

PYRIMIDINONE DERIVATIVES AS ANTIMALARIAL AGENTS

The present invention relates to pyrimidinone derivatives, and to the preparation
5 and therapeutic use thereof.

Malaria is one of the prime causes of infection-mediated mortality worldwide. Infection with the parasite of the type *Plasmodium falciparum* affects close to 225 million people, causes more than 781 000 deaths annually and predominantly concerns
10 children under 5 years old. The substantial return of the disease observed in recent years is due to several factors, including:

- the vectors, namely anopheles, which become resistant to the standard cheap insecticides,
- the increase in the population in the at-risk zones and, mainly,
- 15 - the resistance of numerous strains of *Plasmodium falciparum*, the parasite responsible for the mortal forms of the disease, to the medicaments conventionally used, such as chloroquine and mefloquine. Since 2001, artemisinin and derivatives thereof have been considered by the World Health Organization as the treatment of choice for *Plasmodium falciparum*-mediated uncomplicated malaria. However, clear
20 signs of development of resistance to artemisinins have been observed.

The propagation of resistance among *Plasmodium* strains, in particular *P. falciparum*, towards the majority of the antimalarial drugs demonstrates the urgent need to develop novel compounds having a novel mode of action thus enabling a
25 decrease of the risk of cross-resistance. Human kinases are valid targets in the treatment of numerous pathologies and the kinome of *P. falciparum* has been proposed as a reservoir of novel targets for the development of novel medicaments, which have not yet been explored in the treatment of malaria (Doerig and Meijer (2007) Expert Opin. Ther. Targets 11, 279-290).

30 The kinome of *Plasmodium falciparum* is composed of 64 kinases, some of which are orthologous to human kinases (Ward et al. (2004) BMC Genomics 5,79). Following this orthologous approach, a group of CF₃-pyrimidinone derivatives, which are active on human phosphatidylinositol-3-kinases, has been identified as being parasite growth inhibitors in human erythrocytes. Moreover, a plasmodial
35 phosphatidylinositol-3-kinase, known as PfPI3K, has recently been identified, and the existence of a relationship between this kinase and human phosphatidylinositol kinases

has been demonstrated (Vaid et al. (2010) Blood 115, 2500-2507). PfPI3K intervenes in the mechanism of endocytosis and in trafficking the host hemoglobin and as such plays an important role in maintaining the parasite growth in the infected human erythrocyte. It might thus be thereby deduced that the plasmodial kinase PfPI3K would be a target for the compounds of the present invention.

Human PI3Ks play a major role in signaling and traffic in human cells (Engelman et al. (2006) Nature Rev. Genetics 7, 606-619). The PI3K/Akt/mTOR signaling mechanism is an essential regulator of cell life, cell proliferation and protein synthesis. The insulin signaling pathway via the PI3K/Akt axis involving class 1A of PI3Ks (PI3K α and β) is essential in glucose homeostasis. Downstream attenuation of insulin receptor signaling plays an important role in the development of type-2 diabetes. The other isoforms of class I PI3K, PI3K γ and PI3K δ , are involved in the immune function and inflammation (Ihle and Povis (2010) Current Opinion in Drug Discovery & Development 13, 41-49). Inhibition of PI3K α or PI3K β in mice results in embryonic lethality (Bi et al. (1999) J. Biol. Chem. 274, 10963-10968; Bi et al. (2002) Mamm Genome 13, 169-172). Moreover, mice showing a deficiency in PI3K γ or PI3K δ show deficiencies in immune functions (Okkenhaug et al. (2002) Science 297, 1031-1034). A summary of the potential and observable side effects of PI3K inhibition may be found in the articles by Cully et al. ((2006) Nature Rev. 6, 184-192) and Ihle and Powis ((2009) Mol. Cancer Ther. 8, 1-9).

Inhibition of class III PI3K, PIK3C3/VPS34, may also give rise to adverse side effects such as rapid neuron degeneration in mice following the conditional suppression of VPS34 in the sensory neurons (Zhou et al. (2010) PNAS 107, 9424-9429).

In summary, non-limiting examples that may be mentioned of potential side effects due to PI3K inhibition in man include metabolic disturbances associated with inhibition of insulin signaling with an increase of blood glucose, reduction of insulin sensitivity, diabetes, deregulation of the cerebral functions with the potential for inducing symptoms of schizophrenia and of Parkinson's disease, and neurodegeneration, and also immunosuppression. It should also be noted that nausea, diarrhea, tiredness, vomiting, skin eruptions and liver damage have been observed during clinical studies with inhibitors of the PI3K/mTOR axis.

On the basis of these observations, it is obvious that inhibiting human PI3K lipid kinases may have highly undesirable effects and should be avoided when the lipid kinome of *Plasmodium* is targeted for the treatment of malaria.

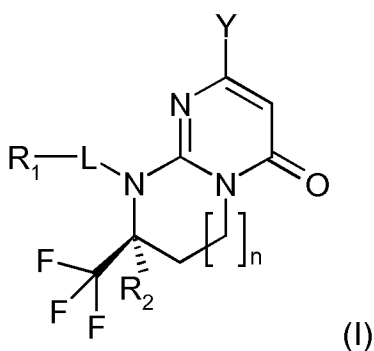
CF₃-pyrimidinone derivatives have been described in patent applications WO 2011/001112 and WO 2011/001113 for the preparation of medicaments for treating various cancers and also for treating parasitic diseases such as malaria. These compounds are described as inhibitors of human PI3Ks.

5 The compounds of the present invention have the advantage, although being derived from inhibitors of human PI3K and in particular PI3K α , they do not inhibit this class of human kinases, while nonetheless remaining inhibitors of parasite growth.

10 Similar kinomes are present in all species of *Plasmodium*, such as *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. The compounds of the invention may thus be useful in the treatment of malaria induced by all the parasites mentioned above. In addition, the kinases are found in other parasites, such as *Trypanosoma* (for example *T. brucei*, *T. cruzi*) and *Leishmania* (for example *L. major*, *L. donovani*). The compounds of the invention may thus be used in the treatment of
15 sleeping sickness, Chagas disease, the various forms of leishmaniasis and other parasitic infections.

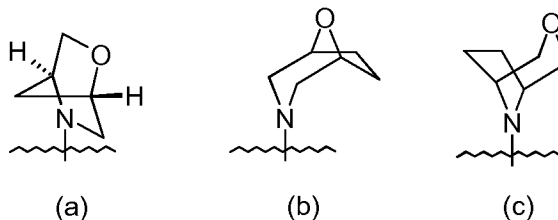
Other parasites, such as schistosomes, toxoplasms and *Eimeria*, also use kinases for their cell regulation. Consequently, the compounds of the present invention may be useful in the treatment of schistosomiasis (bilharzia), toxoplasmosis and
20 coccidiosis.

The present invention relates to compounds corresponding to formula (I):



in which:

- n represents 0 or 1;
- Y represents a bridged morpholine chosen from



➤ L represents a linker $-\text{CH}_2\text{CO}-$ such that the carbonyl function is attached to the substituent R_1 , or a $(\text{C}_1\text{-C}_2)$ alkyl, said alkyl being optionally substituted with one or more substituents chosen from a $(\text{C}_1\text{-C}_3)$ alkyl group and a hydroxyl group;

➤ R_1 represents:

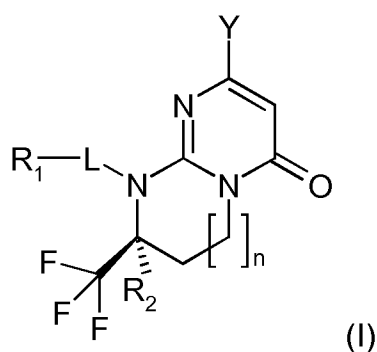
- a linear, branched, cyclic or partially cyclic $(\text{C}_1\text{-C}_5)$ alkyl group, optionally substituted with one or more substituents chosen from a hydroxyl group, an aryl group, a trifluoromethyl group and a $(\text{C}_3\text{-C}_5)$ cycloalkyl group,
- a $(\text{C}_3\text{-C}_6)$ cycloalkyl group, optionally substituted with a hydroxyl group,
- an aryl group, optionally substituted with one or more substituents chosen from a halogen atom, a hydroxyl group, a cyano group, an $-\text{NH}_2$ group, a urea group of formula $-\text{NH}\text{CO}\text{NH}(\text{C}_1\text{-C}_4)\text{alkyl}$, a morpholine group, a group of formula $-\text{SO}_2(\text{C}_1\text{-C}_5)\text{alkyl}$, a $(\text{C}_1\text{-C}_5)$ alkoxy group, said alkoxy being optionally substituted with one or more substituents chosen from:
 - a halogen atom,
 - a hydroxyl group or a $(\text{C}_1\text{-C}_5)$ alkoxy group,
 - a group $-\text{COR}_3$, in which R_3 represents a substituent chosen from a heterocycloalkyl group and a hydroxyl group,
 - a group $-\text{CONR}_4\text{R}_4'$ in which R_4 and R_4' are as defined below,
 - a group $-\text{NR}_4\text{R}_4'$ in which R_4 and R_4' are as defined below,
 - a heterocycloalkyl group comprising one or two heteroelements chosen from a nitrogen atom and an oxygen atom,
 - a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a $(\text{C}_1\text{-C}_3)$ alkyl group, a hydroxyl group and an $-\text{NH}_2$ group;
- a heteroaryl group, comprising one or more heteroatoms chosen from a nitrogen atom, a sulfur atom and an oxygen atom, optionally substituted with one or more substituents chosen from:
 - a halogen atom,
 - a $(\text{C}_1\text{-C}_3)$ alkyl group optionally substituted with one or more halogen atoms,

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- a (C₁-C₅)alkoxy group, optionally substituted with one or more substituents chosen from a halogen atom, a (C₃-C₅)cycloalkyl group, a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group,
 - a group -NR₅R_{5'} in which R₅ and R_{5'}, independently, which may be identical or different, represent a substituent chosen from a hydrogen atom, a -CO₂-(C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group and a linear or branched (C₁-C₃)alkyl group, said alkyl group being optionally substituted with one or more hydroxyl groups,
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- a pyridine group bearing two linked adjacent groups forming, together with the two carbons that bear them, a heterocycle comprising a nitrogen atom and an oxygen atom,
 - a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group, an acetyl group and a -CO₂-(C₁-C₄)alkyl group,
 - a group -NR₆R_{6'} in which R₆ and R_{6'}, which are different, represent a (C₁-C₅)alkyl group and a (C₁-C₅)alkoxy group,
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- R₂ represents a hydrogen atom when n represents 1 and a methyl group when n represents 0;
 - R₄ and R_{4'}, independently, which may be identical or different, represent a hydrogen atom or a (C₁-C₃)alkyl group,
- in the form of the base or of an addition salt with an acid or with a base.
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- The compounds of formula (I) can comprise one or more asymmetric carbon atoms. They can therefore exist in the form of enantiomers or diastereoisomers. These enantiomers, diastereoisomers and also mixtures thereof, including racemic mixtures, are part of the invention.
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- The compounds of formula (I) may exist in the form of bases or salified with acids or bases, especially pharmaceutically acceptable acids or bases. Such addition salts are part of the invention.
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- These salts are prepared with pharmaceutically acceptable acids, but salts of other acids that are of use, for example, for purifying or isolating the compounds of formula (I) also form part of the invention. In particular, use will be made in the context of the invention of the hydrogen chloride salt.

In the context of the present invention, and unless otherwise mentioned in the text:

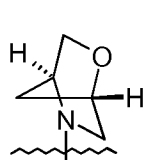
- a halogen atom: a fluorine atom, a chlorine atom, a bromine atom or an iodine atom; in particular, the halogen atom is a fluorine atom;
- an alkyl group: unless otherwise mentioned in the text, a linear or branched saturated aliphatic group containing from 1 to 5 carbons. Examples that may be mentioned include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl and pentyl groups;
- a partially cyclic (C₁-C₅)alkyl group: unless otherwise mentioned in the text, a linear saturated aliphatic group substituted with a (C₃-C₄)cycloalkyl group. Examples that may be mentioned include methylcyclopropyl, methylcyclobutyl and ethylcyclopropyl groups;
- a cycloalkyl group: a cyclic (C₃-C₆)alkyl group. Examples that may be mentioned include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups;
- an alkoxy group: a radical -O-alkyl in which the alkyl group is as defined previously, in particular the alkyl group is a methyl or ethyl;
- an aryl group: a cyclic aromatic group comprising between 5 and 6 carbon atoms. An example of an aryl group that may be mentioned is the phenyl group;
- a heteroaryl group: a monocyclic or bicyclic aromatic group comprising between 2 and 9 carbon atoms and comprising between 1 and 4 heteroatoms, such as nitrogen, oxygen or sulfur. In particular, the bicyclic aromatic groups comprise a phenyl group. Examples of monocyclic heteroaryl groups that may be mentioned include imidazolyl, pyrimidyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrazolyl, oxazolyl and 1,2,4-oxadiazolyl groups. Examples of bicyclic heteroaryl groups that may be mentioned include 1H-indazolyl, benzo[1,2,3]thiadiazolyl, benzo[1,2,5]thiadiazolyl, benzothiophenyl, imidazo[1,2-a]pyridyl, quinolinyl and isoquinolinyl groups;
- a heterocycloalkyl: a monocyclic or bicyclic alkyl group comprising from 4 to 8 atoms, 1 or 2 of which are heteroatoms, chosen from an oxygen atom and a nitrogen atom. Examples of monocyclic heterocycloalkyl groups that may especially be mentioned include piperidyl, morpholinyl and tetrahydropyranyl groups, and examples of bicyclic heterocycloalkyl groups that may be mentioned include groups of bridged morpholine type: 8-oxa-3-azabicyclo[3.2.1]oct-3-yl, 3-oxa-8-azabicyclo[3.2.1]oct-8-yl.

Among the compounds of the invention, mention may be made of a first subgroup of compounds corresponding to formula (I):

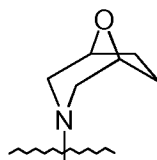


in which:

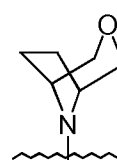
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- n represents 0 or 1, and/or
 - Y represents a bridged morpholine chosen from



(a)



(b)



(c)

10 and/or

➤ L represents a linker $-\text{CH}_2\text{CO}-$ such that the carbonyl function is attached to the substituent R_1 , or a $(\text{C}_1\text{-C}_2)$ alkyl, said alkyl being optionally substituted with one or more substituents chosen from a $(\text{C}_1\text{-C}_3)$ alkyl group and a hydroxyl group, and/or

➤ R_1 represents:

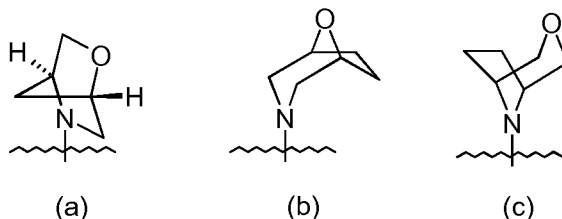
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- a linear, branched, cyclic or partially cyclic $(\text{C}_1\text{-C}_5)$ alkyl group, optionally substituted with one or more substituents chosen from a hydroxyl group, an aryl group, a trifluoromethyl group and a $(\text{C}_3\text{-C}_5)$ cycloalkyl group,
 - a $(\text{C}_3\text{-C}_6)$ cycloalkyl group, optionally substituted with a hydroxyl group,
 - an aryl group, optionally substituted with one or more substituents chosen from
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- a halogen atom, a hydroxyl group, a cyano group, an $-\text{NH}_2$ group, a urea group of formula $-\text{NH-CO-NH-}(\text{C}_1\text{-C}_4)$ alkyl, a morpholine group, a group of formula $-\text{SO}_2\text{-(C}_1\text{-C}_5)$ alkyl, a $(\text{C}_1\text{-C}_5)$ alkoxy group, said alkoxy being optionally substituted with one or more substituents chosen from:
 - a halogen atom,
 - a hydroxyl group or a $(\text{C}_1\text{-C}_5)$ alkoxy group,
 - a group $-\text{COR}_3$, in which R_3 represents a substituent chosen from a
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- heterocycloalkyl group and a hydroxyl group,
- a group $-\text{CONR}_4\text{R}_{4'}$ in which R_4 and $\text{R}_{4'}$ are as defined below,
 - a group $-\text{NR}_4\text{R}_{4'}$ in which R_4 and $\text{R}_{4'}$ are as defined below,
 - a heterocycloalkyl group comprising one or two heteroelements chosen from a nitrogen atom and an oxygen atom,
 - a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a $(\text{C}_1\text{-C}_3)$ alkyl group, a hydroxyl group and an $-\text{NH}_2$ group;
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- a heteroaryl group, comprising one or more heteroatoms chosen from a nitrogen atom, a sulfur atom and an oxygen atom, optionally substituted with one or more substituents chosen from:
 - a halogen atom,
 - a $(\text{C}_1\text{-C}_3)$ alkyl group optionally substituted with one or more halogen atoms,
 - a $(\text{C}_1\text{-C}_5)$ alkoxy group, optionally substituted with one or more substituents chosen from a halogen atom, a $(\text{C}_3\text{-C}_5)$ cycloalkyl group, a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a $(\text{C}_1\text{-C}_3)$ alkyl group, a hydroxyl group and an $-\text{NH}_2$ group,
 - a group $-\text{NR}_5\text{R}_5$ in which R_5 and R_5 , independently, which may be identical or different, represent a substituent chosen from a hydrogen atom, a $-\text{CO}_2\text{-(C}_1\text{-C}_3)$ alkyl group, a $(\text{C}_3\text{-C}_5)$ cycloalkyl group and a linear or branched $(\text{C}_1\text{-C}_3)$ alkyl group, said alkyl group being optionally substituted with one or more hydroxyl groups,
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- a pyridine group bearing two linked adjacent groups forming, together with the two carbons that bear them, a heterocycle comprising a nitrogen atom and an oxygen atom,
 - a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group, an acetyl group and a $-\text{CO}_2\text{-(C}_1\text{-C}_4)$ alkyl group,
 - a group $-\text{NR}_6\text{R}_{6'}$ in which R_6 and $\text{R}_{6'}$, which are different, represent a $(\text{C}_1\text{-C}_5)$ alkyl group and a $(\text{C}_1\text{-C}_5)$ alkoxy group, and/or
 - R_2 represents a hydrogen atom when n represents 1 and a methyl group when n represents 0, and/or
 - R_4 and $\text{R}_{4'}$, independently, which may be identical or different, represent a
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hydrogen atom or a (C₁-C₃)alkyl group,
in the form of the base or of an addition salt with an acid or with a base.

5 Among the compounds of the present invention, mention may be made of a second subgroup of compounds of formula (I) in which:

- n represents 0 or 1;
- Y represents a bridged morpholine chosen from



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➤ L represents a linker -CH₂-CO- such that the carbonyl function is attached to the substituent R₁, or a (C₁-C₂)alkyl, said alkyl being optionally substituted with one or more substituents chosen from a (C₁-C₃)alkyl group and a hydroxyl group;

➤ R₁ represents:

- a linear or branched (C₁-C₅) alkyl group, optionally substituted with one or more substituents chosen from a hydroxyl group and an aryl group,
- a group (C₃-C₆)cycloalkyl,
- an aryl group, optionally substituted with one or more substituents chosen from a halogen atom, a hydroxyl group, a cyano group, an -NH₂ group, a urea group of formula -NH-CO-NH-(C₁-C₄)alkyl, a morpholine group, a group of formula -SO₂-(C₁-C₅)alkyl, a (C₁-C₅)alkoxy group, said alkoxy being optionally substituted with one or more substituents chosen from:

- a halogen atom,
- a hydroxyl group or a (C₁-C₅)alkoxy group,
- a group -COR₃, in which R₃ represents a substituent chosen from a heterocycloalkyl group and a hydroxyl group,
- a group -CONR₄R_{4'} in which R₄ and R_{4'} are as defined below,
- a group -NR₄R_{4'} in which R₄ and R_{4'} are as defined below,
- a heterocycloalkyl group comprising one or two heteroelements chosen from a nitrogen atom and an oxygen atom,

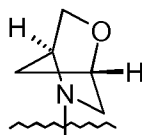
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- a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group,
 - a heteroaryl group, comprising one or more heteroatoms chosen from a nitrogen atom, a sulfur atom and an oxygen atom, optionally substituted with one or more substituents chosen from:
 - a halogen atom,
 - a (C₁-C₃)alkyl group optionally substituted with one or more halogen atoms,
 - a (C₁-C₅)alkoxy group, optionally substituted with one or more substituents chosen from a halogen atom, a (C₃-C₅)cycloalkyl group, a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group,
 - a group -NR₅R_{5'} in which R₅ and R_{5'}, independently, which may be identical or different, represent a substituent chosen from a hydrogen atom, a -CO₂-(C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group and a linear or branched (C₁-C₃)alkyl group, said alkyl group being optionally substituted with one or more hydroxyl groups,
 - a pyridine group bearing two linked adjacent groups forming, together with the two carbons that bear them, a heterocycle comprising a nitrogen atom and an oxygen atom,
 - a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group and an acetyl group,
 - a group -NR₆R_{6'} in which R₆ and R_{6'}, which are different, represent a (C₁-C₅)alkyl group and a (C₁-C₅)alkoxy group,
 - R₂ represents a hydrogen atom when n represents 1 and a methyl group when n represents 0;
 - R₄ and R_{4'}, independently, which may be identical or different, represent a hydrogen atom or a (C₁-C₃)alkyl group,
- in the form of the base or of an addition salt with an acid or with a base.

Among the compounds of the present invention, mention may be made of a third subgroup of compounds of formula (I) in which:

- n represents 0 or 1;

- Y represents a bridged morpholine (a)



(a)

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➤ L represents a linker $-\text{CH}_2\text{-CO}-$ such that the carbonyl function is attached to the substituent R_1 , or $(\text{C}_1\text{-C}_2)\text{alkyl}$, said alkyl being optionally substituted with one or more substituents chosen from a $(\text{C}_1\text{-C}_3)\text{alkyl}$ group and a hydroxyl group;

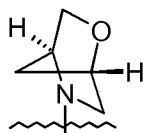
➤ R_1 represents:

- 10 - a linear, branched, cyclic or partially cyclic $(\text{C}_1\text{-C}_5)\text{alkyl}$ group, optionally substituted with one or more substituents chosen from a hydroxyl group, an aryl group, a trifluoromethyl group and a $(\text{C}_3\text{-C}_5)\text{cycloalkyl}$ group,
- a $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$ group, optionally substituted with a hydroxyl group,
- 15 - an aryl group, optionally substituted with one or more substituents chosen from a halogen atom, a hydroxyl group, an $-\text{NH}_2$ group, a urea group of formula $-\text{NH}-\text{CO}-\text{NH}-(\text{C}_1\text{-C}_4)\text{alkyl}$, a morpholine group, a group of formula $-\text{SO}_2-(\text{C}_1\text{-C}_5)\text{alkyl}$, a $(\text{C}_1\text{-C}_5)\text{alkoxy}$ group, said alkoxy being optionally substituted with one or more substituents chosen from:
- 20 ○ a halogen atom,
- a hydroxyl group or a $(\text{C}_1\text{-C}_5)\text{alkoxy}$ group,
- a group $-\text{COR}_3$, in which R_3 represents a substituent chosen from a heterocycloalkyl group and a hydroxyl group,
- a group $-\text{CONR}_4\text{R}_{4'}$ in which R_4 and $\text{R}_{4'}$ are as defined below,
- a group $-\text{NR}_4\text{R}_{4'}$ in which R_4 and $\text{R}_{4'}$ are as defined below,
- 25 ○ a heterocycloalkyl group comprising one or two heteroelements chosen from a nitrogen atom and an oxygen atom,
- a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a $(\text{C}_1\text{-C}_3)\text{alkyl}$ group, a hydroxyl group and an $-\text{NH}_2$ group,
- 30 - a heteroaryl group, comprising one or more heteroatoms chosen from a nitrogen atom, a sulfur atom and an oxygen atom, optionally substituted with one or more substituents chosen from:
- a halogen atom,

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- a (C₁-C₃)alkyl group optionally substituted with one or more halogen atoms,
 - a (C₁-C₅)alkoxy group, optionally substituted with one or more substituents chosen from a halogen atom, a (C₃-C₅)cycloalkyl group, a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group,
 - a group -NR₅R_{5'} in which R₅ and R_{5'}, independently, which may be identical or different, represent a substituent chosen from a hydrogen atom, a -CO₂-(C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group and a linear or branched (C₁-C₃)alkyl group, said alkyl group being optionally substituted with one or more hydroxyl groups,
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- a pyridine group bearing two linked adjacent groups forming, together with the two carbons that bear them, a heterocycle comprising a nitrogen atom and an oxygen atom,
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- a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, in particular a morpholinyl group, a bridged morpholinyl group, a tetrahydropyranyl group and a piperidyl group, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group, an acetyl group and a -CO₂-(C₁-C₄)alkyl group,
- 20
- a group -NR₆R_{6'} in which R₆ and R_{6'}, which are different, represent a (C₁-C₅)alkyl group and a (C₁-C₅)alkoxy group,
 - R₂ represents a hydrogen atom when n represents 1 and a methyl group when n represents 0;
- 25
- R₄ and R_{4'}, independently, which may be identical or different, represent a hydrogen atom or a (C₁-C₃)alkyl group,
- in the form of the base or of an addition salt with an acid or with a base.

Among the compounds of the present invention, mention may be made of a fourth subgroup of compounds of formula (I) in which:

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- n represents 0 or 1;
 - Y represents a bridged morpholine (a)



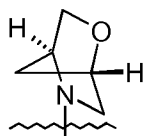
(a)

- L represents a linker $-\text{CH}_2\text{CO}-$ such that the carbonyl function is attached to the substituent R_1 , or $(\text{C}_1\text{-C}_2)\text{alkyl}$, said alkyl being optionally substituted with one or more substituents chosen from a $(\text{C}_1\text{-C}_3)\text{alkyl}$ group and a hydroxyl group;
- R_1 represents:
- a linear or branched $(\text{C}_1\text{-C}_5)$ alkyl group, optionally substituted with one or more substituents chosen from a hydroxyl group and an aryl group,
 - a $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$ group,
 - an aryl group, optionally substituted with one or more substituents chosen from a halogen atom, a hydroxyl group, an $-\text{NH}_2$ group, a urea group of formula $-\text{NH}-\text{CO}-\text{NH}-(\text{C}_1\text{-C}_4)\text{alkyl}$, a morpholine group, a group of formula $-\text{SO}_2-(\text{C}_1\text{-C}_5)\text{alkyl}$, a $(\text{C}_1\text{-C}_5)\text{alkoxy}$ group, said alkoxy being optionally substituted with one or more substituents chosen from:
 - a halogen atom,
 - a hydroxyl group or a $(\text{C}_1\text{-C}_5)\text{alkoxy}$,
 - a group $-\text{COR}_3$, in which R_3 represents a substituent chosen from a heterocycloalkyl group and a hydroxyl group,
 - a group $-\text{CONR}_4\text{R}_{4'}$ in which R_4 and $\text{R}_{4'}$ are as defined below,
 - a group $-\text{NR}_4\text{R}_{4'}$ in which R_4 and $\text{R}_{4'}$ are as defined below,
 - a heterocycloalkyl group comprising one or two heteroelements chosen from a nitrogen atom and an oxygen atom,
 - a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a $(\text{C}_1\text{-C}_3)\text{alkyl}$ group, a hydroxyl group and an $-\text{NH}_2$ group;
 - a heteroaryl group, comprising one or more heteroatoms chosen from a nitrogen atom, a sulfur atom and an oxygen atom, optionally substituted with one or more substituents chosen from:
 - a halogen atom,
 - a $(\text{C}_1\text{-C}_3)\text{alkyl}$ group optionally substituted with one or more halogen atoms,
 - a $(\text{C}_1\text{-C}_5)\text{alkoxy}$ group, optionally substituted with one or more

- substituents chosen from a halogen atom, a (C₃-C₅)cycloalkyl group, a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group,
- 5 ○ a group -NR₅R_{5'} in which R₅ and R_{5'}, independently, which may be identical or different, represent a substituent chosen from a hydrogen atom, a -CO₂-(C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group and a linear or branched (C₁-C₃)alkyl group, said alkyl group being optionally substituted with one or more hydroxyl groups,
- 10 - a pyridine group bearing two linked adjacent groups forming, together with the two carbons that bear them, a heterocycle comprising a nitrogen atom and an oxygen atom,
- a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, in particular a morpholinyl group, a bridged morpholinyl group and a piperidyl group, said nitrogen atom being optionally
- 15 substituted with a substituent chosen from a formyl group and an acetyl group,
- a group -NR₆R_{6'} in which R₆ and R_{6'}, which are different, represent a (C₁-C₅)alkyl group and a (C₁-C₅)alkoxy group,
- R₂ represents a hydrogen atom when n represents 1 and a methyl group when
- 20 n represents 0;
- R₄ and R_{4'}, independently, which may be identical or different, represent a hydrogen atom or a (C₁-C₃)alkyl group,
- in the form of the base or of an addition salt with an acid or with a base.

25 Among the compounds of the present invention, mention may be made of a fifth subgroup of compounds of formula (I) in which:

- n represents 0 or 1;
- Y represents a bridged morpholine (a)



(a)

30

- L represents a linker -CH₂-CO- such that the carbonyl function is attached to the substituent R₁, or (C₁-C₂)alkyl, said alkyl being optionally substituted with one or more (C₁-C₃)alkyl groups;

➤ R₁ represents:

- a linear, branched, cyclic or partially cyclic (C₁-C₅)alkyl group, in particular an isopropyl or tert-butyl group, optionally substituted with one or more substituents chosen from a hydroxyl group, an aryl group, a trifluoromethyl group and a (C₃-C₅)cycloalkyl group, 5
- a (C₃-C₆)cycloalkyl group, optionally substituted with a hydroxyl group,
- an aryl group, in particular a phenyl group, optionally substituted with one or more substituents chosen from a halogen atom, a cyano group, an -NH₂ group, a urea group of formula -NH-CO-NH-(C₁-C₄)alkyl, a morpholine group, a group of formula -SO₂-(C₁-C₅)alkyl, a (C₁-C₅)alkoxy group, in particular a methoxy group, said alkoxy being optionally substituted with one or more substituents chosen from: 10
 - a halogen atom, in particular a fluorine atom,
 - a hydroxyl group or a (C₁-C₅)alkoxy group,
 - 15 ○ a group -COR₃, in which R₃ represents a substituent chosen from a heterocycloalkyl group and a hydroxyl group,
 - a heterocycloalkyl group comprising one or two heteroelements chosen from a nitrogen atom and an oxygen atom, in particular a morpholinyl group,
 - 20 ○ a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group;
- a heteroaryl group, comprising one or more heteroatoms chosen from nitrogen atoms, in particular a pyridyl group, and sulfur and oxygen atoms, optionally substituted with one or more substituents chosen from: 25
 - a halogen atom,
 - a (C₁-C₃)alkyl group optionally substituted with one or more halogen atoms,
 - a (C₁-C₅)alkoxy group, optionally substituted with one or more substituents chosen from a halogen atom, a (C₃-C₅)cycloalkyl group, a 30 heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group,
 - a group -NR₅R_{5'}, in which R₅ and R_{5'}, independently, which may be identical or different, represent a substituent chosen from a hydrogen 35 atom, a -CO₂-(C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group and a linear

or branched (C₁-C₃)alkyl group, said alkyl group being optionally substituted with one or more hydroxyl groups,

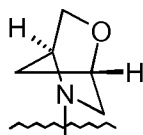
- a pyridine group bearing two linked adjacent groups forming, together with the two carbons that bear them, a heterocycle comprising a nitrogen atom and an oxygen atom, in particular a 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine group,
 - a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group, an acetyl group and a -CO₂-(C₁-C₄)alkyl group,
 - a group -NR₆R_{6'} in which R₆ and R_{6'}, which are different, represent an alkyl group and a (C₁-C₅)alkoxy group,
- R₂ represents a hydrogen atom when n represents 1 and a methyl group when n represents 0;

in the form of the base or of an addition salt with an acid or with a base.

