) δ ppm: 8.99 (d, 2H), 8.94 (s, 1H), 7.64 (t, 1H), 6.87 (s, 1H), 6.48-6.46 (m, 1H), 5.68-5.66 (m, 1H), 4.55-4.40 (m, 1H), 4.32-4.21 (m, 2H), 3.91 - 3.77 (m, 4H), 3.55-3.40 (m, 1H), 2.09-2.06 (m, 3H), 1.54 (d, 3H). MS obsd (ESI) [(M+H) $^+$]: 463.

5

Example 128

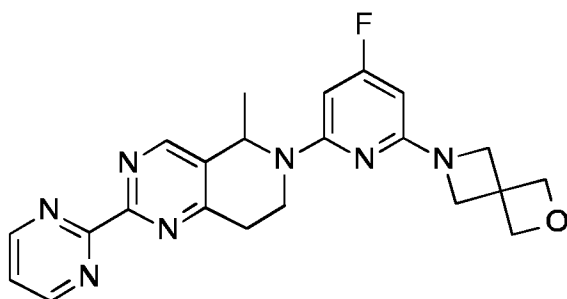
1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-methylsulfonyl-piperazin-2-one



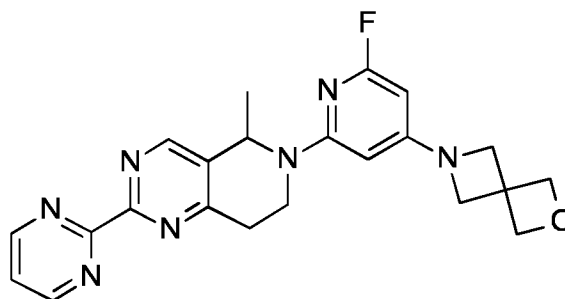
To a solution of 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-2-one (the product of step 2 in Example 127, 150 mg) in DCM (3 mL) was added triethylamine (68.2 mg, 674 μmol) and methanesulfonic anhydride (58.7 mg, 337 μmol) successively at 0 $^\circ\text{C}$. After being slowly warmed to rt and stirred for 2 hrs at rt, the resulting mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-methylsulfonyl-piperazin-2-one (5 mg) as a light yellow solid. ^1H NMR (400MHz, DMSO- d_6) δ ppm: 8.99 (d, 2H), 8.94 (s, 1H), 7.64 (t, 1H), 6.90 (s, 1H), 6.47 (s, 1H), 5.71-5.62 (m, 1H), 4.50-4.40 (m, 1H), 4.01 (s, 2H), 3.94 - 3.87 (m, 2H), 3.59-3.56 (m, 2H), 3.51-3.37 (m, 1H), 3.07 (s, 3H), 3.07 - 3.01 (m, 2H), 1.54 (d, 3H). MS obsd (ESI) [(M+H) $^+$]: 499.

Example 129 and 130

6-[4-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-6-azaspiro[3.3]heptane and 6-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-6-azaspiro[3.3]heptane



Example 129



Example 130

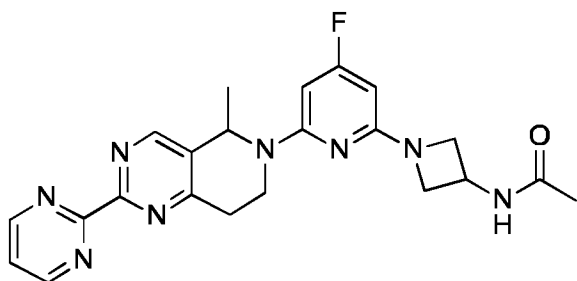
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), 2-oxa-6-azaspiro[3.3]heptane (87 mg, 0.88 mmol) and potassium carbonate (122 mg, 0.88 mmol) in NMP (1 mL) was heated at 140 °C with stirring in a microwave reactor for 2 hrs. The resulting reaction mixture was diluted with MeOH (4 mL), filtered and purified by prep-HPLC to give 6-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-6-azaspiro[3.3]heptane (5.4 mg) as a yellow solid and 6-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-6-azaspiro[3.3]heptane (37 mg) as a yellow solid.

Example 129: 6-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-6-azaspiro[3.3]heptane, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.88 (s, 1 H), 7.65 (t, 1 H), 5.98 (m, 1 H), 5.76 (q, 1 H), 5.47 (m, 1 H), 4.84 (s, 4 H), 4.50 - 4.59 (m, 1 H), 4.09 - 4.15 (m, 4 H), 3.40 - 3.51 (m, 1 H), 3.09 - 3.17 (m, 2 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 420.

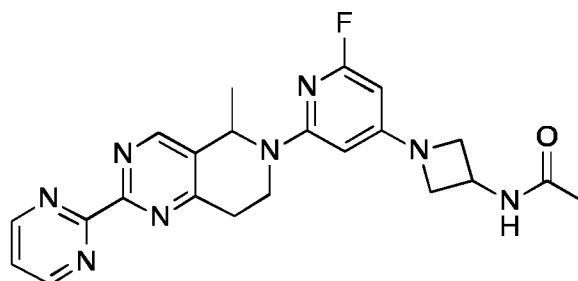
Example 130: 6-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-6-azaspiro[3.3]heptane, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.02 (d, 2 H), 8.86 (s, 1 H), 7.64 (t, 1 H), 5.68 (q, 1 H), 5.62 (s, 1 H), 5.36 (d, 1 H), 4.84 (s, 3 H), 4.81 - 4.87 (m, 1 H), 4.40 - 4.50 (m, 1 H), 4.08 - 4.16 (m, 4 H), 3.40 - 3.52 (m, 1 H), 3.04 - 3.22 (m, 2 H), 1.55 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 420.

Example 131 and 132

N-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]acetamide and *N*-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]acetamide

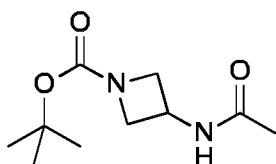


Example 131



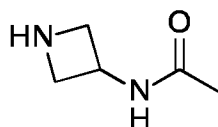
Example 132

Step 1: Preparation of *tert*-butyl 3-acetamidoazetidine-1-carboxylate



- 5 To a solution of 1-Boc-3-(amino)azetidine (1.0 g, 5.81 mmol) in DCM (10 mL) was added acetyl chloride (0.5 mL, 6.97 mmol) at 0 °C. After being warmed to rt and stirred for 2 hrs, the resulting mixture was diluted with DCM (80 mL) and washed with water (20 mL) and brine successively. The organic layer were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give crude *tert*-butyl 3-acetamidoazetidine-1-carboxylate (500 mg) which was used directly in
- 10 the next step without any further purification.

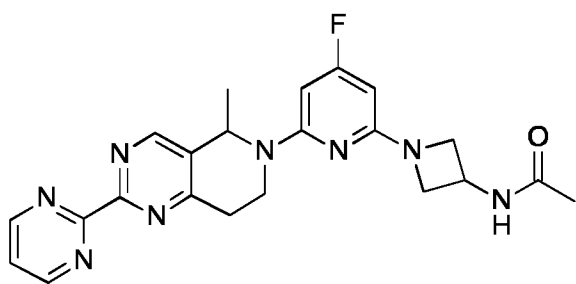
Step 2: Preparation of *N*-(azetidin-3-yl)acetamide



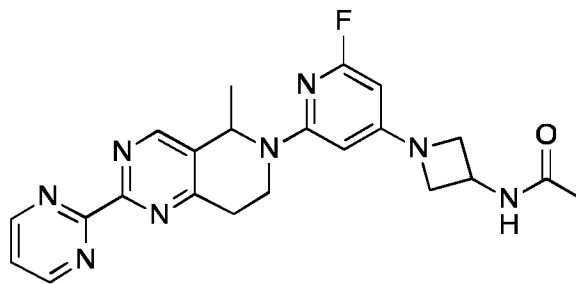
- To a solution of *tert*-butyl 3-acetamidoazetidine-1-carboxylate (500 mg, 2.33 mmol) in DCM (3 mL) was added trifluoroacetic acid (1.5 mL, 19.47 mmol) at 0 °C. The mixture was
- 15 warmed to rt with stirring for 12 hrs. The reaction mixture was concentrated *in vacuo* to give crude *N*-(azetidin-3-yl)acetamide (250 mg) as a yellow oil which was used directly in the next step.

Step 3: Preparation of *N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]acetamide and *N*-[1-[2-fluoro-6-(5-

methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]acetamide



Example 131



Example 132

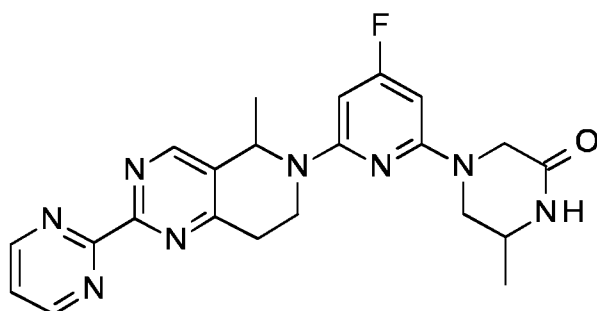
- 5 A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), *N*-(azetidin-3-yl)acetamide (101 mg, 0.88 mmol) and potassium carbonate (122 mg, 0.88 mmol) in NMP (1 mL) was heated at 140 °C with stirring for 2 hrs in a microwave reactor. The resulting reaction mixture was diluted with DCM (5 mL) and filtered. The filtrate was concentrated *in vacuo* and
- 10 the residue was purified by prep-HPLC to give *N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]acetamide (5.2 mg) as a red solid and *N*-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]acetamide (59 mg) as a light red solid.

Example 131: *N*-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]acetamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.88 (s, 1 H), 7.65 (t, 1 H), 5.99 (d, 1 H), 5.76 (d, 1 H), 5.48 (d, 1 H), 4.65 - 4.71 (m, 1 H), 4.55 (d, 1 H), 4.21 - 4.31 (m, 2 H), 3.74 - 3.84 (m, 2 H), 3.43 - 3.52 (m, 1 H), 3.13 (s, 2 H), 1.97 (s, 3 H), 1.58 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 435.

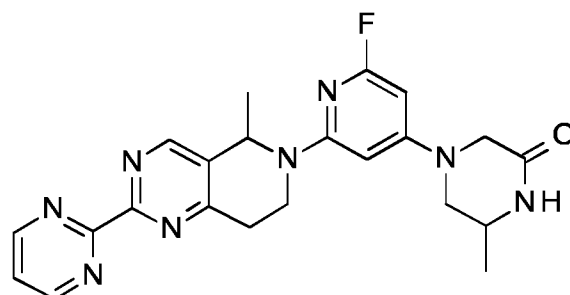
Example 132: *N*-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]acetamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.86 (s, 1 H), 7.64 (t, 1 H), 5.68 (q, 1 H), 5.63 (s, 1 H), 5.37 (d, 1 H), 4.68 - 4.81 (m, 1 H), 4.38 - 4.54 (m, 1 H), 4.21 - 4.34 (m, 2 H), 3.78 (m, 2 H), 3.39 - 3.53 (m, 1 H), 3.04 - 3.20 (m, 2 H), 1.95 - 2.00 (m, 3 H), 1.56 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 435.

Example 133 and 134

4-[4-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-6-methyl-piperazin-2-one and 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-6-methyl-piperazin-2-one



Example 133



Example 134

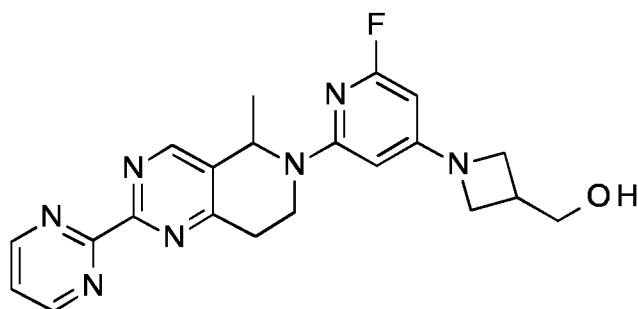
A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), 6-methylpiperazin-2-one (101 mg, 0.88 mmol) and DIPEA (114 mg, 0.88 mmol) in NMP (1 mL) was heated at 200 °C with stirring in a microwave reactor for 2 hrs. The resulting reaction mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC to give 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-6-methyl-piperazin-2-one (27 mg) as a yellow solid and 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-6-methyl-piperazin-2-one (38 mg) as a yellow solid.

Example 133: 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-6-methyl-piperazin-2-one, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.91 (s, 1 H), 7.64 (t, 1 H), 6.05 (dd, 1 H), 5.88 (d, 1 H), 5.77 (m, 1 H), 4.47 - 4.58 (m, 1 H), 4.27 (dd, 1 H), 3.94 - 4.04 (m, 2 H), 3.64 - 3.75 (m, 1 H), 3.44 - 3.55 (m, 1 H), 3.26 - 3.30 (m, 1 H), 3.09 - 3.20 (m, 2 H), 1.59 (dd, 3 H), 1.26 (dd, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 435.

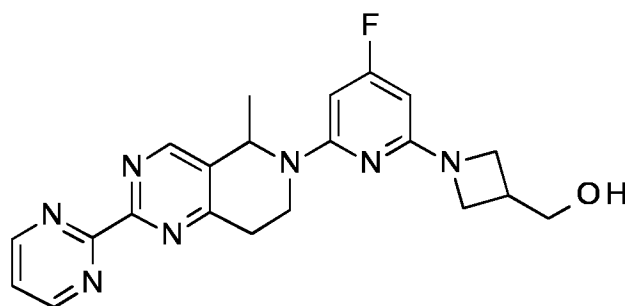
Example 134: 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-6-methyl-piperazin-2-one, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 6.04 (s, 1 H), 5.82 (s, 1 H), 5.75 (d, 1 H), 4.47 - 4.58 (m, 1 H), 3.85 - 4.10 (m, 2 H), 3.80 (m, 1 H), 3.66 - 3.76 (m, 1 H), 3.42 - 3.55 (m, 1 H), 3.05 - 3.25 (m, 3 H), 1.58 (d, 3 H), 1.28 (dd, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 435.

Example 135 and 136

[1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]methanol and [1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]methanol



Example 135



Example 136

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100.0 mg, 0.290 mmol), azetidin-3-ylmethanol (76.8 mg, 0.880 mmol) and DIPEA (0.15 mL, 0.880 mmol) in NMP (2 mL) was heated at 120 °C with stirring in a microwave reactor for 1 hr. The resulting reaction mixture was cooled to rt and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford [1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]methanol (46.1 mg) as a white solid and [1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]methanol (14.4 mg) as a white solid.

Example 135: [1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]methanol, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 5.68 (q, 1 H), 5.59 (s, 1 H), 5.34 (d, 1 H), 4.45 (br dd, 1

-153-

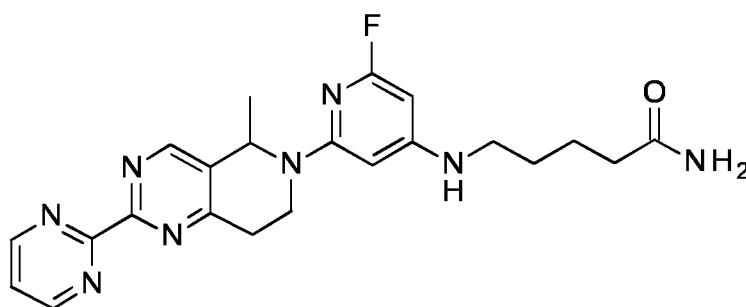
H), 4.01 (td, 2 H), 3.66 - 3.81 (m, 4 H), 3.41 - 3.53 (m, 1 H), 3.04 - 3.24 (m, 2 H), 2.83 - 2.98 (m, 1 H), 1.56 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 408.

Example 136: [1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]methanol, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm:

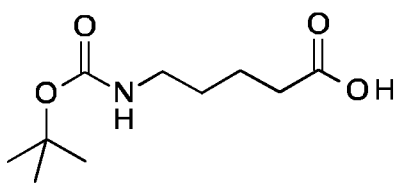
5 9.03 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 5.94 (dd, 1 H), 5.75 (q, 1 H), 5.42 (dd, 1 H), 4.51 - 4.60 (m, 1 H), 4.01 (td, 2 H), 3.68 - 3.78 (m, 4 H), 3.39 - 3.51 (m, 1 H), 3.04 - 3.23 (m, 2 H), 2.84 (dq, 1 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 408.

Example 137

10 **5-[[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]pentanamide**

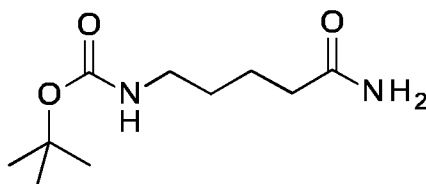


Step 1: Preparation of 5-(*tert*-butoxycarbonylamino)pentanoic acid

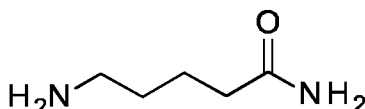


To a stirred solution of 5-aminovaleric acid (5.0 g, 42.68 mmol) in dioxane (100 mL) was
 15 added a solution of sodium hydroxide (1.79 g, 44.81 mmol) in water (100 mL) and the resulting mixture was stirred at rt for 0.5 hr. Then to the resulting mixture was added Boc₂O (9.78 g, 44.81 mmol) slowly. And the reaction mixture was stirred further at rt for 16 hrs, and then concentrated *in vacuo*. The residue was diluted with H₂O (100 mL), then acidified with HCl solution (6 M) to pH=3 and extracted with EA (50 mL) for three times. The combined organic layer was dried
 20 over anhydrous Na₂SO₄ and concentrated *in vacuo* to give 5-(*tert*-butoxycarbonylamino)-pentanoic acid (8.7 g) as colorless oil which was used in the next step directly without any further purification.

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Step 2: Preparation of *tert*-butyl *N*-(5-amino-5-oxo-pentyl)carbamate

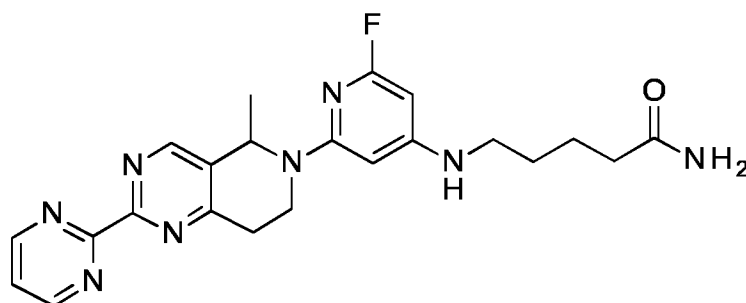
To a stirred solution of 5-(*tert*-butoxycarbonylamino)pentanoic acid (1.0 g, 4.6 mmol) and 4-methylmorpholine (0.51 g, 5.06 mmol) in THF (20 mL) was added isobutyl chloroformate (0.69 g, 5.06 mmol) at -20 °C. The resulting mixture was warmed to 0 °C and stirred for 1 hr. Then to the resulting mixture was added a solution of NH₃ in MeOH (saturated at 0 °C) drop wise. After being stirred at 0 °C for 0.5 hr and warmed up to rt, The resulting mixture was stirred under N₂ for 16 hrs at rt, and then concentrated *in vacuo*. The residue was diluted with H₂O (30 mL) and extracted with EA (30 mL) for three times. The combined organic phase was washed with brine (20 mL), dried over anhydrous Na₂SO₄, concentrated *in vacuo* to give *tert*-butyl *N*-(5-amino-5-oxo-pentyl)carbamate (780 mg) as a white solid, which was used in the next step directly without any further purification.

Step 3: Preparation of 5-aminopentanamide

To a stirred solution of *tert*-butyl *N*-(5-amino-5-oxo-pentyl)carbamate (770.0 mg, 3.56 mmol) in EA (15 mL) was added a solution of HCl in dioxane (2.67 mL, 10.68 mmol). The resulting mixture was stirred at rt for 16 hrs and filtered. The filter cake was dried *in vacuo* to give 5-aminopentanamide (400 mg) as a white solid.

Step 4: Preparation of 5-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]pentanamide

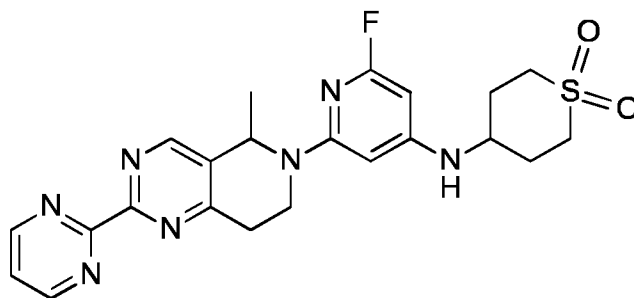
-155-



A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 99.41 mg, 0.290 mmol), 5-aminopentanamide (101.79 mg, 0.880 mmol) and potassium carbonate (121.11 mg, 0.880 mmol) in NMP (2 mL) was heated at 160 °C with stirring for 2 hrs in a microwave reactor. The resulting reaction mixture was cooled to rt and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by prep-HPLC to afford 5-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]pentanamide (11 mg) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 5.83 (s, 1 H), 5.64 (q, 1 H), 5.54 (d, 1 H), 4.40 (dd, 1 H), 3.41 - 3.53 (m, 1 H), 3.05 - 3.23 (m, 4 H), 2.22 - 2.33 (m, 2 H), 1.60 - 1.79 (m, 4 H), 1.56 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 437.

Example 138

***N*-(1,1-dioxothian-4-yl)-2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)pyridin-4-amine**



15

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 170 mg, 0.5 mmol), potassium carbonate (207 mg, 1.5 mmol) and 4-aminotetrahydro-2H-thiopyran 1,1-dioxide (224 mg, 1.5 mmol) in NMP (5 mL) was heated at 130 °C with stirring for 15 hrs. After being cooled to rt, the mixture was poured into water (50 mL) and extracted with DCM (75 mL) twice. The organic

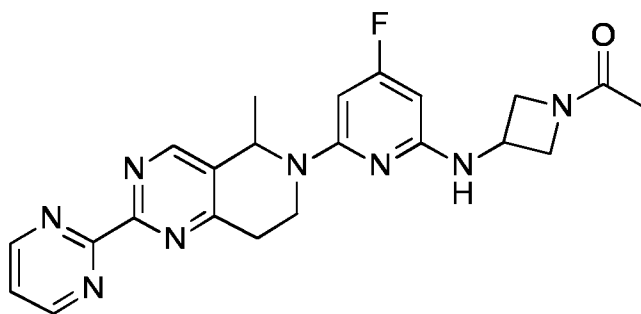
20

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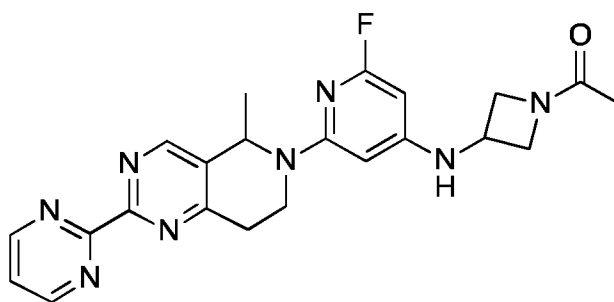
layers were combined, then washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-HPLC to provide *N*-(1,1-dioxothian-4-yl)-2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)pyridin-4-amine (2 mg) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ ppm: 8.93 (d, 2H), 8.76 (s, 1H), 7.54 (m, 1H), 5.78 (s, 1H), 5.53-5.60 (m, 1H), 5.50-5.53 (m, 1H), 4.26-4.36 (m, 1H), 3.68 (m, 1H), 3.32-3.43 (m, 1H), 3.11-3.17 (m, 2H), 2.94-3.09 (m, 4H), 2.23 (m, 2H), 1.93-2.14 (m, 2H), 1.46 (d, 3H). MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 470

Example 139 and 140

1-[3-[[4-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]amino]azetidin-1-yl]ethanone and 1-[3-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]amino]azetidin-1-yl]ethanone



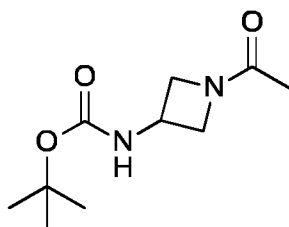
Example 139



Example 140

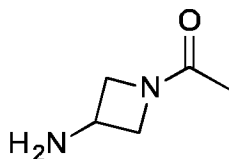
Step 1: Preparation of *tert*-butyl *N*-(1-acetylazetidin-3-yl)carbamate

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To a stirred solution of 3-Boc-aminoazetidine hydrochloride (2.0 g, 9.58 mmol) and triethylamine (4.01 mL, 28.75 mmol) in DCM (40 mL) was added acetyl chloride (1.02 mL, 14.38 mmol) slowly at 0 °C and the resulting mixture was stirred at 0 °C for 1 hr. The resulting reaction mixture was diluted with DCM (20 mL), then washed with H₂O (10 mL) and brine (10 mL) successively. The organic phase was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by the flash column (eluting with PE/EA=5/1, v:v) to afford *tert*-butyl *N*-(1-acetylazetidin-3-yl)carbamate (1.85 g) as a yellow oil.

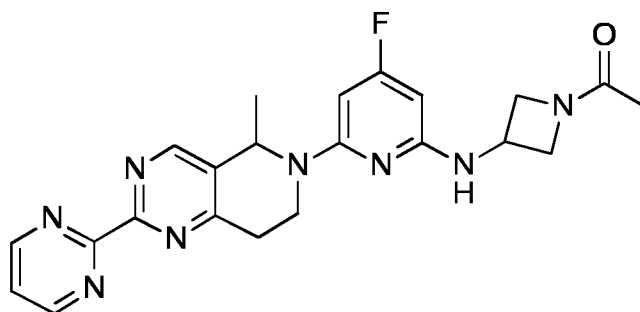
Step 2: Preparation of 1-(3-aminoazetidin-1-yl)ethanone



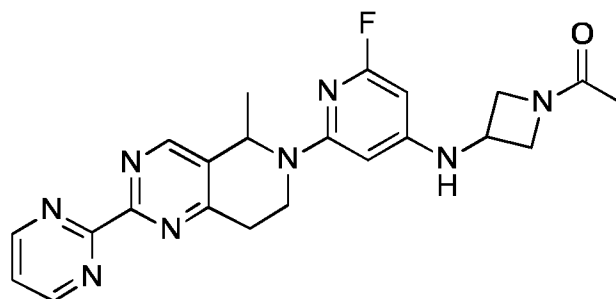
A mixture of *tert*-butyl *N*-(1-acetylazetidin-3-yl)carbamate (1.0 g, 4.67 mmol) and TFA (2.0 mL, 25.96 mmol) in DCM (10 mL) was stirred at 20 °C for 1 hr. The resulting reaction mixture was concentrated *in vacuo* to give crude 1-(3-aminoazetidin-1-yl)ethanone (450 mg) which was used directly in the next step without any further purification.

Step 3: Preparation of 1-[3-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]amino]azetidin-1-yl]ethanone and 1-[3-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]azetidin-1-yl]ethanone

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Example 139



Example 140

5 A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 201.13 mg, 0.880 mmol), 1-(3-aminoazetidin-1-yl)ethanone (100.0 mg, 0.290 mmol) and potassium carbonate (203.05 mg, 1.47 mmol) in NMP (0.500 mL) was heated at 170 °C with stirring in a microwave reactor for 2 hrs. The resulting reaction mixture was filtered and concentrated *in vacuo*. The residue was purified
10 by prep-HPLC to afford 1-[3-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]amino]azetidin-1-yl]ethanone (6.8 mg) as yellow solid and 1-[3-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]azetidin-1-yl]ethanone (12.2 mg) as a yellow solid.

Example 139: 1-[3-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-
15 d]pyrimidin-6-yl)-2-pyridyl]amino]azetidin-1-yl]ethanone, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.90 (s, 1 H), 7.65 (t, 1 H), 5.94 (d, 1 H), 5.70 - 5.82 (m, 1 H), 5.60 (dd, 1 H), 4.54 - 4.67 (m, 2 H), 4.44 - 4.53 (m, 1 H), 4.34 (q, 1 H), 4.05 - 4.13 (m, 1 H), 3.90 (dt, 1 H), 3.41 - 3.54 (m, 1 H), 3.06 - 3.21 (m, 2 H), 1.91 (s, 3 H), 1.58 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 435.

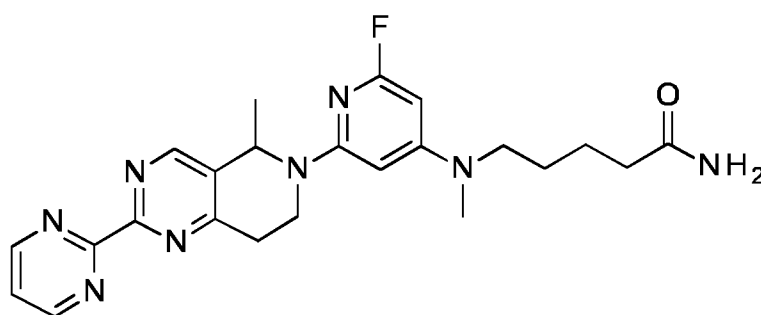
20 **Example 140:** 1-[3-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]azetidin-1-yl]ethanone, ¹H NMR (400 MHz, Methanol-*d*₄) δ

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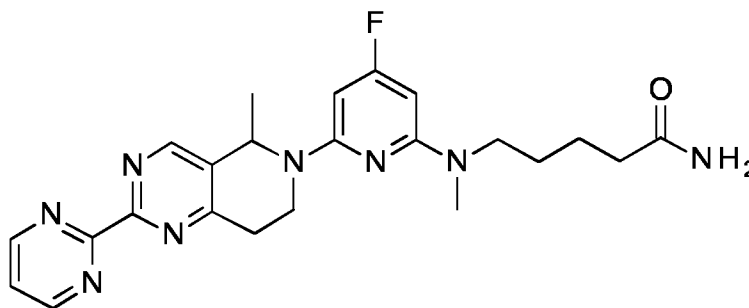
ppm: 9.03 (d, 2 H), 8.87 (s, 1 H), 7.64 (t, 1 H), 5.78 (s, 1 H), 5.66 (q, 1 H), 5.51 (d, 1 H), 4.59 (br t, 1 H), 4.32 - 4.47 (m, 3 H), 4.01 (dd, 1 H), 3.77 - 3.87 (m, 1 H), 3.42 - 3.55 (m, 1 H), 3.06 - 3.24 (m, 2 H), 1.90 (d, 3 H), 1.56 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 435.