15

Among the compounds of the present invention, mention may be made of a sixth subgroup of compounds of formula (I) in which:

- n represents 0 or 1;
- Y represents a bridged morpholine (a)



(a)

20

➤ L represents a linker -CH₂-CO- such that the carbonyl function is attached to the substituent R₁, or (C₁-C₂)alkyl, said alkyl being optionally substituted with one or more (C₁-C₃)alkyl groups;

25

- R₁ represents:
 - a linear or branched (C₁-C₅)alkyl group, in particular an isopropyl or tert-butyl group, optionally substituted with one or more hydroxyl groups,
 - a (C₃-C₆)cycloalkyl group,
 - an aryl group, in particular a phenyl group, optionally substituted with one or more substituents chosen from a halogen atom, a cyano group, an -NH₂ group, a urea group of formula -NH-CO-NH-(C₁-C₄)alkyl, a morpholine group, a group of formula -SO₂-(C₁-C₅)alkyl, a (C₁-C₅)alkoxy group, in particular a methoxy group, said alkoxy being optionally substituted with one or more substituents

30

chosen from:

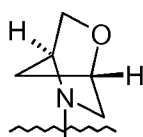
- a halogen atom, in particular a fluorine atom,
 - a hydroxyl group or a (C₁-C₅)alkoxy,
 - a group -COR₃, in which R₃ represents a substituent chosen from a heterocycloalkyl group and a hydroxyl group,
 - a heterocycloalkyl group comprising one or two heteroelements chosen from a nitrogen atom and an oxygen atom, in particular a morpholinyl group,
 - a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group;
 - a heteroaryl group, comprising one or more heteroatoms chosen from nitrogen atoms, in particular a pyridyl group, and sulfur and oxygen atoms, optionally substituted with one or more substituents chosen from:
 - a halogen atom,
 - a (C₁-C₃)alkyl group optionally substituted with one or more halogen atoms,
 - a (C₁-C₅)alkoxy group, optionally substituted with one or more substituents chosen from a halogen atom, a (C₃-C₅)cycloalkyl group, a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group,
 - a group -NR₅R_{5'} in which R₅ and R_{5'}, independently, which may be identical or different, represent a substituent chosen from a hydrogen atom, a -CO₂-(C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group and a linear or branched (C₁-C₃)alkyl group, said alkyl group being optionally substituted with one or more hydroxyl groups,
 - a pyridine group bearing two linked adjacent groups forming, together with the two carbons that bear them, a heterocycle comprising a nitrogen atom and an oxygen atom, in particular a 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine group,
 - a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group and an acetyl group,
 - a group -NR₆R_{6'} in which R₆ and R_{6'}, which are different, represent an alkyl group and a (C₁-C₅)alkoxy group,
- R₂ represents a hydrogen atom when n represents 1 and a methyl group when

n represents 0;

in the form of the base or of an addition salt with an acid or with a base.

Among the compounds of the present invention, mention may be made of a
 5 seventh subgroup of compounds of formula (I) in which:

- Y represents a bridged morpholine (a)



(a)

➤ L represents a linker $-\text{CH}_2\text{-CO}-$ such that the carbonyl function is attached
 10 to the substituent R_1 ,

- R_1 represents:

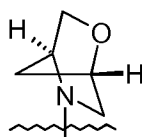
- a linear or branched $(\text{C}_1\text{-C}_5)$ alkyl group, in particular an isopropyl or tert-butyl group,
- a $(\text{C}_3\text{-C}_6)$ cycloalkyl group,
- 15 - an aryl group, in particular a phenyl group, optionally substituted with one or more substituents chosen from a halogen atom, a cyano group, an $-\text{NH}_2$ group, a urea group of formula $-\text{NH-CO-NH-}(\text{C}_1\text{-C}_4)\text{alkyl}$, a morpholinyl group, a group of formula $-\text{SO}_2\text{-(C}_1\text{-C}_5)\text{alkyl}$, a $(\text{C}_1\text{-C}_5)$ alkoxy group, in particular a methoxy group, said alkoxy being optionally substituted with one or more substituents
- 20 chosen from:
 - a halogen atom, in particular a fluorine atom,
 - a hydroxyl group or a $(\text{C}_1\text{-C}_5)$ alkoxy group,
 - a group $-\text{COR}_3$, in which R_3 represents a substituent chosen from a heterocycloalkyl group and a hydroxyl group,
 - 25 ○ a heterocycloalkyl group comprising one or two heteroelements chosen from a nitrogen atom and an oxygen atom, in particular a morpholinyl group,
 - a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a $(\text{C}_1\text{-C}_3)$ alkyl group, a hydroxyl group and
 - 30 an $-\text{NH}_2$ group;
- a heteroaryl group, comprising one or more heteroatoms chosen from nitrogen atoms, in particular a pyridyl group, and sulfur and oxygen atoms, optionally substituted with one or more substituents chosen from:

- a halogen atom,
- a (C₁-C₃)alkyl group optionally substituted with one or more halogen atoms,
- an alkoxy group, optionally substituted with one or more substituents chosen from a halogen atom, a (C₃-C₅)cycloalkyl group, a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group,
- a group -NR₅R_{5'} in which R₅ and R_{5'}, independently, which may be identical or different, represent a substituent chosen from a hydrogen atom, a -CO₂-(C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group and a linear or branched (C₁-C₃)alkyl group, said alkyl group being optionally substituted with one or more hydroxyl groups,
- a pyridine group bearing two linked adjacent groups forming, together with the two carbons that bear them, a heterocycle comprising a nitrogen atom and an oxygen atom, in particular a 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine group,
- a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group, an acetyl group and a -CO₂-(C₁-C₅)alkyl group,
- a group -NR₆R_{6'} in which R₆ and R_{6'}, which are different, represent an alkyl group and a (C₁-C₅)alkoxy group,

in the form of the base or of an addition salt with an acid or with a base.

Among the compounds of the present invention, mention may be made of an eighth subgroup of compounds of formula (I) in which:

- Y represents a bridged morpholine (a)



(a)

➤ L represents a linker -CH₂-CO- such that the carbonyl function is attached to the substituent R₁,

- R₁ represents:

- a linear or branched (C₁-C₅)alkyl group, in particular an isopropyl or tert-butyl

group,

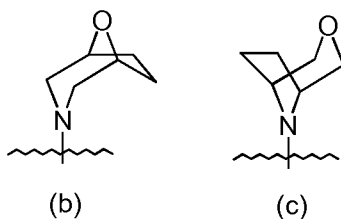
- a (C₃-C₆)cycloalkyl group,
- an aryl group, in particular a phenyl group, optionally substituted with one or more substituents chosen from a halogen atom, a cyano group, an -NH₂ group,
5 a urea group of formula -NH-CO-NH-(C₁-C₄)alkyl, a morpholinyl group, a group of formula -SO₂-(C₁-C₅)alkyl, a (C₁-C₅)alkoxy group, in particular a methoxy group, said alkoxy being optionally substituted with one or more substituents chosen from:
 - a halogen atom, in particular a fluorine atom,
 - 10 ○ a hydroxyl group or a (C₁-C₅)alkoxy group,
 - a group -COR₃, in which R₃ represents a substituent chosen from a heterocycloalkyl group and a hydroxyl group,
 - a heterocycloalkyl group comprising one or two heteroelements chosen from a nitrogen atom and an oxygen atom, in particular a morpholinyl
15 group,
 - a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group;
- a heteroaryl group, comprising one or more heteroatoms chosen from nitrogen
20 atoms, in particular a pyridyl group, and sulfur and oxygen atoms, optionally substituted with one or more substituents chosen from:
 - a halogen atom,
 - a (C₁-C₃)alkyl group optionally substituted with one or more halogen atoms,
 - 25 ○ an alkoxy group, optionally substituted with one or more substituents chosen from a halogen atom, a (C₃-C₅)cycloalkyl group, a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group,
 - 30 ○ a group -NR₅R_{5'}, in which R₅ and R_{5'}, independently, which may be identical or different, represent a substituent chosen from a hydrogen atom, a -CO₂-(C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group and a linear or branched (C₁-C₃)alkyl group, said alkyl group being optionally substituted with one or more hydroxyl groups,
 - 35 - a pyridine group bearing two linked adjacent groups forming, together with the two carbons that bear them, a heterocycle comprising a nitrogen atom and an

- oxygen atom, in particular a 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine group,
- a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, in particular a morpholinyl group, a bridged morpholinyl group and a piperidyl group, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group and an acetyl group,
- 5 - a group $-NR_6R_{6'}$ in which R_6 and $R_{6'}$, which are different, represent an alkyl group and an alkoxy group,

in the form of the base or of an addition salt with an acid or with a base.

10 A ninth subgroup of compounds of formula (I) according to the invention is such that:

- n represents 0 or 1;
- Y represents a bridged morpholine chosen from (b) and (c)



15

➤ L represents a linker $-CH_2-CO-$ such that the carbonyl function is attached to the substituent R_1 , or (C_1-C_2) alkyl, said alkyl being optionally substituted with a hydroxyl group;

20

➤ R_1 represents:

- a linear or branched (C_1-C_5) alkyl group, optionally substituted with an aryl group,
 - an aryl group, optionally substituted with one or more substituents chosen from a halogen atom, a hydroxyl group and a (C_1-C_5) alkoxy group, said alkoxy being optionally substituted with one or more substituents chosen from:
 - a group $-CONR_4R_{4'}$ in which R_4 and $R_{4'}$ are as defined below,
 - a group $-NR_4R_{4'}$ in which R_4 and $R_{4'}$ are as defined below,
 - a heteroaryl group comprising one or more heteroatoms chosen from a nitrogen atom, a sulfur atom and an oxygen atom, optionally substituted with one or more (C_1-C_3) alkyl groups, optionally substituted with one or more halogen atoms,
- 25
- 30

➤ R_2 represents a hydrogen atom when n represents 1 and a methyl group when n represents 0;

➤ R_4 and R_4' , independently, which may be identical or different, represent a hydrogen atom or a (C_1 - C_3)alkyl group,

5 in the form of the base or of an addition salt with an acid or with a base.

A tenth subgroup of compounds of formula (I) according to the invention is such that L represents a linker $-\text{CH}_2\text{-CO}-$ such that the carbonyl function is attached to the substituent R_1 , in the form of the base or of an addition salt with an acid or with a base.

10

An eleventh subgroup of compounds of formula (I) according to the invention is such that n represents 1, in the form of the base or of an addition salt with an acid or with a base.

15 A twelfth subgroup of compounds of formula (I) according to the invention is such that n represents 0, in the form of the base or of an addition salt with an acid or with a base.

20 A thirteenth subgroup of compounds of formula (I) according to the invention is such that R_1 represents a heteroaryl group, in particular a pyridyl group, in the form of the base or of an addition salt with an acid or with a base.

25 A fourteenth subgroup of compounds of formula (I) according to the invention is such that R_1 represents a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, in particular a morpholinyl group, a bridged morpholinyl group, a tetrahydropyranyl group and a piperidyl group, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group, an acetyl group and a $-\text{CO}_2-(C_1-C_4)\text{alkyl}$ group, in the form of the base or of an addition salt with an acid or with a base.

30

The subgroups defined above, taken separately or in combination, also form part of the invention. It should be noted that the eleventh and twelfth subgroups cannot be combined together.

35 Among the compounds of formula (I) that are subjects of the invention, mention may be made especially of the following compounds:

- 1 (8S)-9-(2-Methyl-2-pyrid-4-ylpropyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 2 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 5 3 (8S)-9-[2-(6-Aminopyrid-3-yl)-2-oxoethyl]-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 4 (8S)-9-[2-(6-Methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 10 5 (8S)-9-[2-(6-Methylaminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 6 (8S)-9-[2-(6-Dimethylaminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 15 7 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 8 1-[2-(6-Dimethylaminopyrid-3-yl)-2-oxoethyl]-2-(S)-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 20 9 2-(S)-Methyl-1-[2-(6-methylaminopyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 10 (8S)-1-[2-(4-Methoxyphenyl)ethyl]-2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 25 11 (S)-1-[2-(6-Aminopyrid-3-yl)-2-oxoethyl]-2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 30 12 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 13 2-Methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-1-(2-pyrid-3-ylethyl)-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 14 (8S)-9-{2-[6-(2-Hydroxyethylamino)pyrid-3-yl]-2-oxoethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 35

- 15 (8S)-9-[2-(5-Methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 16 2-Methyl-1-[2-(5-methylpyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 17 2-Methyl-1-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 10 18 2-Methyl-1-[2-(2-methylpyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 19 (8S)-9-[2-(2-Methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 15 20 (8S)-9-[2-(4-Methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 21 2-Methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-1-(2-oxo-2-pyrid-3-ylethyl)-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 20 22 (8S)-9-[2-(6-Cyclopropylaminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 23 1-Ethyl-3-{4-[2-((S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]phenyl}urea
- 25 24 1-Ethyl-3-{4-[2-((S)-2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-5-oxo-2-trifluoromethyl-2,3-dihydro-5H-imidazo[1,2-a]pyrimidin-1-yl)ethyl]phenyl}urea
- 25 25 (8S)-9-[2-(4-Methylthiazol-5-yl)ethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 30 26 2-Methyl-1-[2-(4-methylthiazol-5-yl)ethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 27 (8S)-9-[2-(3,5-Dimethyl-1H-pyrazol-4-yl)ethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 35 28 1-[2-(3,5-Dimethyl-1H-pyrazol-4-yl)ethyl]-2-methyl-7-(1S,4S)-2-oxa-5-

- azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 29 (8S)-9-(3,3-Dimethyl-2-oxobutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 5 30 1-(3,3-Dimethyl-2-oxobutyl)-2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 31 (8S)-9-[2-(6-Amino-5-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 10 32 1-[2-(4-Aminophenyl)ethyl]-2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 33 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-oxo-2-(6-trifluoromethylpyrid-3-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 15 34 (8S)-9-(2-{6-[(2-Hydroxyethyl)methylamino]pyrid-3-yl}-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 35 (8S)-9-[2-(6-Ethoxypyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 20 36 (8S)-9-[2-(6-Amino-4,5-dimethylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 37 (S)-9-[2-(4-Difluoromethoxyphenyl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 25 38 (8S)-9-[2-(3,4-Dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 30 39 (8S)-9-[2-(4-Methyloxazol-5-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 40 (S)-9-[2-(3,4-Difluorophenyl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 35 41 (8S)-9-[2-(4-Morpholin-4-ylphenyl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-

- azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 42 4-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]benzonitrile
- 5 43 (8S)-9-[2-(4-Methylthiazol-5-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 44 (8S)-9-[2-(5-Chloropyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-
- 10 4-one
- 45 (8S)-9-[2-(6-Methoxypyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 46 (8S)-9-[2-(3-Methylisoxazol-4-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-
- 15 azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 47 (8S)-9-(2-Benzo[1,2,3]thiadiazol-5-yl-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 20 48 (8S)-9-[2-(2,4-Difluorophenyl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 49 (8S)-9-(3-Ethyl-3-hydroxypentyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 25 50 (8S)-9-(3-Hydroxy-3-methylbutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 51 (8S)-9-(1-Methyl-1H-indazol-3-ylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 30 52 (8S)-9-[2-(2-Cyclopropylmethoxypyrimidin-5-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 53 (8S)-9-[2-(3,5-Dimethylisoxazol-4-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-
- 35 4-one
- 54 (8S)-9-(2-Ethyl-2-hydroxybutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-

- trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 55 3-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]benzonitrile
- 56 (8S)-9-(3-Methyl-2-oxobutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-
- 5 trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 57 {5-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]pyrid-2-yl}carbamic acid ethyl ester
- 58 {5-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]pyrid-2-yl}carbamic acid methyl ester
- 10 59 (8S)-9-(5-Methyl-[1,2,4]oxadiazol-3-ylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 15 60 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-oxo-2-(2-trifluoromethylpyrid-3-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 61 (8S)-9-(2-Benzo[1,2,5]thiadiazol-5-yl-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-
- 20 4-one
- 62 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-oxo-2-(tetrahydropyran-4-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 63 (8S)-9-{2-[6-(2-Fluoroethoxy)pyrid-3-yl]-2-oxoethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-
- 25 4-one
- 64 (8S)-9-{2-[3-Fluoro-4-(2-fluoroethoxy)phenyl]-2-oxoethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 65 (8S)-9-[2-(2-Methoxypyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-
- 30 4-one
- 66 (8S)-9-[2-(3-Methyl-3H-imidazol-4-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 35 67 (8S)-9-(2-Cyclopropyl-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

- 68 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-2-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 69 (8S)-9-[2-(2-Methyl-2H-pyrazol-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 5 4-one
- 70 N,N-Dimethyl-2-(4-{2-[(S)-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-5-oxo-2-trifluoromethyl-2,3-dihydro-5H-imidazo[1,2-a]pyrimidin-1-yl]ethyl}phenoxy)acetamide
- 71 (8S)-9-[(S)-2-(4-Fluoro-2-methoxyphenyl)-2-hydroxyethyl]-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 10 one
- 72 (2S)-1-[2-(4-Hydroxyphenyl)ethyl]-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 73 (8S)-2-(8-Oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(2-oxo-2-phenylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 15 74 (2S)-1-{2-[4-(2-Dimethylaminoethoxy)phenyl]ethyl}-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- one
- 75 (8S)-2-(8-Oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(2-oxo-2-pyrid-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 20 76 (S)-1-[2-(4-Methoxyphenyl)ethyl]-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 77 (S)-2-Methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-1-(3-phenylpropyl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 78 (S)-1-{2-[4-(3-Dimethylaminopropoxy)phenyl]ethyl}-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 25 one
- 79 (2S)-1-((S)-2-Hydroxy-2-phenylethyl)-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 80 (8S)-9-((S)-2-Hydroxy-2-phenylethyl)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 30 one
- 81 (8S)-9-[2-(4-Methoxyphenyl)ethyl]-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 82 (8S)-9-((R)-2-Benzo[b]thiophen-2-yl-2-hydroxyethyl)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 35 one
- 83 (8S)-9-[2-(4-Hydroxyphenyl)ethyl]-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-

- trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 84 (8S)-2-(8-Oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(3-phenylpropyl)-8-trifluoromethylmethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 85 (8S)-2-(3-Oxa-8-azabicyclo[3.2.1]oct-8-yl)-9-(2-oxo-2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 5 86 (8S)-9-(1-Difluoromethyl-1H-pyrazol-3-ylmethyl)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 87 (8S)-2-(8-Oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(2-oxo-2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 10 88 (8S)-2-(8-Oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(2-oxo-2-pyrid-2-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 89 (S)-9-[2-(1-Acetylpiperid-4-yl)ethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 15 90 4-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]piperidine-1-carbaldehyde
- 91 4-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]piperidine-1-carboxylic acid ethyl ester
- 20 92 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-(tetrahydropyran-4-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 93 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(tetrahydropyran-4-ylmethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 94 (8S)-9-(1-Acetylpiperid-4-ylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 25 95 4-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-ylmethyl)piperidine-1-carbaldehyde
- 96 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(3,3,3-trifluoro-2-hydroxy-2-trifluoromethylpropyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 30 97 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(4,4,4-trifluoro-3-hydroxy-3-trifluoromethylbutyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 98 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 35

- 99 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 100 (8S)-9-[2-(1-Hydroxycyclopentyl)ethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 101 (8S)-9-(1-Hydroxycyclopentylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 102 (8S)-9-(3,3-Dicyclopropyl-3-hydroxypropyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 103 (8S)-9-(2,2-Dicyclopropyl-2-hydroxyethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 104 (8S)-9-(1-Hydroxycyclopropylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 105 (8S)-9-[2-(1-Hydroxycyclopropyl)ethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 106 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-quinolin-5-ylmethyl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 107 (8S)-9-[2-(3-Methylisothiazol-4-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 108 (8S)-9-[2-(4-Methanesulfonylphenyl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 109 (8S)-9-Isoquinolin-5-ylmethyl-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 110 (8S)-9-(2-Morpholin-4-yl-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 111 (8S)-9-{2-[4-(2-Morpholin-4-ylethoxy)phenyl]ethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 112 N-Methoxy-N-methyl-2-((S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetamide
- 113 (8S)-9-(2-Imidazo[1,2-a]pyrid-6-yl-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-

4-one

114 (8S)-9-[2-(6-Difluoromethoxy-pyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

5 115 (S)-9-{2-[4-(2-Morpholin-4-yl-2-oxoethoxy)phenyl]ethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

116 (8S)-9-(1-Methyl-3-trifluoromethyl-1H-pyrazol-4-ylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

10 117 (8S)-9-{2-[4-(2-Dimethylaminoethoxy)phenyl]ethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

118 4-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]piperidine-1-carbaldehyde

15 119 (8S)-9-[2-(1-Acetylpiperid-4-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

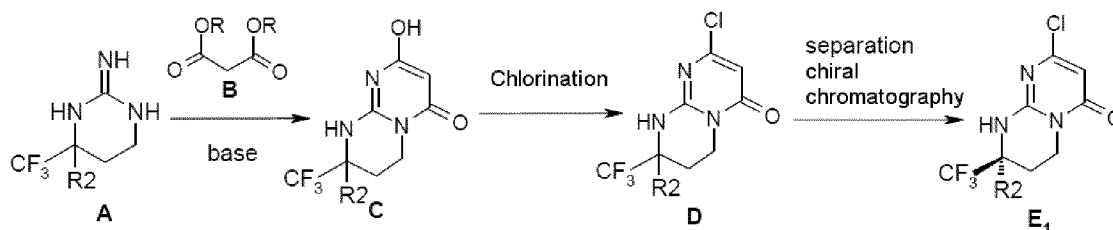
in the form of the base or of an addition salt with an acid or with a base.

20

It should be noted that the above compounds were named according to the IUPAC nomenclature by means of the Autonom software.

25 In accordance with the invention, the compounds of general formula (I) may be prepared according to the processes that follow.

The synthesis of the intermediate compounds E₁ in which n = 1 and R₂ represents a hydrogen atom is described in Scheme 1:

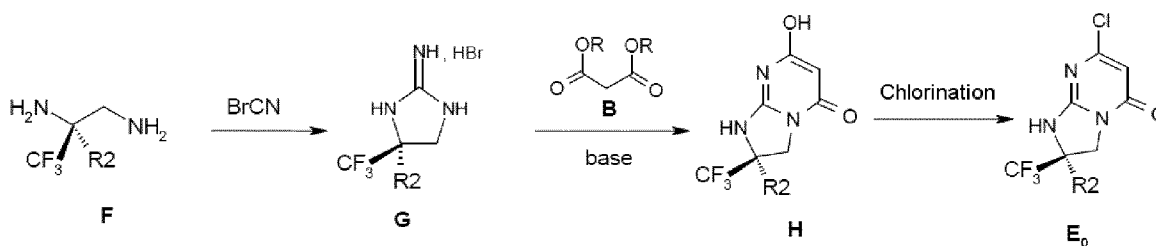


Scheme 1

30 The guanidine A is prepared according to the processes described in patent application

EP 1 460 076 by Lothead, A.W. et al.. Compound C may be obtained by condensation of a guanidine A with a dialkyl malonate B, in which R is an alkyl group, preferably an ethyl group, in the presence of a strong base such as sodium methoxide, at a temperature of between 60°C and 100°C, under the conditions described, for example, by Badawey E.-S.A.M. et al. (Eur. J. Med. Chem., 1998, 33(5), 349-361). Compound D may be obtained from a compound C by treatment with a chlorinating agent such as phosphorus oxychloride, in the absence of solvent, at a temperature between 20°C and 120°C, or in the presence of a polar solvent such as 1,2-dichloroethane, at a temperature of between 20°C and the boiling point of the solvent, as described by Yamashita, A. et al. (Syn. Commun. (2004), 34(5), 795-803). Compound E₁ is obtained after separation of the enantiomers of the compound of formula D by chromatography on a chiral support.

The synthesis of the intermediate compounds E₀ in which n = 0 and R₂ represents a methyl group is described in Scheme 2:

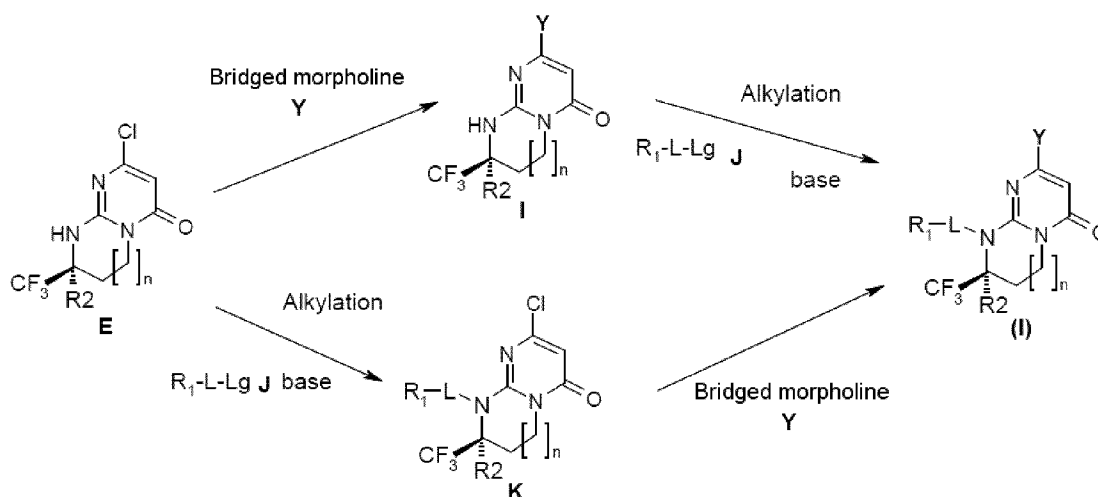


Scheme 2

The diamine F is either commercially available or prepared according to the process described in Journal of Organic Chemistry (2006, 71(18), 7075-7078) by Brigaud, T. et al. The guanidine G is obtained by reacting a diamine F and cyanogen bromide in a polar solvent such as water or acetonitrile, at a temperature of between 0°C and the boiling point of the solvent, according to the conditions described in patent application EP 1 340 761 by Gallet, T. et al. As previously, the compounds H may be obtained by condensation of a guanidine G with a dialkyl malonate B, in which R is an alkyl group, preferably an ethyl group, in the presence of a strong base such as sodium methoxide, at a temperature of between 60°C and 100°C.

The compounds E₀ are obtained from a compound H by treatment with a chlorinating agent such as phosphorus oxychloride, in the absence of solvent, at a temperature between 20°C and 120°C, or in the presence of a polar solvent such as 1,2-dichloroethane, at a temperature of between 20°C and the boiling point of the solvent.

Thereafter, the products of formula (I) as defined above according to the present invention may thus be prepared according to Scheme 3.



Scheme 3

- The compounds I are obtained from a compound E, in which n represents 0 or 1, and R₂ represents a hydrogen atom if n = 1, or a methyl group if n = 0, by reaction with a bridged morpholine Y, in the absence of solvent, at a temperature of between 20°C and 140°C, or in the presence of a polar solvent such as methyl isobutyl ketone or butyronitrile, at a temperature of between 20°C and the reflux temperature of the solvent. The compounds (I) may then be obtained via an alkylation reaction, by addition of a compound J of formula R₁-L-Lg with R₁ and L as defined above and Lg being a leaving group such as Cl, Br, I or OTf (trifluoromethanesulfonate), with compound I and a base such as sodium hydride, cesium carbonate or potassium tert-butoxide in excess, in a polar solvent such as acetonitrile, N,N-dimethylformamide or tetrahydrofuran, at a temperature of between 0°C and 150°C, as described by Ting P.C. et al. (J. Med. Chem. (1990), 33(10), 2697-2706).
- By following the procedure described by E. P. Seest et al. in Tet. Asymmetry 17 (2006) 2154-2182, the compounds J, corresponding to chiral 1-aryl-2-chloroethanols or 1-heteroaryl-2-chloroethanols, were synthesized from the corresponding chloro ketone derivatives, which were themselves derived from chlorination of commercially available acetyl derivatives under standard conditions.
- Alternatively, the compounds (I) may be obtained from a compound K by reaction with a bridged morpholine, in the absence of solvent, at a temperature of between 20°C and

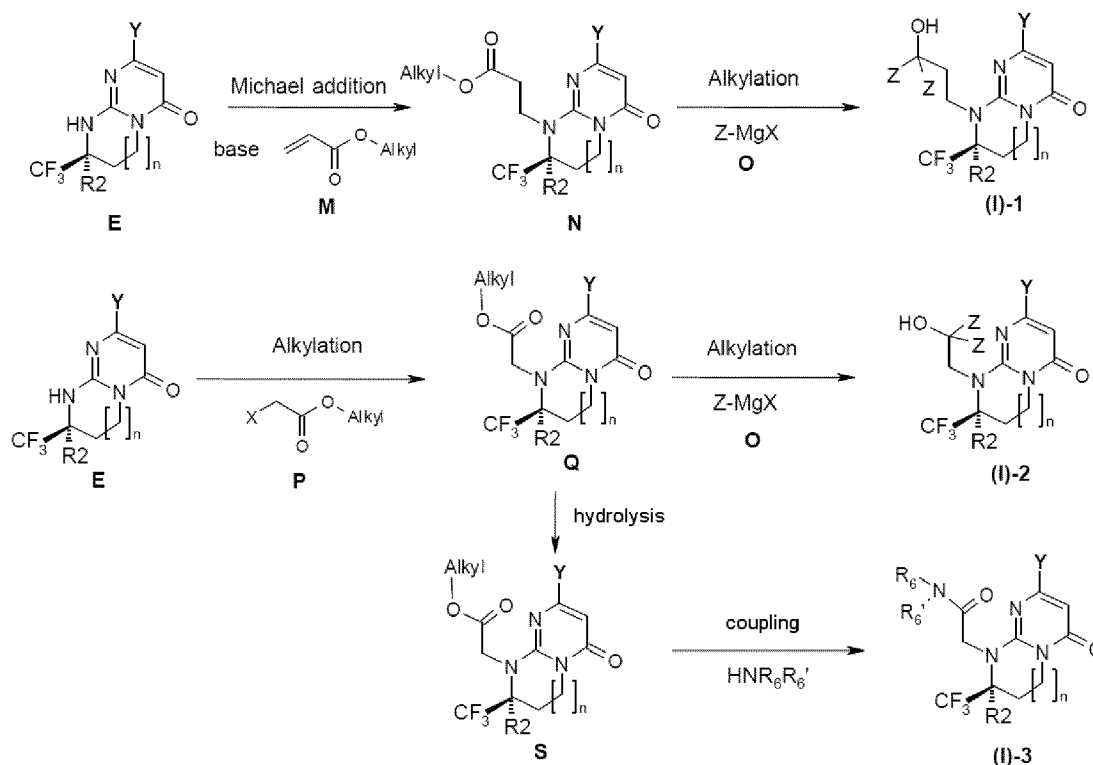
140°C, or in the presence of a solvent such as methyl isobutyl ketone or butyronitrile, at a temperature of between 20°C and the reflux temperature of the solvent.

The compounds K may be obtained via an alkylation reaction, by addition of a compound J of formula R_1-L-Lg with R_1 and L as defined above and Lg being a leaving group such as Cl, Br, I or OTf, with compound E and a base such as sodium hydride, cesium carbonate or potassium tert-butoxide in excess, in a solvent such as acetonitrile, N,N-dimethylformamide or tetrahydrofuran, at a temperature of between 0°C and 150°C, as described, for example, by Ting P.C. et al. (J. Med. Chem. (1990), 33(10), 2697-2706).

10

The compounds of formula (I) for which the linker L is an ethyl group, R_1 is a linear or branched (C_1-C_5)alkyl group substituted with a hydroxyl group, Y represents a bridged morpholine chosen from (a), (b) and (c), n represents 1 or 0, and R_2 represents a hydrogen atom when $n = 1$ and a methyl group when $n = 0$, are noted (I)-1. The compounds for which the linker L is a methyl group, R_1 is a linear or branched (C_1-C_5)alkyl group substituted with a hydroxyl group, Y represents a bridged morpholine chosen from (a), (b) and (c), n represents 1 or 0, and R_2 represents a hydrogen atom when $n = 1$ and a methyl group when $n = 0$, are noted (I)-2. The compounds of formula (I) for which the linker L is a methyl group, R_1 is a group $-NR_6R_6'$ with R_6 et R_6' being either different and representing an alkyl group and an alkoxy group, or R_6 and R_6' together forming a monocyclic or bicyclic heterocycloalkyl, Y represents a bridged morpholine chosen from (a), (b) and (c), n represents 1 or 0, and R_2 represents a hydrogen atom when $n = 1$ and a methyl group when $n = 0$, are noted (I)-3. The compounds of formulae (I)-1, (I)-2 and (I)-3 may be obtained according to Scheme 4.