Example 141 and 142

- 5 5-[[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-methyl-amino]pentanamide and 5-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-methyl-amino]pentanamide

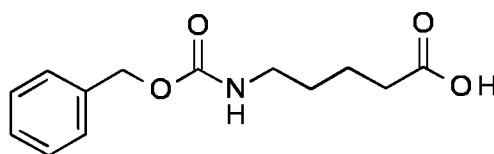


Example 141



Example 142

Step 1: Preparation of 5-(benzyloxycarbonylamino)pentanoic acid

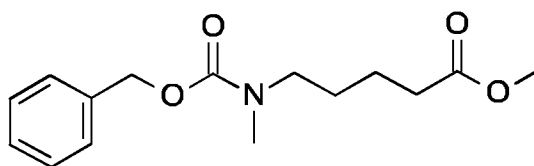


- 15 To a mixture of 5-aminovaleric acid (10.0 g, 0.085 mol) and an aqueous solution of NaOH (50 mL, 2.0 M) which was cooled to 0 °C, were added CbzCl (16.0 g, 0.094 mol) and an aqueous solution of NaOH (50 mL, 2.0 M) simultaneously. The resulting mixture was warmed to rt and stirred for 0.5 hrs, then extracted with EA (300 mL) for three times. The combined organic phase

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was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give crude 5-(benzyloxycarbonylamino)-pentanoic acid (20.0 g) as a white solid, which was used directly in the next step without any further purification.

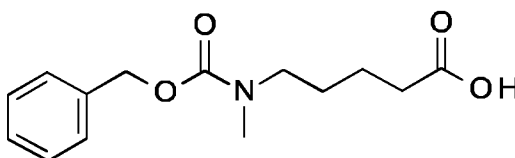
Step 2: Preparation of methyl 5-[benzyloxycarbonyl(methyl)amino]pentanoate



5

To a solution of 5-(benzyloxycarbonylamino)-pentanoic acid (2.0 g, 7.96 mmol) in DMF (40 mL) was added NaH (60% in oil, 0.57 g, 23.88 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 hr and then to the resulting mixture was added MeI (4.88 mL, 47.76 mmol) at 0 °C. The resulting mixture was warmed to rt and stirred for 2 hrs, then quenched with saturated
10 NH_4Cl (150 mL) and extracted with EA (100 mL) for three times. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column (eluting with PE/EA=10/1, v:v) to give methyl 5-[benzyloxycarbonyl(methyl)amino]pentanoate (2.2 g) as a yellow oil.

Step 3: Preparation of 5-[benzyloxycarbonyl(methyl)amino]pentanoic acid

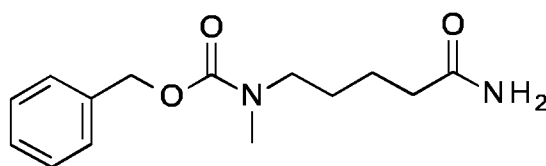


15

To a solution of methyl 5-[benzyloxycarbonyl(methyl)amino]pentanoate (2.2 g, 7.88 mmol) in THF (22 mL) was added a solution of LiOH (1.32 g, 31.5 mmol) in water (10 mL) at 0 °C. After being heated at 60°C with stirring for 1 hr and cooled to rt, the resulting mixture was concentrated *in vacuo* until the volume was around 25 mL, and the residue was acidified to
20 pH=5 with 1M HCl and extracted with EA (100 mL) for three times. The combined organic phase was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to give 5-[benzyloxycarbonyl(methyl)amino]pentanoic acid (1.6 g) as a yellow oil, which was used directly in the next step without any further purification.

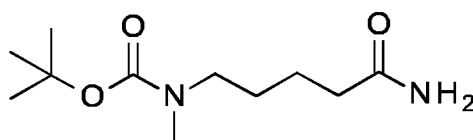
Step 4: Preparation of benzyl N-(5-amino-5-oxo-pentyl)-N-methyl-carbamate

-161-



To a solution of 5-[benzyloxycarbonyl(methyl)amino]pentanoic acid (1.5 g, 5.65 mmol) in DMF (20 mL) was added HATU (4.3 g, 11.31 mmol), NH₄Cl (0.91 g, 16.96 mmol) and DIPEA (2.95 mL, 16.96 mmol) at rt. The resulting mixture was stirred for 3 hrs at rt, then diluted with
5 water (100 mL) and extracted with EA (100 mL) for three times. The combined organic phase was dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by prep-HPLC to give benzyl *N*-(5-amino-5-oxo-pentyl)-*N*-methyl-carbamate (1.2 g) as a light yellow oil.

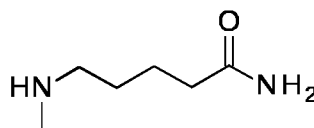
Step 5: Preparation of *tert*-butyl *N*-(5-amino-5-oxo-pentyl)-*N*-methyl-carbamate



10

To a solution of benzyl *N*-(5-amino-5-oxo-pentyl)-*N*-methyl-carbamate (1.2 g, 4.54 mmol) in MeOH (20 mL) was added Pd/C (10%, 300 mg) and Boc₂O (1.98 g, 9.08 mmol). The resulting mixture was degassed, charged with H₂ (15 psi), and then stirred at rt for 2 hrs. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by
15 column (eluting with PE/EA=5/1, v:v) to give *tert*-butyl *N*-(5-amino-5-oxo-pentyl)-*N*-methyl-carbamate (0.9 g) as a colorless oil.

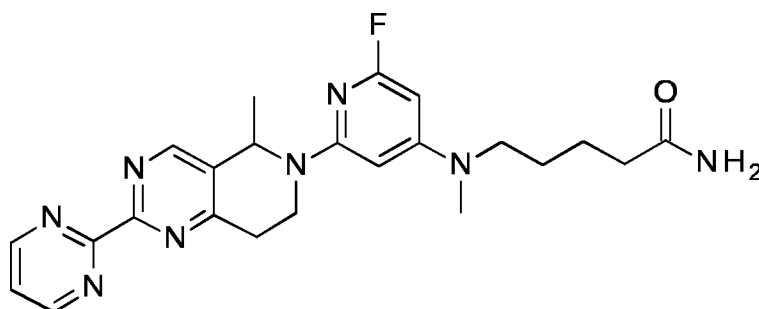
Step 6: Preparation of 5-(methylamino)pentanamide



To a solution of *tert*-butyl *N*-(5-amino-5-oxo-pentyl)-*N*-methyl-carbamate (0.5 g, 2.17
20 mmol) in EA (5 mL) was added a solution of HCl in EA (3.0 mL, 4 M). The resulting mixture was stirred for 2 hrs at rt and then concentrated *in vacuo* to give 5-(methylamino)pentanamide (0.4 g) as a yellow gum, which was used directly in the next step without any further purification.

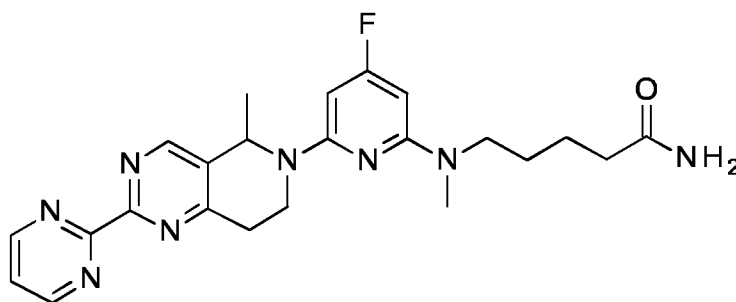
-162-

Step 7: Preparation of 5-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-methyl-amino]pentanamide and 5-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-methyl-amino]pentanamide



5

Example 141



Example 142

A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100.0 mg, 0.290 mmol), K₂CO₃ (203.05 mg, 1.47 mmol) and 5-(methylamino)pentanamide (45.9 mg, 0.350 mmol) in DMSO (2 mL) was heated at 150 °C with stirring for 1 hr in a microwave reactor. The resulting reaction mixture was diluted with DCM (100 mL), washed with water (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 5-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-methyl-amino]pentanamide (8 mg) as a yellow solid and 5-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-methyl-amino]pentanamide (5.5 mg) as a yellow solid.

Example 141: 5-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-methyl-amino]pentanamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.05 (d, 2 H), 8.90 (s, 1 H), 7.66 (t, 1 H), 5.84 (s, 1 H), 5.68 - 5.73 (m, 1 H), 5.66 (s, 1 H),

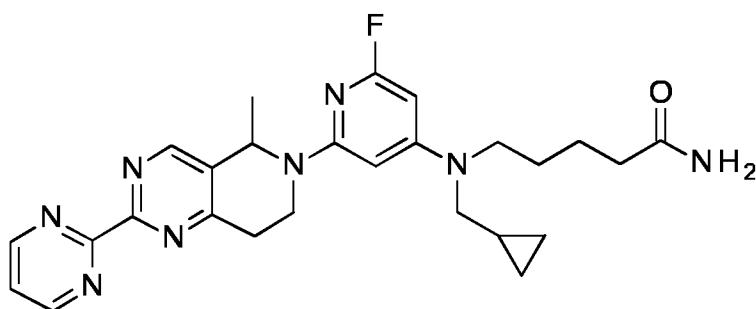
-163-

4.67 (br s, 2 H), 4.47 (br dd, 1 H), 3.48 - 3.53 (m, 1 H), 3.41 - 3.47 (m, 2 H), 3.13 - 3.25 (m, 2 H), 3.03 (s, 3 H), 2.24 - 2.32 (m, 2 H), 1.67 (br d, 4 H), 1.59 (d, 3 H). MS obsd (ESI) [(M+H)⁺]: 451.

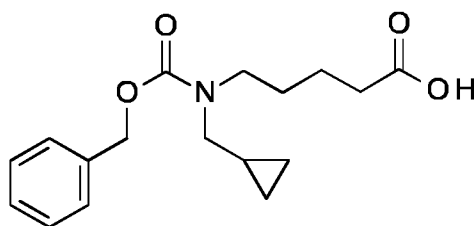
Example 142: 5-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-methyl-amino]pentanamide, ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.05 (d, 2 H), 8.91 (s, 1 H), 7.66 (t, 1 H), 5.91 (d, 1 H), 5.78 (q, 1 H), 5.65 (d, 1 H), 4.48 - 4.69 (m, 2 H), 4.45 - 4.56 (m, 1 H), 3.58 (br s, 2 H), 3.46 - 3.54 (m, 1 H), 3.12 - 3.23 (m, 2 H), 3.01 (s, 3 H), 2.23 - 2.30 (m, 2 H), 1.64 - 1.72 (m, 4 H), 1.60 (d, 3 H). MS obsd (ESI) [(M+H)⁺]: 451.

Example 143

10 **5-[Cyclopropylmethyl-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]pentanamide**



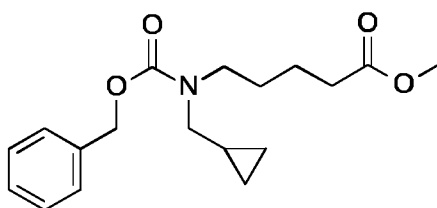
Step 1: Preparation of 5-[benzyloxycarbonyl(cyclopropylmethyl)amino]pentanoic acid



To a solution of 5-(benzyloxycarbonylamino)pentanoic acid (3.0 g, 11.94 mmol) in DMF (50 mL) was added NaH (60% in oil, 1.19 g, 29.85 mmol) at 0 °C. The resulting mixture was stirred for 1 hr at 0 °C. To the mixture was added (bromomethyl)-cyclopropane (2.9 mL, 29.85 mmol) at 0 °C. After being heated at 50 °C with stirring for 2 hrs, the resulting mixture was quenched with saturated NH₄Cl (100 mL) and extracted with EA (100 mL) twice. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was

concentrated *in vacuo* to give crude 5-[benzyloxycarbonyl(cyclopropylmethyl)amino]pentanoic acid (4.9 g) as a light yellow oil.

Step 2: Preparation of methyl 5-[benzyloxycarbonyl(cyclopropylmethyl)amino]-pentanoate



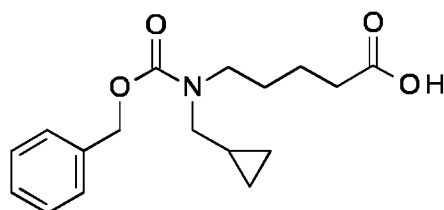
5

To a solution of 5-[benzyloxycarbonyl(cyclopropylmethyl)amino]pentanoic acid (4.9 g, 9.63 mmol) in DMF (30 mL) was added K_2CO_3 (3.99 g, 28.88 mmol) and MeI (5.9 mL, 57.77 mmol). The resulting mixture was stirred for 2 hrs at rt, then diluted with saturated aqueous NH_4Cl (100 mL) and extracted with EA (80 mL) for three times. The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column (eluting with PE/EA=5/1, v:v) to give methyl 5-[benzyloxycarbonyl(cyclopropylmethyl)amino]-pentanoate (2 g) as a light yellow oil.

10

Step 3: Preparation of 5-[benzyloxycarbonyl(cyclopropylmethyl)amino]pentanoic acid

15 acid



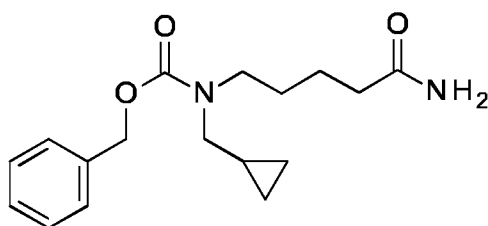
20

To a solution of methyl 5-[benzyloxycarbonyl(cyclopropylmethyl)amino]-pentanoate (2.9 g, 9.08 mmol) in THF (20 mL) was added a solution of LiOH monohydrate (1.52 g, 36.32 mmol) in water (10 mL) drop wise at 0 °C. After being heated at 60 °C with stirring for 1 hr, the resulting mixture was cooled to rt and concentrated *in vacuo* until the volume is around 25 mL. The residue was acidified to pH=5 with 1M HCl and extracted with EA (100 mL) twice. The combined organic phase was dried over anhydrous Na_2SO_4 and filtered. The filtrate was

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concentrated *in vacuo* to give 5-[benzyloxycarbonyl-(cyclopropylmethyl)amino]pentanoic acid (2.6 g) as a yellow oil, which was used directly in the next step without any further purification.

Step 4: Preparation of benzyl *N*-(5-amino-5-oxo-pentyl)-*N*-(cyclopropylmethyl)-carbamate

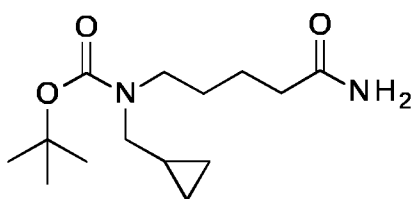


5

To a solution of 5-[benzyloxycarbonyl-(cyclopropylmethyl)amino]pentanoic acid (2.5 g, 8.19 mmol) in DMF (25 mL) was added HATU (4.67 g, 12.28 mmol), NH₄Cl (1.31 g, 24.56 mmol) and DIPEA (4.28 mL, 24.56 mmol). After being stirred for 3 hrs at rt, the resulting mixture was diluted with water (100 mL) and extracted with EA (100 mL) for three times. The combined organic phase was dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by prep-HPLC to give benzyl *N*-(5-amino-5-oxo-pentyl)-*N*-(cyclopropylmethyl)-carbamate (1.6 g) as a light yellow oil.