25



Scheme 4

The compounds (I)-1 may be obtained via an alkylation reaction, by addition to a compound N of a compound O, of formula $Z-Mg-X$ in which Z represents a linear or branched alkyl radical and X is a halogen atom such as Cl or Br, in a polar solvent such as tetrahydrofuran, at a temperature of between 0°C and 25°C, as described, for example, by Ting P.C. et al. (J. Med. Chem. (1990), 33(10), 2697-2706). The compounds N may be obtained via an addition reaction of Michael type of a compound E with a compound M, of formula $CH_2=CH_2-CO_2Alkyl$, in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene, in a polar aprotic solvent such as N,N-dimethylformamide, at a temperature of 25°C.

Similarly, the compounds (I)-2 may be obtained via an alkylation reaction, by addition of a compound O, as described above, to compound Q, in a polar solvent such as tetrahydrofuran, at a temperature of between 0°C and 25°C. The compounds Q may be obtained via an alkylation reaction, by addition of a compound P, of formula X-CH₂-CO₂Alkyl in which X is a halogen atom such as Cl, Br or I, to compound E and an alkaline base such as sodium hydride or cesium carbonate in excess, in a polar solvent such as N,N-dimethylformamide or acetonitrile, at a temperature of 25°C.

20

The compounds (I)-3 may be obtained via a coupling reaction between a compound S

and a compound of formula $\text{HNR}_6\text{R}_{6'}$ with R_6 and $\text{R}_{6'}$ being either different and representing an alkyl group and an alkoxy group, or R_6 and $\text{R}_{6'}$ together forming a monocyclic or bicyclic heterocycloalkyl, in a polar solvent such as N,N-dimethylformamide, in the presence of coupling agents such as 1-hydroxy
5 benzotriazole with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. Compound S is obtained by hydrolysis of compound Q, for example using lithium hydroxide monohydrate in a water/tetrahydrofuran mixture.

It is clear to a person skilled in the art that, in order to perform the processes according to the invention described previously, it may be necessary to introduce protecting
10 groups for the amino, carboxyl and alcohol functions in order to avoid side reactions.

Examples of protecting groups and also of protection and deprotection methods are given in *Protective Groups in Organic Synthesis*, Greene et al., 3rd Edition (John Wiley & Sons, Inc., New York). As examples of protection of reactive functions, the following non-exhaustive list may be mentioned:

- 15 - the hydroxyl groups may be protected, for example, with alkyl radicals such as tert-butyl, trimethylsilyl, tert-butyldimethylsilyl, methoxymethyl, tetrahydropyranyl, benzyl or acetyl,
- the amino groups may be protected, for example, with acetyl, trityl, benzyl, tert-butoxycarbonyl, benzyloxycarbonyl or phthalimido radicals or other radicals known in
20 peptide chemistry,
- the acid functions may be protected, for example, in the form of esters formed with readily cleavable esters such as benzyl or tert-butyl esters or esters known in peptide chemistry.

25 In the text hereinabove, the term "leaving group Lg" means a group that can be readily cleaved from a molecule by breaking a heterolytic bond, with loss of an electron pair. This group can thus be easily replaced with another group in a substitution reaction, for example. Such leaving groups are, for example, halogens or an activated hydroxyl group, such as a mesylate, tosylate, triflate, acetyl, etc. Examples of leaving
30 groups and also references for preparing them are given in *Advanced Organic Chemistry*, J. March, 4th Edition, Wiley Interscience, p. 310-316.

In schemes 1, 2, 3 and 4, the starting compounds and the reagents, when the method for preparing them is not described, are commercially available or described in

the literature, or else can be prepared according to methods which are described therein or which are known to those skilled in the art.

According to another of its aspects, a subject of the invention is also the
5 compounds of formulae I, N, Q and S. These compounds are useful as intermediates in the synthesis of the compounds of formula (I).

The following abbreviations and molecular formulae are used:

- 10 EtOAc: ethyl acetate
Br: bromine
CDCl₃: deuterated chloroform
Cl: chlorine
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
15 DCM: dichloromethane
DMF: N,N-dimethylformamide
DMSO: dimethyl sulfoxide
DMSO-d₆: deuterated dimethyl sulfoxide
HPLC: high performance liquid chromatography
20 HCl: hydrochloric acid
K₂CO₃: potassium carbonate
LC/MS: liquid chromatography/mass spectrometry
MeOH: methanol
MgSO₄: magnesium sulfate
25 MHz: Megahertz
Na₂CO₃: sodium carbonate
NaCl: sodium chloride
NaOH: sodium hydroxide
NaHCO₃: sodium hydrogen carbonate
30 Na₂SO₄: sodium sulfate
Ph: phenyl
Pd/C: palladium-on-charcoal
Pd(OH)₂/C: palladium hydroxide-on-charcoal
TFA: trifluoroacetic acid
35 THF: tetrahydrofuran
°C: degrees Celsius

Tr: retention time

min: minutes

ESI+: positive-mode electrospray ionization

5

The following examples describe the preparation of certain compounds in accordance with the invention. These examples are not limiting and merely illustrate the present invention. The numbers of the compounds exemplified refer to those given in the table hereinafter, which shows the chemical structures and the physical properties of some compounds according to the invention.

It should be noted that the compounds described in the experimental section were named according to the IUPAC nomenclature by means of the Autonom software.

In the procedures and examples below:

- 15 - the microwave oven used is a Biotage, InitiatorTM Eight, 400 W max, 2450 MHz apparatus.
- the proton magnetic resonance spectra (¹H NMR), as described below, are recorded at a temperature of 300 K (exchangeable protons not recorded) at 300, 400 or 600 MHz in DMSO-d₆ or CDCl₃, using the DMSO-d₆ or CDCl₃ peak as reference. The chemical shifts δ are expressed in parts per million (ppm). The signals observed are expressed as follows: s = singlet, d = doublet, m = multiplet, bs = broad signal, t = triplet, q = quartet.
- 20 - the LC/MS characteristics, as described below (A, B, C, D, E, F and G) indicate, successively, the analytical method used and detailed below, the retention time (Tr) of the compound expressed in minutes and the peak [M+H]⁺ identified by mass spectrometry.
- 25

*** Method A**

- 30 Instrument: Acquity UPLC chain (Waters); SQD mass spectrometer (Waters)
Column: Ascentis Express C18 50 x 2.1 mm 2.7 μ m, T° = 55°C
Solvent A: H₂O + 0.02% TFA; Solvent B: acetonitrile + 0.014% TFA
Flow rate: 1 mL/min
Gradient A/B: t 0 min 2% B, t 1 min 98% B, t 1.3 min 98% B, t 1.33 min 2% B
35 Detection: UV 220 nm

Ionization: electrospray positive mode

*** Method B**

Instrument: Acquity UPLC chain (Waters); LCT mass spectrometer (Waters)

5 Column: BHE C8 50 x 2.1 mm 1.7 μ m, T° = 55°C

Solvent A: H₂O + 0.02% TFA; Solvent B: acetonitrile + 0.014% TFA

Flow rate: 1 mL/min

Gradient A/B: t 0 min 2% B, t 1 min 98% B, t 1.3 min 98% B, t 1.33 min 2% B

Detection: UV 220 nm

10 Ionization: electrospray positive mode

*** Method C**

Instrument: Acquity UPLC chain (Waters); SQD mass spectrometer (Waters)

Column: BHE C18 50 x 2.1 mm 1.7 μ m, T° = 50°C

15 Solvent A: H₂O + 0.02% HCO₂H; Solvent B: acetonitrile + 0.02% HCO₂H

Flow rate: 1 mL/min

Gradient A/B: t 0 min 5% B, t 2 min 100% B, t 2.5 min 100% B

Detection: UV 220 nm

Ionization: electrospray positive mode

20

*** Method D**

Instrument: Acquity UPLC chain (Waters); SQD mass spectrometer (Waters)

Column: Acquity BHE C18 50 x 2.1 mm 1.7 μ m, T° = 50°C

Solvent A: H₂O + 0.1% HCO₂H; Solvent B: acetonitrile + 0.1% HCO₂H

25 Flow rate: 1 mL/min

Gradient A/B: t 0 min 5% B, t 0.8 min 50% B, t 1.2 min 100% B, t 1.85 min 100%

B, t 1.95 min 5% B

Detection: UV 220 nm

Ionization: electrospray positive mode

30

*** Method E**

Instrument: HPLC chain (Waters); ZQ mass spectrometer (Waters)

Column: XBridge C18 50 x 3 mm 2.5 μ m, T° = 70°C

Solvent A: H₂O + 0.1% HCO₂H; Solvent B: acetonitrile + 0.1% HCO₂H

35 Flow rate: 0.9 mL/min

Gradient A/B: t 0 min 5% B, t 5.3 min 100% B, t 5.5 min 100% B, t 6.3 min 5% B

Detection: UV 220 nm

Ionization: electrospray positive mode

*** Method F**

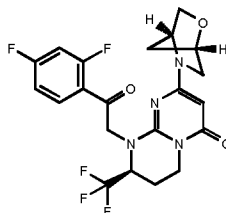
- 5 Instrument: Acquity UPLC type HPLC chain (Waters); SQD mass spectrometer (Waters)
Column: BHE C18 30 x 2.1 mm 1.7 μ m, T° = 50°C
Solvent A: H₂O + 0.1% HCO₂H; Solvent B: acetonitrile + 0.1% HCO₂H
Flow rate: 1 mL/min
10 Gradient A/B: t 0 min 5% B, t 2 min 100% B, t 2.5 min 100% B
Detection: UV 220 nm
Ionization: electrospray positive mode

*** Method G**

- 15 Instrument: Alliance HPLC chain (Waters); ZQ mass spectrometer (Waters)
Column: X Bridge C18 30 x 2.1 mm 2.5 μ m, T° = 55°C
Solvent A: H₂O + 0.02% TFA; Solvent B: MeOH
Flow rate: 0.7 mL/min
Gradient A/B: t 0 min 2% B, t 3 min 100% B, t 3.5 min 100% B, t 3.6 min 2% B
20 Detection: UV 220 nm
Ionization: electrospray positive mode

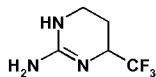
The optical rotations $[\alpha]_D^{25}$ were measured on a model 341 polarimeter from Perkin-Elmer. Wavelength: sodium α line (589 nm).

- 25 **Example 1:**
(8S)-9-[2-(2,4-difluorophenyl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 48)



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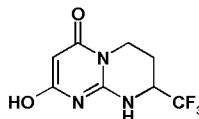
Step 1.1: 4-trifluoromethyl-1,4,5,6-tetrahydropyrimidin-2-ylamine



A mixture of 6 g of 10% Pd/C and 60 g (370 mmol) of 2-amino-4-(trifluoromethyl)pyrimidine dissolved in 80 mL of water, 250 mL of isopropanol and 24 mL (370 mmol) of methanesulfonic acid is hydrogenated at 5 bar, at 40°C, for 5 hours in an autoclave. The resulting mixture is then filtered and rinsed with isopropanol and with water. The filtrate is then concentrated under reduced pressure and the residue obtained is dried under vacuum to give 93.5 g of 4-trifluoromethyl-1,4,5,6-tetrahydropyrimidin-2-ylamine methanesulfonate in the form of a white solid. The white solid is dissolved in 250 mL of methyl isobutyl ketone. 100 mL of 10 N sodium hydroxide are then added. The mixture is stirred at room temperature for 15 minutes. The phases are separated by settling and the aqueous phase is re-extracted with methyl isobutyl ketone. The organic phases are combined and then evaporated under vacuum. 59.50 g of 4-trifluoromethyl-1,4,5,6-tetrahydropyrimidin-2-ylamine are thus obtained, the characteristics of which are as follows:

¹H NMR (300 MHz, δ in ppm, DMSO- d_6): 1.46 (m, 1H), 1.84 (m, 1H), 3.15 (m, 2H), 3.80 (m, 1H), 4.51-5.20 (bs, 2H), 5.55-6.30 (bs, 1H).

Step 1.2: 2-hydroxy-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



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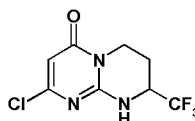
62.10 g (1150 mmol) of sodium methoxide are added to a mixture of 340 mL (2230 mmol) of diethyl malonate heated to 40°C. The mixture is heated at 100°C until a clear solution is obtained. 59.50 g (360 mmol) of 4-trifluoromethyl-1,4,5,6-tetrahydropyrimidin-2-ylamine dissolved in 100 mL of methanol are then added to the reaction medium. The mixture obtained is maintained at 100°C for 1 hour and then cooled to room temperature overnight. The reaction mixture is evaporated to dryness under reduced pressure. The residue obtained is taken up in 250 mL of water. 12 N hydrochloric acid is added to the thick suspension obtained, to pH = 5-6. The suspension obtained is filtered through a sinter funnel and the insoluble matter is rinsed with acetonitrile to give 68.10 g of 2-hydroxy-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in the form of a yellow solid, the characteristics of which are as follows:

30

LC/MS (method D), ESI+: [M+H]⁺: m/z 236; tr (min) = 0.26

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 1.46 (m, 1H), 1.84 (m, 1H), 3.15 (m, 2H), 3.80 (m, 1H), 4.51-5.20 (bs, 2H), 5.55-6.30 (bs, 1H).

5 **Step 1.3: 2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one**

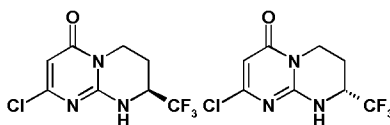


136 mL (1440 mmol) of phosphorus oxychloride are added, at room temperature and under an argon atmosphere, to a suspension of 68.10 g (290 mmol) of 2-hydroxy-8-(trifluoromethyl)-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one in 950 mL of 1,2-dichloroethane. The mixture obtained is then heated at 65°C for 3 hours. After cooling, the reaction mixture is evaporated to dryness under reduced pressure. The residue obtained is taken up in 140 mL of cold water and 430 mL of ethyl acetate. 32% sodium hydroxide is added to the mixture obtained, to pH = 5. The resulting organic phase is separated out and then dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 60 g of 2-chloro-8-(trifluoromethyl)-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one in the form of an orange solid, the characteristics of which are as follows:

LC/MS (method D), ESI+: [M+H]⁺: m/z 254; tr (min) = 0.51

20 ¹H NMR (300 MHz, δ in ppm, DMSO-d₆) 2.16 (m, 2H) 3.45 (m, 1H) 4.12 (m, 1H) 4.42 (m, 1H) 5.83 (s, 1H) 9.12 (s, 1H)

Step 1.4: (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



25

The separation of the two enantiomers of 2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one (100 g) is performed by chiral chromatography: stationary phase: Chiralpak IA (250 mm x 4.6) 5 μ m; temperature 25°C; mobile phase: methanol (100%). The levorotatory enantiomer is concentrated to give 49.10 g of (8R)-2-chloro-8-(trifluoromethyl)-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one, in the form of a white powder. The dextrorotatory enantiomer is concentrated to obtain 48.5 g

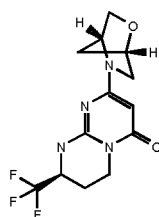
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of (8S)-2-chloro-8-(trifluoromethyl)-6,7,8,9-tetrahydro-4H-pyrimido[1,2-a]pyrimidin-4-one, in the form of a white powder, the characteristics of which are as follows: LC/MS (method D), ESI+: [M+H]⁺: m/z 254; tr (min) = 0.51

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 2.14 (m, 2H), 3.47 (m, 1H), 4.12 (m, 1H), 4.36 (m, 1H), 5.81 (s, 1H), 9.31 (s, 1H).

[α]_D²⁵ at 589 nm = + 21.3 $\pm$ 0.5° (MeOH)

Step 1.5: (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

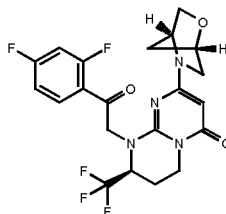


1.60 g (6.31 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 1.30 g (9.46 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride are mixed together. The powder obtained is placed in a tube and 2.21 mL (15.77 mmol) of triethylamine are added. The tube is sealed and heated at 130°C in an oil bath for 6 hours. After cooling, the crude product is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH). After evaporating the fractions under reduced pressure, 1.20 g of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, the characteristics of which are as follows:

LC/MS (method G): ESI+: [M+H]⁺: m/z 317 tr (min) = 1.37

¹H NMR (300 MHz, δ in ppm, CDCl₃): 2 (m, 2H), 2.35 (m, 2H), 3.45 (m, 2H), 3.92 (s, 1H), 3.95-4.32 (m, 4H), 4.78 (s, 1H), 4.89-5.2 (bs, 1H), 5.49-5.77 (bs, 1H).

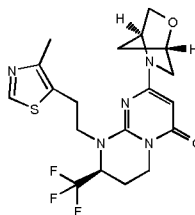
Step 1.6: (8S)-9-[2-(2,4-difluorophenyl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



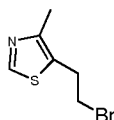
A suspension of 150 mg (0.47 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 463.57 mg (1.42 mmol) of cesium carbonate in 10 mL of acetonitrile is stirred for 15 minutes at room temperature. 222.93 mg (0.95 mmol) of 2-bromo-1-(2,4-difluorophenyl)ethanone are then added. After stirring overnight at room temperature, the reaction mixture is evaporated and the residue is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and then evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 130 mg of (8S)-9-[2-(2,4-difluorophenyl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:
 LC/MS (method A): ESI+ [M+H]⁺: m/z 471 tr (min) = 0.68
¹H NMR (600 MHz, δ in ppm, DMSO- d_6): 1.58-1.76 (m, 2H), 2.13-2.29 (m, 1H), 2.39-2.47 (m, 1H), 2.95-3.13 (bs, 4H), 3.16-3.29 (m, 1H), 4.34 (m, 1H), 4.41 (s, 1H), 4.51 (s, 1H), 4.58-4.71 (m, 3H), 5.38 (m, 1H), 7.3 (m, 1H), 7.51 (m, 1H), 8 (q, 1H)

Example 2:

(8S)-9-[2-(4-methylthiazol-5-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 25)



Step 2.1: 5-(2-bromoethyl)-4-methylthiazole



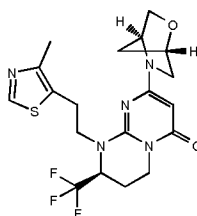
A solution of 1 g (7 mmol) of 4-methyl-5-thiazolyethanol in 15 mL of dichloromethane is cooled to 0°C under argon. In a first stage, 1.8 g (7 mmol) of

triphenylphosphine are added. Next, 1.30 g (7 mmol) of N-bromosuccinimide are added portionwise over 5 minutes. After stirring for 2 hours at 0°C, the solvent is evaporated off under vacuum. The residue obtained is purified by chromatography on silica gel (eluent: 50/50 EtOAc/heptane) to give 900 mg of 5-(2-bromoethyl)-4-methylthiazole, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 207 tr (min) = 1.52

¹H NMR (300 MHz, δ in ppm, CDCl₃): 2.42 (s, 3H), 3.3-3.35 (t, 2H), 3.5-3.55 (t, 2H), 8.62 (s, 1H).

Step 2.2: (8S)-9-[2-(4-methylthiazol-5-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



A suspension of 160 mg (0.50 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 415 mg (1.25 mmol) of cesium carbonate in 4 mL of N,N-dimethylformamide is heated at 80°C for 15 minutes. After cooling to room temperature, a solution of 150 mg (0.76 mmol) of 5-(2-bromoethyl)-4-methylthiazole in 1 mL of N,N-dimethylformamide is added dropwise. The reaction medium is heated at 80°C overnight. The reaction mixture obtained is evaporated to dryness. The residue obtained is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness.

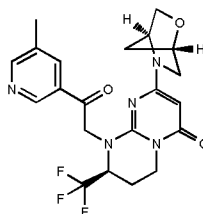
The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 40 mg of (8S)-9-[2-(4-methylthiazol-5-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

LC/MS (method A): ESI+ [M+H]⁺: m/z 442 tr (min) = 0.55

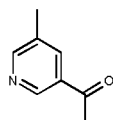
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.85 (t, 2H), 2.13 (m, 1H), 2.32 (s, 3H), 2.36 (m, 1H), 3.05-3.32 (m, 4H), 3.36 (d, 1H), 3.45 (m, 1H), 3.67 (d, 1H), 3.75 (d, 1H), 4.15-4.22 (m, 2H), 4.57 (m, 1H), 4.63 (s, 1H), 4.71 (s, 1H), 4.8 (s, 1H), 8.8 (s, 1H).

Example 3:

(8S)-9-[2-(5-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 15)

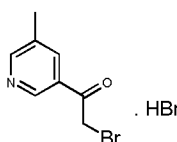


5

Step 3.1: 1-(5-methylpyrid-3-yl)ethanone

The following are successively introduced into a microwave tube:

- 10 484 μ l (4.07 mmol) of 3-bromo-5-methylpyridine in 20 mL of H₂O/DMF: (1/3: v/v), 2.03 mL (5.70 mmol) of tributyl(1-ethoxyvinyl)tin, 57.12 mg (0.081 mmol) of bis(triphenylphosphine)palladium(II) chloride, 1.12 g (8.14 mmol) of potassium carbonate. This mixture is subjected to microwave irradiation at 110°C for 1 hour. The reaction mixture is evaporated to dryness and the residue is then taken up in water and
- 15 extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue obtained is taken up in 6 mL of methanol and 1 mL of 6 N HCl, and the solution is stirred overnight at room temperature. The reaction medium is evaporated to dryness and the residue is taken up in saturated aqueous NaHCO₃ solution and extracted with ethyl acetate. The organic phase is dried over
- 20 magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 50/50 EtOAc/heptane) to give 300 mg of 1-(5-methylpyrid-3-yl)ethanone, the characteristics of which are as follows:
- LC/MS (method G): ESI+ [M+H]⁺: m/z 136 tr (min) = 0.78
- ¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 2.37 (s, 3H), 2.62 (s, 3H), 8.1 (s, 1H), 8.63 (s,
- 25 1H), 8.93 (s, 1H).

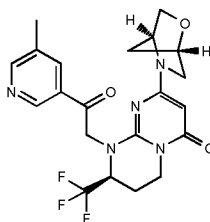
Step 3.2: 2-bromo-1-(5-methylpyrid-3-yl)ethanone hydrobromide

300 mg (2.22 mmol) of 1-(5-methylpyrid-3-yl)ethanone are dissolved in 15 mL of glacial acetic acid. 365 μ L (2.22 mmol) of hydrobromic acid and 126 μ L (2.44 mmol) of bromine are added to the medium. The reaction mixture is placed under magnetic stirring at room temperature for 2 hours. Ethyl ether is added to the solution until a precipitate appears. The precipitate corresponding to 2-bromo-1-(5-methylpyrid-3-yl)ethanone hydrobromide is filtered off, washed with ether and dried. The 600 mg of product obtained have the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 214 tr (min) = 1.17

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 2.46 (s, 3H), 5.05 (s, 2H), 8.48 (s, 1H), 8.82 (s, 1H), 9.12 (s, 1H).

Step 3.3: (8S)-9-[2-(5-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



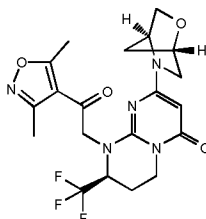
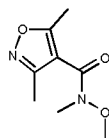
150 mg (0.474 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 5 mL of DMF are added to a suspension of 50.08 mg (1.04 mmol) of sodium hydride in 5 mL of DMF. The reaction mixture is placed under magnetic stirring at room temperature for 15 minutes. A solution of 153.88 mg (0.522 mmol) of 3-(bromoacetyl)pyridine hydrobromide in 5 mL of DMF is added dropwise to the reaction medium. The reaction is stirred at room temperature overnight. The reaction medium is evaporated to dryness. The crude product is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 70 mg of (8S)-9-[2-(5-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

LC/MS (method A): ESI+ [M+H]⁺: m/z 450 tr (min) = 0.51

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.62-1.7 (dd, 2H), 2.25 (m, 1H), 2.4 (s, 3H), 2.43 (m, 1H), 2.96-3.2 (m, 3H), 3.2-3.33 (m, 2H), 4.37 (m, 1H), 4.42 (s, 1H), 4.47 (s, 1H), 4.57 (m, 1H), 4.63-4.7 (m, 2H), 5.6 (d, 1H), 8.16 (s, 1H), 8.67 (s, 1H), 8.98 (s, 1H).

Example 4:

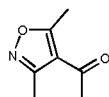
(8S)-9-[2-(3,5-dimethylisoxazol-4-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 53)

**Step 4.1: N-methoxy-N-methyl-3,5-dimethylisoxazole-4-carboxamide**

659 μ l (8.15 mmol) of pyridine are added to a suspension of 343.07 mg (3.45 mmol) of N,O-dimethylhydroxylamine hydrochloride in 10 mL of dichloromethane. The mixture is stirred at room temperature until fully dissolved. A solution of 526.32 mg (3.13 mmol) of 3,5-dimethylisoxazole-4-carbonyl chloride in 5 mL of dichloromethane is then added. After stirring for 1 hour at room temperature, the reaction mixture is taken up in saturated aqueous NaHCO_3 solution and stirred for a few minutes, and the phases are separated by settling. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue obtained is taken up in toluene and evaporated, the operation being repeated a second time. 570 mg of N-methoxy-N-methyl-3,5-dimethylisoxazole-4-carboxamide are then obtained, corresponding to the following characteristics:

LC/MS (method G): ESI+ $[\text{M}+\text{H}]^+$: m/z 185 tr (min) = 1.08

^1H NMR (300 MHz, δ in ppm, CDCl_3): 2.32 (s, 3H), 2.46 (s, 3H), 3.34 (s, 3H), 3.52 (s, 3H).

Step 4.2: 1-(3,5-dimethylisoxazol-4-yl)ethanone

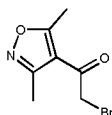
A solution of 580 mg (3.15 mmol) of N-methoxy-N-methyl-3,5-dimethylisoxazole-4-carboxamide in 20 mL of THF is cooled to 0°C . A solution of 1.57 mL (4.72 mmol) of 3 M methylmagnesium bromide in ether is added. After stirring for 4

hours at room temperature, the reaction medium is taken up in 10 mL of 1 N HCl and stirred for a further 1 hour at room temperature. The mixture is then basified with K_2CO_3 and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness to give 420 mg of 1-(3,5-dimethylisoxazol-4-yl)ethanone, corresponding to the following characteristics:

LC/MS (method G): $[M+H]^+$: m/z 140 tr (min) = 1.06

^1H NMR spectrum (300 MHz, δ in ppm, $CDCl_3$): 2.48 (s, 6H), 2.70 (s, 3H).

Step 4.3: 2-bromo-1-(3,5-dimethylisoxazol-4-yl)ethanone

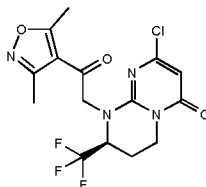


400 mg (2.87 mmol) of 1-(3,5-dimethylisoxazol-4-yl)ethanone are dissolved in 20 mL of glacial acetic acid. 1.42 mL (8.62 mmol) of hydrobromic acid and 163 μ L (3.16 mmol) of bromine are added to the medium. The reaction mixture is placed under magnetic stirring at room temperature for 2 hours. The solution is diluted with water, basified with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness to give 540 mg of 2-bromo-1-(3,5-dimethylisoxazol-4-yl)ethanone, corresponding to the following characteristics:

LC/MS (method G): ESI+ $[M+H]^+$: m/z 218 tr (min) = 1.35

^1H NMR (300 MHz, δ in ppm, $CDCl_3$): 2.52 (s, 3H), 2.74 (s, 3H), 4.18 (s, 2H).

Step 4.4: (8S)-2-chloro-9-[2-(3,5-dimethylisoxazol-4-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



A suspension of 150 mg (0.591 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 578.13 mg (1.77 mmol) of cesium carbonate in 10 mL of acetonitrile is stirred for 15 minutes at room temperature. 154.76 mg (0.709 mmol) of 2-bromo-1-(3,5-dimethylisoxazol-4-yl)ethanone are then added. After stirring overnight at room temperature, the reaction mixture is evaporated and the residue is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness to give 230 mg of (8S)-2-

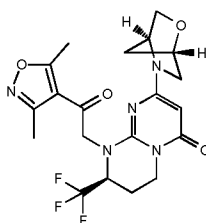
chloro-9-[2-(3,5-dimethylisoxazol-4-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 391 tr (min) = 2.06

- 5 ¹H NMR (300 MHz, δ in ppm, CDCl₃): 2.44 (s, 2H), 2.7 (s, 3H), 3.46 (m, 1H), 4 (m, 2H), 4.54 (m, 1H), 5.23 (s, 3H), 5.53 (d, 1H), 5.92 (s, 1H).

Step 4.5: (8S)-9-[2-(3,5-dimethylisoxazol-4-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

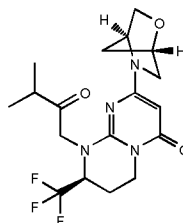
10



- 200 mg (0.51 mmol) of (8S)-2-chloro-9-[2-(3,5-dimethylisoxazol-4-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 83.28 mg (0.61 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride are mixed together. The powder obtained is placed in a tube and 178 μ l (1.28 mmol) of triethylamine are added. The tube is sealed and heated at 130°C in an oil bath for 6 hours. The crude product obtained is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and then evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 130 mg of (8S)-9-[2-(3,5-dimethylisoxazol-4-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:
- LC/MS (method A): ESI+ [M+H]⁺: m/z 454 tr (min) = 0.58
- 25 ¹H NMR (300 MHz, δ in ppm, CDCl₃): 2.44 (s, 2H), 2.7 (s, 3H), 3.46 (m, 1H), 4 (m, 2H), 4.54 (m, 1H), 5.23 (s, 3H), 5.53 (d, 1H), 5.92 (s, 1H).

Example 5:

- (8S)-9-(3-methyl-2-oxobutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 56)
- 30



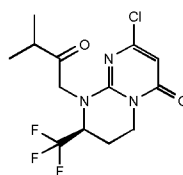
Step 5.1: 1-bromo-3-methylbutan-2-one



A solution of 1 g (11.61 mmol) of 3-methylbutan-2-one in 6 mL of methanol is
 5 cooled to a temperature of 10°C. When the temperature is reached, 597 µl (11.61 mmol) of bromine are added. The reaction mixture is stirred at 10°C until fully decolorized, and stirring is then continued for 30 minutes at room temperature. After adding 10 mL of water to the solution, stirring is continued for 1 hour at room temperature. The reaction mixture is then taken up in water and extracted with ethyl
 10 ether. The organic phase is washed with aqueous 10% Na₂CO₃ solution and then with saturated NaCl solution, dried and evaporated to give 1.50 g of 1-bromo-3-methylbutan-2-one, corresponding to the following characteristics:
¹H NMR (300 MHz, δ in ppm, CDCl₃): 1.15 (s, 3H), 1.18 (s, 3H), 2.92-3.06 (m, 1H), 4 (s, 2H).

15

Step 5.2: (8S)-2-chloro-9-(3-methyl-2-oxobutyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

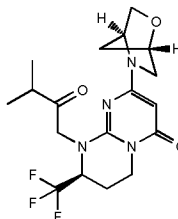


20 A suspension of 170 mg (0.670 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 655.21 mg (2.01 mmol) of cesium carbonate in 10 mL of acetonitrile is stirred for 15 minutes at room temperature. 132.75 mg (0.804 mmol) of 1-bromo-3-methylbutan-2-one are then added. After stirring overnight at room temperature, the reaction mixture is evaporated and the residue is
 25 taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness to give 220 mg of (8S)-2-chloro-9-(3-methyl-2-oxobutyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 338 tr (min) = 2.20

¹H NMR (300 MHz, δ in ppm, CDCl₃): 1.13 (m, 6H), 2.38 (m, 2H), 2.68 (m, 1H), 3.41 (m, 1H), 3.87 (m, 2H), 4.51 (m, 1H), 5.2 (d, 1H), 5.9 (s, 1H).