10

Step 5: Preparation of *tert*-butyl *N*-(5-amino-5-oxo-pentyl)-*N*-(cyclopropylmethyl)-carbamate



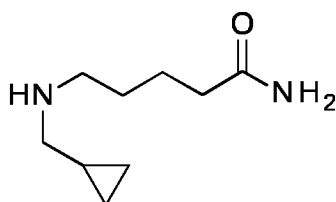
15

To a solution of benzyl *N*-(5-amino-5-oxo-pentyl)-*N*-(cyclopropylmethyl)-carbamate (1.6 g, 5.26 mmol) in methanol (20 mL) was added Pd/C (1.12 g, 10%wt) and Boc₂O (2.29 g, 10.51 mmol). The resulting mixture was degassed, charged with H₂ (15 psi) and stirred at rt for 2 hrs. The resulting reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column (eluting with PE/EA=5/1, v:v) to give *tert*-butyl *N*-(5-amino-5-oxo-pentyl)-*N*-(cyclopropylmethyl)-carbamate (1.4 g) as a colorless oil.

20

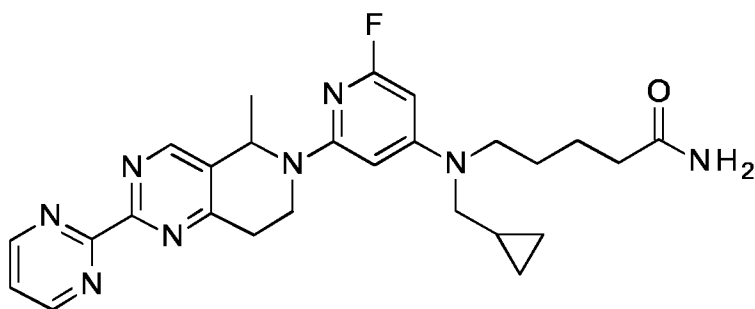
Step 6: Preparation of 5-(cyclopropylmethylamino)pentanamide

-166-



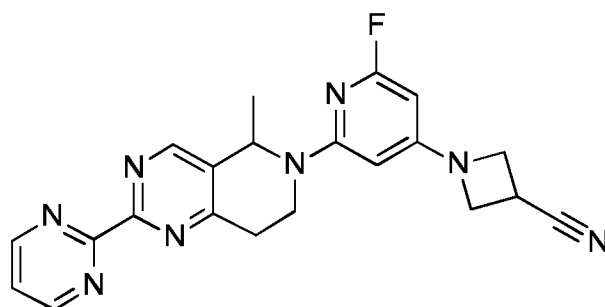
Tert-butyl *N*-(5-amino-5-oxo-pentyl)-*N*-(cyclopropylmethyl)-carbamate (400 mg, 1.48 mmol) was stirred in a solution of HCl in MeOH (4 mL, 1M) at rt for 2 hrs. The resulting reaction mixture was basified by basic resin and filtered. The filtrate was concentrated *in vacuo* to give 5-(cyclopropylmethyl-amino)pentanamide (300 mg) as a yellow oil which was used directly in the next step without any further purification.

Step 7: Preparation of 5-[cyclopropylmethyl-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]amino]pentanamide



A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), 5-(cyclopropylmethylamino)pentanamide (150 mg, 0.88 mmol) and K₂CO₃ (122 mg, 0.88 mmol) in DMSO (1 mL) was heated at 160 °C with stirring for 1 hr in a microwave reactor. The resulting reaction mixture was diluted with EA (30 mL), then washed with H₂O (20 mL) and brine (20 mL) successively, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 5-[cyclopropylmethyl-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]amino]pentanamide (5 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.90 (s, 1 H), 7.64 (t, 1 H), 5.86 (s, 1 H), 5.61 - 5.74 (m, 2 H), 4.45 (d, 1 H), 3.54 - 3.55 (m, 1 H), 3.42 - 3.55 (m, 2 H), 3.21 - 3.29 (m, 2 H), 3.07 - 3.20 (m, 2 H), 2.27 (s, 2 H), 1.67 (br. s, 4 H), 1.58 (d, 3 H), 1.07 (d, 1 H), 0.57 (d, 2 H), 0.31 (d, 2 H). MS obsd. (ESI⁺) [(M+H)⁺]: 491.

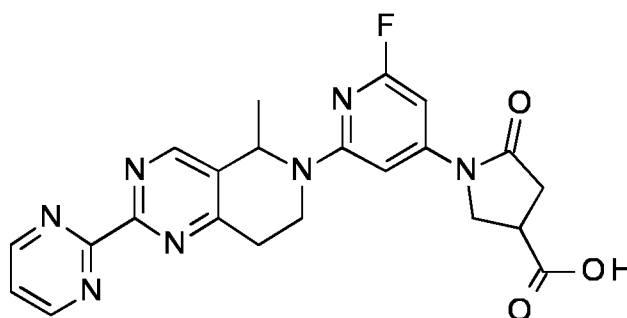
Example 144

1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carbonitrile

- 5 A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 100 mg, 0.29 mmol), azetidine-3-carbonitrile (72 mg, 0.88 mmol) and DIPEA (114 mg, 0.88 mmol) in NMP (1 mL) was heated at 160 °C with stirring for 1 hr in a microwave reactor. The resulting reaction mixture was diluted with MeOH (4 mL), filtered and purified by prep-HPLC to afford 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carbonitrile (8 mg) as a red solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.86 (s, 1 H), 7.64 (t, 1 H), 5.63 - 5.76 (m, 2 H), 5.42 (s, 1 H), 4.41 - 4.52 (m, 1 H), 4.28 (m, 2 H), 4.08 - 4.19 (m, 2 H), 3.81 (m, 1 H), 3.40 - 3.55 (m, 1 H), 3.03 - 3.23 (m, 2 H), 1.57 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 403.
- 10

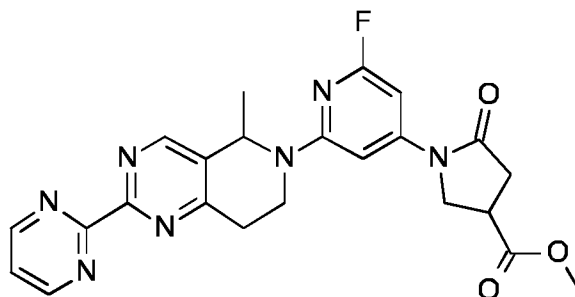
15

Example 145

1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-5-oxo-pyrrolidine-3-carboxylic acid

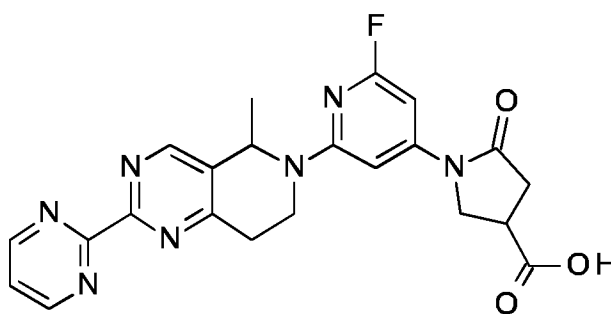
-168-

Step 1: Preparation of methyl 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-5-oxo-pyrrolidine-3-carboxylate



To a solution of 6-(6-fluoro-4-iodo-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 1 in Example 96, 150mg, 335 μ mol) in dioxane (3mL) was added methyl 5-oxopyrrolidine-3-carboxylate (95.8 mg, 669 μ mol), cesium carbonate (218 mg, 669 μ mol), Xantphos (38.7 mg, 66.9 μ mol) and Pd(OAc)₂ (7.51 mg, 33.5 μ mol). The resulting mixture was heated at 100 °C with stirring for 20 hrs under argon. After being cooled to rt, the resulting reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give crude methyl 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-5-oxo-pyrrolidine-3-carboxylate (210 mg) which was directly used in the next step without any further purification.

Step 2: Preparation of 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-5-oxo-pyrrolidine-3-carboxylic acid



15

To a solution of the crude methyl 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-5-oxo-pyrrolidine-3-carboxylate (210mg) in a mixture solvent of MeOH (3 mL) and water (1 mL) was added lithium hydroxide monohydrate (49.4 mg) at rt. The resulting mixture was stirred for 2 hrs at rt, then acidified with acetic acid and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 1-[2-fluoro-6-(5-

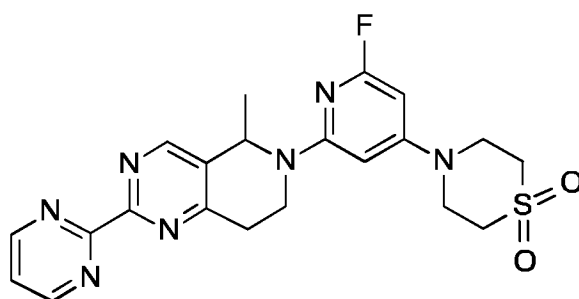
20

-169-

methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-5-oxo-pyrrolidine-3-carboxylic acid (18 mg) as a light yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm: 8.99 (d, 2H), 8.95 (s, 1H), 7.64 (t, 1H), 6.90 (d, 1H), 6.84 (d, 1H), 5.73-5.65 (m, 1H), 4.53-4.43 (m, 1H), 4.15 - 4.07 (m, 1H), 4.07 - 3.99 (m, 1H), 3.53 - 3.44 (m, 1H), 3.13 - 2.98 (m, 2H),
 5 2.88 - 2.71 (m, 3H), 1.52 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 450.

Example 146

4-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-1,4-thiazinane 1,1-dioxide

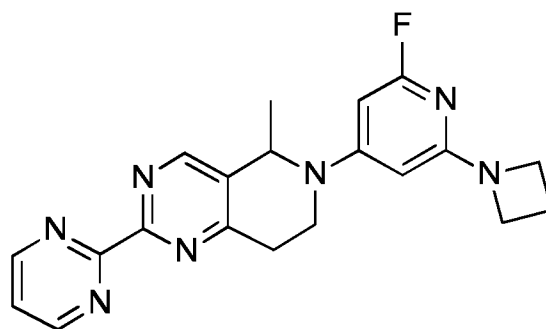


10 A mixture of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 170 mg, 0.5 mmol), thiomorpholine 1,1-dioxide (203 mg, 1.5 mmol) and potassium carbonate (207 mg, 1.5 mmol) in NMP (5 mL) was heated at 110 °C with stirring for 15 hrs under nitrogen. After being cooled to rt, the resulting mixture was diluted with water (25 mL) and extracted with DCM (75 mL) twice.
 15 The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to provide 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-1,4-thiazinane 1,1-dioxide (2 mg) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.99 (d, 2H), 8.90 (s, 1H), 7.63 (t, 1H), 6.20 (s, 1H), 6.03 (s, 1H), 5.73 (q, 1H), 4.49 (br dd, 1H), 3.94 (br s, 4H), 3.35-
 20 3.49 (m, 1H), 3.09-3.18 (m, 4H), 2.90-3.08 (m, 2H), 1.50 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 456.

Example 147

6-[2-(Azetidin-1-yl)-6-fluoro-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine

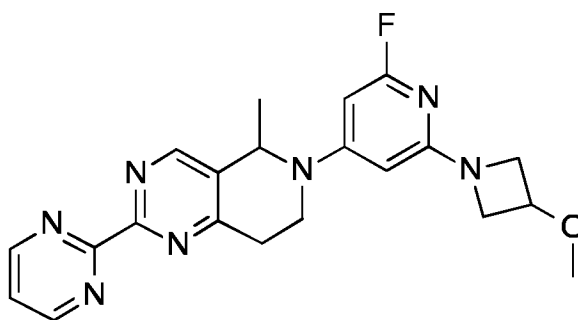
-170-



A mixture of 6-(2,6-difluoro-4-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 170 mg, 0.5 mmol), azetidine hydrochloride (94 mg, 1.0 mmol) and potassium carbonate (207 mg, 1.5 mmol) in NMP (5 mL) was heated at 110 °C with stirring for 15 hrs under nitrogen. After being cooled to rt, the resulting mixture was diluted with water (25 mL) and extracted with DCM (75 mL) twice. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to provide 6-[2-(azetidin-1-yl)-6-fluoro-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (85 mg) as a light yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.05 (d, 2H), 8.90 (s, 1H), 7.67 (t, 1H), 5.97 (t, 1H), 5.61 (s, 1H), 5.36 (q, 1H), 4.08-4.19 (m, 1H), 4.01 (t, 4H), 3.55-3.64 (m, 1H), 3.14-3.31 (m, 2H), 2.34-2.42 (m, 2H), 1.61 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 378.

Example 148

6-[2-Fluoro-6-(3-methoxyazetidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



A mixture of 6-(2,6-difluoro-4-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 170 mg, 0.5 mmol), 3-methoxyazetidine hydrochloride (124 mg, 1.0 mmol) and potassium carbonate (207 mg, 1.5

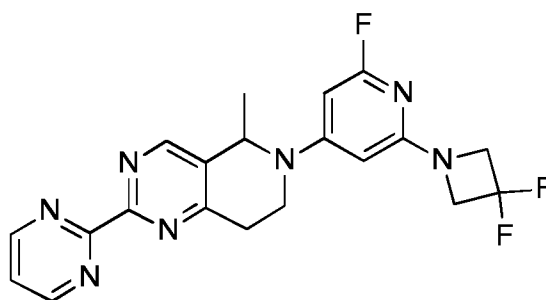
-171-

mmol) in NMP (5 mL) was heated at 110 °C with stirring for 15 hrs under nitrogen. After being cooled to rt, the resulting mixture was diluted with water (25 mL) and extracted with DCM (75 mL) twice. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to provide 6-[2-fluoro-6-(3-methoxyazetidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (100 mg) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.05 (d, 2H), 8.89 (s, 1H), 7.66 (t, 1H), 5.99 (t, 1H), 5.66 (s, 1H), 5.36 (d, 1H), 4.34 (tt, 1H), 4.08-4.21 (m, 3H), 3.81 (dd, 2H), 3.53-3.65 (m, 1H), 3.35 (s, 3H), 3.13-3.27 (m, 2H), 1.61 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 408.

10

Example 149

6-[2-(3,3-Difluoroazetidin-1-yl)-6-fluoro-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



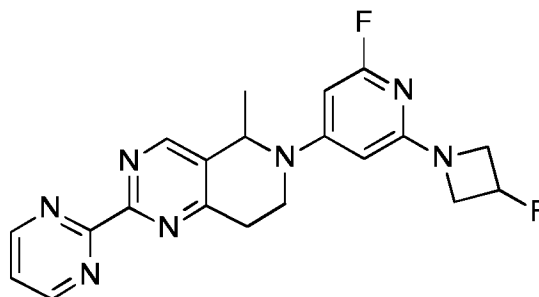
A mixture of 6-(2,6-difluoro-4-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 170 mg, 0.5 mmol), 3,3-difluoroazetidine hydrochloride (156 mg, 1.0 mmol) and potassium carbonate (207 mg, 1.5 mmol) in NMP (5 mL) was heated at 110 °C with stirring for 15 hrs under nitrogen. After being cooled to rt, the resulting mixture was diluted with water (25 mL) and extracted with DCM (75 mL) twice. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to provide 6-[2-(3,3-difluoroazetidin-1-yl)-6-fluoro-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (35 mg) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.05 (d, 2H), 8.89 (s, 1H), 7.67 (t, 1H), 6.10 (t, 1H), 5.84 (s, 1H), 5.39 (q, 1H), 4.34 (t, 4H), 4.08-4.28 (m, 1H), 3.56-3.69 (m, 1H), 3.11-3.30 (m, 2H), 1.62 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 414.