5 **Step 5.3: (8S)-9-(3-methyl-2-oxobutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one**



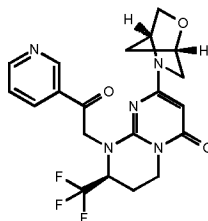
220 mg (0.51 mmol) of (8S)-2-chloro-9-(3-methyl-2-oxobutyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 105.99 mg (0.78 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride are mixed together. The powder obtained is placed in a tube and 227 μ l (1.63 mmol) of triethylamine are added. The tube is sealed and heated at 130°C in an oil bath for 3 hours. The crude product obtained is taken up in ethyl acetate and the organic phase is washed with water, dried over magnesium sulfate and then evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 100 mg of (8S)-9-(3-methyl-2-oxobutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

20 LC/MS (method A): ESI+ [M+H]⁺: m/z 401 tr (min) = 0.6

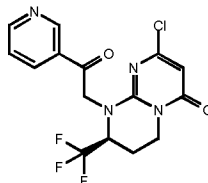
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.02 (m, 6H), 1.79 (m, 2H), 2.16 (m, 1H), 2.37 (m, 1H), 2.68 (m, 1H), 2.84-3.26 (bs, 3H), 3.30-3.75 (bs, 2H), 4.18 (d, 1H), 4.30 (m, 1H), 4.46 (m, 1H), 4.60 (s, 1H), 4.63-4.96 (bs, 2H), 5 (m, 1H).

25 **Example 6:**

(8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 7)



Step 6.1: (8S)-2-chloro-9-(2-oxo-2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



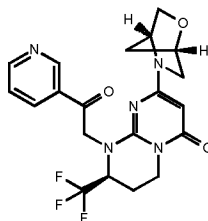
5

A suspension of 750 mg (15.77 mmol) of sodium hydride in 50 mL of DMF is cooled to 0°C under argon. A solution of 2 g (7.89 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 50 mL of DMF is added dropwise. The mixture is stirred for 10 minutes at room temperature. After cooling the reaction medium to 0°C, 2.92 g (9.86 mmol) of 3-(bromoacetyl)pyridine hydrobromide are added portionwise. The reaction mixture is allowed to warm to room temperature and is stirred overnight. The reaction medium is evaporated to dryness and the residue is taken up in water and extracted with EtOAc. The organic phase is dried over magnesium sulfate and evaporated to dryness. The crude product obtained is purified by chromatography on silica gel (eluent: 100% EtOAc). After evaporating the fractions under reduced pressure, 1.90 g of (8S)-2-chloro-9-(2-oxo-2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 373 tr (min) = 1.76

¹H NMR (300 MHz, δ in ppm, CDCl₃): 1.66 (s, 1H), 2.3-2.52 (m, 2H), 3.48 (m, 1H), 4 (m, 1H), 4.37 (d, 1H), 4.56 (m, 1H), 5.92 (s, 1H), 7.45 (m, 1H), 8.22 (m, 1H), 8.81 (s, 1H), 9.15 (s, 1H).

Step 6.2: (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



1 g (2.68 mmol) of (8S)-2-chloro-9-(2-oxo-2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 545.67 mg (4.02 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride are mixed together. The powder obtained is placed in a tube and 934.86 μ l (6.71 mmol) of triethylamine are added. The tube is sealed and heated at 130°C in an oil bath for 6 hours. The crude product obtained is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and then evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 980 mg of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

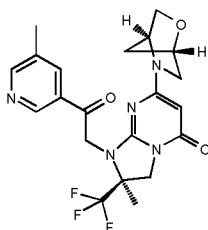
LC/MS (method A): ESI+ [M+H]⁺: m/z 436 tr (min) = 0.51

¹H NMR (600 MHz, δ in ppm, DMSO- d_6): 1.67 (d, 1H), 1.75 (d, 1H), 2.32 (m, 1H), 2.5 (m, 1H), 3.04 (d, 1H), 3.17-3.25 (bs, 1H), 3.25-3.4 (bs, 3H), 4.44 (dd, 1H), 4.48 (s, 1H), 4.52 (s, 1H), 4.66 (m, 1H), 4.72 (s, 1H), 4.77 (d, 1H), 5.7 (d, 1H), 7.64 (m, 1H), 8.41 (m, 1H) 8.88 (m, 1H), 9.24 (s, 1H).

20

Example 7:

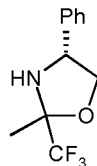
2-methyl-1-[2-(5-methylpyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one (compound 16)



25

Step 7.1: (R)-2-methyl-4-phenyl-2-trifluoromethyloxazolidine

55



25 g (180 mmol) of (R)-phenylglycinol and then 4 g (16 mmol) of pyridinium para-toluenesulfonate are added to a solution of 25.8 g (230 mmol) of trifluoroacetone in 200 mL of toluene in a three-necked flask on which is mounted Dean-Stark apparatus. The mixture obtained is then heated at 110°C for 5 hours. After cooling, the reaction mixture is concentrated under reduced pressure. The residue obtained is purified by filtration on silica (eluent: dichloromethane) to give 35.10 g of (R)-2-methyl-4-phenyl-2-trifluoromethyloxazolidine in the form of a colorless liquid, the characteristics of which are as follows:

LC/MS (method D): ESI+ [M+H]⁺: m/z 232 tr (min) = 0.96

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 1.55 (s, 3H), 3.58 (m, 1H), 3.80 (m, 1H), 4.28 (m, 1H), 4.42 (m, 1H), 7.34 (m, 5H).

$[\alpha]_D^{25}$ at 589 nm = -23.4 $\pm$ 0.8° (c = 1.794 mg / 0.5 mL MeOH)

Step 7.2: (S)-3,3,3-trifluoro-2-((R)-2-hydroxy-1-phenylethylamino)-2-methylpropionitrile



25 mL (200 mmol) of trimethylsilyl cyanide are added dropwise to a solution, cooled to 2°C, of 30.10 g (130 mmol) of (R)-2-methyl-4-phenyl-2-trifluoromethyloxazolidine in 300 mL of dichloromethane in a three-necked flask under argon, followed by dropwise addition of 25 mL (200 mmol) of boron trifluoride etherate. The cold bath is then removed to allow the mixture to warm to room temperature. The resulting mixture is stirred at room temperature for 3 hours, followed by addition of saturated sodium bicarbonate solution to pH = 7. The organic phase is separated out and then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue obtained is purified by chromatography on silica (eluent A/B: pentane/EtOAc, A/B gradient: t 0 min 0% B, t 20 min 10% B, t 40 min 40% B) to give 3.50 g of (R)-3,3,3-trifluoro-2-((R)-2-hydroxy-1-phenylethylamino)-2-methylpropionitrile in the form of a colorless oil and 10 g of (S)-3,3,3-trifluoro-2-((R)-2-hydroxy-1-phenylethylamino)-2-methylpropionitrile in the form of a white solid, the characteristics of which are:

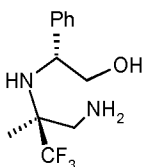
LC/MS (method D): ESI+ [M+H]⁺: m/z 259 tr (min) = 0.86

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 1.71 (s, 3H), 3.43 (m, 2H), 3.57 (m, 1H), 3.96 (m, 1H), 4.97 (m, 1H), 7.29 (m, 5H).

$[\alpha]_D^{25}$ at 589 nm = $-77.6 \pm 1.4^\circ$ (c = 1.818 mg/ 0.5 mL DMSO) for (S)-3,3,3-trifluoro-2-

5 ((R)-2-hydroxy-1-phenylethylamino)-2-methylpropionitrile

Step 7.3: (R)-2-((S)-1-aminomethyl-2,2,2-trifluoro-1-methylethylamino)-2-phenylethanol



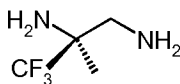
- 10 65.10 mL (65.10 mmol) of a 1 M solution of lithium aluminum hydride in tetrahydrofuran are added to a solution, cooled to 2°C, of 16.80 g (65.10 mmol) of (S)-3,3,3-trifluoro-2-((R)-2-hydroxy-1-phenylethylamino)-2-methylpropionitrile in 50 mL of anhydrous tetrahydrofuran in a three-necked flask under argon. At the end of the addition, the reaction mixture is allowed to warm to room temperature and is then stirred overnight.
- 15 The mixture obtained is cooled to 0°C, followed by very slow dropwise addition of 12 mL of water. Substantial evolution of gas and a temperature rise to 4°C are observed. 12 mL of 15% potassium hydroxide and then 25 mL of water are added to the resulting mixture, maintained at 0°C. The white precipitate formed is filtered off and the filtrate obtained is dried over magnesium sulfate and then concentrated under reduced
- 20 pressure to give 10.50 g of (R)-2-((S)-1-aminomethyl-2,2,2-trifluoro-1-methylethylamino)-2-phenylethanol, the characteristics of which are as follows:

LC/MS (method D): ESI+ [M+H]⁺: m/z 263 tr (min) = 0.43

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 0.90 (s, 3H), 2.48 (m, 2H), 2.72 (m, 2H), 3.31 (m, 4H), 3.95 (m, 1H), 7.27 (m, 5H).

25 $[\alpha]_D^{25}$ at 589 nm = $-51.2 \pm 1.3^\circ$ (c = 1.576 mg / 0.5 mL DMSO)

Step 7.4: (S)-3,3,3-trifluoro-2-methylpropane-1,2-diamine



- A mixture of 10.50 g (70 mmol) of (R)-2-((S)-1-aminomethyl-2,2,2-trifluoro-1-methylethylamino)-2-phenylethanol in methanol, 4.5 mL (68 mmol) of methanesulfonic acid and 1.50 g of Pd(OH)₂/C (20% w/w) is hydrogenated at 25°C in an autoclave,
- 30

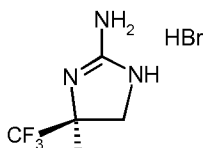
under a hydrogen pressure of 5 bar, for 24 hours. The mixture obtained is then filtered and the filtrate is evaporated to dryness. The oil obtained is taken up in 3 M hydrochloric acid solution (42 mL). The mixture obtained is extracted with ethyl ether. Ethyl ether and 15 mL of 35% sodium hydroxide are then added to the aqueous phase, to pH 12. The aqueous phase is then separated out by settling and extracted with 3 times 200 mL of ethyl ether. The organic phases are combined, dried over magnesium sulfate, filtered and then concentrated under vacuum to give 4.50 g of (S)-3,3,3-trifluoro-2-methylpropane-1,2-diamine in the form of a pale yellow oil, the characteristics of which are as follows:

LC/MS (method E): ESI+ [M+H]⁺: m/z 143 tr (min) = 0.34

¹H NMR (300 MHz, DMSO-d₆): 1.10 (s, 3 H), 1.60-1.85 (bs, 2H), 2.48 (d, 1 H), 2.72 (d, 1 H), 3.20-3.50 (bs, 2H).

[α]_D²⁵ at 589 nm = -4.3 ± 0.6° (c = 1.778 mg/ 0.5 mL DMSO)

Step 7.5: (S)-4-methyl-4-trifluoromethyl-4,5-dihydro-1H-imidazol-2-ylamine hydrobromide



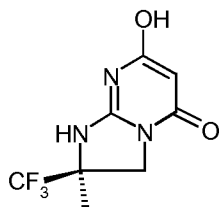
11.60 mL (34.90 mmol) of cyanogen bromide dissolved in dichloromethane are added portionwise to a solution, cooled to 4°C, of 4.50 g (31.70 mmol) of (S)-3,3,3-trifluoro-2-methylpropane-1,2-diamine in 20 mL of acetonitrile, while maintaining the temperature between 5 and 10°C. At the end of the addition, the reaction mixture is left at 5°C for 30 minutes. The mixture obtained is then stirred at room temperature overnight. The resulting mixture is then concentrated under vacuum. The residue obtained is taken up twice with ethanol and then twice with toluene, and evaporated to dryness each time. The solid obtained is triturated with ethyl ether and then filtered off to give 4.50 g of (S)-4-methyl-4-trifluoromethyl-4,5-dihydro-1H-imidazol-2-ylamine hydrobromide in the form of a white solid, the characteristics of which are as follows:

LC/MS (method D): ESI+ [M+H]⁺: m/z 168 tr (min) = 0.14

¹H NMR (300 MHz, DMSO-d₆): 1.52 (s, 3 H), 3.57 (m, 1H), 3.81 (m, 1 H), 7.45 (s, 2H), 8.09 (s, 1H), 9.45 (s, 1H).

[α]_D²⁵ at 589 nm: -5.2 ± 0.3° (c = 4.909 mg/ 0.5 mL DMSO)

Step 7.6: (S)-7-hydroxy-2-methyl-2-trifluoromethyl-2,3-dihydro-1H-

imidazo[1,2-a]pyrimidin-5-one

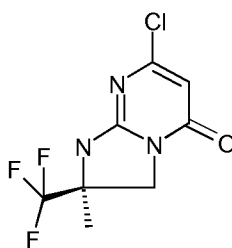
36.90 g (148.76 mmol) of (S)-4-methyl-4-trifluoromethyl-4,5-dihydro-1H-imidazol-2-ylamine hydrobromide and 24.10 g (446 mmol) of sodium methoxide are added to a mixture of 29.50 g (216.43 mmol) of diethyl malonate in 200 mL of methanol. The resulting mixture is refluxed for 18 hours. After cooling, the mixture obtained is concentrated to dryness under vacuum. 65 mL of cold water are added to the residue obtained, to obtain a thick suspension, to which is added 25% hydrochloric acid to pH 5. The resulting suspension is stirred in an ice bath for 3 hours and then filtered. The insoluble matter obtained is rinsed with water and then dried to give 37.60 g of (S)-7-hydroxy-2-methyl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one in the form of a white solid, the characteristics of which are as follows:

LC/MS (method D): ESI+ [M+H]⁺: m/z 236 tr (min) = 0.32

¹H NMR (400 MHz, DMSO-d₆): 1.53 (s, 3H), 3.95 (m, 1H), 4.10 (m, 1H), 4.79 (s, 1H), 5.80-7.01 (bs, 1H), 9.09 (s, 1H).

[α]_D²⁵ at 589 nm = -5.6 ± 0.6° (c = 1.789 mg/ 0.5 mL DMSO)

Step 7.7: (S)-7-chloro-2-methyl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one



20

41.60 mL (446.50 mmol) of phosphorus oxychloride are added, at room temperature and under an argon atmosphere, to a suspension of 35 g (148.80 mmol) of (S)-7-hydroxy-2-methyl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one in 350 mL of 1,2-dichloroethane. The resulting mixture is then heated at 70°C for 4 hours. After cooling, the reaction mixture is evaporated to dryness under vacuum. The residue obtained is taken up in 35 mL of cold water and 500 mL of ethyl acetate. 32% sodium hydroxide is added to the mixture obtained, to pH = 6-7. The organic phase is then separated out and then dried over magnesium sulfate, filtered and concentrated under

25

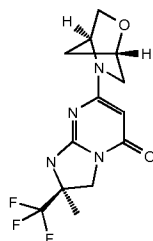
reduced pressure to give 20 g of (S)-7-chloro-2-methyl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one, the characteristics of which are as follows:

LC/MS (method D): ESI+ [M+H]⁺: m/z 254 tr (min) = 0.51

¹H NMR (400 MHz, DMSO-d₆): 1.57 (s, 3H), 4.00 (d, 1H), 4.21 (d, 1H), 5.84 (s, 1H), 9.64 (s, 1H).

[α]_D²⁵ at 589 nm = -64.8 ± 1.1° (c = 2.2 mg/ 0.5 mL DMSO)

Step 7.8: 2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one

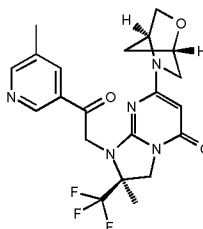


1 g (3.84 mmol) of (S)-7-chloro-2-methyl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one and 844.18 mg (5.91 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride are mixed together. The powder obtained is placed in a tube and 1.38 mL (9.86 mmol) of triethylamine are added. The tube is sealed and heated at 140°C in an oil bath for 4 hours. After cooling, the crude product is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH). After evaporating the fractions under reduced pressure, 750 mg of 2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one are obtained, the characteristics of which are as follows:

LC/MS (method G): ESI+: [M+H]⁺: m/z 317 tr (min) = 1.34

¹H NMR (300 MHz, δ in ppm, CDCl₃): 1.34 (s, 3H), 1.65 (m, 2H), 3.13 (m, 2H), 3.43 (m, 1H), 3.53 (m, 1H), 3.72 (d, 1H), 3.89 (d, 1H), 4.1-4.81 (bs, 3H), 8.77 (s, 1H).

Step 7.9: 2-methyl-1-[2-(5-methylpyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one



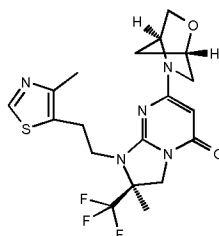
150 mg (0.474 mmol) of 2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one in 5 mL of DMF are added to a suspension of 50.08 mg (1.04 mmol) of sodium hydride in 5 mL of DMF. The reaction mixture is placed under magnetic stirring at room temperature for 15 minutes. A solution of 153.88 mg (0.521 mmol) of 3-(bromoacetyl)pyridine hydrobromide in 5 mL of DMF is added dropwise to the reaction medium. The reaction is stirred at room temperature overnight. The reaction medium is evaporated to dryness. The crude product is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 100 mg of 2-methyl-1-[2-(5-methylpyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one, the characteristics of which are as follows:

LC/MS (method A): ESI+ [M+H]⁺: m/z 450 tr (min) = 0.52

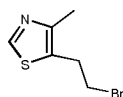
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.65 (s, 3H), 1.71 (m, 2H), 2.4 (s, 3H), 3-3.2 (m, 2H), 3.42 (s, 2H), 4 (d, 1H), 4.24 (d, 1H), 4.52 (t, 3H) 4.81 (d, 1H), 5.12 (d, 1H), 8.19 (s, 1H), 8.67 (s, 1H), 8.99 (s, 1H).

Example 8:

20 **2-methyl-1-[2-(4-methylthiazol-5-yl)ethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one (compound 26)**



25 **Step 8.1: 5-(2-bromoethyl)-4-methylthiazole**



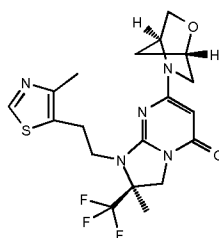
1 g (6.98 mmol) of 2-(4-methylthiazol-5-yl)ethanol is dissolved in 15 mL of dichloromethane. The solution is cooled to 0°C. When the temperature is reached, 1.85

g (6.98 mmol) of triphenylphosphine are added, followed by portionwise addition of 1.30 g (6.98 mmol) of N-bromosuccinimide. After stirring for 2 hours at 0°C, the mixture is evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 50/50 EtOAc/heptane) to give 900 mg of 5-(2-bromoethyl)-4-methylthiazole, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 206 tr (min) = 1.52

¹H NMR (300 MHz, δ in ppm, CDCl₃): 2.42 (s, 3H) 3.3-3.35 (t, 2H) 3.5-3.55 (t, 2H) 8.62 (s, 1H)

Step 8.2: 2-methyl-1-[2-(4-methylthiazol-5-yl)ethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one



15 150 mg (0.474 mmol) of 2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one in 5 mL of DMF are added to a suspension of 45.53 mg (0.95 mmol) of sodium hydride in 5 mL of DMF. The reaction mixture is heated for 15 minutes at 80°C. A solution of 293.24 mg (1.42 mmol) of 5-(2-bromoethyl)-4-methylthiazole in 5 mL of DMF is added dropwise to the reaction medium. The reaction is heated at 80°C overnight. The reaction medium is evaporated to dryness. The crude product is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 45 mg of 2-methyl-1-[2-(4-methylthiazol-5-yl)ethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one, the characteristics of which are as follows:

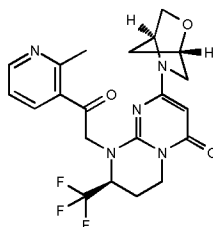
LC/MS (method A): ESI+ [M+H]⁺: m/z 442 tr (min) = 0.56

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.55 (s, 3H), 1.86 (m, 2H), 2.34 (s, 3H), 3-3.48 (m, 7H), 3.6 (m, 1H), 3.66 (m, 1H), 3.76 (m, 1H), 3.86 (d, 1H), 4.13 (d, 1H), 4.66 (s, 1H), 8.86 (s, 1H).

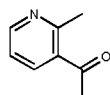
Example 9:

(8S)-9-[2-(2-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-

azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 19)



5 **Step 9.1: 1-(2-methylpyrid-3-yl)ethanone**



The following are successively introduced into a microwave tube:

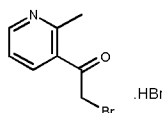
469.80 μ l (4.07 mmol) of 3-bromo-5-methylpyridine in 20 mL of H₂O/DMF: (1/3:
 10 v/v), 2.03 mL (5.70 mmol) of tributyl(1-ethoxyvinyl)tin, 57.12 mg (81.38 mmol) of
 bis(triphenylphosphine)palladium(II) chloride, 1.12 g (8.14 mmol) of potassium
 carbonate. After irradiating with microwaves for 1 hour at 110°C, the reaction mixture is
 evaporated to dryness and the residue is taken up in water and extracted with ethyl
 acetate. The organic phase is dried over magnesium sulfate and evaporated to
 15 dryness. The residue is taken up in a solution consisting of 6 mL of methanol and 1 mL
 of 1 N hydrochloric acid. After stirring overnight at room temperature, the reaction
 mixture is evaporated to dryness and the residue is taken up in saturated aqueous
 NaHCO₃ solution and extracted with ethyl acetate. The organic phase is dried over
 magnesium sulfate and evaporated to dryness. The residue is purified by
 20 chromatography on silica gel (eluent: 50/50 EtOAc/heptane) to give 160 mg of 1-(2-
 methylpyrid-3-yl)ethanone, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 136 tr (min) = 0.38

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 2.58 (s, 3H), 2.61 (s, 3H), 7.38 (m, 1H), 8.2
 (m, 1H), 8.57 (m, 1H).

25

Step 9.2: 2-bromo-1-(2-methylpyrid-3-yl)ethanone hydrobromide

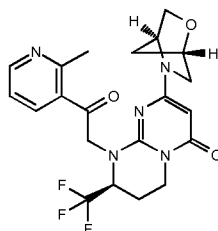


150 mg (1.11 mmol) of 1-(2-methylpyrid-3-yl)ethanone are dissolved in 10 mL of glacial acetic acid. 365 μ l (2.22 mmol) of hydrobromic acid and 63 μ l (1.22 mmol) of bromine are added to the medium. The reaction mixture is placed under magnetic stirring at room temperature for 1 hour. Ethyl ether is added to the solution until a precipitate appears. The precipitate corresponding to 2-bromo-1-(2-methylpyrid-3-yl)ethanone hydrobromide is filtered off, washed with ethyl ether and dried. The 280 mg of product obtained have the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 214 tr (min) = 0.72

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 2.73 (s, 3H), 5 (s, 2H), 7.86 (m, 1H), 8.76 (m, 1H), 8.86 (m, 1H).

Step 9.3: (8S)-9-[2-(2-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



140 mg (0.474 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 3 mL of DMF are added to a suspension of 46.74 mg (0.97 mmol) of sodium hydride in 4 mL of DMF. The reaction mixture is placed under magnetic stirring at room temperature for 15 minutes. A solution of 143.62 mg (0.443 mmol) of 2-bromo-1-(2-methylpyrid-3-yl)ethanone hydrobromide in 3 mL of DMF is added dropwise to the reaction medium. The reaction is stirred at room temperature for 1 hour. The reaction medium is evaporated to dryness. The crude product is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 100 mg of (8S)-9-[2-(2-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

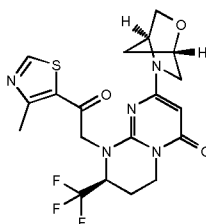
LC/MS (method A): ESI+ [M+H]⁺: m/z 450 tr (min) = 0.48

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.71 (m, 2H), 2.25 (m, 1H), 2.43 (m, 1H), 2.6 (s, 3H), 3.1-3.15 (m, 2H), 3.28 (m, 1H), 3.33-3.52 (bs, 2H), 4.37 (m, 1H), 4.52 (d, 2H), 4.59 (m, 1H), 4.64 (d, 1H), 4.69 (s, 1H), 5.5 (d, 1H), 7.4 (m, 1H), 8.28 (m, 1H), 8.61 (m,

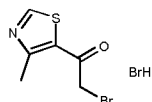
1H).

Example 10:

(8S)-9-[2-(4-methylthiazol-5-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 43)

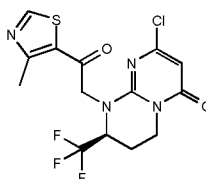


Step 10.1: 2-bromo-1-(4-methylthiazol-5-yl)ethanone hydrobromide



220 mg (1.56 mmol) of 1-(4-methylthiazol-5-yl)ethanone are dissolved in 10 mL of glacial acetic acid. 769 μ l (4.67 mmol) of hydrobromic acid and 88 μ l (1.71 mmol) of bromine are added to the medium. The reaction mixture is placed under magnetic stirring at room temperature for 2 hours. Ethyl ether is added to the solution until a precipitate appears. The precipitate corresponding to 2-bromo-1-(4-methylthiazol-5-yl)ethanone hydrobromide is filtered off, washed with ethyl ether and dried. The 350 mg of product obtained have the following characteristics:
LC/MS (method G): ESI+ [M+H]⁺: m/z 220 tr (min) = 1.32
¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 2.67 (s, 3H), 4.79 (s, 2H), 9.31 (s, 1H).

Step 10.2: (8S)-2-chloro-9-[2-(4-methylthiazol-5-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



A suspension of 150 mg (0.591 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 578.13 mg (1.77 mmol) of cesium carbonate in 10 mL of acetonitrile is stirred for 15 minutes at room temperature. 213.64 mg (0.709 mmol) of 2-bromo-1-(4-methylthiazol-5-yl)ethanone hydrobromide are then

added. After stirring overnight at room temperature, the reaction mixture is evaporated and the residue is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness to give 190 mg of (8S)-2-chloro-9-[2-(4-methylthiazol-5-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-

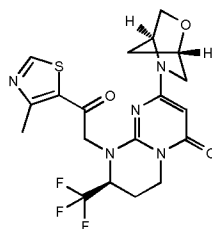
5 tetrahydropyrimido[1,2-a]pyrimidin-4-one, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 393 tr (min) = 1.95

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 2.3 (m, 1H), 2.49 (s, 1H), 2.72 (s, 3H), 3.37 (m, 1H), 4.4 (m, 1H), 4.77 (m, 1H), 4.81 (s, 1H), 5.22 (d, 1H), 5.96 (s, 1H), 9.58 (s, 1H).

10

Step 10.3: (8S)-9-[2-(4-methylthiazol-5-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



15 170 mg (0.511 mmol) of (8S)-2-chloro-9-[2-(4-methylthiazol-5-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 70.42 mg (0.52 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride are mixed together. The powder obtained is placed in a tube and 151 µl (1.08 mmol) of triethylamine are added. The tube is sealed and heated at 130°C in an oil bath for 3 hours. The crude product obtained is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and then evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 120 mg of (8S)-9-[2-(4-methylthiazol-5-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

25

LC/MS (method A): ESI+ [M+H]⁺: m/z 456 tr (min) = 0.55

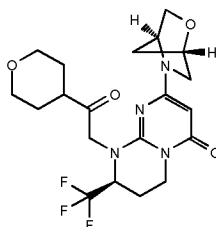
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.69 (m, 2H), 2.28 (m, 1H), 2.43 (m, 1H), 2.7 (s, 3H), 2.98 (d, 1H), 3.12 (d, 1H), 3.21-3.33 (m, 3H), 4.37 (m, 1H), 4.42 (s, 1H), 4.5 (s, 1H), 4.55-4.62 (m, 2H), 4.67 (s, 1H), 5.22 (d, 1H), 9.19 (s, 1H).

30

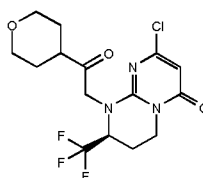
Example 11:

(8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-oxo-2-

(tetrahydropyran-4-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 62)



5 **Step 11.1:** (8S)-2-chloro-9-[2-oxo-2-(tetrahydropyran-4-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

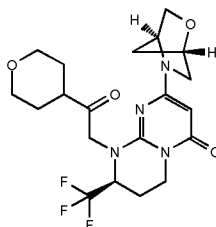


A suspension of 150 mg (0.591 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 578.13 mg (1.77 mmol) of cesium carbonate in 10 mL of acetonitrile is stirred for 15 minutes at room temperature. 146.97 mg (0.709 mmol) of 2-bromo-1-(tetrahydropyran-4-yl)ethanone are then added. After stirring overnight at room temperature, the reaction mixture is evaporated and the residue is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness to give 220 mg of (8S)-2-chloro-9-[2-oxo-2-(tetrahydropyran-4-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 380 tr (min) = 1.94

¹H NMR (300 MHz, δ in ppm, CDCl₃): 1.58-2.04 (m, 2H), 2.37 (m, 1H), 2.5 (m, 1H), 2.76 (m, 1H), 3.5 (4H), 3.9 (d, 1H), 3.96-4.02 (m, 4H), 4.6 (m, 1H), 5.25 (d, 1H), 5.99 (s, 1H).

25 **Step 11.2:** (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-oxo-2-(tetrahydropyran-4-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



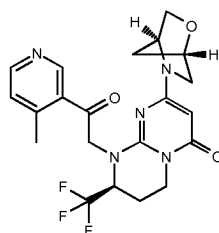
- 220 mg (0.58 mmol) of (8S)-2-chloro-9-[2-oxo-2-(tetrahydropyran-4-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 94.26 mg (0.69 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride are mixed together.
- 5 The powder obtained is placed in a tube and 202 μ l (1.45 mmol) of triethylamine are added. The tube is sealed and heated at 130°C in an oil bath for 3 hours. The crude product obtained is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and then evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 220 mg of
- 10 (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-oxo-2-(tetrahydropyran-4-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

LC/MS (method A): ESI+ [M+H]⁺: m/z 443 tr (min) = 0.52

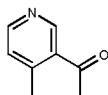
- ¹H NMR (600 MHz, δ in ppm, DMSO- d_6): 1.49 (m, 1H), 1.52 (m, 1H), 1.7 (m, 2H), 1.79 (bs, 2H), 2.15 (m, 1H), 2.36 (m, 1H), 2.7 (m, 1H), 2.84-3.25 (bs, 3H), 3.31-3.59 (bs, 3H), 3.65 (d, 1H), 3.86 (m, 2H), 4.17 (d, 1H), 4.3 (m, 1H), 4.35-5.3 (bs, 5H).
- 15

Example 12:

- (8S)-9-[2-(4-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 20)
- 20



Step 12.1: 1-(4-methylpyrid-3-yl)ethanone



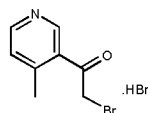
- 25 671 μ l (5.81 mmol) of 3-bromo-4-methylpyridine in 15 mL of H₂O/DMF (1/4: v/v), 1.93 mL (14.53 mmol) of N-butyl vinyl ether, 39.15 mg (0.17 mmol) of palladium(II) acetate,

163.14 mg (0.38 mmol) of 1,3-bis(diphenylphosphino)propane and 973.84 mg (6.98 mmol) of potassium carbonate are placed in a microwave tube. After irradiating with microwaves at 120°C for 2 hours, 20 mL of 5% hydrochloric acid solution are added. The reaction mixture is stirred for 1 hour at room temperature and then basified with potassium carbonate and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 50/50 EtOAc/heptane) to give 320 mg of 1-(4-methylpyrid-3-yl)ethanone, the characteristics of which are as follows:

LC/MS (method G): ESI+ $[M+H]^+$: m/z 136 tr (min) = 0.56

¹H NMR (300 MHz, δ in ppm, DMSO- d_6): 2.46 (s, 3H), 2.62 (s, 3H), 7.35 (d, 1H), 8.56 (d, 1H), 9 (s, 1H).