25

Example 150

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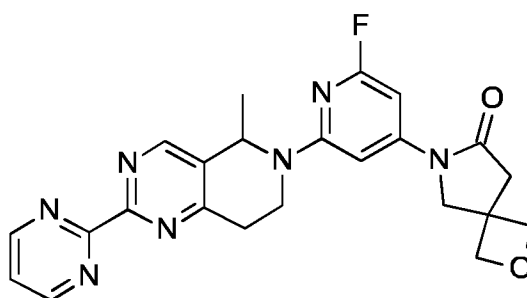
6-[2-Fluoro-6-(3-fluoroazetidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine



A mixture of 6-(2,6-difluoro-4-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 170 mg, 0.5 mmol), 3-fluoroazetidine hydrochloride (110 mg, 1.0 mmol) and potassium carbonate (207 mg, 1.5 mmol) in NMP (5 mL) was heated at 110 °C with stirring for 15 hrs under nitrogen. After being cooled to rt, the resulting mixture was diluted with water (25 mL) and extracted with DCM (75 mL) twice. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to provide 6-[2-fluoro-6-(3-fluoroazetidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (75 mg) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 8.93 (d, 2H), 8.78 (s, 1H), 7.55 (t, 1H), 5.91 (t, 1H), 5.59 (s, 1H), 5.19-5.31 (m, 2H), 4.12-4.23 (m, 2H), 3.87-4.07 (m, 3H), 3.33-3.56 (m, 1H), 3.02-3.20 (m, 2H), 1.49 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 396.

Example 151

7-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-7-azaspiro[3.4]octan-6-one



20

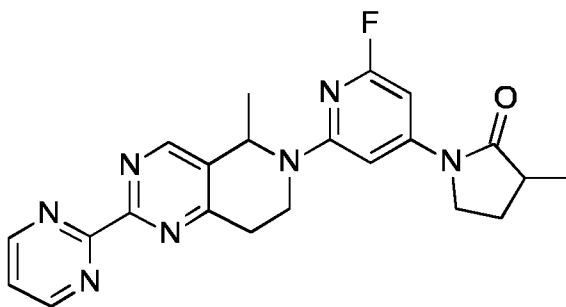
To a solution of 6-(6-fluoro-4-iodo-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-

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5H-pyrido[4,3-d]pyrimidine (the product of step 1 in Example 96, 100mg, 223 μ mol) in dioxane (3mL) was added 2-oxa-6-azaspiro[3.4]octan-7-one (42.5 mg, 335 μ mol), cesium carbonate (145 mg, 446 μ mol), Xantphos (25.8 mg, 44.6 μ mol) and Pd(OAc)₂ (5.01 mg, 22.3 μ mol). The resulting mixture was heated at 100 °C with stirring for 20 hrs under argon. After being cooled to rt, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by prep-HPLC to give 7-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7, 8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-7-azaspiro[3.4]octan-6-one (12 mg) as a light yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm: 8.99 (d, 2H), 8.96 (s, 1H), 7.64 (t, 1H), 6.88 (s, 1H), 6.84 (s, 1H), 5.74-5.64 (m, 1H), 4.65 - 4.58 (m, 4H), 4.50 - 4.43 (m, 1H), 4.22 (s, 2H), 3.55 - 3.45 (m, 1H), 3.13 - 3.03 (m, 2H), 2.98 (s, 2H), 1.53 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 448.

Example 152

1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-methyl-pyrrolidin-2-one



15

To a solution of 6-(6-fluoro-4-iodo-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 1 in Example 96, 100 mg, 223 μ mol) in dioxane (3 mL) was added 3-methylpyrrolidin-2-one (33.2 mg, 335 μ mol), cesium carbonate (145 mg, 446 μ mol), Xantphos (25.8 mg, 44.6 μ mol) and Pd(OAc)₂ (5.01 mg, 22.3 μ mol). The resulting mixture was heated at 100 °C with stirring for 20 hrs under argon. After being cooled to rt, the resulting reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by prep-HPLC to give 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-methyl-pyrrolidin-2-one (15 mg) as a light yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm: 8.99 (d, 2H), 8.95 (s, 1H), 7.64 (t, 1H), 6.98 (d, 1H), 6.81 (d, 1H), 5.72-5.66 (m, 1H), 4.50-4.39 (m, 1H), 3.91 - 3.72 (m, 2H), 3.55 - 3.44 (m, 1H),

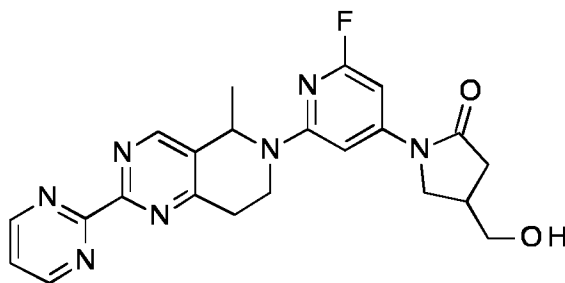
25

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3.13 - 2.98 (m, 2H), 2.78 - 2.66 (m, 1H), 2.38 - 2.27 (m, 1H), 1.76 - 1.64 (m, 1H), 1.53 (d, 3H), 1.17 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 420.

Example 153

1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-(hydroxymethyl)pyrrolidin-2-one

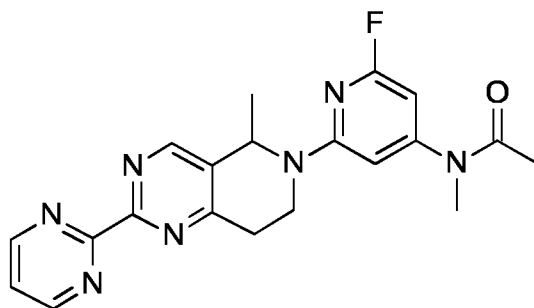


To a solution of 6-(6-fluoro-4-iodo-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 1 in Example 96, 100mg, 223 μ mol) in dioxane (3mL) was added 4-(hydroxymethyl)pyrrolidin-2-one (38.5 mg, 335 μ mol), cesium carbonate (145 mg, 446 μ mol), XantPhos (25.8 mg, 44.6 μ mol) and Pd(OAc)₂ (5.01 mg, 22.3 μ mol). The resulting mixture was heated at 100 °C with stirring for 20 hrs under argon. After being cooled to rt, the resulting reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by prep-HPLC to give 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-(hydroxymethyl)pyrrolidin-2-one (12 mg) as a light yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm: 8.99 (d, 2H), 8.95 (s, 1H), 7.64 (t, 1H), 6.90 - 6.87 (m, 1H), 6.87-6.85 (m, 1H), 5.73-5.63 (m, 1H), 4.96-4.84 (m, 1H), 4.54 - 4.39 (m, 1H), 4.01-3.90 (m, 1H), 3.72-3.64 (m, 1H), 3.53 - 3.41 (m, 3H), 3.12 - 2.99 (m, 2H), 2.72 - 2.63 (m, 1H), 2.60 - 2.53 (m, 1H), 2.41 - 2.33 (m, 1H), 1.53 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 436.

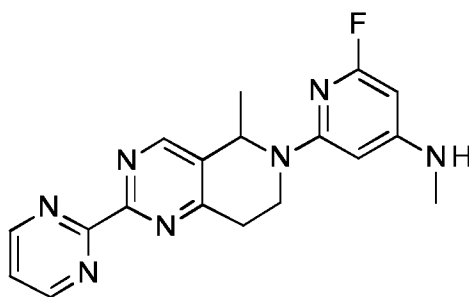
Example 154

N-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-acetamide

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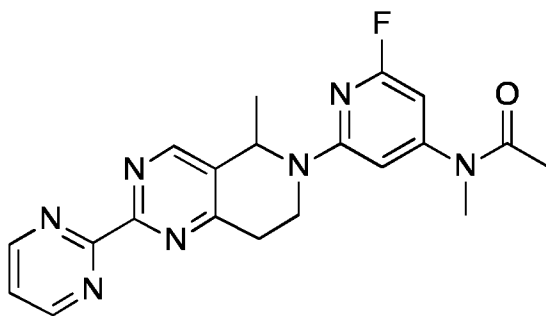


Step 1: Preparation of 2-fluoro-N-methyl-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)pyridin-4-amine



- 5 To a stirring solution of 6-(4,6-difluoro-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 600.0 mg, 1.76 mmol) in DMA (10 mL) was added K₂CO₃ (3.66 g, 26.44 mmol) and methylamine hydrochloride (1.79 g, 26.44 mmol). The resulting mixture was heated at 40 °C with stirring for 12 hrs and then filtrated. The filtrate was concentrated *in vacuo*. The residue was purified by prep-HPLC to give 2-fluoro-N-methyl-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)pyridin-4-amine (280 mg) as a yellow solid.
- 10

Step 2: Preparation of N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-acetamide



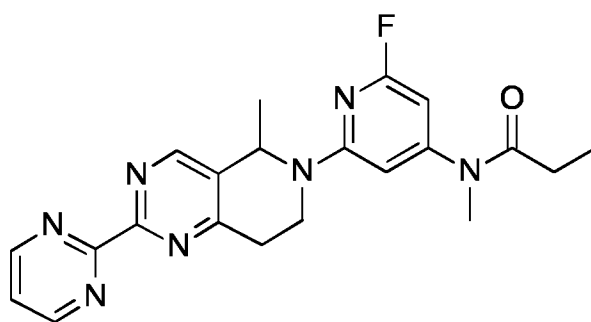
-176-

To a solution of 2-fluoro-*N*-methyl-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)pyridin-4-amine (20 mg, 0.06 mmol) in DCM (0.5 mL) was added acetyl chloride (13.4 mg, 0.17 mmol) and DIPEA (22.07 mg, 0.17 mmol) at rt. The resulting mixture was stirred at rt for 1 h, then diluted with MeOH (1 mL) and concentrated *in vacuo*. The residue was purified by prep-HPLC to give *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methyl-acetamide (18 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.90 (s, 1 H), 7.65 (t, 1 H), 6.76 (s, 1 H), 6.24 (s, 1 H), 5.77 (q, 1 H), 4.55 - 4.61 (m, 1 H), 3.51 - 3.64 (m, 1 H), 3.29 (s, 3 H), 3.14 - 3.22 (m, 2 H), 2.07 (s, 3 H), 1.62 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 394.

10

Example 155

***N*-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methyl-propanamide**



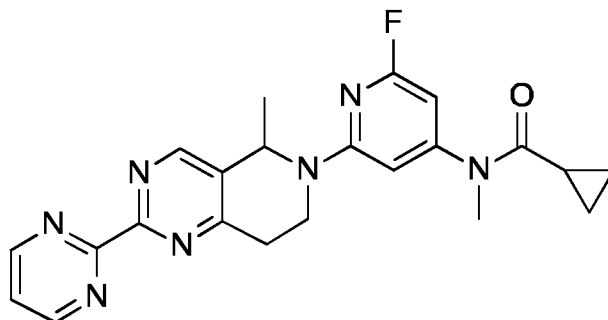
To a solution of 2-fluoro-*N*-methyl-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)pyridin-4-amine (the product of step 1 in Example 154, 20 mg, 0.06 mmol) in DCM (0.5 mL) was added propionyl chloride (22.1 mg, 0.17 mmol) and DIPEA (22.07 mg, 0.17 mmol) at rt. The resulting mixture was stirred for 1 h at rt, then diluted with MeOH (1 mL) and concentrated *in vacuo*. The residue was purified by prep-HPLC to give *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methyl-propanamide (3 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.90 (s, 1 H), 7.65 (t, 1 H), 6.75 (s, 1 H), 6.23 (s, 1 H), 5.76 (q, 1 H), 4.58 (d, 1 H), 3.49 - 3.66 (m, 1 H), 3.28 (s, 3 H), 3.14 - 3.22 (m, 2 H), 2.35 (q, 2 H), 1.62 (d, 3 H), 1.09 (t, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 408.

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Example 156

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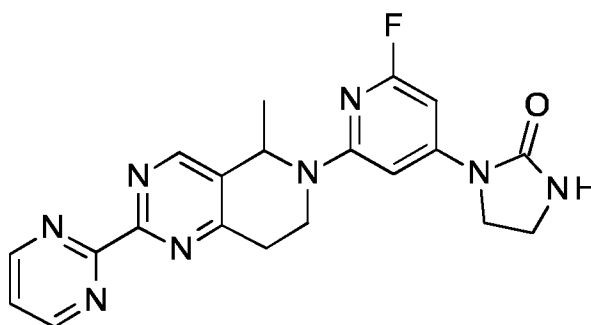
***N*-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methyl-cyclopropanecarboxamide**



To a solution of 2-fluoro-*N*-methyl-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)pyridin-4-amine (the product of step 1 in Example 154, 20 mg, 0.06 mmol) in DCM (0.5 mL) was added cyclopropanecarbonyl chloride (17.9 mg, 0.17 mmol) and DIPEA (22.07 mg, 0.17 mmol) at rt. The resulting mixture was stirred at rt for 1 hr, then diluted with MeOH (1 mL) and concentrated *in vacuo*. The residue was purified by prep-HPLC to give *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methyl-cyclopropanecarboxamide (6 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.90 (s, 1 H), 7.64 (t, 1 H), 6.80 (s, 1 H), 6.28 (s, 1 H), 5.77 (q, 1 H), 4.52 - 4.63 (m, 1 H), 3.50 - 3.67 (m, 1 H), 3.13 - 3.23 (m, 2 H), 1.67 - 1.78 (m, 1 H), 1.62 (d, 3 H), 0.94 - 1.01 (m, 2 H), 0.74 - 0.85 (m, 2 H). MS obsd. (ESI⁺) [(M+H)⁺] : 420.

Example 157

1-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido [4, 3-*d*] pyrimidin-6-yl)-4-pyridyl] imidazolidin-2-one



To a solution of 6-(6-fluoro-4-iodo-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidine (the product of step 1 in Example 96, 100mg, 223 μmol) in dioxane

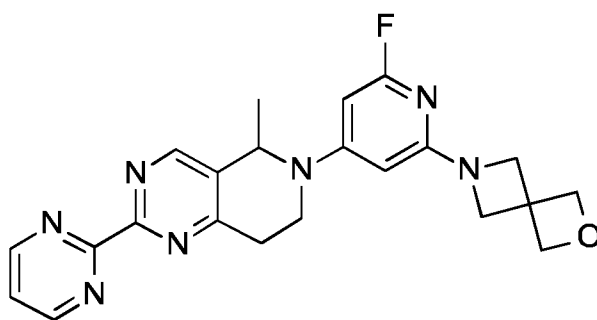
-178-

(3mL) was added imidazolidin-2-one (28.8 mg, 335 μ mol), cesium carbonate (145 mg, 446 μ mol), XantPhos (25.8 mg, 44.6 μ mol) and Pd(OAc)₂ (5.01 mg, 22.3 μ mol). The resulting mixture was heated at 100 °C with stirring for 20 hrs under argon. After being cooled to rt, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by prep-HPLC to give 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]imidazolidin-2-one (8 mg) as a light yellow solid. ¹H NMR (400MHz, DMSO-*d*₆) δ ppm: 8.99 (d, 2H), 8.94 (s, 1H), 7.64 (t, 1H), 7.37 (s, 1H), 6.76 (s, 1H), 6.71 (s, 1H), 5.71-5.62 (m, 1H), 4.45 - 4.38 (m, 1H), 3.96-3.86 (m, 2H), 3.51 - 3.41 (m, 3H), 3.12 - 2.99 (m, 2H), 1.51 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]: 407.