Step 12.2: 2-bromo-1-(4-methylpyrid-3-yl)ethanone hydrobromide

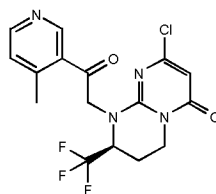


300 mg (2.22 mmol) of 1-(4-methylpyrid-3-yl)ethanone are dissolved in 20 mL of glacial acetic acid. 730 μ L (4.44 mmol) of hydrobromic acid and 126 μ L (2.44 mmol) of bromine are added to the medium. The reaction mixture is placed under magnetic stirring at room temperature for 2 hours. Ethyl ether is added to the solution until a precipitate appears. The precipitate corresponding to 2-bromo-1-(4-methylpyrid-3-yl)ethanone hydrobromide is filtered off, washed with ethyl ether and dried. The 550 mg of product obtained have the following characteristics:

LC/MS (method G): ESI+ $[M+H]^+$: m/z 214 tr (min) = 1.01

¹H NMR (300 MHz, δ in ppm, DMSO- d_6): 2.59 (s, 3H), 5.04 (s, 2H), 7.85 (d, 1H), 8.84 (d, 1H), 9.25 (s, 1H).

Step 12.3: (8S)-2-chloro-9-[2-(4-methylpyrid-3-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



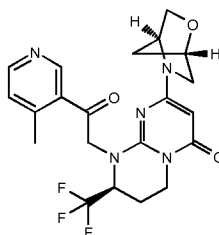
A suspension of 100 mg (0.394 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-

tetrahydropyrimido[1,2-a]pyrimidin-4-one and 385.42 mg (1.18 mmol) of cesium carbonate in 10 mL of acetonitrile is stirred for 15 minutes at room temperature. 139.57 mg (0.473 mmol) of 2-bromo-1-(4-methylpyrid-3-yl)ethanone hydrobromide are then added. After stirring overnight at room temperature, the reaction mixture is evaporated and the residue is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness to give 140 mg of (8S)-2-chloro-9-[2-(4-methylpyrid-3-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 387 tr (min) = 1.87

¹H NMR (300 MHz, δ in ppm, CDCl₃): 2.27 (m, 1H), 2.44 (s, 3H), 2.5 (m, 1H), 3.4 (m, 1H), 4.4 (m, 1H), 4.77 (m, 1H), 4.86 (d, 1H), 5.32 (d, 1H), 5.97 (s, 1H), 7.4 (d, 1H), 8.6 (d, 1H), 9 (s, 1H).

Step 12.4: (8S)-9-[2-(4-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



140 mg (0.36 mmol) of (8S)-2-chloro-9-[2-(4-methylpyrid-3-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 94.26 mg (0.69 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride are mixed together. The powder obtained is placed in a tube and 126 μ L (0.90 mmol) of triethylamine are added. The tube is sealed and heated at 120°C in an oil bath for 2 hours. The crude product obtained is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and then evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 120 mg of (8S)-9-[2-(4-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

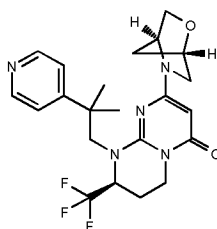
LC/MS (method A): ESI+ [M+H]⁺: m/z 450 tr (min) = 0.48

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.7 (m, 2H), 2.25 (m, 1H), 2.42 (m, 1H), 2.45 (s, 3H), 3-3.2 (m, 2H), 3.24-3.53 (bs, 3H), 3.36 (m, 1H), 4.51 (s, 1H), 4.54 (s, 1H), 4.59

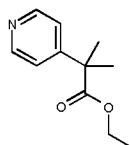
(m, 1H), 4.65-4.76 (m, 2H), 5.55 (d, 1H), 7.37 (d, 1H), 8.59 (d, 1H), 9.05 (s, 1H).

Example 13:

- 5 **(8S)-9-(2-methyl-2-pyrid-4-ylpropyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 1)**

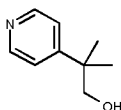


Step 13.1: ethyl 2-methyl-2-pyrid-4-ylpropionate



- 10 The reaction is performed under argon: 2 g (12.12 mmol) of ethyl pyrid-4-ylacetate are dissolved in 30 mL of DMF. After addition of 15.25 mL (15.15 mmol) of a 1 M solution of lithium bis(trimethylsilyl)amide in THF, the reaction mixture is stirred at room temperature for 30 minutes. 1.21 mL (19.39 mmol) of iodomethane are then added gently, and the solution obtained is stirred at room temperature for 1 hour 30
- 15 minutes. A second portion of 15.25 mL (15.15 mmol) of a 1 M solution of lithium bis(trimethylsilyl)amide in THF is added, and the mixture is stirred at room temperature for 1 hour. A second portion of 1.21 mL (19.39 mmol) of iodomethane is also added, and stirring is continued for 2 hours at room temperature. The precipitate formed is filtered off, the filtrate is evaporated to dryness and the residue is taken up in
- 20 dichloromethane. The organic phase is washed with water and with aqueous ammonium chloride solution, dried and evaporated to dryness to give 1.80 g of ethyl 2-methyl-2-pyrid-4-ylpropionate, corresponding to the following characteristics:
- LC/MS (method G): ESI+ [M+H]⁺: m/z 194 tr (min) = 1.03
- ¹H NMR (300 MHz, δ in ppm, DMSO- d_6): 1.11 (t, 3H), 1.49 (s, 6H), 4.09 (q, 2H), 7.31
- 25 (d, 2H), 8.52 (d, 2H).

Step 13.2: 2-methyl-2-pyrid-4-ylpropan-1-ol

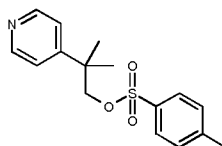


A solution of 1.58 g (7.36 mmol) of ethyl 2-methyl-2-pyrid-4-ylpropionate in 30 mL of THF is cooled to 10°C. When the temperature is reached, 22.08 mL (22.08 mmol) of 1 M diisobutylaluminum hydride solution in toluene are added dropwise. The reaction mixture is allowed to warm to room temperature and is stirred overnight. 1 N hydrochloric acid solution is added to the reaction medium, which is then extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness to give 1.60 g of 2-methyl-2-pyrid-4-ylpropan-1-ol, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 152 tr (min) = 0.40

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 1.19 (s, 6H), 3.42 (d, 2H), 4.76 (t, 1H), 7.34 (d, 2H), 8.44 (d, 2H).

Step 13.3: 2-methyl-2-pyrid-4-ylpropyl benzenesulfonate



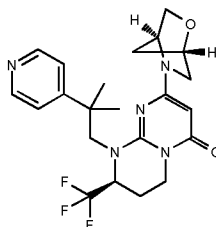
15

710 µl (4.07 mmol) of N,N-diisopropylethylamine and 33.13 mg (0.27 mmol) of 4-dimethyl amino pyridine are added to a solution of 410 mg (2.71 mmol) of 2-methyl-2-pyrid-4-ylpropan-1-ol in 10 mL of dichloromethane. The mixture is cooled to 0°C and a solution of 775.42 mg (4.07 mmol) of 4-methylbenzene-1-sulfonyl chloride in 2 mL of dichloromethane is then added. After allowing the reaction medium to warm to room temperature and stirring overnight, it is washed with water and with saturated NaCl solution. The organic phase is dried over magnesium sulfate and evaporated to dryness to give 660 mg of 2-methyl-2-pyrid-4-ylpropyl benzenesulfonate, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 306 tr (min) = 1.49

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 1.22 (s, 6H), 2.43 (s, 3H), 4.11 (s, 2H), 7.27 (d, 2H), 7.42 (d, 2H), 7.66 (d, 2H), 8.43 (d, 2H).

Step 13.4: (8S)-9-(2-methyl-2-pyrid-4-ylpropyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



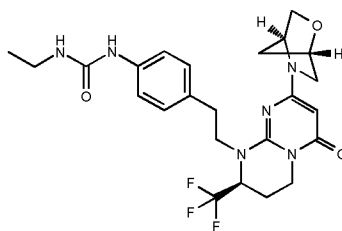
The following are placed in a tube: 130 mg (0.411 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, 133.92 mg (0.411 mmol) of cesium carbonate, 6.16 mg (0.041 mmol) of sodium iodide and 175.74 mg (0.575 mmol) of 2-methyl-2-pyrid-4-ylpropyl benzenesulfonate in 5 mL of DMF. The reaction mixture is heated overnight at 150°C in the sealed tube. After allowing the mixture to cool to room temperature, the solvent is evaporated off. The residue is taken up in ethyl acetate, washed with water, dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 18 mg of (8S)-9-(2-methyl-2-pyrid-4-ylpropyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

LC/MS (method B): ESI+ [M+H]⁺: m/z 450 tr (min) = 0.53

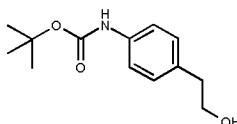
¹H NMR (600 MHz, δ in ppm, DMSO- d_6): 1.24 (s, 1H), 1.31 (s, 3H), 1.35 (s, 3H), 1.83 (m, 2H), 2.09 (m, 1H), 2.18 (m, 1H), 3.02 (m, 1H), 3.21 (m, 2H), 3.57 (m, 1H), 3.75 (m, 2H), 3.98 (m, 1H), 4.65 (m, 2H), 4.76 (d, 1H), 4.99 (m, 1H), 7.49 (s, 2H), 8.53 (s, 2H).

Example 14:

1-ethyl-3-{4-[2-((8S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]phenyl}urea (compound 23)



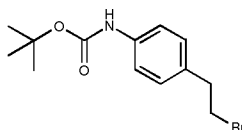
Step 14.1: tert-butyl [4-(2-hydroxyethyl)phenyl]carbamate



5 g (35.36 mmol) of 2-(4-aminophenyl)ethanol and 6.17 mL (35.36 mmol) of N,N-diisopropylethylamine are added to a solution of 8.49 g (38.89 mmol) of di-*tert*-butyl dicarbonate in 10 mL of dioxane. After stirring for 4 hours at room temperature, the reaction mixture is evaporated to dryness. The residue is taken up in ethyl acetate and the solution is washed with 1 N hydrochloric acid solution and then with water. The organic phase is dried over magnesium sulfate and evaporated to dryness to give 7.85 g of *tert*-butyl [4-(2-hydroxyethyl)phenyl]carbamate, the characteristics of which are as follows:

¹H NMR spectrum (300 MHz, δ in ppm, DMSO-*d*₆): 1.47 (s, 9H), 2.65 (t, 2H), 3.54 (q, 2H), 4.60 (t, 1H), 7.07 (d, 2H), 7.33 (d, 2H), 9.13-9.3 (bs, 1H).

Step 14.2: *tert*-butyl [4-(2-bromoethyl)phenyl]carbamate



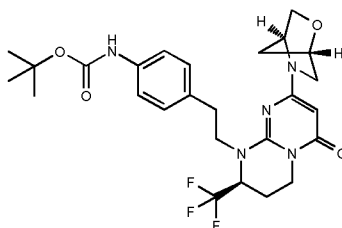
8.68 g (33.08 mmol) of triphenylphosphine are added, under an argon atmosphere, to a solution of 7.85 g (33.08 mmol) of *tert*-butyl [4-(2-hydroxyethyl)phenyl]carbamate in 85 mL of dichloromethane. The mixture is cooled to 0°C and 5.95 g (33.08 mmol) of N-bromosuccinimide are added portionwise over 25 minutes. Stirring is continued for 3 hours at 0°C. The solvent is then evaporated off, the oil obtained is taken up in ether and the precipitate formed is filtered off and discarded.

The filtrate is evaporated and the residue is purified by chromatography on silica gel (eluent: 10/90 EtOAc/heptane) to give 6.90 g of *tert*-butyl [4-(2-bromoethyl)phenyl]carbamate, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+Na]⁺: 322 tr (min) = 2.46

¹H NMR spectrum (300 MHz, δ in ppm, DMSO-*d*₆): 1.47 (s, 9H), 3.04 (t, 2H), 3.68 (t, 2H), 7.15 (d, 2H), 7.38 (d, 2H), 9.29 (s, 1H).

Step 14.3: *tert*-butyl {4-[2-((8*S*)-8-(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*a*]pyrimidin-1-yl)ethyl]phenyl}carbamate

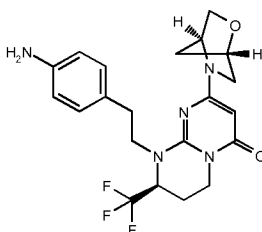


300 mg (0.95 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 3 mL of DMF are added to a suspension of 75.87 mg (1.89 mmol) of sodium hydride in 2 mL of 2-methyltetrahydrofuran. The reaction mixture is placed under magnetic stirring at room temperature for 10 minutes. A solution of 569.48 mg (1.89 mmol) of tert-butyl [4-(2-bromoethyl)phenyl]carbamate in 3 mL of DMF is added dropwise to the reaction medium. The reaction is stirred at room temperature overnight. The reaction medium is evaporated to dryness. The crude product is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 240 mg of tert-butyl {4-[2-((8S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]phenyl}carbamate, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 536 tr (min) = 2.46

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 1.45 (s, 9H), 1.9 (s, 3H), 2.32 (m, 1H), 2.70-2.98 (m, 2H), 3.13 (m, 2H), 3.24-3.47 (bs, 2H), 3.7 (m, 1H), 3.77 (m, 1H), 4.17 (m, 2H), 4.47-5 (bs, 4H), 7.01 (d, 2H), 7.38 (d, 2H), 9.28 (s, 1H).

20 **Step 14.4: (8S)-9-[2-(4-aminophenyl)ethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one**



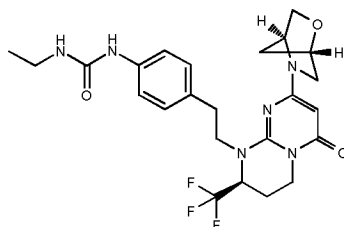
25 4 mL (17.93 mmol) of a 4 N HCl/dioxane solution are added to a solution of 240 mg (0.45 mmol) of tert-butyl {4-[2-((8S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]phenyl}carbamate. The reaction mixture is stirred for 1 hour 30 minutes at room temperature. The solvent is evaporated off and the residue is taken up in a methanol/dichloromethane mixture and then evaporated to give 245 mg of (8S)-9-[2-(4-aminophenyl)ethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as

follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 436 tr (min) = 1.60

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 1.79-2.12 (m, 3H), 2.33 (m, 1H), 2.82-3.09 (m, 2H), 3.17 (m, 2H), 3.37 (m, 1H), 3.58 (s, 1H), 3.69 (m, 2H), 3.79 (d, 1H), 4.2 (m, 2H), 4.67 (bs, 3H), 7.33 (s, 4H), 9.8-10.6 (bs, 2H).

Step 14.5: 1-ethyl-3-{4-[2-((8S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]phenyl}urea



10

50 μl (0.63 mmol) of ethyl isocyanate are added to a solution of 150 mg (0.32 mmol) of (8S)-9-[2-(4-aminophenyl)ethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 139 μl (0.79 mmol) of N,N-diisopropylethylamine in 1 mL of dichloromethane. After stirring overnight at room temperature, the solvent is evaporated off. The residue is taken up in ethyl acetate and washed with water and with saturated aqueous NaCl solution. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by reverse-phase chromatography (RP18 column) (eluent: 50/50 H₂O/MeOH) to give 92 mg of 1-ethyl-3-{4-[2-((8S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]phenyl}urea, the characteristics of which are as follows:

LC/MS (method A): ESI+ [M+H]⁺: m/z 507 tr (min) = 0.6

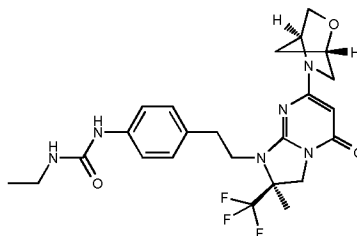
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.05 (t, 3H), 1.88 (m, 3H), 2.31 (m, 1H), 2.78 (m, 1H), 2.9 (m, 1H), 3.1 (m, 4H), 3.36 (m, 2H), 3.71 (d, 1H), 3.79 (d, 1H), 4.18 (d, 2H), 4.55 (m, 1H), 4.6-5.1 (bs, 3H), 6 (t, 1H), 7 (d, 2H), 7.3 (d, 2H), 8.3 (s, 1H).

25

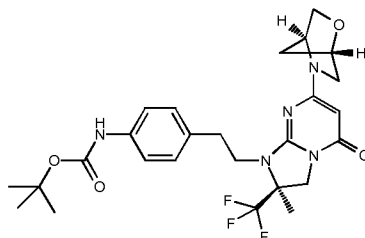
Example 15:

1-ethyl-3-(4-{2-[(1S,4S)-2-methyl-7-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-5-oxo-2-((S)-trifluoromethyl)-2,3-dihydro-5H-imidazo[1,2-a]pyrimidin-1-yl]ethyl}phenyl)urea (compound 24)

30

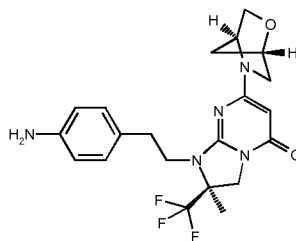


Step 15.1: tert-butyl (4-{2-[(1S,4S)-2-methyl-7-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-5-oxo-2-((S)-trifluoromethyl)-2,3-dihydro-5H-imidazo[1,2-a]pyrimidin-1-yl}ethyl}phenyl)carbamate



A suspension of 300 mg (0.948 mmol) of 2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one and 309.05 mg (0.948 mmol) of cesium carbonate in 5 mL of DMF is stirred at 85°C for 15 minutes. A solution of 284.74 mg (0.948 mmol) of tert-butyl [4-(2-bromoethyl)phenyl]carbamate is added dropwise. After reacting overnight at 85°C, the mixture is evaporated and the residue is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 EtOAc/MeOH) to give 385 mg of tert-butyl (4-{2-[(1S,4S)-2-methyl-7-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-5-oxo-2-((S)-trifluoromethyl)-2,3-dihydro-5H-imidazo[1,2-a]pyrimidin-1-yl}ethyl}phenyl)carbamate, the characteristics of which are as follows:
LC/MS (method G): ESI+ [M+H]⁺: m/z 536 tr (min) = 2.48
¹H NMR (300 MHz, δ in ppm, CDCl₃): 1.47 (s, 9H), 1.53 (s, 3H), 1.85 (s, 2H), 2.77 (m, 1H), 2.93 (m, 1H), 3.29-3.46 (m, 5H), 3.54 (m, 1H), 3.68 (m, 1H), 3.81 (m, 2H), 4.13 (m, 1H), 4.66 (s, 1H), 7.11 (d, 2H), 7.39 (d, 2H), 9.29 (s, 1H).

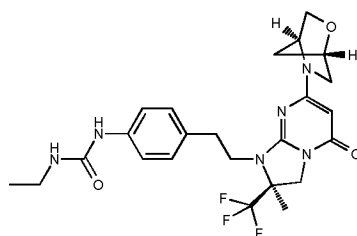
Step 15.2: 1-[2-(4-aminophenyl)ethyl]-2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one



1 mL of trifluoroacetic acid is added to a solution of 385 mg (0.72 mmol) of tert-butyl (4-{2-[(1S,4S)-2-methyl-7-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-5-oxo-2-((S)-trifluoromethyl)-2,3-dihydro-5H-imidazo[1,2-a]pyrimidin-1-yl]ethyl}phenyl)carbamate in
 5 4 mL of dichloromethane. After stirring for 1 hour at room temperature, the solvent is evaporated off. The residue is taken up in ethyl acetate and washed with saturated aqueous NaHCO₃ solution. The organic phase is dried over magnesium sulfate and evaporated to dryness to give 275 mg of 1-[2-(4-aminophenyl)ethyl]-2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-
 10 imidazo[1,2-a]pyrimidin-5-one, the characteristics of which are as follows:
 LC/MS (method A): ESI+ [M+H]⁺: m/z 436 tr (min) = 0.48
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.52 (s, 3H), 1.87 (m, 2H), 2.69 (m, 1H), 2.87 (m, 1H), 3.26-3.53 (bs, 6H), 3.68 (d, 1H), 3.78 (m, 2H), 4.10 (d, 1H), 4.66 (s, 1H), 4.92 (s, 2H), 6.5 (d, 2H), 6.87 (d, 2H).

15

Step 15.3: 1-ethyl-3-(4-{2-[(1S,4S)-2-methyl-7-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-5-oxo-2-((S)-trifluoromethyl)-2,3-dihydro-5H-imidazo[1,2-a]pyrimidin-1-yl]ethyl}phenyl)urea



20 104 μ l (1.29 mmol) of ethyl isocyanate are added to a solution of 140 mg (0.32 mmol) of 1-[2-(4-aminophenyl)ethyl]-2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one in 1 mL of dichloromethane. After stirring for 3 hours at room temperature, the solvent is evaporated off. The residue is taken up in ethyl acetate and washed with water and
 25 with saturated aqueous NaCl solution. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by reverse-phase chromatography (RP18 column) (eluent: 50/50 H₂O/MeOH) to give 83 mg of 1-ethyl-3-

(4-{2-[(1S,4S)-2-methyl-7-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-5-oxo-2-((S)-trifluoromethyl)-2,3-dihydro-5H-imidazo[1,2-a]pyrimidin-1-yl]ethyl}phenyl)urea, the characteristics of which are as follows:

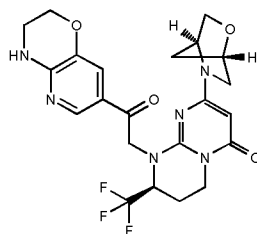
LC/MS (method A): ESI+ $[M+H]^+$: m/z 507 tr (min) = 0.6

- 5 ^1H NMR (600 MHz, δ in ppm, DMSO- d_6): 1.08 (t, 3H), 1.55 (s, 3H), 1.88 (m, 2H), 2.82 (m, 1H), 2.97 (m, 1H), 3.12 (m, 2H), 3.19 (m, 1H), 3.39 (d, 1H), 3.43 (m, 1H), 3.58 (m, 1H), 3.7 (d, 1H), 3.78 (d, 1H), 3.82 (d, 1H), 4.12 (d, 1H), 4.58 (s, 1H), 4.64 (s, 1H), 4.82 (bs, 1H), 5.95 (m, 1H), 7.08 (d, 2H), 7.32 (d, 2H), 8.15 (s, 1H).

10

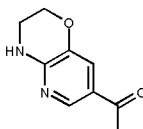
Example 16:

(8S)-9-[2-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 38)



15

Step 16.1: 1-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)ethanone



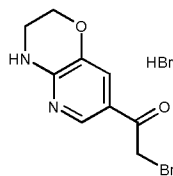
The procedure used is the same as that of step 12.1.

- 20 800 mg (3.61 mmol) of 7-bromo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine were used in the reaction. After purification by chromatography on silica gel (eluent: 90/10 DCM/MeOH), 320 mg of 1-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)ethanone were obtained, the characteristics of which are as follows:

LC/MS (method G): ESI+ $[M+H]^+$: m/z 179 tr (min) = 0.66

- 25 ^1H NMR (300 MHz, δ in ppm, CDCl_3): 2.42 (s, 3H), 3.47 (q, 2H), 4.12 (t, 2H), 7.3 (s, 1H), 7.77 (s, 1H), 8.28 (s, 1H).

Step 16.2: 2-bromo-1-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)ethanone hydrobromide



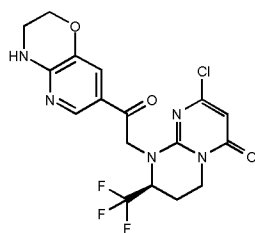
The procedure used is the same as that of step 12.2.

320 mg (1.80 mmol) of 1-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)ethanone were used in the reaction. After precipitation with ethyl ether and filtration, 690 mg of 2-bromo-1-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)ethanone hydrobromide are obtained, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 257 tr (min) = 1.10

¹H NMR (300 MHz, δ in ppm, CDCl₃): 3.57 (t, 2H), 4.23 (t, 2H), 4.78 (s, 2H), 7.55 (s, 1H), 8.38 (s, 1H), 8.5-9 (bs, 1H).

Step 16.3: (8S)-2-chloro-9-[2-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



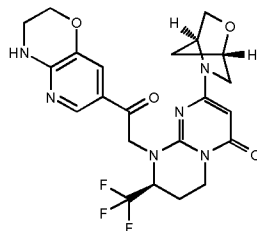
The procedure used is the same as that of step 12.3.

200 mg (0.79 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 319.86 mg (0.95 mmol) of 2-bromo-1-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)ethanone hydrobromide were used in the reaction. After purification by chromatography on silica gel (eluent: 90/10 DCM/MeOH), 110 mg of (8S)-2-chloro-9-[2-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 430 tr (min) = 1.77

¹H NMR (300 MHz, δ in ppm, CDCl₃): 2.27 (m, 1H), 2.44 (s, 1H), 3.17 (d, 1H), 3.39 (m, 1H), 3.49 (s, 2H), 4.13 (m, 2H), 4.37 (m, 1H), 4.58-4.77 (m, 2H), 5.48 (d, 1H), 7.36 (s, 1H), 7.97 (s, 1H), 8.38 (s, 1H).

Step 16.4: (8S)-9-[2-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-

tetrahydropyrimido[1,2-a]pyrimidin-4-one

The procedure used is the same as that of step 12.4.

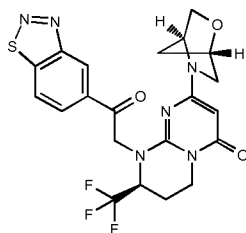
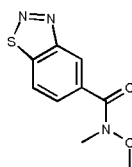
110 mg (0.25 mmol) of (8S)-2-chloro-9-[2-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 41.64 mg (0.31 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride were used in the reaction. After purification by passing through an RP18 reverse-phase column (eluent: from 100% H₂O to 100% CH₃CN over 30 minutes), 30 mg of (8S)-9-[2-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, the characteristics of which are as follows:

LC/MS (method A): ESI+ [M+H]⁺: m/z 493 tr (min) = 0.49

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.65 (d, 1H), 1.72 (d, 1H), 2.25 (m, 1H), 2.4 (m, 1H), 2.99 (m, 1H), 3.13 (m, 1H), 3.2 (m, 1H), 3.26 (m, 2H), 3.49 (m, 2H), 4.13 (t, 2H) 4.36 (m, 1H), 4.41 (d, 1H), 4.48 (d, 2H) 4.52 (m, 1H), 4.63 (s, 1H), 5.52 (d, 1H), 7.36 (s, 1H), 7.57 (s, 1H), 8.37 (s, 1H).

Example 17:

20 **(8S)-9-(2-benzo[1,2,3]thiadiazol-5-yl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 47)**

**Step 17.1: N-methoxy-N-methylbenzo[1,2,3]thiadiazole-5-carboxamide**

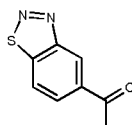
The procedure used is the same as that of step 4.1.

500 mg (2.44 mmol) of benzo[1,2,3]thiadiazole-5-carbonyl chloride are used in the reaction. 620 mg of N-methoxy-N-methylbenzo[1,2,3]thiadiazole-5-carboxamide are obtained, the characteristics of which are as follows:

5 LC/MS (method G): ESI+ [M+H]⁺: m/z 224 tr (min) = 1.36

¹H NMR (300 MHz, δ in ppm, CDCl₃): 3.34 (s, 3H), 3.57 (s, 3H), 7.99 (d, 1H), 8.5 (d, 1H), 8.9 (s, 1H).

Step 17.2: 1-benzo[1,2,3]thiadiazol-5-ylethanone



10

The procedure used is the same as that of step 4.2.

620 mg (2.78 mmol) of N-methoxy-N-methylbenzo[1,2,3]thiadiazole-5-carboxamide were used in the reaction. The mixture is basified with aqueous 1 N NaOH solution and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness to give 430 mg of 1-benzo[1,2,3]thiadiazol-5-ylethanone, corresponding to the following characteristics:

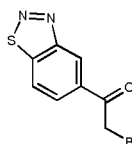
15

LC/MS (method G): ESI+ [M+H]⁺: m/z 224 tr (min) = 1.49

¹H NMR (300 MHz, δ in ppm, CDCl₃): 2.78 (s, 3H), 8.29 (d, 1H), 8.53 (d, 1H), 9.32 (s, 1H).

20

Step 17.3: 1-benzo[1,2,3]thiadiazol-5-yl-2-bromoethanone



The procedure used is the same as that of step 12.2.

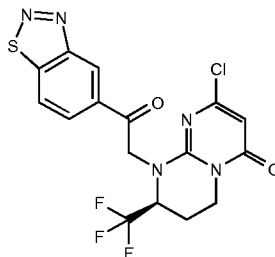
430 mg (2.41 mmol) of 1-benzo[1,2,3]thiadiazol-5-ylethanone were used in the reaction. The reaction mixture is evaporated to dryness and taken up in dichloromethane. The organic phase is washed with aqueous NaHCO₃ solution and with saturated NaCl solution, dried and evaporated to dryness to give 300 mg of 1-benzo[1,2,3]thiadiazol-5-yl-2-bromoethanone, corresponding to the following characteristics:

25

30 LC/MS (method G): ESI+ [M+H]⁺: m/z 257 tr (min) = 1.71

¹H NMR (300 MHz, δ in ppm, CDCl₃): 5.19 (s, 2H), 8.31 (d, 1H), 8.57 (d, 1H), 9.43 (s, 1H).

Step 17.4: (8S)-9-(2-benzo[1,2,3]thiadiazol-5-yl-2-oxoethyl)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



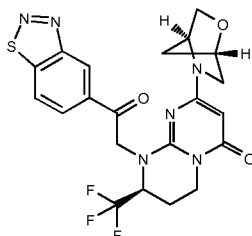
5 The procedure used is the same as that of step 12.3.

150 mg (0.59 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 167.25 mg (0.65 mmol) of 1-benzo[1,2,3]thiadiazol-5-yl-2-bromoethanone were used in the reaction. After purification by chromatography on silica gel (eluent: 90/10 DCM/MeOH), 210 mg of (8S)-9-(2-benzo[1,2,3]thiadiazol-5-yl-2-oxoethyl)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 430 tr (min) = 2.29

¹H NMR (300 MHz, δ in ppm, CDCl₃): 2.32 (m, 1H), 2.42-2.62 (m, 2H), 3.36-3.48 (m, 1H), 4.42 (m, 1H), 4.8 (m, 1H), 5.14 (d, 1H), 5.76 (m, 1H), 8.35 (d, 1H), 8.61 (d, 1H), 9.51 (s, 1H).

Step 17.5: (8S)-9-(2-benzo[1,2,3]thiadiazol-5-yl-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



20

The procedure used is the same as that of step 12.4.

210 mg (0.49 mmol) of (8S)-9-(2-benzo[1,2,3]thiadiazol-5-yl-2-oxoethyl)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 79.50 mg (0.58 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride were used in the reaction. After purification by chromatography on silica gel (eluent: 60/40 DCM/MeOH), 100 mg of (8S)-9-(2-benzo[1,2,3]thiadiazol-5-yl-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-

25

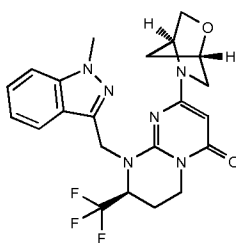
4-one are obtained, the characteristics of which are as follows:

LC/MS (method A): ESI+ [M+H]⁺: m/z 493 tr (min) = 0.64

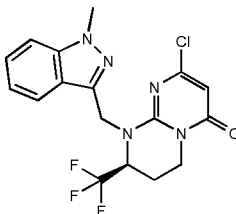
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.36-1.78 (bs, 2H), 2.27 (m, 1H), 2.45-2.5 (m, 2H), 2.75-3.25 (bs, 4H), 4.23-4.98 (bs, 6H), 5.9 (m, 1H), 8.34 (d, 1H), 8.58 (d, 1H), 9.5 (s, 1H).

Example 18:

(8S)-9-(1-methyl-1H-indazol-3-ylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 51)



Step 18.1: (8S)-2-chloro-9-(1-methyl-1H-indazol-3-ylmethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



The procedure used is the same as that of step 12.3.

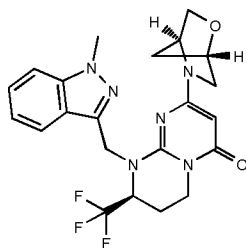
180 mg (0.71 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 145.39 mg (0.78 mmol) of 3-chloromethyl-1-methyl-1H-indazole were used in the reaction. After purification by chromatography on silica gel (eluent: 80/20 DCM/MeOH), 250 mg of (8S)-2-chloro-9-(1-methyl-1H-indazol-3-ylmethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 398 tr (min) = 2.2

¹H NMR (300 MHz, δ in ppm, CDCl₃): 2.01 (m, 1H), 2.44 (m, 1H), 3.24-3.41 (m, 2H), 4.02 (s, 3H), 4.23 (m, 1H), 4.66 (d, 1H), 4.75 (m, 1H), 5.89 (d, 1H), 7.15 (t, 1H), 7.42 (t, 1H), 7.62 (d, 1H), 7.84 (d, 1H).

Step 18.2: (8S)-9-(1-methyl-1H-indazol-3-ylmethyl)-2-(1S,4S)-2-oxa-5-

azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



The procedure used is the same as that of step 12.4.

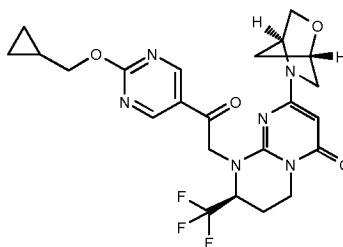
5 250 mg (0.63 mmol) of (8S)-2-chloro-9-(1-methyl-1H-indazol-3-ylmethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 102.26 mg (0.75 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride were used in the reaction. After purification by chromatography on silica gel (eluent: 60/40 DCM/MeOH), 230 mg of (8S)-9-(1-methyl-1H-indazol-3-ylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, the characteristics of which are as follows:

LC/MS (method A): ESI+ [M+H]⁺: m/z 461 tr (min) = 0.68

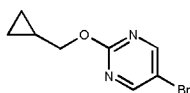
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.75 (m, 2H), 2.08 (m, 1H), 2.4 (d, 1H), 2.6-3.3 (bs, 5H), 3.99 (s, 3H), 4.2 (m, 1H), 4.4-4.67 (t, 3H), 4.66-4.9 (bs, 2H), 5.89 (d, 1H), 7.11 (t, 1H), 7.39 (t, 1H), 7.58 (d, 1H), 7.73 (d, 1H).

Example 19:

(8S)-9-[2-(2-cyclopropylmethoxypyrimidin-5-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 52)



Step 19.1: 5-bromo-2-cyclopropylmethoxypyrimidine



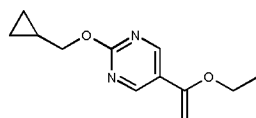
25 A suspension of 607.92 mg (15.20 mmol) of sodium hydride in 50 mL of THF is prepared under argon. A solution of 1.10 g (15.20 mmol) of cyclopropanemethanol in 5

mL of THF is added dropwise. The mixture is stirred for 50 minutes at room temperature. 1 g (5.07 mmol) of 5-bromo-2-chloropyrimidine in 5 mL of THF is then added. The mixture is stirred at room temperature overnight. The reaction mixture is taken up in water and extracted with ethyl acetate. The organic phase is washed with aqueous NaHCO₃ solution and with saturated aqueous NaCl solution, dried and evaporated to dryness to give 1.10 g of 5-bromo-2-cyclopropylmethoxypyrimidine, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 229 tr (min) = 2.06

¹H NMR (300 MHz, δ in ppm, CDCl₃): 0.33 (m, 2H), 0.55 (m, 2H), 1.23 (m, 1H), 4.12 (d, 2H), 8.74 (s, 2H).

Step 19.2: 2-cyclopropylmethoxy-5-(1-ethoxyvinyl)pyrimidine



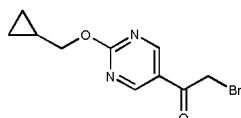
The following are successively introduced into a microwave tube:

760 mg (3.32 mmol) of 5-bromo-2-cyclopropylmethoxypyrimidine in 15 mL of dioxane, 1.36 mL (3.82 mmol) of tributyl(1-ethoxyvinyl)tin, 58.22 mg (0.08 mmol) of bis(triphenylphosphine)palladium(II) chloride, 1.12 g (7.30 mmol) of cesium fluoride. This mixture is subjected to microwave irradiation at 110°C for 1 hour. The reaction mixture is evaporated to dryness and the residue is taken up in 100 mL of ethyl ether. A solution of 2.80 g of cesium fluoride in 10 mL of water is added. After stirring for 1 hour at room temperature, the mixture is filtered through Celite. The filtrate is washed with aqueous NaHCO₃ solution and then with saturated NaCl solution. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 10/90 EtOAc/heptane) to give 480 mg of 2-cyclopropylmethoxy-5-(1-ethoxyvinyl)pyrimidine, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 221 tr (min) = 2.34

¹H NMR (300 MHz, δ in ppm, CDCl₃): 0.35 (m, 2H), 0.57 (m, 2H), 0.86 (m, 1H), 1.34 (t, 3H), 3.91 (q, 2H), 4.16 (d, 2H), 4.35 (s, 1H), 4.85 (s, 1H), 8.78 (s, 2H).

Step 19.3: 2-bromo-1-(2-cyclopropylmethoxypyrimidin-5-yl)ethanone

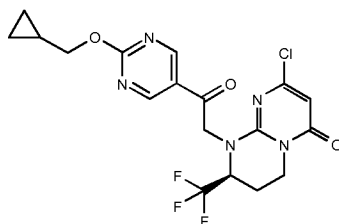


A solution of 480 mg (2.18 mmol) of 2-cyclopropylmethoxy-5-(1-ethoxyvinyl)pyrimidine in 8 mL of a THF/H₂O mixture: (6/2: v/v) is cooled to 0°C under argon. After addition of 380.02 mg (2.11 mmol) of N-bromosuccinimide, the reaction mixture is maintained at 0°C for 1 hour. The solution obtained is taken up in ethyl acetate and washed with aqueous NaHCO₃ solution and then with saturated NaCl solution. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 80/20 DCM/MeOH) to give 410 mg of 2-bromo-1-(2-cyclopropylmethoxypyrimidin-5-yl)ethanone, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 271 tr (min) = 1.87

¹H NMR (300 MHz, δ in ppm, CDCl₃): 0.38 (m, 2H), 0.58 (m, 2H), 1.29 (m, 1H), 4.27 (d, 2H), 4.94 (s, 2H), 9.15 (s, 2H).

Step 19.4: (8S)-2-chloro-9-[2-(2-cyclopropylmethoxypyrimidin-5-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



The procedure used is the same as that of step 12.3.

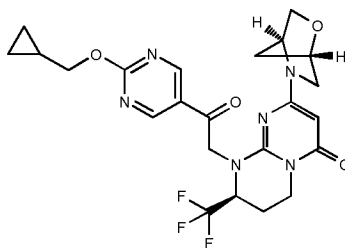
180 mg (0.71 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 211.66 mg (0.78 mmol) of 2-bromo-1-(2-cyclopropylmethoxypyrimidin-5-yl)ethanone were used in the reaction. After purification by chromatography on silica gel (eluent: 80/20 DCM/MeOH), 160 mg of (8S)-2-chloro-9-[2-(2-cyclopropylmethoxypyrimidin-5-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 444 tr (min) = 2.33

¹H NMR (300 MHz, δ in ppm, CDCl₃): 0.38 (m, 2H), 0.58 (m, 2H), 1.30 (m, 1H), 2.25 (m, 1H), 2.51 (m, 1H), 3.35 (m, 2H), 4.28 (d, 2H), 4.50 (m, 1H), 4.70 (m, 1H), 4.90 (d, 1H), 5.53 (d, 1H), 9.21 (s, 2H).

Step 19.5: (8S)-9-[2-(2-cyclopropylmethoxypyrimidin-5-yl)-2-oxoethyl]-2-

(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



The procedure used is the same as that of step 12.4.

5 160 mg (0.36 mmol) of (8S)-2-chloro-9-[2-(2-cyclopropylmethoxypyrimidin-5-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 58.66 mg (0.43 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride were used in the reaction. After purification by chromatography on silica gel (eluent: 60/40 DCM/MeOH), 125 mg of (8S)-9-[2-(2-cyclopropylmethoxypyrimidin-5-yl)-2-oxoethyl]-2-

10 (1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, the characteristics of which are as follows:

LC/MS (method A): ESI+ [M+H]⁺: m/z 507 tr (min) = 0.65

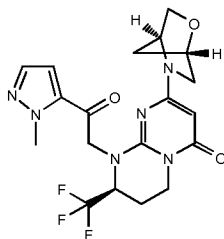
¹H NMR spectrum (600 MHz, δ in ppm, DMSO-d₆): 0.38 (m, 2H), 0.6 (m, 2H), 1.30 (m, 1H), 1.54-1.76 (m, 2H), 2.21 (m, 1H), 2.44 (m, 1H), 2.72-3.9 (bs, 5H), 4.28 (d, 2H), 4.31-4.98 (m, 6H), 5.67 (m, 1H), 9.22 (s, 2H).

15

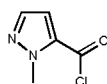
Example 20:

(8S)-9-[2-(2-methyl-2H-pyrazol-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 69)

20



Step 20.1: 2-methyl-2H-pyrazole-3-carbonyl chloride



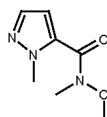
25

A suspension of 800 mg (6.03 mmol) of 2-methyl-2H-pyrazole-3-carboxylic acid

in 30 mL of DCM is placed under argon and cooled to 0°C. When the temperature is reached, 1.32 mL (15.07 mmol) of oxalyl chloride and a catalytic amount of DMF are added. The reaction mixture is stirred at room temperature for 2 hours and then evaporated to dryness and the residue is taken up in DCM and evaporated again to give 850 mg of 2-methyl-2H-pyrazole-3-carbonyl chloride, the characteristics of which are as follows:

¹H NMR (300 MHz, δ in ppm, CDCl₃): 4.10 (s, 3H), 6.82 (s, 1H), 7.50 (s, 1H).

Step 20.2: N-methoxy-N-methyl-2-methyl-2H-pyrazole-3-carboxamide



10

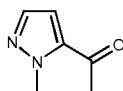
The procedure used is the same as that of step 4.1.

850 mg (5.88 mmol) of 2-methyl-2H-pyrazole-3-carbonyl chloride are used in the reaction. 890 mg of N-methoxy-N-methylbenzo[1,2,3]thiadiazole-5-carboxamide are obtained, the characteristics of which are as follows:

15 LC/MS (method G): ESI+ [M+H]⁺: m/z 170 tr (min) = 1.03

¹H NMR (300 MHz, δ in ppm, CDCl₃): 3.27 (s, 3H), 3.63 (s, 3H), 3.96 (s, 3H), 6.71 (s, 1H), 7.5 (s, 1H).

Step 20.3: 1-(2-methyl-2H-pyrazol-3-yl)ethanone



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The procedure used is the same as that of step 4.2.

890 mg (2.78 mmol) of N-methoxy-N-methylbenzo[1,2,3]thiadiazole-5-carboxamide were used in the reaction. The mixture is taken up in water and a few drops of 1 N HCl, basified with aqueous 1 N NaOH solution and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness to give 570 mg of 1-(2-methyl-2H-pyrazol-3-yl)ethanone, corresponding to the following characteristics:

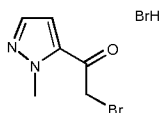
25

LC/MS (method G): ESI+ [M+H]⁺: m/z 125 tr (min) = 0.93

¹H NMR (300 MHz, δ in ppm, CDCl₃): 2.5 (s, 3H) 4.04 (s, 3H) 7.13 (s, 1H) 7.53 (s, 1H)

30

Step 20.4: 1-(2-methyl-2H-pyrazol-3-yl)ethanone hydrobromide



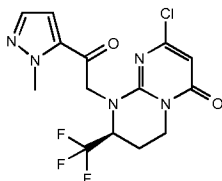
The procedure used is the same as that of step 12.2.

550 mg (4.43 mmol) of 1-(2-methyl-2H-pyrazol-3-yl)ethanone were used in the reaction. The precipitate corresponding to 1-(2-methyl-2H-pyrazol-3-yl)ethanone hydrobromide is filtered off, washed with ethyl ether and dried. The 1.15 g of product obtained have the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 203 tr (min) = 1.19

¹H NMR (300 MHz, δ in ppm, CDCl₃): 4.78 (s, 2H), 7.19 (s, 1H), 7.56 (s, 1H).

Step 20.5: (8S)-2-chloro-9-[2-(2-methyl-2H-pyrazol-3-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



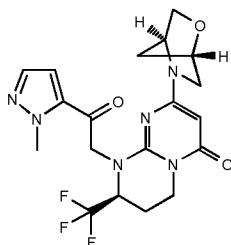
The procedure used is the same as that of step 12.3.

180 mg (0.71 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 262 mg (0.92 mmol) of 1-(2-methyl-2H-pyrazol-3-yl)ethanone hydrobromide were used in the reaction. After purification by chromatography on silica gel (eluent: 80/20 DCM/MeOH), 230 mg of (8S)-2-chloro-9-[2-(2-methyl-2H-pyrazol-3-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 376 tr (min) = 1.98

¹H NMR (300 MHz, δ in ppm, CDCl₃): 2.28 (m, 1H), 3.4 (m, 2H), 4.06 (s, 3H), 4.39 (m, 1H), 4.66-4.84 (m, 2H), 5.41 (d, 1H), 5.96 (s, 1H), 7.36 (s, 1H), 7.63 (s, 1H).

Step 20.6: (8S)-9-[2-(2-methyl-2H-pyrazol-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

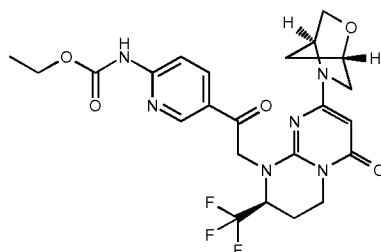


The procedure used is the same as that of step 12.4.

- 230 mg (0.61 mmol) of (8S)-2-chloro-9-[2-(2-methyl-2H-pyrazol-3-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 107.90 mg (0.79 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride were used in the reaction. After purification by chromatography on silica gel (eluent: 60/40 DCM/MeOH), 160 mg of (8S)-9-[2-(2-methyl-2H-pyrazol-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, the characteristics of which are as follows:
- LC/MS (method A): ESI+ [M+H]⁺: m/z 439 tr (min) = 0.54
- ¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.48-1.8 (bs, 2H), 2.22 (m, 1H), 2.43 (d, 1H), 2.66-3.26 (bs, 5H), 4 (s, 3H), 4.28-4.88 (bs, 6H), 5.5 (d, 1H), 7.42 (s, 1H), 7.59 (s, 1H).

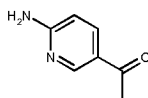
Example 21:

- ethyl {5-[2-((S)8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]pyridin-2-yl}carbamate (compound 57)



Step 21.1: 1-(6-aminopyrid-3-yl)ethanone

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- 2 g (11.57 mmol) of 1-(6-chloropyrid-3-yl)ethanone and 70 mL of ammonium hydroxide are placed in a Parr reactor. The solution is heated at 130°C overnight. The mixture obtained is evaporated to dryness, and the residue is taken up in ethyl acetate and washed with water and with saturated NaCl solution. The organic phase is dried over sodium sulfate and evaporated to dryness to give 1.14 g of 1-(6-aminopyrid-3-

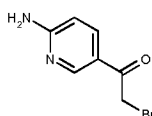
yl)ethanone, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 137 tr (min) = 0.35

¹H NMR (300 MHz, δ in ppm, CDCl₃): 2.41 (s, 3H), 6.45 (d, 1H), 6.88 (s, 2H), 7.86 (d, 1H), 8.58 (s, 1H).

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Step 21.2: 2-bromo-1-(6-aminopyrid-3-yl)ethanone



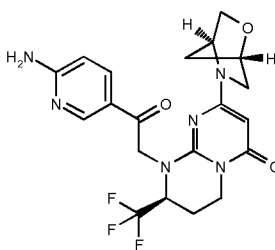
The procedure used is the same as that of step 12.2.

1.14 g (8.37 mmol) of 1-(6-aminopyrid-3-yl)ethanone were used in the reaction. The reaction mixture is taken up in dichloromethane. The organic phase is washed with aqueous K₂CO₃ solution and with saturated NaCl solution, dried and evaporated to dryness. After purification by chromatography on silica gel (eluent: 60/40 DCM/EtOAc), 530 mg of 2-bromo-1-(6-chloropyrid-3-yl)ethanone are obtained, the characteristics of which are as follows:

15 LC/MS (method G): ESI+ [M+H]⁺: m/z 215 tr (min) = 0.44

¹H NMR (300 MHz, δ in ppm, CDCl₃): 4.70 (s, 2H), 6.47 (d, 1H), 7.08 (s, 2H), 7.89 (d, 1H), 8.64 (s, 1H).

Step 21.3: (8S)-9-[2-(6-aminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



500 mg (1.58 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 10 mL of DMF are added to a suspension of 69.55 mg (1.74 mmol) of sodium hydride in 10 mL of DMF. The reaction mixture is placed under magnetic stirring at room temperature for 15 minutes. A solution of 373.96 mg (1.74 mmol) of 2-bromo-1-(6-chloropyrid-3-yl)ethanone in 5 mL of DMF is added dropwise to the reaction medium. The reaction is stirred at room temperature for 2 hours. The reaction medium is taken up in methanol

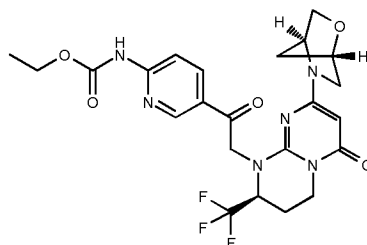
30

and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 60/40 EtOAc/MeOH) to give 530 mg of (8S)-9-[2-(6-aminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

5 LC/MS (method A): ESI+ [M+H]⁺: m/z 451 tr (min) = 0.38

¹H NMR (600 MHz, δ in ppm, CDCl₃): 1.5-1.81 (m, 2H), 2.23 (m, 1H), 2.41 (m, 1H), 2.74-3.33 (bs, 5H), 4.23-4.76 (m, 6H), 5.6 (d, 1H), 6.47 (d, 1H), 6.97 (s, 2H), 7.92 (d, 1H) 8.71 (s, 1H).

10 **Step 21.4: ethyl {5-[2-((S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]pyrid-2-yl}carbamate**



15 168 μ L (1 mmol) of N,N-diisopropylethylamine and 65 μ L (0.66 mmol) of ethyl chloroformate are added to a solution of 150 mg (0.33 mmol) of (8S)-9-[2-(6-aminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 5 mL of DCM.

The heterogeneous mixture is stirred at room temperature for 15 minutes. The solution is taken up in DCM and washed with water and with saturated NaCl solution. The organic phase is dried over sodium sulfate and evaporated to dryness. The residue is dissolved in 10 mL of ethanol, and aqueous 1 N NaOH solution is added. The mixture is stirred for 30 minutes at room temperature and then evaporated to dryness. The crude product is taken up in ethyl acetate and washed with water and with saturated NaCl solution. The organic phase is dried over sodium sulfate and evaporated to dryness. After purification by chromatography on silica gel (eluent: 60/40 DCM/MeOH), 120 mg of ethyl {5-[2-((S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]pyrid-2-yl}carbamate are obtained, the characteristics of which are as follows:

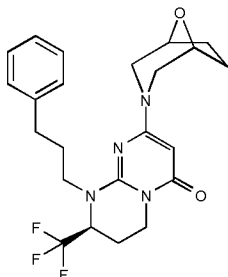
LC/MS (method A): ESI+ [M+H]⁺: m/z 523 tr (min) = 0.6

30 ¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.27 (t, 3H), 1.61 (s, 1H), 1.7 (d, 1H), 2.24 (m, 1H), 2.44 (d, 1H), 2.57-3.17 (bs, 3H), 3.24 (m, 2H), 4.2 (q, 2H), 4.29-4.52 (m, 3H), 4.59

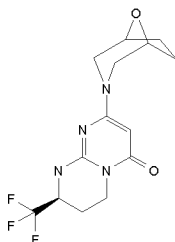
(m, 3H), 5.69 (d, 1H), 7.98 (d, 1H), 8.36 (d, 1H), 8.97 (s, 1H), 10.62 (s, 1H).

Example 22:

(8S)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(3-phenylpropyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 84)



Step 22.1: (8S)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



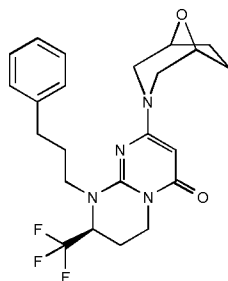
500 mg (1.97 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, 884 mg (5.91 mmol) of 8-oxa-3-azabicyclo[3.2.1]octane and 820 μ l (5.91 mmol) of triethylamine are placed in a microwave tube. The mixture is irradiated for 10 minutes at 150°C. The reaction medium is purified directly by passing through an RP18 reverse-phase column (eluent: H₂O: 100% to CH₃CN: 100%) to give 600 mg of (8S)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

LC/MS (method A): ESI+ [M+H]⁺: m/z 331 tr (min) = 0.53

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.66 (m, 2H), 1.81 (m, 2H), 2.09 (m, 1H), 2.2 (m, 1H), 2.89 (d, 2H), 3.34 (m, 1H), 3.75 (m, 2H), 4.14 (m, 1H), 4.26 (s, 1H), 4.37 (s, 2H), 4.84 (s, 1H), 8.17 (s, 1H).

Step 22.2: (8S)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(3-phenylpropyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

94

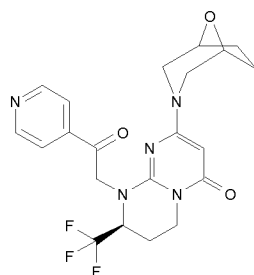


A solution of 200 mg (0.61 mmol) of (8S)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 790 mg (2.42 mmol) of cesium carbonate in 10 mL of DMF is heated at 90°C for 10 minutes. After addition of 600 µl (1.21 mmol) of (3-bromopropyl)benzene, the reaction is continued for 2 hours at 90°C. The solvent is evaporated off. The residue is purified by RP18 reverse-phase chromatography (eluent: H₂O 100% to CH₃CN 100%) to give 100 mg of (8S)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(3-phenylpropyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:
 LC/MS (method B): ESI+ [M+H]⁺: m/z 449 tr (min) = 0.85
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.57 (m, 2H), 1.79 (m, 3H), 2 (m, 2H), 2.31 (d, 1H), 2.62 (m, 2H), 2.8 (d, 2H), 3.13 (m, 2H), 3.53 (m, 2H), 3.94 (m, 1H), 4.15 (m, 1H), 4.31 (s, 2H), 4.62 (m, 1H), 4.82 (s, 1H), 7.18 (m, 3H), 7.27 (m, 2H).

15

Example 23:

(8S)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(2-oxo-2-pyrid-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 75)



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A solution of 200 mg (0.61 mmol) of (8S)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 1.18 g (3.63 mmol) of cesium carbonate in 10 mL of DMF is heated at 90°C for 10 minutes. The mixture is cooled to 0°C and 340 mg (1.21 mmol) of 2-bromo-1-pyrid-4-ylethanone are then added. The reaction is continued for 2 hours at room temperature. The solvent is evaporated off. The residue is purified by chromatography on a column of silica (eluent:

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90/10 DCM/MeOH). The isolated fraction is recrystallized from acetonitrile to give 16 mg of (8S)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(2-oxo-2-pyrid-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

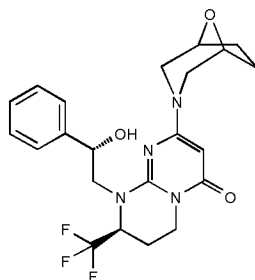
5 LC/MS (method B): ESI+ [M+H]⁺: m/z 450 tr (min) = 0.55

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.32 (m, 1H) 1.5 (m, 1H) 1.62 (m, 2H) 2.2 (m, 1H) 2.42 (d, 1H) 2.51 (d, 1H) 2.69 (d, 1H) 3.2 (m, 1H) 3.38 (d, 2H) 4.05 (d, 2H) 4.31 (d, 1H) 4.61 (m, 1H) 4.85 (s, 2H) 5.45 (d, 1H) 7.89 (s, 2H) 8.85 (s, 2H)

10

Example 24:

(8S)-9-((S)-2-hydroxy-2-phenylethyl)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 80)



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200 mg (0.61 mmol) of (8S)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 5 mL of DMF are added to a suspension of 60 mg (1.51 mmol) of sodium hydride in 5 mL of DMF. The reaction mixture is heated at 50°C for 10 minutes. After addition of 142 mg (0.91 mmol) of (S)-2-chloro-1-phenylethanol, the reaction is continued at 90°C overnight. The reaction medium is evaporated to dryness. The residue is purified by chromatography on a column of silica (eluent: 90/10 DCM/MeOH). The isolated fraction is recrystallized from acetonitrile to give 33 mg of (8S)-9-((S)-2-hydroxy-2-phenylethyl)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

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LC/MS (method B): ESI+ [M+H]⁺: m/z 451 tr (min) = 0.68

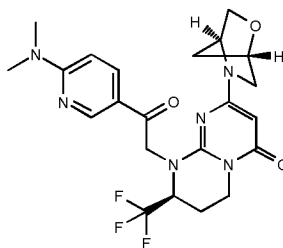
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.70 (m, 2H) 1.84 (m, 2H) 2.25 (m, 1H) 2.4 (m, 1H) 3.02 (m, 3H) 3.2 (m, 1H) 3.77 (m, 2H) 4.26 (m, 2H) 4.41 (s, 2H) 4.80 (m, 1H) 4.92 (s, 1H) 5.01 (m, 1H) 5.71 (d, 1H) 7.37 (m, 5H)

30

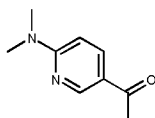
Example 25:

(8S)-9-[2-(6-dimethylaminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-

azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 6)



Step 25.1: 1-(6-dimethylaminopyrid-3-yl)ethanone



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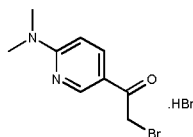
500 mg (2.89 mmol) of 1-(6-chloropyrid-3-yl)ethanone, 2 mL of ethanol and 7.23 mL (14.46 mmol) of 2 M dimethylamine in tetrahydrofuran are placed in a 20 mL microwave reactor. The solution is irradiated with microwaves for 10 minutes at 130°C. The mixture obtained is taken up in water and extracted with ethyl acetate. The organic phase is dried over sodium sulfate and evaporated to dryness to give 470 mg of 1-(6-dimethylaminopyrid-3-yl)ethanone, the characteristics of which are as follows:

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^1H NMR (300 MHz, δ in ppm, CDCl_3): 2.44 (s, 3H), 3.12 (s, 6H), 6.68 (d, 1H), 7.96 (d, 1H), 8.72 (s, 1H).

15

Step 25.2: 2-bromo-1-(6-dimethylaminopyrid-3-yl)ethanone hydrobromide



The procedure used is the same as that of step 12.2.

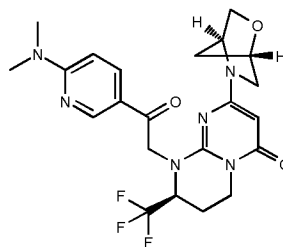
514 mg (3.13 mmol) of 1-(6-dimethylaminopyrid-3-yl)ethanone were used in the reaction. The precipitate corresponding to 2-bromo-1-(6-dimethylaminopyrid-3-yl)ethanone hydrobromide is filtered off, washed with ether and dried. The 950 mg of product obtained have the following characteristics:

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^1H NMR (300 MHz, δ in ppm, CDCl_3): 3.22 (s, 6H), 4.80 (s, 2H), 6.95 (d, 1H), 8.10 (d, 1H), 8.68 (s, 1H).

25

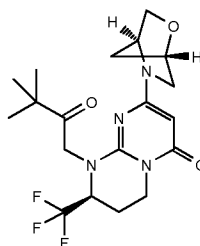
Step 25.3: (8S)-9-[2-(6-dimethylaminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



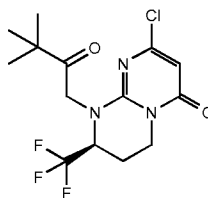
100 mg (0.32 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 2 mL of DMF are added to a suspension of 13.91 mg (0.35 mmol) of sodium hydride in 3 mL of DMF. The reaction mixture is placed under magnetic stirring at room temperature for 15 minutes. A solution of 84.55 mg (0.35 mmol) of 2-bromo-1-(6-dimethylaminopyrid-3-yl)ethanone in 5 mL of DMF is added dropwise to the reaction medium. The reaction is stirred at room temperature for 5 minutes. The reaction medium is taken up in ethanol and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 DCM/MeOH) to give 34 mg of (8S)-9-[2-(6-dimethylaminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:
LC/MS (method A): ESI+ [M+H]⁺: m/z 479 tr (min) = 0.48
¹H NMR (600 MHz, δ in ppm, DMSO-*d*₆): 1.62 (bs, 1H), 1.73 (d, 1H), 2.24 (m, 1H), 2.42 (m, 1H), 2.66-3.27 (m, 11H), 4.05-4.96 (m, 6H), 5.63 (d, 1H), 6.71 (d, 1H), 8.03 (d, 1H), 8.83 (s, 1H).

Example 26:

(8S)-9-(3,3-dimethyl-2-oxobutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 29)



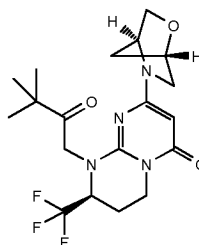
Step 26.1: (8S)-2-chloro-9-(3,3-dimethyl-2-oxobutyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



The procedure used is the same as that of step 12.3.

- 150 mg (0.591 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, 578.71 mg (1.77 mmol) of cesium carbonate, 99 μ l (0.709 mmol) of
 5 1-bromopinacolone and 10 mL of acetonitrile were used in the reaction. After purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 12 min 4% B, t 15 min 4% B, t 30 min 10% B), 188 mg of (8S)-2-chloro-9-(3,3-dimethyl-2-oxobutyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:
- 10 LC/MS (method G): ESI+ [M+H]⁺: m/z 352 tr (min) = 2.38
¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 1.17 (s, 9H), 2.20 (m, 1H), 2.45 (m, 1H), 3.25 (m, 2H), 4.35 (d, 1H), 4.63 (m, 1H), 5.05 (d, 1H), 5.92 (s, 1H).

- Step 26.2: (8S)-9-(3,3-dimethyl-2-oxobutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one**
- 15



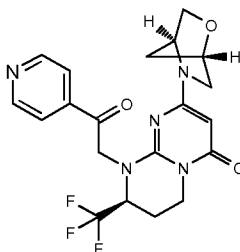
The procedure used is the same as that of step 12.4.

- 180 mg (0.511 mmol) of (8S)-2-chloro-9-(3,3-dimethyl-2-oxobutyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, 76.32 mg (0.563 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride and 179 μ l (1.28 mmol) of triethylamine were used in the reaction. After purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 15 min 4% B, t 18 min 4% B, t 33 min 10% B), 130 mg of (8S)-9-(3,3-dimethyl-2-oxobutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:
- 20
 25 LC/MS (method A): ESI+ [M+H]⁺: m/z 415 tr (min) = 0.67
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.15 (s, 9H), 1.80 (m, 2H), 2.22 (m, 1H), 2.37

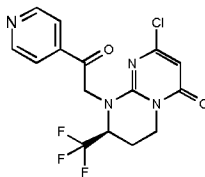
(m, 1H), 3.13 (m, 1H), 3.25 (m, 2H), 3.52 (m, 1H), 3.65 (m, 1H), 4.25 (d, 1H), 4.34 (m, 2H), 4.58 (m, 1H), 4.67 (m, 2H), 5.32 (d, 1H).