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Example 158

6-[6-Fluoro-4-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-6-azaspiro[3.3]heptane

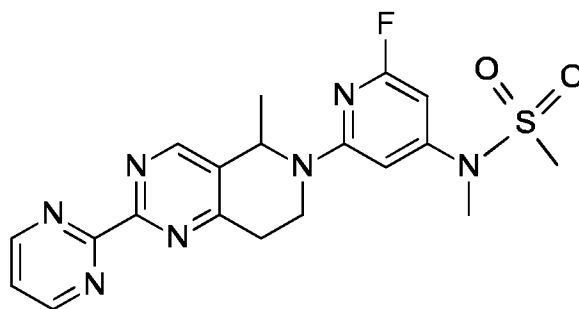


A mixture of 6-(2,6-difluoro-4-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (one product of step 7 in Example 1, 170 mg, 0.5 mmol), 2-oxa-6-azaspiro[3.3]heptane hemioxalate (144 mg, 1.0 mmol) and potassium carbonate (207 mg, 1.5 mmol) in NMP (5 mL) was heated at 110 °C with stirring for 15 hrs under nitrogen. After being cooled to rt, the resulting mixture was diluted with water (25 mL) and extracted with DCM (75 mL) twice. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-HPLC to provide 6-[6-fluoro-4-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-6-azaspiro[3.3]heptane (68 mg) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 9.00 (d, 2H), 8.87 (s, 1H), 7.64 (t, 1H), 5.99 (s, 1H), 5.67 (s, 1H), 5.38 (q, 1H), 4.68-4.75 (m, 4H), 4.00-4.13 (m, 5H), 3.43-3.57 (m, 1H), 2.94-3.14 (m, 2H), 1.49 (d, 3H). MS obsd. (ESI⁺) [(M+H)⁺]:

25 420.

Example 159

***N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methyl-methanesulfonamide**

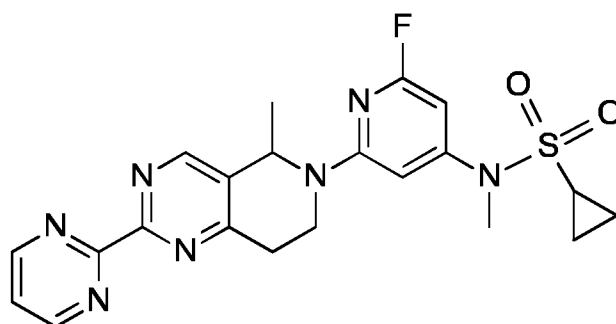


- 5 To a solution of 2-fluoro-*N*-methyl-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)pyridin-4-amine (the product of step 1 in Example 154, 30 mg, 0.09 mmol) in pyridine (0.5 mL) was added methanesulfonyl chloride (29 mg, 0.26 mmol) at rt. The mixture was stirred for 12 hrs at rt and then concentrated *in vacuo*. The residue was purified by prep-HPLC to give *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-
- 10 *d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methyl-methanesulfonamide (10 mg) as a red solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.90 (s, 1 H), 7.65 (t, 1 H), 6.73 (s, 1 H), 6.37 (s, 1 H), 5.69 - 5.81 (m, 1 H), 4.50 - 4.59 (m, 1 H), 3.50 - 3.61 (m, 1 H), 3.36 (s, 3 H), 3.13 - 3.23 (m, 1 H), 3.12 - 3.13 (m, 1 H), 2.96 - 3.06 (m, 3 H), 1.61 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺]: 430.

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Example 160

***N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methyl-cyclopropanesulfonamide**

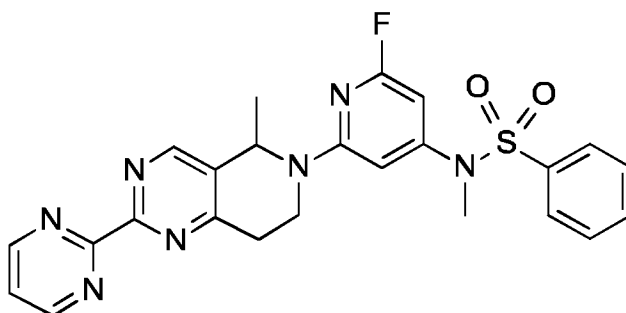


-180-

To a solution of 2-fluoro-*N*-methyl-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)pyridin-4-amine (the product of step 1 in Example 154, 40 mg, 0.11 mmol) in pyridine (0.5 mL) was added cyclopropanesulfonyl chloride (48 mg, 0.34 mmol) at rt. The resulting mixture was stirred for 12 hrs at rt and then concentrated *in vacuo*. The residue was
5 purified by prep-HPLC to give *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methyl-cyclopropanesulfonamide (23 mg) as a light green solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (br d, 2 H), 8.91 (s, 1 H), 7.65 (t, 1 H), 6.76 (s, 1 H), 6.39 (s, 1 H), 5.74 (q, 1 H), 4.54 (m, 1 H), 3.48 - 3.65 (m, 1 H), 3.38 (s, 3 H), 3.10 - 3.21 (m, 2 H), 2.62 - 2.78 (m, 1 H), 1.61 (d, 3 H), 0.96 - 1.14 (m, 4 H). MS obsd. (ESI⁺)
10 [(M+H)⁺] : 456.

Example 161

***N*-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methyl-benzenesulfonamide**



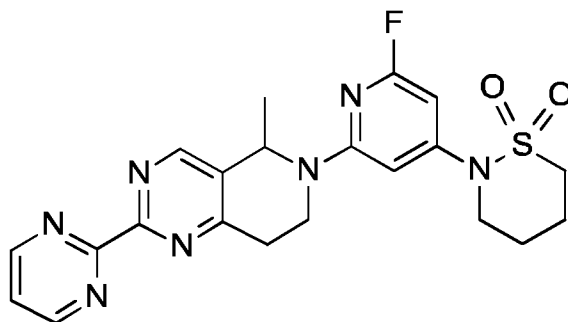
To a solution of 2-fluoro-*N*-methyl-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)pyridin-4-amine (the product of step 1 in Example 154, 20 mg, 0.06 mmol) in pyridine (0.5 mL) was added benzenesulfonyl chloride (0.03 mL, 0.260 mmol) at rt. The resulting mixture was stirred at rt for 1 hr and then concentrated *in vacuo*. The residue was
15 purified by prep-HPLC to give *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methyl-benzenesulfonamide (27 mg) as a light yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.88 (s, 1 H), 7.61 - 7.74 (m, 4 H), 7.50 - 7.60 (m, 1 H), 7.50 - 7.60 (m, 1 H), 6.53 (s, 1 H), 6.13 (s, 1 H), 5.64 (q, 1 H), 4.49 (s, 1 H), 4.46 (s, 1 H), 3.43 - 3.58 (m, 1 H), 3.27 (s, 3 H), 3.06 - 3.16 (m, 2 H), 1.55 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 492.
20

25

Example 162

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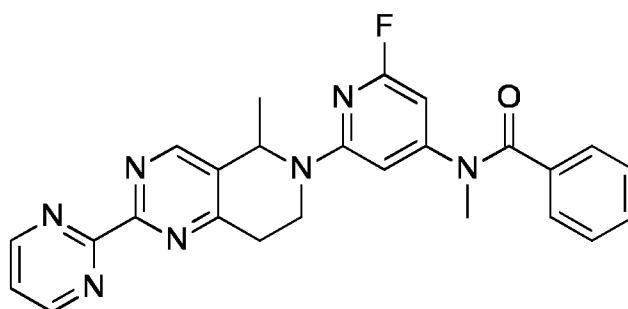
2-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]thiazinane 1,1-dioxide



To a solution of 6-(6-fluoro-4-iodo-2-pyridyl)-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine (the product of step 1 in Example 96, 100mg, 223 μmol) in dioxane (3mL) was added 1,2-thiazinane 1,1-dioxide (30.2 mg, 223 μmol), cesium carbonate (145 mg, 446 μmol), Xantphos (25.8 mg, 44.6 μmol) and $\text{Pd}(\text{OAc})_2$ (5.01 mg, 22.3 μmol). After being heated at 100 $^{\circ}\text{C}$ with stirring for 20 hrs under argon and cooled to rt, the resulting reaction mixture was filtered. The filtrate was concentrated *in vacuo*. The residue was purified by prep-HPLC to give 2-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]thiazinane 1,1-dioxide (15 mg) as a light yellow solid. ^1H NMR (400MHz, Methanol-*d*4) δ ppm: 9.06(d, 2H), 8.92 (s, 1H), 7.67 (t, 1H), 6.67 (s, 1H), 6.26 (s, 1H), 5.75-5.73 (m, 1H), 4.65 - 4.50 (m, 1H), 3.90-3.80 (m, 2H), 3.65 - 3.50 (m, 1H), 3.35 - 3.25 (m, 2H), 3.26 - 3.15 (m, 2H), 2.40 - 2.25 (m, 2H), 2.01 - 1.85 (m, 2H), 1.62 (d, 3H). MS obsd. (ESI^+) [(M+H) $^+$]: 456.

Example 163

N-[2-Fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-benzamide



To a solution of 2-fluoro-*N*-methyl-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)pyridin-4-amine (the product of step 1 in Example 154, 20 mg, 0.06 mmol) in DCM (0.5 mL) was added benzoylchloride (17.9 mg, 0.17 mmol) and DIPEA (22.07 mg, 0.17 mmol) at rt. The resulting mixture was stirred for 1 h at rt and diluted with MeOH (1 mL). The resulting mixture was concentrated *in vacuo*. The residue was purified by prep-HPLC to give *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]-*N*-methyl-benzamide (12 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: 9.03 (d, 2 H), 8.81 (s, 1 H), 7.64 (t, 1 H), 7.38 - 7.44 (m, 2 H), 7.26 - 7.37 (m, 2 H), 7.26 - 7.37 (m, 1 H), 6.36 (s, 1 H), 6.16 (s, 1 H), 5.45 (q, 1 H), 4.34 (m, 1 H), 3.49 (s, 3 H), 3.34 - 3.43 (m, 1 H), 2.90 - 3.10 (m, 2 H), 1.40 (d, 3 H). MS obsd. (ESI⁺) [(M+H)⁺] : 456.

BIOLOGICAL EXAMPLES

Example 164 materials and methods

HBV cell line

HepG2.2.15 cells (Acs et al. *Proc Natl Acad Sci U S A*, 84, (1987), 4641-4), a constitutively HBV-expressing cell line were cultured in DMEM+Glutamax-I medium (Invitrogen, Carlsbad, CA, USA), supplemented with 10% fetal bovine serum (Invitrogen) and G418 (Invitrogen) at a final concentration of 200 mg/L and maintained in 5% CO₂ at 37°C.

HBsAg Assay

HepG2.2.15 cells were seeded in duplicate into white, 96-well plates at 1.5 x 10⁴ cells/well. The cells were treated with a three-fold serial dilution series of the compounds in DMSO. The final DMSO concentration in all wells was 1% and DMSO was used as no drug control.

The HBsAg chemiluminescence immunoassay (CLIA) kit (Autobio Diagnostics Co., Zhengzhou, China, Catalog number: CL0310-2) was used to measure the levels of secreted HBV antigens semi-quantitatively. For the detection 50 µL/well culture supernatant was used and HBsAg was quantified using HBsAg chemiluminescence immunoassay (CLIA) kit (Autobio Diagnostics Co., Zhengzhou, China, Catalog number: CL0310-2), 50 µL of the supernatant was transferred to the CLIA assay plate and 50 µL of enzyme conjugate reagent was added into each well. The plates were sealed and gently agitated for 1 hour at room temperature. The supernatant-enzyme-mixture was discarded and wells were washed 6 times with 300 µL of PBS.

The residual liquid was removed by plating the CLIA plate right side down on absorbent tissue paper. 25 μ L of substrates A and B were added to each well. Luminance was measured using a luminometer (Mithras LB 940 Multimode Microplate Reader) after 10 minutes incubation. Dose-response curves were generated and the IC₅₀ value was extrapolated by using the E-WorkBook Suite (ID Business Solutions Ltd., Guildford, UK). The IC₅₀ was defined as the compound concentration (or conditioned media log dilution) at which HBsAg secretion was reduced by 50% compared to the no drug control.

The compounds according to formula I were tested for their capacity to inhibit HBsAg as described herein. The Examples were tested in the above assay and found to have IC₅₀ below 50 μ M. Particular compounds of formula I were found to have IC₅₀ below 0.50 μ M. More Particular compounds of formula I were found to have IC₅₀ below 0.100 μ M. Results of HBsAg assay are given in Table 1.

Table 1: Activity data in HBsAg assay

Example No.	IC ₅₀ (μ M)	Example No.	IC ₅₀ (μ M)	Example No.	IC ₅₀ (μ M)	Example No.	IC ₅₀ (μ M)
1	1.501	42	0.319	83	0.02	124	0.033
2	0.155	43	0.134	84	0.023	125	0.038
3	0.06	44	0.054	85	0.264	126	0.012
4	0.008	45	0.018	86	1.244	127	0.494
5	0.02	46	0.036	87	0.005	128	0.417
6	0.009	47	0.033	88	0.018	129	0.036
7	0.042	48	0.055	89	0.012	130	0.012
8	0.011	49	0.056	90	0.005	131	0.043
9	0.029	50	1.94	91	0.012	132	0.024
10	0.039	51	0.346	92	0.139	133	0.009
11	0.188	52	1.036	93	0.497	134	0.015
12	0.008	53	4.706	94	8.856	135	0.008
13	0.016	54	6.342	95	3.779	136	0.023
14	0.017	55	0.072	96	0.125	137	0.12
15	0.03	56	0.037	97	0.003	138	0.663
16	0.014	57	0.028	98	0.41	139	1.55
17	0.015	58	0.015	99	0.026	140	0.972
18	0.003	59	0.026	100	0.013	141	0.043
19	0.011	60	0.023	101	0.06	142	0.025

Example No.	IC ₅₀ (μM)	Example No.	IC ₅₀ (μM)	Example No.	IC ₅₀ (μM)	Example No.	IC ₅₀ (μM)
20	0.01	61	0.022	102	0.029	143	0.176
21	0.013	62	0.035	103	1.35	144	0.028
22	0.004	63	5.418	104	0.22	145	5.342
23	0.005	64	2.381	105	0.023	146	0.038
24	0.038	65	4.438	106	0.007	147	0.018
25	0.046	66	1.935	107	0.01	148	0.021
26	2.315	67	0.532	108	0.013	149	0.02
27	3.763	68	0.215	109	0.021	150	0.02
28	1.815	69	0.014	110	0.008	151	0.027
29	0.722	70	0.016	111	0.026	152	0.003
30	0.007	71	0.008	112	0.006	153	0.032
31	0.014	72	0.058	113	0.004	154	0.069
32	0.391	73	0.01	114	0.008	155	0.086
33	0.093	74	0.019	115	0.004	156	0.03
34	0.054	75	0.039	116	0.103	157	0.006
35	0.033	76	0.044	117	0.106	158	0.048
36	0.012	77	0.554	118	0.094	159	0.014
37	0.011	78	0.263	119	0.057	160	0.006
38	1.006	79	0.071	120	33.266	161	0.005
39	0.108	80	0.124	121	0.496	162	0.015
40	0.01	81	0.206	122	0.028	163	0.091
41	0.017	82	0.149	123	0.012		

HBV DNA assay

The assay employs real-time qPCR (TaqMan) to directly measure extracellular HBV DNA copy number in the cell supernatant. HepG2.2.15 cells were plated in 96-well microtiter plates before treatment with complete medium (DMEM, Glutamax, 10% FBS, 1% Penicillin/Streptomycin, 250 μg/mL Genetecin, final DMSO concentration is 1%). Only the interior wells were utilized to reduce “edge effects” observed during cell culture, the exterior wells were filled with complete medium to help minimize sample evaporation. The HepG2.2.15 cells were treated 1h later with various concentrations of a test compound in duplicate (top concentration used at 5 μM, 2 μM or 0.5 μM according to the HBsAg IC₅₀ observed, with 1/3 successive dilutions (total of 10 dilutions). Six days following the initial administration of the test compound, the cell culture supernatant was collected; DNA extraction was performed by

automated system (Magnapure) and then used in a real-time qPCR/TaqMan assay to determine HBV DNA copy numbers. Antiviral activity was calculated from the reduction in HBV DNA levels (IC_{50}).

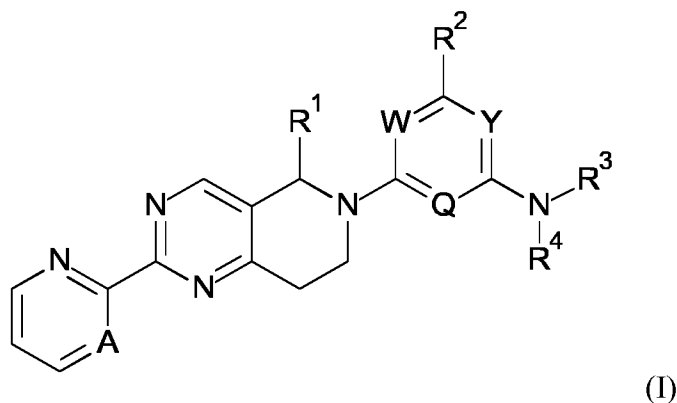
The compounds of the present invention were tested for their capacity to inhibit HBV DNA as described herein. The Examples were tested in the above assay and found to have IC_{50} below 50 μ M. Results of HBV DNA assay are given in Table 2.

Table 2: Anti HBV DNA production activity in HepG2.2.15 cells

Example No.	IC_{50} (nM)
20	0.15
90	1.1
97	1.9
112	0.6
115	3.2
123	0.43

Claims

1. A compound of formula I,



5 wherein

R^1 is aminoC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, C₁₋₆alkyl, C₃₋₇cycloalkyl, carboxyC₁₋₆alkyl, cyanoC₁₋₆alkyl, haloC₁₋₆alkyl, hydrogen or hydroxyC₁₋₆alkyl;

R^2 is C₁₋₆alkoxy, C₁₋₆alkyl, haloC₁₋₆alkoxy, haloC₁₋₆alkyl, halogen or hydrogen;

One of R^3 and R^4 is C₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkyl or hydrogen; the other one is 1,1-

10 dioxothianyl, aminocarbonylC₁₋₆alkyl, azetidiny, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonylazetidiny, C₁₋₆alkylsulfonylpiperidiny, C₁₋₆alkylsulfonyl, C₃₋₇cycloalkylcarbonyl, C₃₋₇cycloalkylsulfonyl, carboxyC₁₋₆alkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkylcarbonyl, phenylcarbonyl, phenylsulfonyl or tetrahydropyranyl; or

R^3 and R^4 together with the nitrogen to which they are attached form 1,1-dioxo-thiazolidiny;

15 1,1-dioxo-thiazinany; 2-oxa-6-azaspiro[3.3]heptany; 2-oxa-7-azaspiro[4.4]nonany; 3-oxa-8-azabicyclo[3.2.1]octany; 6-oxo-2-oxa-7-azaspiro[3.4]octany; azetidiny; oxoimidazolidiny; oxopyrrolidiny; substituted azetidiny; substituted morpholiny; substituted oxooxazolidiny; substituted oxopiperaziny; substituted oxopyrrolidiny; substituted piperaziny; substituted piperidiny or substituted pyrrolidiny; wherein said

20 substituted azetidiny, substituted morpholiny, substituted oxooxazolidiny, substituted oxopiperaziny, substituted oxopyrrolidiny, substituted piperaziny, substituted piperidiny and substituted pyrrolidiny are substituted with one, two or three substituents independently selected from aminocarbonyl, aminocarbonylC₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkylsulfonyl, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfonylamino, C₁₋

25

alkylsulfonylaminocarbonyl, carboxy, carboxyC₁₋₆alkyl, cyano, halogen, hydroxy and hydroxyC₁₋₆alkyl;

A is N or CH;

One of W, Q and Y is N, the others are CH;

- 5 with the proviso that *N*-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-4-pyridyl]methanesulfonamide and *N*-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5*H*-pyrido[4,3-*d*]pyrimidin-6-yl)-2-pyridyl]methanesulfonamide are excluded; or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

2. A compound according to claim 1, wherein

10 R¹ is C₁₋₆alkyl;

R² is halogen;

One of R³ and R⁴ is C₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkyl or hydrogen; the other one is 1,1-

dioxothianyl, aminocarbonylC₁₋₆alkyl, azetidiny, C₁₋₆alkylcarbonyl, C₁₋

alkylcarbonylazetidiny, C₁₋₆alkylsulfonylpiperidiny, C₁₋₆alkylsulfonyl, C₃₋

15 7cycloalkylcarbonyl, C₃₋₇cycloalkylsulfonyl, carboxyC₁₋₆alkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkylcarbonyl, phenylcarbonyl, phenylsulfonyl or tetrahydropyrany; or

R³ and R⁴ together with the nitrogen to which they are attached form 1,1-dioxo-thiazolidiny;

1,1-dioxo-thiazinany; 2-oxa-6-azaspiro[3.3]heptany; 2-oxa-7-azaspiro[4.4]nonany; 3-

oxa-8-azabicyclo[3.2.1]octany; 6-oxo-2-oxa-7-azaspiro[3.4]octany; azetidiny;

20 oxoimidazolidiny; oxopyrrolidiny; substituted azetidiny; substituted morpholin;

substituted oxooxazolidiny; substituted oxopiperazinyl; substituted oxopyrrolidiny;

substituted piperazinyl; substituted piperidiny or substituted pyrrolidiny; wherein said

substituted azetidiny, substituted morpholin, substituted oxooxazolidiny, substituted

oxopiperazinyl, substituted oxopyrrolidiny, substituted piperazinyl, substituted

25 piperidiny and substituted pyrrolidiny are substituted with one, two or three substituents

independently selected from aminocarbonyl, aminocarbonylC₁₋₆alkyl, C₁₋₆alkoxy, C₁₋

alkoxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkylsulfonyl, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, C₁₋

alkylcarbonylamino, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfonylamino, C₁₋

alkylsulfonylaminocarbonyl, carboxy, carboxyC₁₋₆alkyl, cyano, halogen, hydroxy and

30 hydroxyC₁₋₆alkyl;

A is N or CH;

One of W, Q and Y is N, the others are CH;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

3. A compound according to claim 1, wherein

R¹ is C₁₋₆alkyl;

R² is halogen;

One of R³ and R⁴ is C₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkyl or hydrogen; the other one is 1,1-

5 dioxothianyl, aminocarbonylC₁₋₆alkyl, azetidiny, C₁₋₆alkylcarbonylazetidiny, C₁₋₆alkylsulfonylpiperidiny, carboxyC₁₋₆alkyl, haloC₁₋₆alkyl, hydroxyC₁₋₆alkylcarbonyl, phenylcarbonyl, phenylsulfonyl or tetrahydropyrany; or

R³ and R⁴ together with the nitrogen to which they are attached form

2-oxa-6-azaspiro[3.3]heptany;

10 2-oxa-7-azaspiro[4.4]nonany;

3-oxa-8-azabicyclo[3.2.1]octany;

6-oxo-2-oxa-7-azaspiro[3.4]octany;

azetidiny substituted with one or two substituents independently selected from

15 aminocarbonyl, C₁₋₆alkoxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylsulfonylamino, C₁₋₆alkylsulfonylaminocarbonyl, carboxy, cyano, halogen, hydroxy and hydroxyC₁₋₆alkyl;

morpholinyl substituted with one or two substituents independently selected from

aminocarbonyl, C₁₋₆alkoxyC₁₋₆alkylcarboxy, carboxyC₁₋₆alkyl and hydroxyC₁₋₆alkyl;

oxopyrrolidinyl substituted with one or two substituents independently selected from

20 carboxy and hydroxyC₁₋₆alkyl;

piperazinyl substituted with one, two or three substituents independently selected from

aminocarbonylC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkylsulfonyl, carboxy and carboxyC₁₋₆alkyl;

piperidinyl substituted with one or two substituents independently selected from

25 aminocarbonyl, C₁₋₆alkylsulfonylamino, C₁₋₆alkylsulfonylaminocarbonyl and carboxy; or

pyrrolidinyl substituted with one, two or three substituents independently selected from

aminocarbonyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkylsulfonylaminocarbonyl, C₁₋₆alkyl, carboxy, halogen, hydroxy and hydroxyC₁₋₆alkyl;

A is N or CH;

30 One of W, Q and Y is N, the others are CH;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

4. A compound according to claim 1, wherein

R¹ is C₁₋₆alkyl;

R² is halogen;

One of R³ and R⁴ is C₃₋₇cycloalkylC₁₋₆alkyl, C₁₋₆alkyl or hydrogen; the other one is 1,1-dioxothianyl, aminocarbonylC₁₋₆alkyl, azetidiny, C₁₋₆alkylcarbonylazetidiny, C₁₋₆alkylsulfonylpiperidiny, carboxyC₁₋₆alkyl, hydroxyC₁₋₆alkylcarbonyl, phenylcarbonyl; 5 phenylsulfonyl or tetrahydropyrany; or

R³ and R⁴ together with the nitrogen to which they are attached form

2-oxa-6-azaspiro[3.3]heptany;

2-oxa-7-azaspiro[4.4]nonany;

3-oxa-8-azabicyclo[3.2.1]octany;

10 6-oxo-2-oxa-7-azaspiro[3.4]octany;

azetidiny substituted with one or two substituents independently selected from

aminocarbonyl, C₁₋₆alkoxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylsulfonylamino, C₁₋₆alkylsulfonylaminocarbonyl, carboxy, cyano, halogen, hydroxy and hydroxyC₁₋₆alkyl;

15 morpholiny substituted with one or two substituents independently selected from

aminocarbonyl, C₁₋₆alkoxyC₁₋₆alkyl, carboxy, carboxyC₁₋₆alkyl and hydroxyC₁₋₆alkyl;

oxopyrrolidiny substituted with one or two substituents independently selected from

carboxy and hydroxyC₁₋₆alkyl;

piperaziny substituted with one, two or three substituents independently selected from

20 aminocarbonylC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkylsulfonyl, carboxy and carboxyC₁₋₆alkyl;

piperidiny substituted with one or two substituents independently selected from

aminocarbonyl, C₁₋₆alkylsulfonylamino, C₁₋₆alkylsulfonylaminocarbonyl and carboxy; or

pyrrolidiny substituted with one, two or three substituents independently selected from

25 aminocarbonyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, carboxy, halogen, hydroxy and hydroxyC₁₋₆alkyl;

A is N;

One of W, Q and Y is N, the others are CH;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

30 5. A compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R¹ is methyl.

6. A compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R² is fluoro.

7. A compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R³ and R⁴ together with the nitrogen to which they are attached form 2-oxa-6-azaspiro[3.3]heptanyl; 2-oxa-7-azaspiro[4.4]nonanyl; azetidinyl substituted with one or two substituents independently selected from C₁₋₆alkoxy, halogen and hydroxyc₁₋₆alkyl; (C₁₋₆alkoxyc₁₋₆alkyl)morpholinyl; (C₁₋₆alkoxyc₁₋₆alkylsulfonyl)piperazinyl; (C₁₋₆alkylsulfonylamino)piperidinyl; or pyrrolidinyl substituted with one or two substituents independently selected from aminocarbonyl, C₁₋₆alkoxy, halogen, hydroxy and hydroxyc₁₋₆alkyl.

8. A compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R³ and R⁴ together with the nitrogen to which they are attached form 2-oxa-6-azaspiro[3.3]heptanyl; 2-oxa-7-azaspiro[4.4]nonanyl; azetidinyl substituted with one or two substituents independently selected from fluoro, hydroxymethyl and methoxy; (methoxymethyl)morpholinyl; (methoxyethylsulfonyl)piperazinyl; (methylsulfonylamino)piperidinyl; or pyrrolidinyl substituted with one or two substituents independently selected from aminocarbonyl, fluoro, hydroxy, hydroxymethyl and methoxy.

9. A compound according to claim 1, wherein

R¹ is C₁₋₆alkyl;

R² is halogen;

R³ and R⁴ together with the nitrogen to which they are attached form

azetidinyl substituted with one or two substituents independently selected from C₁₋₆alkoxy and halogen;

(C₁₋₆alkylsulfonylamino)-piperidinyl; or

pyrrolidinyl substituted with one or two substituents independently selected from C₁₋

₆alkoxy and halogen;

A is N;

One of W, Q and Y is N, the others are CH;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

10. A compound according to claim 1, wherein

R¹ is methyl;

R² is fluoro;

R³ and R⁴ together with the nitrogen to which they are attached form

azetidinyl substituted with one or two substituents independently selected from fluoro and methoxy;

(methylsulfonylamino)-piperidiny; or

5 pyrrolidinyl substituted with one or two substituents independently selected from methoxy and fluoro;

A is N;

One of W, Q and Y is N, the others are CH;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

10 11. A compound according to claim 1, selected from

6-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]hexanoic acid ;

6-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]amino]hexanoic acid;

15 N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-hydroxy-acetamide;

8-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-oxa-8-azabicyclo[3.2.1]octane;

20 8-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-3-oxa-8-azabicyclo[3.2.1]octane;

7-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-7-azaspiro[4.4]nonane;

7-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-7-azaspiro[4.4]nonane;

25 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-(methoxymethyl)morpholine;

4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-(methoxymethyl)morpholine;

30 6-[6-fluoro-4-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-fluoro-6-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-(3,3-difluoropyrrolidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-(3,3-difluoropyrrolidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

5 [4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholin-2-yl]methanol;

[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholin-2-yl]methanol;

10 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine-2-carboxylic acid;

4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholine-2-carboxylic acid;

2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholin-2-yl]acetic acid;

15 2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholin-2-yl]acetic acid;

[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-2-yl]methanol;

20 [1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidin-2-yl]methanol;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-2-carboxylic acid;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-2-carboxylic acid;

25 6-[6-fluoro-4-[2-(methoxymethyl)pyrrolidin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-fluoro-6-[2-(methoxymethyl)pyrrolidin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

30 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-3-ol;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidin-3-ol;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-3-carboxylic acid;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-3-carboxylic acid;

5 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-2-carboxamide;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-2-carboxamide;

10 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidine-3-carboxamide;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]pyrrolidine-3-carboxamide;

4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine-2-carboxamide;

15 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholine-2-carboxamide;

2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-N-tetrahydropyran-4-yl-pyridin-4-amine;

20 4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-N-tetrahydropyran-4-yl-pyridin-2-amine;

4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazine-2-carboxylic acid;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperidine-4-carboxylic acid;

25 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperidine-4-carboxylic acid;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidine-3-carboxylic acid;

30 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carboxylic acid;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperidine-4-carboxamide;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperidine-4-carboxamide;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-N-methylsulfonyl-azetidine-3-carboxamide;

5 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methylsulfonyl-azetidine-3-carboxamide;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-N-methylsulfonyl-piperidine-4-carboxamide;

10 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methylsulfonyl-piperidine-4-carboxamide;

N-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]benzenesulfonamide;

N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]benzenesulfonamide;

15 1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidine-3-carboxamide;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carboxamide;