Example 27:

- 5 **(8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 2)**



- 10 **Step 27.1: (8S)-2-chloro-9-(2-oxo-2-pyrid-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one**



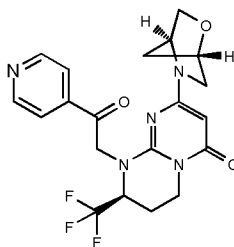
The procedure used is the same as that of step 12.3.

- 1 g (3.94 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, 3.85 g (11.83 mmol) of cesium carbonate, 1.33 g (4.73 mmol) of 2-bromo-1-pyrid-4-ylethanone hydrobromide and 100 mL of acetonitrile were used in the reaction. After purification by chromatography on silica gel (eluent A/B: heptane/EtOAc, gradient A/B: t 0 min 60% B, t 25 min 100% B, t 30 min 100% B), 804 mg of (8S)-2-chloro-9-(2-oxo-2-pyrid-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 373 tr (min) = 1.77

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 2.28 (m, 1H), 3.36 (m, 2H), 4.40 (m, 1H), 4.73 (m, 1H), 4.98 (d, 1H), 5.54 (d, 1H), 5.95 (s, 1H), 7.92 (m, 2H), 8.87 (m, 2H).

- 25 **Step 27.2: (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one**



The procedure used is the same as that of step 12.4.

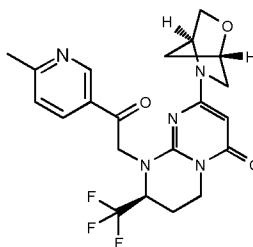
250 mg (0.67 mmol) of (8S)-2-chloro-9-(2-oxo-2-pyrid-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, 109 mg (0.80 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride and 230 μ l (1.68 mmol) of triethylamine were used in the reaction. After purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 25 min 10% B, t 30 min 10%) 230 mg of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:

LC/MS (method A): ESI+ $[M+H]^+$: m/z 436 tr (min) = 0.50

^1H NMR (600 MHz, δ in ppm, DMSO- d_6): 1.65 (m, 1H), 1.72 (m, 1H), 2.25 (m, 1H), 2.45 (m, 1H), 3.00 (m, 1H), 3.10 (m, 1H), 3.20 (m, 1H), 3.30 (m, 2H), 4.38 (m, 1H), 4.42 (m, 1H), 4.48 (m, 1H), 4.62 (m, 1H), 4.37 (m, 1H), 4.75 (d, 1H), 5.58 (d, 1H), 7.88 (m, 2H), 8.85 (m, 2H).

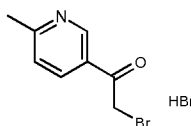
Example 28:

(8S)-9-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 4)



Step 28.1:

2-bromo-1-(6-methylpyrid-3-yl)ethanone hydrobromide

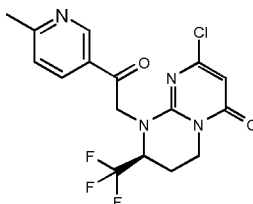


The procedure used is the same as that of step 12.2.

500 mg (3.59 mmol) of 1-(6-methylpyrid-3-yl)ethanone, 590 μ l (3.59 mmol) of hydrobromic acid, 204 μ l (3.95 mmol) of bromine and 10 mL of glacial acetic acid were used in the reaction. After precipitation with ethyl ether and filtration, 1.02 g of 2-bromo-1-(6-methylpyrid-3-yl)ethanone hydrobromide are obtained, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 214 tr (min) = 1.00

Step 28.2: (8S)-2-chloro-9-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

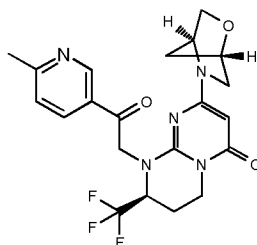


1 g (3.94 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one is added to a suspension of 394.27 mg (9.86 mmol) of sodium hydride in 40 mL of DMF. The reaction mixture is placed under magnetic stirring at room temperature for 15 minutes. A solution of 1.16 g (3.94 mmol) of 2-bromo-1-(6-methylpyrid-3-yl)ethanone hydrobromide in 10 mL of DMF is added dropwise to the reaction medium at 0°C. The reaction is stirred at room temperature overnight. The reaction medium is evaporated to dryness. The crude product is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness. After purification by chromatography on silica gel (eluent A/B: heptane/EtOAc, gradient A/B: t 0 min 30% B, t 35 min 60% B, t 40 min 60% B), 480 mg of (8S)-2-chloro-9-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 387 tr (min) = 1.85

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 2.30 (m, 1H), 2.58 (s, 3H), 3.29 (m, 2H), 4.40 (m, 1H), 4.75 (m, 1H), 4.93 (d, 1H), 5.55 (d, 1H), 5.94 (s, 1H), 7.46 (m, 1H), 8.26 (m, 1H), 9.09 (m, 1H).

Step 28.3: (8S)-9-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



The procedure used is the same as that of step 12.4.

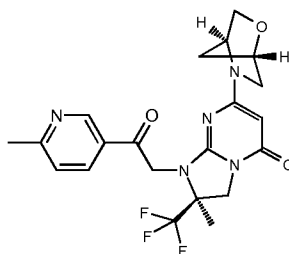
480 mg (1.24 mmol) of (8S)-2-chloro-9-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, 201.94 mg (1.49 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride and 313.97 mg (3.10 mmol) of triethylamine were used in the reaction. After purification by chromatography on silica gel (eluent A/B: heptane/EtOAc, gradient A/B: t 0 min 30% B, t 35 min 60% B, t 40 min 60% B), 335 mg of (8S)-9-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:

LC/MS (method A): ESI+ [M+H]⁺: m/z 450 tr (min) = 0.49

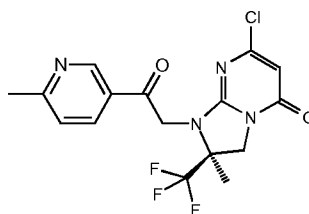
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.65 (m, 2H), 2.30 (m, 1H), 2.42 (m, 1H), 2.55 (s, 3H), 2.70-3.10 (bs, 3H), 3.20 (m, 2H), 4.40 (m, 3H), 4.65 (m, 3H), 5.70 (m, 1H), 7.49 (m, 1H), 8.30 (m, 1H), 9.10 (m, 1H).

Example 29:

2-methyl-1-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one (compound 17)



Step 29.1: (S)-7-chloro-2-methyl-1-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one

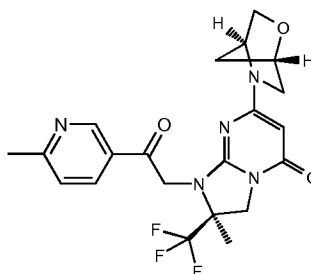


500 mg (1.97 mmol) of (S)-7-chloro-2-methyl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one are added to a suspension of 141.94 mg (5.91 mmol) of sodium hydride in 20 mL of DMF. The reaction mixture is placed under magnetic stirring at room temperature for 15 minutes. A solution of 872.32 mg (2.96 mmol) of 2-bromo-1-(6-methylpyrid-3-yl)ethanone hydrobromide in 10 mL of DMF is added dropwise to the reaction medium at 0°C. The reaction is stirred at room temperature overnight. The reaction medium is evaporated to dryness. The crude product is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness. After purification by chromatography on silica gel (eluent A/B: heptane/EtOAc, gradient A/B: t 0 min 30% B, t 35 min 60% B, t 40 min 60% B), 150 mg of (S)-7-chloro-2-methyl-1-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one were obtained, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 387 tr (min) = 1.79

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 1.54 (s, 3H), 2.46 (s, 3H), 4.10 (d, 1H), 4.27 (d, 1H), 4.88 (d, 1H), 5.20 (d, 1H), 5.83 (s, 1H), 7.36 (m, 1H), 7.8.17 (m, 1H), 9.00 (m, 1H).

Step 29.2: 2-methyl-1-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one



The procedure used is the same as that of step 12.4.

150 mg (0.388 mmol) of (S)-7-chloro-2-methyl-1-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one, 63.11 mg (0.465 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride and 98.61 mg (0.970 mmol) of triethylamine were used in the reaction. After purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 35 min 10% B, t 40 min 10% B), 65 mg of 2-methyl-1-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one were obtained, corresponding to the following

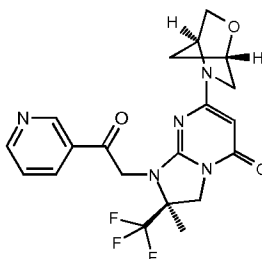
characteristics:

LC/MS (method A): ESI+ [M+H]⁺: m/z 450 tr (min) = 0.49

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.65 (s, 3H), 1.67-1.76 (bs, 2H), 2.96-3.24 (bs, 2H), 3.28 (m, 2H), 2.58 (s, 3H), 4.02 (d, 1H), 4.24 (d, 1H), 4.48 (m, 3H), 4.85 (d, 1H), 5.20 (d, 1H), 7.49 (m, 1H), 8.30 (m, 1H), 9.10 (m, 1H).

Example 30:

2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-1-(2-oxo-2-pyrid-3-ylethyl)-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one (compound 21)



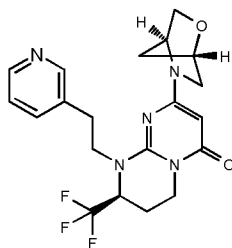
150 mg (0.474 mmol) of 2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one are added to a suspension of 47.42 mg (1.19 mmol) of sodium hydride in 10 mL of DMF. The reaction mixture is placed under magnetic stirring at room temperature for 15 minutes. A solution of 168.31 mg (0.569 mmol) of 2-bromo-1-pyrid-3-ylethanone hydrobromide in 5 mL of DMF is added dropwise to the reaction medium at 0°C. The reaction is stirred at room temperature overnight. The reaction medium is evaporated to dryness. The crude product is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness. After purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 35 min 10% B, t 40 min 10% B), 58 mg of 2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-1-(2-oxo-2-pyrid-3-ylethyl)-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one were obtained, corresponding to the following characteristics:

LC/MS (method A): ESI+ [M+H]⁺: m/z 436 tr (min) = 0.51

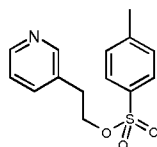
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.58 (s, 3H), 1.62 (m, 2H), 2.80-3.25 (bs, 5H) 3.95 (d, 1H), 4.15 (d, 1H), 4.50 (m, 2H), 4.80 (d, 1H), 5.15 (d, 1H), 7.51 (m, 1H), 8.30 (m, 1H), 8.78 (m, 1H), 9.20 (m, 1H).

Example 31:

(8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 12)



Step 31.1: 2-pyrid-3-ylethyl toluene-4-sulfonate



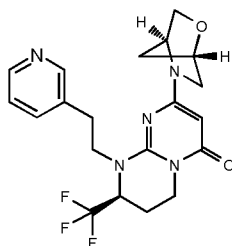
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6.62 mL (47.26 mmol) of triethylamine and 8.26g (43.32 mmol) of 4-methylbenzenesulfonyl chloride are added at 0°C to a solution of 5 g (39.38 mmol) of 2-pyrid-3-ylethanol in 300 mL of dichloromethane. After allowing the reaction medium to warm to room temperature and stirring overnight, it is washed with water and with saturated NaCl solution. The organic phase is dried over magnesium sulfate and evaporated to dryness. After purification by chromatography on silica gel (eluent: 4/6 heptane/EtOAc), 8 g of 2-pyrid-3-ylethyl toluene-4-sulfonate were obtained, corresponding to the following characteristics:

¹H NMR (300 MHz, δ in ppm, DMSO- d_6): 2.41 (s, 3H), 2.91 (m, 2H), 4.27 (m, 2H), 7.27 (m, 1H), 7.43 (m, 2H), 7.56 (m, 1H), 7.68 (m, 2H), 8.40 (m, 2H).

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Step 31.2: (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



A suspension of 150 mg (0.474 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 170.15 mg (0.522 mmol) of cesium carbonate in 10 mL of acetonitrile is stirred for 15 minutes at 85°C. 131.53 mg (0.474 mmol) of 2-pyrid-3-ylethyl toluene-4-sulfonate are then added. After stirring overnight at 85°C, the reaction mixture is evaporated and the residue is taken up in water and extracted with ethyl acetate. The

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organic phase is dried over magnesium sulfate and evaporated to dryness. After purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 35 min 10% B, t 40 min 10% B) 145 mg of (8S)-2-(1S,4S)-2-oxa-5-

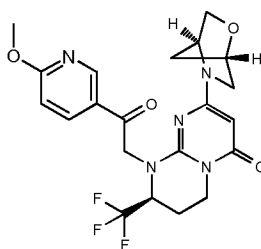
5 tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, the characteristics of which are as follows:

LC/MS (method A): ESI+ [M+H]⁺: m/z 422 tr (min) = 0.39

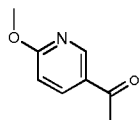
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.25 (m, 2H), 1.85 (m, 2H), 2.01 (m, 1H), 2.35 (m, 1H), 2.95 (m, 3H), 3.15 (m, 1H), 3.42 (m, 1H), 3.75 (m, 2H), 4.22 (m, 2H), 4.72 (m, 10 3H), 7.35 (m, 1H), 7.65 (m, 1H), 8.45 (m, 2H).

Example 32:

(8S)-9-[2-(6-methoxypyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-
azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-
15 a]pyrimidin-4-one (compound 45)



Step 32.1: 1-(6-methoxypyrid-3-yl)ethanone



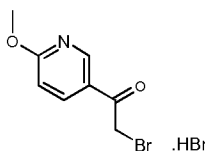
A mixture of 15 mL of methanol, 500 mg (2.89 mmol) of 1-(6-chloropyrid-3-yl)ethanone and 1.17 g (21.69 mmol) of sodium methoxide is heated in a microwave reactor at 160°C for 4 hours. The reaction medium is evaporated to dryness. After purification by chromatography on silica gel (eluent A/B: heptane/EtOAc, gradient A/B: t 0 min 0% B, t 5 min 20% B, t 30 min 40% B), 230 mg of 1-(6-methoxypyrid-3-yl)ethanone were obtained, corresponding to the following characteristics:

25 LC/MS (method G): ESI+ [M+H]⁺: m/z 152 tr (min) = 1.33

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 2.50 (s, 3H), 3.94 (s, 3H), 6.92 (m, 1H), 8.18 (m, 1H), 8.83 (m, 1H).

Step 32.2: 2-bromo-1-(6-methoxypyrid-3-yl)ethanone hydrobromide

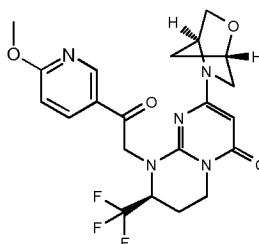
107



The procedure used is the same as that of step 12.2.

230 mg (1.52 mmol) of 1-(6-methoxypyrid-3-yl)ethanone, 413 μ l (7.61 mmol) of
 5 hydrobromic acid, 87 μ l (1.67 mmol) of bromine and 5 mL of glacial acetic acid were
 used in the reaction. After precipitation with ethyl ether and filtration, 430 mg of 2-
 bromo-1-(6-methoxypyrid-3-yl)ethanone hydrobromide are obtained, the characteristics
 of which are as follows:
 LC/MS (method G): ESI+ [M+H]⁺: m/z 230 tr (min) = 1.61
 10 ¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 3.96 (s, 3H), 4.91 (s, 2H), 6.96 (m, 1H), 8.21
 (m, 1H), 8.88 (m, 1H).

Step 32.3: (8S)-9-[2-(6-methoxypyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-
 azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-
 15 a]pyrimidin-4-one



The procedure used is the same as that of step 12.3.

150 mg (0.474 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-
 trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, 464.04 mg (1.42
 20 mmol) of cesium carbonate, 176.98 mg (0.569 mmol) of 2-bromo-1-(6-methoxypyrid-3-
 yl)ethanone hydrobromide and 10 mL of acetonitrile were used in the reaction. After
 purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0
 min 0% B, t 25 min 10% B, t 30 min 10% B), 100 mg of (8S)-9-[2-(6-methoxypyrid-3-yl)-
 2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-
 25 tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following
 characteristics:

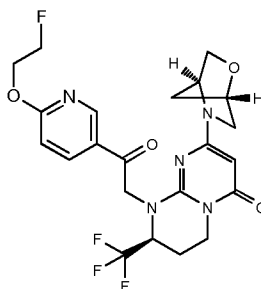
LC/MS (method A): ESI+ [M+H]⁺: m/z 466 tr (min) = 0.61

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.62 (m, 1H), 1.71 (m, 1H), 2.25 (m, 1H), 2.41
 (m, 1H), 2.61-3.17 (bs, 3H), 3.25 (m, 2H), 3.95 (s, 3H), 3.38 (m, 1H), 4.48 (m, 2H), 4.62

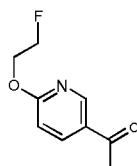
(m, 3H), 5.70 (m, 1H), 6.97 (m, 1H), 8.28 (m, 1H), 8.98 (s, 1H).

Example 33:

(S)-9-{2-[6-(2-fluoroethoxy)pyrid-3-yl]-2-oxoethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 63)



Step 33.1: 1-[6-(2-fluoroethoxy)pyrid-3-yl]ethanone



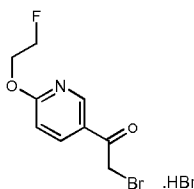
530 μ l (8.68 mmol) of 2-fluoroethanol are added to a suspension of 347.05 mg (8.68 mmol) of sodium hydride in 10 mL of DMF. The reaction mixture is placed under magnetic stirring at room temperature for 15 minutes. A solution of 500 mg (2.89 mmol) of 1-(6-chloropyrid-3-yl)ethanone in 3 mL of DMF is added dropwise to the reaction medium. The reaction is stirred at room temperature overnight. The reaction medium is evaporated to dryness. The crude product is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness. After purification by chromatography on silica gel (eluent A/B: heptane/EtOAc, gradient A/B: t 0 min 0% B, t 5 min 10% B, t 30 min 30% B), 362 mg of 1-[6-(2-fluoroethoxy)pyrid-3-yl]ethanone were obtained, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 184 tr (min) = 1.41

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 2.57 (s, 3H), 4.56 (m, 1H), 4.67 (m, 1H), 4.86 (m, 1H), 7.00 (m, 1H), 8.21 (m, 1H), 8.83 (m, 1H).

Step 33.2: 2-bromo-1-[6-(2-fluoroethoxy)pyrid-3-yl]ethanone hydrobromide

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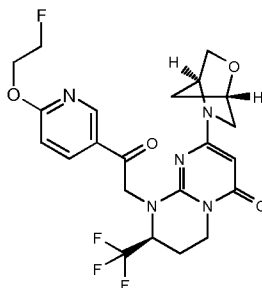
The procedure used is the same as that of step 12.2.

362 mg (1.98 mmol) of 1-[6-(2-fluoroethoxy)pyrid-3-yl]ethanone, 413 μ l (7.61 mmol) of hydrobromic acid, 537 μ l (9.88 mmol) of bromine and 5 mL of glacial acetic acid were used in the reaction. After precipitation with ethyl ether and filtration, 602 mg of 2-bromo-1-[6-(2-fluoroethoxy)pyrid-3-yl]ethanone hydrobromide are obtained, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 264 tr (min) = 1.69

¹H NMR spectrum (300 MHz, δ in ppm, DMSO-d₆): 4.56 (m, 1H), 4.69 (m, 1H), 4.86 (m, 1H), 4.92 (s, 2H), 7.00 (m, 1H), 8.23 (m, 1H), 8.85 (m, 1H), 9.80 (bs, 1H).

Step 33.3: (8S)-9-{2-[6-(2-fluoroethoxy)pyrid-3-yl]-2-oxoethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



The procedure used is the same as that of step 12.3.

150 mg (0.474 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, 464.04 mg (1.42 mmol) of cesium carbonate, 195.20 mg (0.569 mmol) of 2-bromo-1-[6-(2-fluoroethoxy)pyrid-3-yl]ethanone hydrobromide and 10 mL of acetonitrile were used in the reaction. After purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 25 min 10% B, t 30 min 10% B), 130 mg of (8S)-9-{2-[6-(2-fluoroethoxy)pyrid-3-yl]-2-oxoethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:

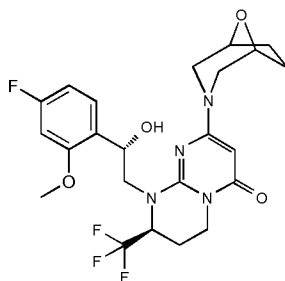
LC/MS (method A): ESI+ [M+H]⁺: m/z 498 tr (min) = 0.62

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.62 (m, 1H), 1.72 (m, 1H), 2.25 (m, 1H), 2.45

(m, 1H), 2.61-3.17 (bs, 3H), 2.25 (m, 2H), 4.38 (m, 1H), 4.50 (m, 2H), 4.55-4.70 (m, 5H), 4.74 (m, 1H), 4.83 (m, 1H), 5.70 (m, 1H), 7.12 (m, 1H), 8.30 (m, 1H), 8.97 (m, 1H).

Example 34:

- 5 **(8S)-9-[(S)-2-(4-fluoro-2-methoxyphenyl)-2-hydroxyethyl]-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 71)**



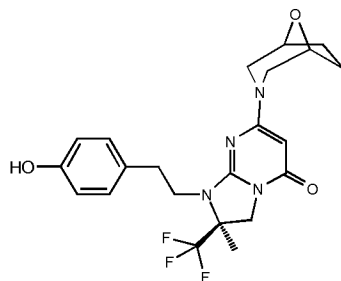
- 200 mg (0.61 mmol) of (8S)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 5 mL of DMF are added to a suspension of 60 mg (1.51 mmol) of sodium hydride in 10 mL of DMF. The reaction mixture is heated at 50°C for 10 minutes. After addition of 162 mg (0.79 mmol) of (S)-2-chloro-1-(4-fluoro-2-methoxyphenyl)ethanol, the reaction is continued at room temperature overnight. The reaction medium is evaporated to dryness. The residue is purified by chromatography on a column of silica (eluent: 90/10 DCM/MeOH). 40 mg of (8S)-9-[(S)-2-(4-fluoro-2-methoxyphenyl)-2-hydroxyethyl]-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:

LC/MS (method B): ESI+ [M+H]⁺: m/z 499 tr (min) = 0.71

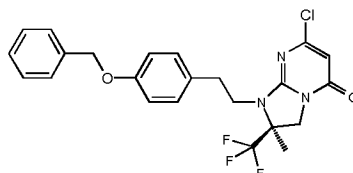
- 20 ¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.65 (m, 2H), 1.83 (m, 2H), 2.25 (m, 1H), 2.35 (m, 1H), 2.92 (m, 3H), 3.22 (m, 1H), 3.75 (m, 1H), 3.75 (s, 3H), 3.85 (m, 1H), 4.15 (m, 1H), 4.35 (m, 3H), 4.71 (m, 1H), 4.89 (s, 1H), 5.35 (m, 1H), 5.53 (m, 1H), 6.78 (m, 1H), 6.87 (m, 1H), 7.51 (m, 1H).

- 25 **Example 35:**

(S)-1-[2-(4-hydroxyphenyl)ethyl]-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one (compound 72)



Step 35.1: (S)-1-[2-(4-benzyloxyphenyl)ethyl]-7-chloro-2-methyl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one

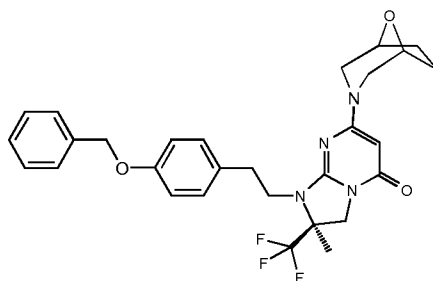


- 5 A mixture of 40 mL of DMF, 2 g (7.89 mmol) of (S)-7-chloro-2-methyl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one, 3.44 g (11.84 mmol) of 1-benzyloxy-4-(2-bromoethyl)benzene and 5.14 g (15.78 mmol) of cesium carbonate is heated in a Biotage microwave reactor at 120°C for 20 minutes. The reaction medium is evaporated to dryness. After purification by chromatography on silica gel (eluent A/B: heptane/EtOAc, gradient A/B: t 0 min 20% B, t 25 min 50% B, t 35 min 50% B), 2.8 g of (S)-1-[2-(4-benzyloxyphenyl)ethyl]-7-chloro-2-methyl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one were obtained, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 464 tr (min) = 2.91

- 15 ¹H NMR (300 MHz, δ in ppm, CDCl₃): 1.36 (s, 3H), 2.90 (m, 1H), 3.11 (m, 1H), 3.49 (m, 1H), 3.75 (m, 1H), 4.38 (d, 1H), 5.07 (m, 2H), 5.32 (s, 1H), 5.97 (s, 1H), 6.94 (m, 2H), 7.12 (m, 2H), 7.43 (m, 5H).

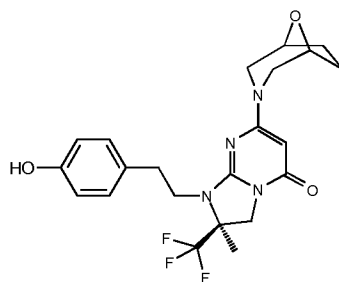
- 20 **Step 35.2: (S)-1-[2-(4-benzyloxyphenyl)ethyl]-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one**



The procedure used is the same as that of step 12.4.

1.40 g (3.02 mmol) of (S)-1-[2-(4-benzyloxyphenyl)ethyl]-7-chloro-2-methyl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one, 903 mg (6.04 mmol) of 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride and 763 mg (7.54 mmol) of triethylamine were used in the reaction. After purification by chromatography on silica gel (eluent A/B: 2/8 heptane/EtOAc), 1.2 g of (S)-1-[2-(4-benzyloxyphenyl)ethyl]-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one were obtained, corresponding to the following characteristics:
 LC/MS (method G): ESI+ [M+H]⁺: m/z 541 tr (min) = 2.84
¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 1.49 (s, 3H), 1.66 (m, 2H), 1.83 (m, 2H), 2.79 (m, 1H), 2.96 (m, 3H), 3.45 (m, 2H), 3.86 (m, 3H), 4.10 (d, 1H), 4.39 (m, 2H), 4.78 (m, 1H), 5.08 (s, 2H), 6.96 (m, 2H), 7.15 (m, 2H), 7.41 (m, 5H).

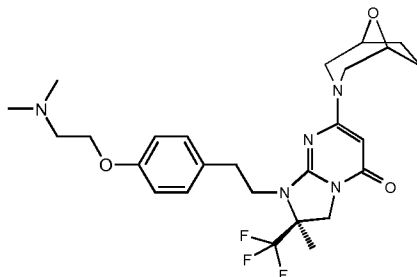
Step 35.3: (S)-1-[2-(4-hydroxyphenyl)ethyl]-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one



700 mg (11.10 mmol) of ammonium formate and 156 mg (0.22 mmol) of 20% palladium hydroxide are added at 0°C to a solution of 1.20 g (2.22 mmol) of (S)-1-[2-(4-benzyloxyphenyl)ethyl]-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one in 15 mL of methanol. The mixture is refluxed for 1 hour and then allowed to cool to room temperature. The reaction medium is filtered through Celite and the filtrate is then evaporated to dryness. After purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 25 min 10% B, t 30 min 10% B), 732 mg of (S)-1-[2-(4-hydroxyphenyl)ethyl]-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one were obtained, corresponding to the following characteristics:
 LC/MS (method B): ESI+ [M+H]⁺: m/z 451 tr (min) = 0.68
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.48 (s, 3H), 1.64 (m, 2H), 1.80 (m, 2H), 2.72 (m, 1H), 2.87 (m, 1H), 3.00 (m, 2H), 3.35 (m, 1H), 3.52 (m, 1H), 3.78 (m, 3H), 4.09 (d, 1H), 4.39 (m, 2H), 4.77 (s, 1H), 6.68 (m, 2H), 6.97 (m, 2H), 9.16 (s, 1H).

Example 36:

(S)-1-{2-[4-(2-dimethylaminoethoxy)phenyl]ethyl}-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one (compound 74)



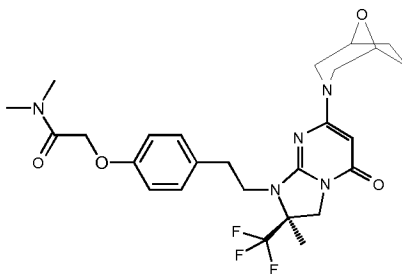
282 mg (0.87 mmol) of cesium carbonate are added to a solution of 130 mg (0.29 mmol) of (S)-1-[2-(4-hydroxyphenyl)ethyl]-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one in 10 mL of DMF. After heating at 80°C for 20 minutes, 62.40 mg (0.43 mmol) of (2-chloroethyl)dimethylamine are added. The reaction medium is heated at 80°C overnight. The reaction medium is evaporated to dryness. After purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 25 min 10% B, t 30 min 10% B), 116 mg of (S)-1-{2-[4-(2-dimethylaminoethoxy)phenyl]ethyl}-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one were obtained, corresponding to the following characteristics:

LC/MS (method B): ESI+ [M+H]⁺: m/z 522 tr (min) = 0.56

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.48 (s, 3H), 1.62 (m, 2H), 1.77 (m, 2H), 2.77 (m, 7H), 2.88 (m, 1H), 2.93 (m, 2H), 3.40 (m, 4H), 3.57-3.78 (bs, 2H), 3.82 (m, 1H), 4.06 (m, 1H), 4.26 (m, 2H), 4.33 (m, 2H), 4.72 (s, 1H), 6.90 (m, 2H), 7.12 (m, 2H), 10.2 (bs, 1H).

Example 37:

N,N-dimethyl-2-(4-{2-[(S)-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-5-oxo-2-trifluoromethyl-2,3-dihydro-5H-imidazo[1,2-a]pyrimidin-1-yl]ethyl}phenoxy)acetamide (compound 70)



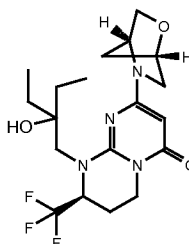
235 mg (0.72 mmol) of cesium carbonate are added to a solution of 130 mg (0.29 mmol) of (S)-1-[2-(4-hydroxyphenyl)ethyl]-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one in 10 mL of DMF. After heating at 80°C for 20 minutes, 52.60 mg (0.43 mmol) of 2-chloro-N,N-dimethylacetamide and 43.30 mg (0.29 mmol) of sodium iodide are added. The reaction medium is heated at 80°C overnight. The reaction medium is evaporated to dryness. After purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 25 min 10% B, t 30 min 10% B), 138 mg of N,N-dimethyl-2-(4-{2-[(S)-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-5-oxo-2-trifluoromethyl-2,3-dihydro-5H-imidazo[1,2-a]pyrimidin-1-yl]ethoxy}phenyl)acetamide were obtained, corresponding to the following characteristics:

LC/MS (method B): ESI+ [M+H]⁺: m/z 536 tr (min) = 0.69

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.53 (s, 3H), 1.68 (m, 2H), 1.82 (m, 2H), 2.75 (m, 1H), 2.81 (s, 3H), 2.95 (m, 3H), 2.97 (s, 3H), 3.38 (m, 1H), 3.52 (m, 1H), 3.73 (m, 2H), 3.82 (d, 1H), 4.13 (d, 1H), 4.41 (m, 2H), 4.74 (s, 2H), 4.76 (s, 1H), 6.85 (m, 2H), 7.12 (m, 2H).