20 6-[6-fluoro-4-[4-(2-methoxyethylsulfonyl)piperazin-1-yl]-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

N-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-piperidyl]methanesulfonamide;

N-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-4-piperidyl]methanesulfonamide;

25 2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]acetic acid;

2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]acetic acid;

30 2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-N-(1-methylsulfonyl-4-piperidyl)pyridin-4-amine;

2-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]acetamide;

2-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]acetamide;

3-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]propanamide;

5 3-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]propanamide;

6-[2-fluoro-6-(3-methoxypyrrolidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

10 6-[4-fluoro-6-(3-methoxyazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-fluoro-4-(3-methoxyazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

N-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]methanesulfonamide;

15 N-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]methanesulfonamide;

N-(azetidin-3-yl)-4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)pyridin-2-amine;

20 N-(azetidin-3-yl)-2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)pyridin-4-amine;

6-[4-fluoro-6-(3-fluoroazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-fluoro-4-(3-fluoroazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

25 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-ol;

6-[6-(3,3-difluoroazetidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

30 6-[4-(3,3-difluoroazetidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-6-azaspiro[3.3]heptane;

6-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-6-azaspiro[3.3]heptane;

N-[1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]acetamide;

5 N-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]acetamide;

[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidin-3-yl]methanol;

10 [1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]azetidin-3-yl]methanol;

5-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]pentanamide;

N-(1,1-dioxothian-4-yl)-2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)pyridin-4-amine;

15 1-[3-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]amino]azetidin-1-yl]ethanone;

1-[3-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]azetidin-1-yl]ethanone;

20 5-[[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-methyl-amino]pentanamide;

5-[[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-methyl-amino]pentanamide;

5-[cyclopropylmethyl-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]amino]pentanamide;

25 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]azetidine-3-carbonitrile;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-5-oxo-pyrrolidine-3-carboxylic acid;

30 6-[2-fluoro-6-(3-methoxyazetidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[2-(3,3-difluoroazetidin-1-yl)-6-fluoro-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[2-fluoro-6-(3-fluoroazetidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

7-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-oxa-7-azaspiro[3.4]octan-6-one;

5 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-(hydroxymethyl)pyrrolidin-2-one;

6-[6-fluoro-4-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-oxa-6-azaspiro[3.3]heptane;

10 N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-benzenesulfonamide; and

N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-benzamide;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

15 12. A compound according to claim 1, selected from

6-[6-fluoro-4-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-(3,3-difluoropyrrolidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

20 6-[6-(3,3-difluoropyrrolidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

N-[1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-piperidyl]methanesulfonamide;

25 6-[2-fluoro-6-(3-methoxypyrrolidin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-fluoro-4-(3-methoxyazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-fluoro-4-(3-fluoroazetidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine; and

30 6-[4-(3,3-difluoroazetidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

13. A compound according to claim 1, wherein

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R¹ is C₁₋₆alkyl;

R² is halogen;

One of R³ and R⁴ is hydrogen; the other one is haloC₁₋₆alkyl; or

R³ and R⁴ together with the nitrogen to which they are attached form aminocarbonylpiperidinyl,

5 aminocarbonylpyrrolidinyl, C₁₋₆alkylsulfonylaminocarbonylpyrrolidinyl, C₁₋₆alkoxy-
pyrrolidinyl, carboxypyrrolidinyl or hydroxypyrrolidinyl;

A is CH;

One of W and Q is N, the other one is CH;

Y is CH;

10 or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

14. A compound according to any one of claims 1, 2, 3 and 13, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R¹ is methyl.

15. A compound according to any one of claims 1, 2, 3, 13 and 14, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R² is fluoro.

15 16. A compound according to any one of claims 1, 2, 3 and 13 to 15, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R³ and R⁴ together with the nitrogen to which they are attached form aminocarbonylpiperidinyl, hydroxypyrrolidinyl or C₁₋₆alkoxy-
pyrrolidinyl.

17. A compound according to any one of claims 1 to 3 and 13 to 16, or a pharmaceutically
20 acceptable salt, or enantiomer, or diastereomer thereof, wherein R³ and R⁴ together with the nitrogen to which they are attached form aminocarbonylpiperidinyl, hydroxypyrrolidinyl or methoxypyrrolidinyl.

18. A compound according to claim 1, selected from

1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-
25 pyridyl]pyrrolidin-3-ol;

1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-
pyridyl]pyrrolidin-3-ol;

1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-
pyridyl]pyrrolidine-3-carboxamide;

1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidine-3-carboxamide;

1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]pyrrolidine-3-carboxylic acid;

5 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]pyrrolidine-3-carboxylic acid;

1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperidine-4-carboxamide;

10 1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperidine-4-carboxamide;

1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperidine-3-carboxamide;

1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperidine-3-carboxamide;

15 N-(2,2-difluoroethyl)-2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]pyridin-2-amine;

N-(2,2-difluoroethyl)-4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]pyridin-2-amine;

20 6-[6-fluoro-4-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-fluoro-6-(3-methoxypyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

1-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]-N-methylsulfonyl-pyrrolidine-3-carboxamide; and

25 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]-N-methylsulfonyl-pyrrolidine-3-carboxamide;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

19. A compound according to claim 1, is

30 1-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperidine-4-carboxamide; or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

20. A compound according to claim 1, wherein

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R¹ is C₁₋₆alkyl;

R² is halogen;

One of R³ and R⁴ is C₁₋₆alkyl; the other one is C₁₋₆alkylcarbonyl, C₁₋₆alkylsulfonyl, C₃₋₇cycloalkylcarbonyl or C₃₋₇cycloalkylsulfonyl; or

- 5 R³ and R⁴ together with the nitrogen to which they are attached form
 1,1-dioxo-thiazolidinyl;
 1,1-dioxo-thiazinanyl;
 azetidinyll;
 morpholinyl substituted once or twice by C₁₋₆alkyl;
- 10 oxoimidazolidinyl;
 diC₁₋₆alkyl-oxooxazolidinyl;
 oxopiperazinyl substituted with one or two substituents independently selected from C₁₋₆alkyl, C₁₋₆alkylcarbonyl and C₁₋₆alkylsulfonyl;
 oxopyrrolidinyl;
- 15 C₁₋₆alkyloxopyrrolidinyl;
 piperazinyl substituted with one, two or three substituents independently selected from C₁₋₆alkyl, C₁₋₆alkylcarbonyl and C₁₋₆alkylsulfonyl; or
 pyrrolidinyl substituted with one, two or three substituents independently selected from C₁₋₆alkyl and carboxy;
- 20 A is N or CH;
 One of W, Q and Y is N, the others are CH;
 or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.
21. A compound according to any one of claims 1, 2 and 20, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R¹ is methyl.
- 25 22. A compound according to any one of claims 1, 2, 20 and 21, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R² is fluoro.
23. A compound according to any one of claims 1, 2 and 20 to 22, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R³ and R⁴ together with the nitrogen to which they are attached form azetidinyll; morpholinyl substituted once or twice by C₁₋₆alkyl; C₁₋₆alkyloxopiperazinyl; C₁₋₆alkyloxopyrrolidinyl; piperazinyl substituted with one, two or three substituents independently selected from C₁₋₆alkyl, C₁₋₆alkylcarbonyl and C₁₋₆alkylsulfonyl; or C₁₋₆alkylpyrrolidinyl.
- 30

24. A compound according to any one of claims 1, 2 and 20 to 23, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein R³ and R⁴ together with the nitrogen to which they are attached form azetidiny; methylmorpholinyl; ethylmorpholinyl; dimethylmorpholinyl; methyloxopiperazinyl; methyloxopyrrolidinyl; piperazinyl substituted with one, two or three substituents independently selected from acetyl, ethylsulfonyl, methyl and methylsulfonyl; or methylpyrrolidinyl.

25. A compound according to any one of claims 1, 2 and 20 to 24, or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof, wherein A is N.

26. A compound according to claim 1, wherein

R¹ is C₁₋₆alkyl;

R² is halogen;

R³ and R⁴ together with the nitrogen to which they are attached form

piperazinyl substituted with one, two or three substituents independently selected from C₁₋₆alkyl, C₁₋₆alkylcarbonyl and C₁₋₆alkylsulfonyl;

A is N or CH;

One of W, Q and Y is N, the others are CH;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

27. A compound according to claim 1, wherein

R¹ is methyl;

R² is fluoro;

piperazinyl substituted with one, two or three substituents independently selected from acetyl, ethylsulfonyl, methyl and methylsulfonyl;

A is N or CH;

One of W, Q and Y is N, the others are CH;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

28. A compound according to claim 1, selected from

4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2-methyl-morpholine;

4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2-methyl-morpholine;

2-ethyl-4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]morpholine;

5 2-ethyl-4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]morpholine;

4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-2,2-dimethyl-morpholine;

10 4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-2,2-dimethyl-morpholine;

1-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]ethanone;

1-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]ethanone;

15 6-[6-fluoro-4-(3-methylpyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-fluoro-6-(3-methylpyrrolidin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

20 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-methyl-morpholine;

4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-3-methyl-morpholine;

6-[4-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

25 6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

1-[4-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperazin-1-yl]ethanone;

30 1-[4-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperazin-1-yl]ethanone;

6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-(4-ethylsulfonylpiperazin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

5 6-[6-(4-ethylsulfonylpiperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

1-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-4,4-dimethyl-pyrrolidine-3-carboxylic acid;

10 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4,4-dimethyl-pyrrolidine-3-carboxylic acid;

(5R)-6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

(5S)-6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

15 6-[6-(3,3-dimethyl-4-methylsulfonyl-piperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-(3,3-dimethyl-4-methylsulfonyl-piperazin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

20 6-[4-fluoro-6-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-fluoro-4-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[2-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

25 6-[6-(azetidin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[4-(azetidin-1-yl)-6-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

30 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]pyrrolidin-2-one;

3-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-5,5-dimethyl-oxazolidin-2-one;

2-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-1,2-thiazolidine 1,1-dioxide;

4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-3-methyl-piperazin-2-one;

5 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-methyl-piperazin-2-one;

4-acetyl-1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-2-one;

10 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-4-methylsulfonyl-piperazin-2-one;

4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]-6-methyl-piperazin-2-one;

4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-6-methyl-piperazin-2-one;

15 4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-1,4-thiazinane 1,1-dioxide;

6-[2-(azetidin-1-yl)-6-fluoro-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

20 1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-3-methyl-pyrrolidin-2-one;

N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-acetamide;

N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-propanamide;

25 N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-cyclopropanecarboxamide;

1-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]imidazolidin-2-one;

30 N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-methanesulfonamide;

N-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]-N-methyl-cyclopropanesulfonamide; and

2-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]thiazinane 1,1-dioxide;

or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

29. A compound according to claim 1, selected from

5 1-[4-[2-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-4-pyridyl]piperazin-1-yl]ethanone;

1-[4-[4-fluoro-6-(5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-2-pyridyl]piperazin-1-yl]ethanone;

10 6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

1-[4-[2-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-4-pyridyl]piperazin-1-yl]ethanone;

1-[4-[4-fluoro-6-[5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl]-2-pyridyl]piperazin-1-yl]ethanone;

15 6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-(2-pyridyl)-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

6-[6-(4-ethylsulfonylpiperazin-1-yl)-4-fluoro-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

(5R)-6-[6-fluoro-4-(4-methylsulfonylpiperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

20 6-[6-fluoro-4-(3-methyl-4-methylsulfonyl-piperazin-1-yl)-2-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine; and

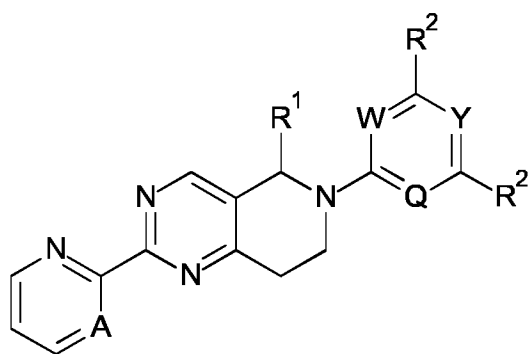
6-[2-fluoro-6-(4-methylsulfonylpiperazin-1-yl)-4-pyridyl]-5-methyl-2-pyrimidin-2-yl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine;

25 or a pharmaceutically acceptable salt, or enantiomer, or diastereomer thereof.

30. A process for the preparation of a compound according to any one of claims 1 to 29 comprising

(a) coupling of a compound of formula (A)

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(A)

with a compound of formula (B)

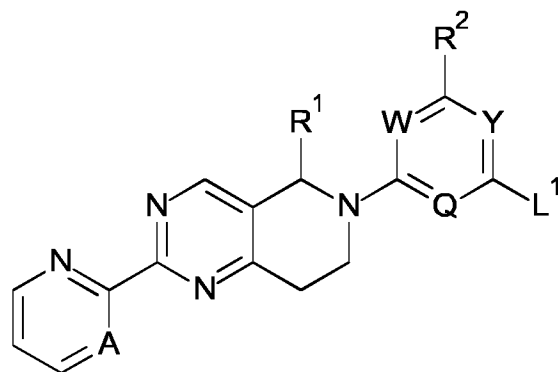
NHR^3R^4 (B)

in the presence of a base;

- 5 wherein R^1 , R^3 and R^4 , A, U, W, Q and Y are defined as in any one of claims 1 to 29;
 R^2 is F, Cl or Br;

or

(b) coupling of a compound of formula (C)



(C)

- 10 with a compound of formula (B)

NHR^3R^4 (B)

in the presence of a catalyst, a ligand and a base;

wherein R^1 to R^4 , A, U, W, Q and Y are defined as in any one of claims 1 to 29; L^1 is Cl, Br or I.

- 15 31. A compound according to any one of claims 1 to 29 for use as therapeutically active substance.

32. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 29 and a therapeutically inert carrier.

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33. The use of a compound according to any one of claims 1 to 29 for the treatment or prophylaxis of HBV infection.

34. The use of a compound according to any one of claims 1 to 29 for the preparation of a medicament for the treatment or prophylaxis of HBV infection.

5 35. The use of a compound according to any one of claims 1 to 29 for the inhibition of HBsAg production or secretion, or for the inhibition of HBV DNA production.

36. A compound according to any one of claims 1 to 29 for the treatment or prophylaxis of HBV infection.

10 37. A compound according to any one of claims 1 to 29, when manufactured according to a process of claim 30.

38. A method for the treatment or prophylaxis of HBV infection, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 29.

39. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/065690

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D519/00 A61K31/519 A61P31/20
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHANG-AN GENG ET AL: "Small-molecule inhibitors for the treatment of hepatitis B virus documented in patents", MINI REVIEWS IN MEDICINAL CHEMISTRY, vol. 13, no. 5, 2013, pages 749-776, XP009176654, ISSN: 1389-5575, DOI: 10.2174/1389557511313050012 the whole document	1-39
A	WO 2006/035061 A1 (TIBOTEC PHARM LTD [IE]) 6 April 2006 (2006-04-06) the whole document claims 1-3; compounds 22-25,30 ----- -/-	1-39



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

17 July 2017

Date of mailing of the international search report

31/07/2017

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2017/065690

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2016/177655 A1 (F HOFFMANN-LA ROCHE AG [CH]; HOFFMANN-LA ROCHE INC [US]) 10 November 2016 (2016-11-10)	1,2,5,6, 14,15, 20-25, 30-39
A,P	the whole document especially examples 211 and 212; claims 1-32; examples 196-225	3,4, 7-13, 16-19, 26-29
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/065690

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