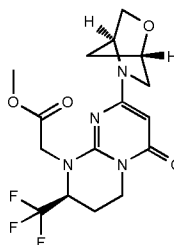
Example 38:

(8S)-9-(2-ethyl-2-hydroxybutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 54)



Step 38.1: methyl ((8S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetate

115

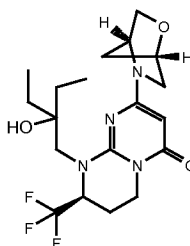


150 mg (0.474 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 3 mL of DMF are added to a suspension of 18.97 mg (0.474 mmol) of sodium hydride in 7 mL of DMF. The reaction mixture is stirred at room temperature for 10 minutes. After addition of 45 μ l (0.474 mmol) of methyl bromoacetate, the reaction is stirred at room temperature overnight. The reaction medium is evaporated to dryness. The residue is purified by chromatography on a column of silica (eluent: 95/5 DCM/MeOH). 147 mg of methyl ((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetate were obtained, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 389 tr (min) = 1.70

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 1.81 (m, 2H), 2.11 (m, 1H), 2.40 (m, 1H), 3.13 (m, 3H), 3.50 (m, 1H), 3.57 (s, 3H), 3.69 (m, 1H), 4.16 (m, 1H), 4.27 (m, 1H), 4.50 (m, 1H), 4.68 (m, 4H).

Step 38.2: (8S)-9-(2-ethyl-2-hydroxybutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



631 μ l (1.89 mmol) of a 3 M solution of ethylmagnesium bromide in ethyl ether are added at 0°C to a solution of 147 mg (0.38 mmol) of methyl ((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetate in 10 mL of THF. The reaction medium is stirred at 0°C for 4

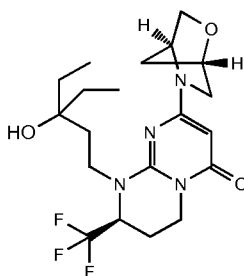
hours, followed by addition of 10 mL of saturated ammonium chloride solution. The resulting mixture is extracted with ethyl acetate and the organic phase is then dried over magnesium sulfate and evaporated to dryness. After purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 25 min 10% B, t 30 min 10% B), 80 mg of (8S)-9-(2-ethyl-2-hydroxybutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:

LC/MS (method A): ESI+ [M+H]⁺: m/z 417 tr (min) = 0.63

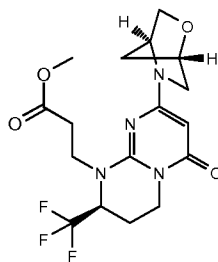
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 0.76 (m, 3H), 0.83 (m, 3H), 1.30 (m, 1H), 1.36 (m, 1H), 1.42 (m, 2H), 1.83 (m, 2H), 2.25 (m, 1H), 2.39 (m, 1H), 2.99 (m, 1H), 3.24 (m, 1H), 3.30 (m, 2H), 3.57 (m, 1H), 3.70 (m, 1H), 4.13 (m, 1H), 4.61 (m, 3H), 4.72 (m, 1H), 4.98 (m, 1H).

Example 39:

(8S)-9-(3-ethyl-3-hydroxypentyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 49)



Step 39.1: methyl 3-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)-propionate



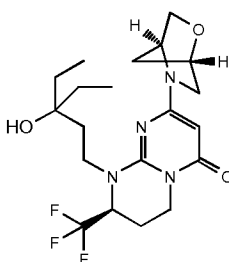
1 μ l (0.006 mmol) of DBU and 274.94 mg (3.16 mmol) of methyl acrylate are added to a solution of 200 mg (0.632 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 5 mL of DMF. The reaction mixture is stirred at room temperature overnight.

The reaction medium is evaporated to dryness. The residue is purified by chromatography on a column of silica (eluent: 95/5 DCM/MeOH). 245 mg of methyl 3-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)-propionate were obtained, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 403 tr (min) = 1.83

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 1.61 (m, 2H), 1.85 (m, 1H), 2.11 (m, 1H), 2.43 (m, 1H), 2.61 (m, 1H), 2.88 (m, 2H), 3.09 (m, 2H), 3.35 (m, 4H), 3.48 (m, 1H), 3.95 (m, 2H), 4.45 (m, 4H).

Step 39.2: (8S)-9-(3-ethyl-3-hydroxypentyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



911 μ l (2.73 mmol) of a 3 M solution of ethylmagnesium bromide in ethyl ether are added at 0°C to a solution of 220 mg (0.55 mmol) of methyl 3-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)-propionate in 10 mL of THF. The reaction medium is stirred at 0°C for 2 hours. 10 mL of saturated ammonium chloride solution are added to the reaction medium. The resulting mixture is extracted with ethyl acetate and the organic phase is then dried over magnesium sulfate and evaporated to dryness. After purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 25 min 10% B, t 30 min 10% B), 128 mg of (8S)-9-(3-ethyl-3-hydroxypentyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:

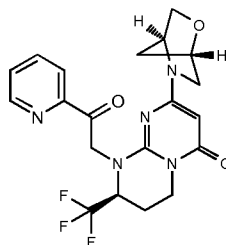
LC/MS (method A): ESI+ [M+H]⁺: m/z 431 tr (min) = 0.63

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 0.80 (m, 6H), 1.36 (m, 4H), 1.63 (m, 1H), 1.71 (m, 1H), 1.82 (m, 2H), 2.05 (m, 1H), 2.34 (m, 1H), 3.15 (m, 1H), 3.23 (m, 1H), 3.62 (m,

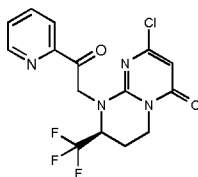
1H), 3.70 (m, 1H), 3.99 (m, 1H), 4.19 (m, 2H), 4.51 (m, 2H), 4.64 (m, 2H), 5.01-5.12 (bs, 1H).

Example 40:

- 5 **(8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-2-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 68)**



- 10 **Step 40.1: (8S)-2-chloro-9-(2-oxo-2-pyrid-2-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one**



The procedure used is the same as that of step 12.3.

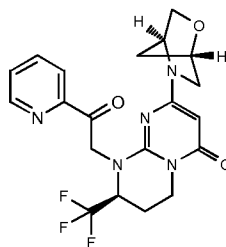
- 15 150 mg (0.591 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, 578.71 mg (1.77 mmol) of cesium carbonate, 199.40 mg (0.709 mmol) of 2-bromo-1-pyrid-2-ylethanone hydrobromide and 10 mL of acetonitrile were used in the reaction. After purification by chromatography on silica gel (eluent A/B: heptane/EtOAc, gradient A/B: t 0 min 0% B, t 15 min 50% B, t 25 min 70% B), 218 mg of (8S)-2-chloro-9-(2-oxo-2-pyrid-2-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following
- 20 characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 373 tr (min) = 2.14

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 2.28 (m, 1H), 3.40 (m, 1H), 4.40 (m, 1H), 4.80 (m, 1H), 5.11 (d, 1H), 5.61 (d, 1H), 5.77 (m, 1H), 5.93 (s, 1H), 7.76 (m, 1H), 8.00 (m, 1H), 8.08 (m, 1H), 8.79 (m, 1H).

25

- Step 40.2: (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-2-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one**



The procedure used is the same as that of step 12.4.

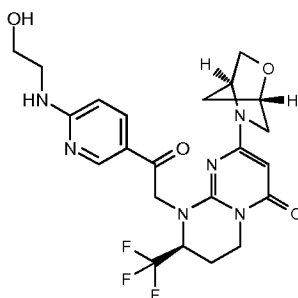
218 mg (0.58 mmol) of (8S)-2-chloro-9-(2-oxo-2-pyrid-2-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, 95.17 mg (0.702 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride and 205 μ l (1.46 mmol) of triethylamine were used in the reaction. After purification by chromatography on silica gel (eluent A/B: 95/5 DCM/MeOH), 103 mg of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-2-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:

LC/MS (method A): ESI+ [M+H]⁺: m/z 436 tr (min) = 0.59

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.59 (m, 1H), 1.68 (m, 1H), 2.24 (m, 1H), 2.44 (m, 1H), 2.90 (m, 2H), 3.08-3.20 (bs, 2H), 3.25 (m, 1H), 4.26 (m, 1H), 4.37 (m, 1H), 4.47 (m, 1H), 4.62 (m, 1H), 4.72 (m, 1H), 4.82 (m, 1H), 5.70 (m, 1H), 7.73 (m, 1H), 7.98 (m, 1H), 8.07 (m, 1H), 8.78 (m, 1H).

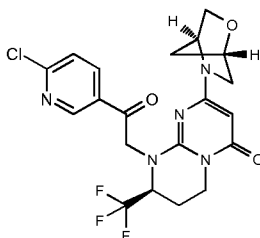
Example 41:

(8S)-9-[2-[6-(2-hydroxyethylamino)pyrid-3-yl]-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 14)



Step 41.1: (8S)-9-[2-(6-chloropyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

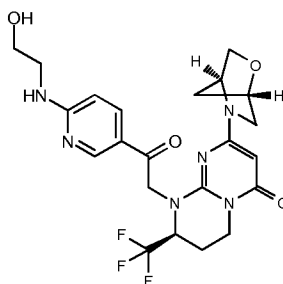
120



- 100 mg (0.32 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 3 mL of DMF are added to a suspension of 41.73 mg (1.04 mmol) of sodium hydride in 5 mL of DMF.
- 5 The reaction mixture is stirred at room temperature for 10 minutes. After addition of 244.65 mg (1.04 mmol) of 2-bromo-1-(6-chloropyrid-3-yl)ethanone, the reaction is continued at room temperature overnight. The reaction medium is evaporated to dryness. The residue is purified by chromatography on a column of silica (eluent: 90/10 DCM/MeOH). 85 mg of (8S)-9-[2-(6-chloropyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-
- 10 azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:
- LC/MS (method G): ESI+ [M+H]⁺: m/z 470 tr (min) = 1.86
- ¹H NMR (600 MHz, δ in ppm, DMSO- d_6): 1.65 (m, 2H), 2.28 (m, 1H), 2.93 (m, 3H), 3.19 (m, 3H), 4.45 (m, 3H), 4.71 (m, 3H), 5.74 (m, 1H), 7.78 (m, 1H), 8.41 (m, 1H), 9.10 (m,
- 15 1H).

Step 41.2: (8S)-9-{2-[6-(2-hydroxyethylamino)pyrid-3-yl]-2-oxoethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

20



- A mixture of 0.50 mL of ethanol, 33 mg (0.070 mmol) of (8S)-9-[2-(6-chloropyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-
- 25 trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 21.41 μ L (0.352 mmol) of ethanolamine is heated in a Biotage microwave reactor at 130°C for 30 minutes. The reaction mixture is evaporated to dryness and the residue is then taken

up in 10 mL of water. The precipitate is filtered off and then dried under vacuum. 17 mg of (8S)-9-[2-[6-(2-hydroxyethylamino)pyrid-3-yl]-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, the characteristics of which are as follows:

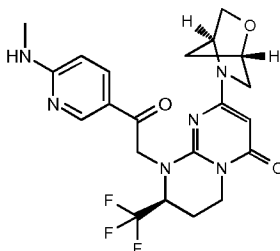
5 LC/MS (method A): ESI+ [M+H]⁺: m/z 495 tr (min) = 0.40

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.62 (m, 1H), 1.73 (m, 1H), 2.23 (m, 1H), 2.41 (m, 1H), 2.91-3.12 (bs, 3H), 3.23 (m, 1H), 3.42 (m, 2H), 3.54 (m, 2H), 4.36 (m, 2H), 4.49 (m, 2H), 4.60 (m, 2H), 4.74 (m, 1H), 5.60 (d, 1H), 6.58 (d, 1H), 7.53 (m, 1H), 7.88 (m, 1H), 8.77 (m, 1H).

10

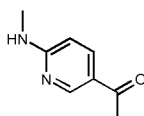
Example 42:

(8S)-9-[2-(6-methylaminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 5)



15

Step 42.1: 1-(6-methylaminopyrid-3-yl)ethanone

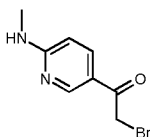


20

A mixture of 2 mL of ethanol, 280 mg (1.80 mmol) of 1-(6-chloropyrid-3-yl)ethanone and 4.50 mL (9 mmol) of a 2 M solution of methylamine in THF is heated in a Biotage microwave reactor at 130°C for 30 minutes. The reaction medium is evaporated to dryness. The crude product is taken up in water and extracted with EtOAc. The organic phase is dried over magnesium sulfate and evaporated to dryness. 258 mg of 1-(6-methylaminopyrid-3-yl)ethanone are obtained, the characteristics of which are as follows:

25 ¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 2.42 (s, 3H), 2.84 (s, 3H), 6.47 (m, 1H), 7.42 (m, 1H), 7.85 (m, 1H), 8.65 (m, 1H).

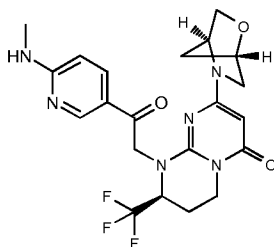
Step 42.2: 2-bromo-1-(6-methylaminopyrid-3-yl)ethanone



The procedure used is the same as that of step 12.2.

- 380 mg (2.53 mmol) of 1-(6-methylaminopyrid-3-yl)ethanone, 416 μ l (2.53 mmol) of hydrobromic acid, 130 μ l (2.53 mmol) of bromine and 5 mL of glacial acetic acid were used in the reaction. After precipitation with ethyl ether and filtration, the precipitate is taken up in water. The solution is basified with saturated NaHCO_3 solution. The precipitate formed is filtered off, washed with water and then dried under vacuum. 370 mg of 2-bromo-1-(6-methylaminopyrid-3-yl)ethanone are obtained, the characteristics of which are as follows:
- ^1H NMR spectrum (300 MHz, δ in ppm, $\text{DMSO}-d_6$): 2.85 (s, 3H), 4.70 (s, 2H), 6.50 (m, 1H), 7.62 (m, 1H), 7.87 (m, 1H), 8.71 (m, 1H).

- Step 42.3:** (8S)-9-[2-(6-methylaminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

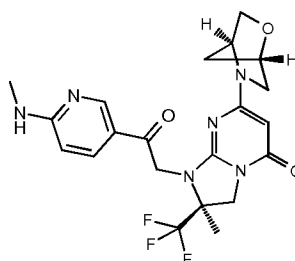


- 100 mg (0.32 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 3 mL of DMF are added to a suspension of 13.91 mg (0.35 mmol) of sodium hydride in 5 mL of DMF. The reaction mixture is stirred at room temperature for 15 minutes. After dropwise addition of 79.67 mg (0.35 mmol) of 2-bromo-1-(6-methylaminopyrid-3-yl)ethanone dissolved in 3 mL of DMF, the reaction is continued at room temperature for 1 hour. The reaction medium is evaporated to dryness. The residue is purified by chromatography on a column of silica (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 25 min 10% B, t 30 min 15% B). 75 mg of (8S)-9-[2-(6-methylaminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:
- LC/MS (method A): ESI+ $[\text{M}+\text{H}]^+$: m/z 465 tr (min) = 0.41

¹H NMR spectrum (600 MHz, δ in ppm, DMSO- d_6): 1.62 (m, 1H), 1.73 (m, 1H), 2.23 (m, 1H), 2.42 (m, 1H), 2.86 (s, 3H), 2.92-3.16 (bs, 3H), 3.23 (m, 2H), 4.37 (m, 2H), 4.49 (m, 2H), 4.60 (m, 2H), 5.60 (m, 1H), 6.51 (m, 1H), 7.47 (m, 1H), 7.92 (m, 1H), 8.78 (m, 1H).

5 **Example 43:**

2-methyl-1-[2-(6-methylaminopyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one (compound 9)



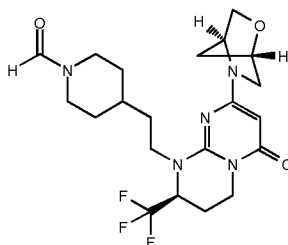
10 100 mg (0.32 mmol) of 2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one in 3 mL of DMF are added to a suspension of 13.91 mg (0.35 mmol) of sodium hydride in 5 mL of DMF. The reaction mixture is stirred at room temperature for 15 minutes. After dropwise addition of 79.67 mg (0.35 mmol) of 2-bromo-1-(6-methylaminopyrid-3-yl)ethanone dissolved in 3 mL of DMF, the reaction is continued at room temperature for 1 hour. The reaction medium is evaporated to dryness. The residue is purified by chromatography on a column of silica (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 25 min 10% B, t 30 min 15% B). 100 mg of 2-methyl-1-[2-(6-methylaminopyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one were obtained, corresponding to the following characteristics:

LC/MS (method A): ESI+ [M+H]⁺: m/z 465 tr (min) = 0.42

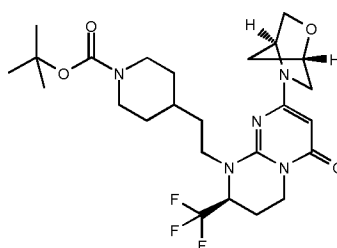
¹H NMR (600 MHz, δ in ppm, DMSO- d_6): 1.61 (s, 3H), 1.70 (m, 1H), 1.75 (m, 1H), 2.86 (d, 3H), 2.93-3.26 (bs, 3H), 3.35 (m, 1H), 3.98 (m, 1H), 4.22 (m, 1H), 4.53 (m, 3H), 4.64 (d, 1H), 5.05 (d, 1H), 6.51 (m, 1H), 7.50 (m, 1H), 7.91 (m, 1H), 8.79 (m, 1H).

Example 44:

4-[2-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]piperidine-1-carbaldehyde (compound 90)



Step 44.1: tert-butyl 4-[2-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]piperidine-1-carboxylate

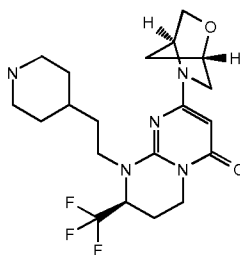


1.03 g (3.54 mmol) of tert-butyl 4-(2-bromoethyl)piperidine-1-carboxylate and 530 mg (3.54 mmol) of sodium iodide are added to a solution of 800 mg (2.53 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 2.47 g (7.59 mmol) of cesium carbonate in 15 mL of acetonitrile. The reaction mixture is heated in a Biotage microwave reactor at 100°C for 1 hour 15 minutes. The reaction medium is evaporated to dryness and the residue is taken up in EtOAc and washed with water and with saturated NaCl. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 90/10 DCM/MeOH) to give 730 mg of tert-butyl 4-[2-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]piperidine-1-carboxylate, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 528 tr (min) = 2.57

¹H NMR spectrum (300 MHz, δ in ppm, DMSO-d₆): 0.98 (m, 2H), 1.24 (m, 1H), 1.38 (s, 9H), 1.47 (m, 1H), 1.61 (m, 3H), 1.84 (m, 2H), 2.03 (m, 1H), 2.33 (m, 1H), 2.68 (m, 2H), 3.13 (m, 3H), 3.32 (m, 3H), 3.57-3.75 (dd, 2H), 3.88 (m, 2H), 7.92 (m, 1H), 4.18 (m, 2H), 4.63 (m, 2H).

Step 44.2: (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-piperidin-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



5

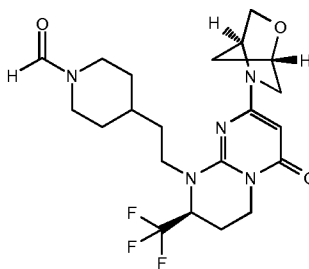
A solution of 250 mg (0.473 mmol) of tert-butyl 4-[2-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]piperidine-1-carboxylate in 10 mL of formic acid is stirred for 1 hour 30 minutes at room temperature.

The reaction mixture is evaporated to dryness and the residue is taken up in DCM and evaporated to give 224 mg of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-piperidin-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 428 tr (min) = 1.34

Step 44.3: 4-[2-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]piperidine-1-carbaldehyde

20



33 mg (0.521 mmol) of ammonium formate are added to a suspension of 224 mg (0.474 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-piperidin-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 10 mL of 1,4-dioxane. The reaction mixture is heated at 100°C for 4 hours and then evaporated

25

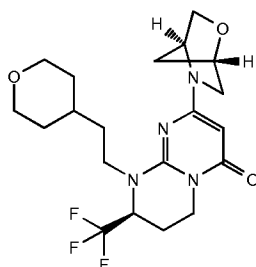
to dryness. The residue is taken up in DCM and the solution is washed with water and with saturated NaCl. The organic phase is dried over sodium sulfate and evaporated to dryness. The product obtained is purified by chromatography on silica gel (eluent: 90/10 DCM/MeOH) to give 85 mg of 4-[2-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]piperidine-1-carbaldehyde, the characteristics of which are as follows:

LC/MS (method A): ESI+ [M+H]⁺: m/z 456 tr (min) = 0.54

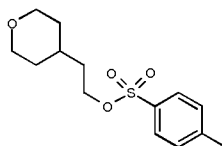
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 0.83-1.11 (m, 2H), 1.5 (m, 2H), 1.58-1.77 (m, 3H), 1.85 (m, 2H), 2.04 (m, 1H), 2.34 (m, 1H), 2.57 (m, 1H), 2.99 (m, 1H), 3.02-3.23 (m, 3H), 3.33 (m, 1H), 3.59-3.75 (m, 3H), 4.07-4.21 (m, 3H), 4.55-4.99 (m, 4H), 7.95 (s, 1H).

Example 45:

(8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-(tetrahydropyran-4-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 92)



Step 45.1: 2-(tetrahydro-2H-pyran-4-yl)ethyl 4-methylbenzenesulfonate

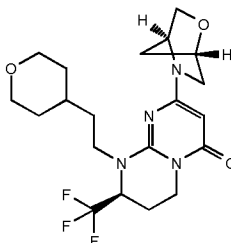


629 μ L (4.47 mmol) of triethylamine and 813 mg (4.10 mmol) of p-toluenesulfonyl chloride are added to a solution of 500 mg (3.73 mmol) of 2-(tetrahydropyran-4-yl)ethanol in 15 mL of DCM previously cooled to 0°C.

The reaction mixture is stirred at room temperature overnight. The solution is taken up in DCM, washed with aqueous NaHCO₃ solution, dried over magnesium sulfate and then evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 20/80 EtOAc/heptane) to give 840 mg of 2-(tetrahydro-2H-pyran-4-yl)ethyl 4-methylbenzenesulfonate, corresponding to the following characteristics:

^1H NMR (300 MHz, δ in ppm, CDCl_3): 1.15-1.32 (m, 2H), 1.45-1.74 (m, 5H), 2.47 (s, 3H), 3.33 (td, 2H), 3.88-3.96 (m, 2H), 4.09 (t, 2H), 7.37 (d, 2H), 7.82 (d, 2H).

5 **Step 45.2: (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-(tetrahydropyran-4-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one**



198 mg (0.698 mmol) of 2-(tetrahydro-2H-pyran-4-yl)ethyl 4-methylbenzenesulfonate and 104 mg (0.698 mmol) of sodium iodide are added to a solution of 170 mg (0.537 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 525 mg (1.61 mmol) of cesium carbonate in 5 mL of acetonitrile. The reaction mixture is heated in a Biotage microwave reactor at 100°C for 1 hour 15 minutes. The reaction medium is evaporated to dryness and the residue is taken up in EtOAc and washed with water and with saturated NaCl. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 DCM/MeOH) to give 140 mg of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-(tetrahydropyran-4-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

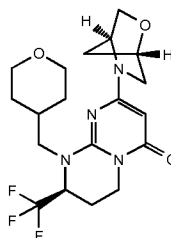
LC/MS (method A): ESI+ $[\text{M}+\text{H}]^+$: m/z 429 tr (min) = 0.61

^1H NMR spectrum (600 MHz, δ in ppm, $\text{DMSO}-d_6$): 1.09-1.25 (m, 2H), 1.46-1.57 (m, 3H), 1.58-1.67 (m, 2H), 1.82-1.89 (m, 2H), 2.04 (m, 1H), 2.34 (m, 1H), 2.96-2-3.22 (m, 3H), 3.23-3.37 (m, 4H), 3.63 (m, 1H), 3.73 (m, 1H), 3.82 (m, 2H), 4.11 (m, 1H), 4.21 (m, 1H), 4.57-5.01 (m, 3H).

Example 46:

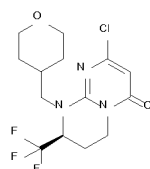
(8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(tetrahydropyran-4-ylmethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 93)

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Step 46.1: (8S)-2-chloro-9-(tetrahydropyran-4-ylmethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

5



A suspension of 200 mg (0.788 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 771 mg (2.37 mmol) of cesium carbonate
10 in 10 mL of acetonitrile is stirred for 15 minutes at room temperature. 187 mg (0.788 mmol) of (bromomethyl)tetrahydropyran are then added.

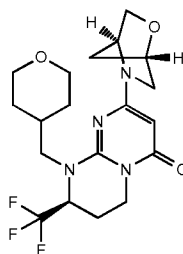
The reaction mixture is heated in a Biotage microwave reactor at 100°C for 50 minutes. The crude product is evaporated and the residue is taken up in water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and
15 evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 DCM/MeOH) to give 220 mg of (8S)-2-chloro-9-(tetrahydropyran-4-ylmethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 352 tr (min) = 2.08

¹H NMR spectrum (300 MHz, δ in ppm, DMSO-d₆): 1.04-1.42 (m, 2H), 1.42-1.57 (m, 2H), 2.04-2.33 (m, 2H), 2.34-2.46 (m, 1H), 2.95-3.07 (m, 1H), 3.17-3.30 (m, 3H), 3.79-3.89 (m, 2H), 4.04-4.21 (m, 2H), 4.72 (m, 1H), 5.89 (s, 1H).
20

Step 46.2: (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(tetrahydropyran-4-ylmethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
25

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220 mg (0.62 mmol) of (8S)-2-chloro-9-(tetrahydropyran-4-ylmethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 127 mg (0.93 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride are mixed together. The powder obtained is placed in a tube and 244 μ L (1.75 mmol) of triethylamine are added. The tube is sealed and heated at 130°C in an oil bath for 4 hours. The crude product obtained is taken up in ethyl acetate and the organic phase is washed with water, dried over magnesium sulfate and then evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 DCM/MeOH) to give 180 mg of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(tetrahydropyran-4-ylmethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

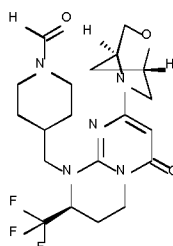
LC/MS (method A): ESI+ [M+H]⁺: m/z 415 tr (min) = 0.57

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.10-1.38 (m, 2H), 1.40-1.56 (m, 2H), 1.79-1.89 (m, 2H), 2.06-2.22 (m, 2H), 2.32 (m, 1H), 2.89 (m, 1H), 2.95-3.14 (m, 2H), 3.20 (m, 3H), 3.61 (m, 1H), 3.73 (m, 1H), 3.83 (m, 2H), 4.07-4.17 (m, 2H), 4.56 (m, 1H), 4.60-4.96 (m, 3H).

20

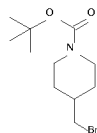
Example 47:

4-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-ylmethyl)piperidine-1-carbaldehyde (compound 95)



25

Step 47.1: tert-butyl 4-bromomethylpiperidine-1-carboxylate



A solution of 1 g (4.41 mmol) of tert-butyl 4-hydroxymethylpiperidine-1-carboxylate in 25 mL of THF is cooled to 0°C. 1.34 g (5.07 mmol) of triphenylphosphine and 2.02 g (5.96 mmol) of carbon tetrabromide are then added.

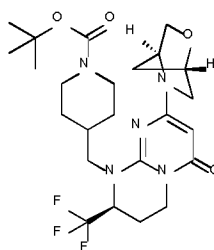
5 The reaction mixture is stirred at room temperature over the weekend.

The solution is taken up in ethyl ether, the insoluble matter is filtered off and the organic phase is evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 80/20 EtOAc/heptane) to give 960 mg of tert-butyl 4-bromomethylpiperidine-1-carboxylate, the characteristics of which are as follows:

10 LC/MS (method G): ESI+ [M+H]⁺: m/z 279 tr (min) = 2.13

¹H NMR (300 MHz, δ in ppm, CDCl₃): 1.09-1.29 (m, 2H), 1.47 (s, 9H), 1.71-1.88 (m, 3H), 2.62-2.78 (m, 2H), 3.31 (d, 2H), 4.07-4.25 (m, 2H).

Step 47.2: tert-butyl 4-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-ylmethyl)piperidine-1-carboxylate



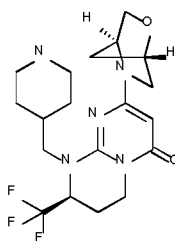
788 mg (2.84 mmol) of tert-butyl 4-bromomethylpiperidine-1-carboxylate and 425 mg (2.84 mmol) of sodium iodide are added to a solution of 690 mg (2.18 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 2.13 g (6.54 mmol) of cesium carbonate in 10 mL of acetonitrile. The reaction mixture is heated in a Biotage microwave reactor at 100°C for 3 hours. The reaction medium is evaporated to dryness and the residue is taken up in EtOAc and washed with water and with saturated NaCl. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 DCM/MeOH) to give 510 mg of tert-butyl 4-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-ylmethyl)piperidine-1-carboxylate, the characteristics

of which are as follows:

LC/MS (method G): ESI+ [M+H]⁺: m/z 514 tr (min) = 2.45

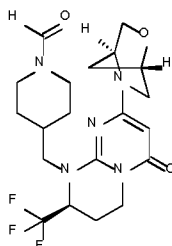
¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 0.93-1.03 (m, 1H), 1.11-1.32 (m, 3H), 1.38 (s, 9H), 1.44-1.64 (m, 2H), 1.76-1.91 (m, 2H), 1.99-2.39 (m, 3H), 2.78-3.32 (m, 5H), 3.60 (m, 1H), 3.71 (m, 1H), 3.86-3.99 (m, 2H), 4.06-4.19 (m, 2H), 4.48-4.92 (m, 3H).

Step 47.3: (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-piperid-4-ylmethyl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



A solution of 280 mg (0.545 mmol) of tert-butyl 4-((S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-ylmethyl)piperidine-1-carboxylate in 10 mL of formic acid is stirred for 2 hours at room temperature. The reaction mixture is evaporated to dryness and the residue is taken up in DCM and evaporated to give 250 mg of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-piperid-4-ylmethyl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:
LC/MS (method G): ESI+ [M+H]⁺: m/z 414 tr (min) = 1.31

Step 47.4: 4-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-ylmethyl)piperidine-1-carbaldehyde



41 mL (0.817 mmol) of ammonium formate are added to a suspension of 250 mg (0.545 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-piperid-4-ylmethyl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one in 10 mL of 1,4-dioxane. The reaction mixture is heated at 100°C for 2 hours and then evaporated to dryness. The residue is taken up in EtOAc and washed with aqueous NaHCO₃

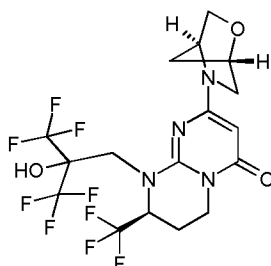
solution and with saturated NaCl. The organic phase is dried over sodium sulfate and evaporated to dryness. The product obtained is purified by chromatography on silica gel (eluent: 90/10 DCM/MeOH) to give 120 mg of 4-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-ylmethyl)piperidine-1-carbaldehyde, the characteristics of which are as follows:

LC/MS (method D): ESI+ [M+H]⁺: m/z 442 tr (min) = 0.82

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 0.91-1.24 (m, 2H), 1.56-1.75 (m, 2H), 1.81-1.91 (m, 2H), 2.14-2.29 (m, 2H), 2.36 (m, 1H), 2.54 (m, 1H), 2.96 (m, 2H), 3.15 (m, 1H), 3.21-3.40 (m, 2H), 3.66 (m, 2H), 3.74 (m, 1H), 4.10-4.23 (m, 3H), 4.51 (m, 1H), 4.58-4.84 (m, 3H), 7.99 (m, 1H).

Example 48:

(8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(3,3,3-trifluoro-2-hydroxy-2-trifluoromethylpropyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 96)



264 mg (1.42 mmol) of bis(trifluoromethyl)oxirane are added to a solution of 300 mg (0.948 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 1.66 ml (1.66 mmol) of 1 M sodium hydroxide in 5 mL of 1,4-dioxane. The reaction mixture is heated in a Biotage microwave reactor at 130°C for 2 hours. The reaction medium is evaporated to dryness and the residue is taken up in EtOAc and washed with water and with saturated NaCl. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 DCM/MeOH) to give 250 mg of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(3,3,3-trifluoro-2-hydroxy-2-trifluoromethylpropyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

LC/MS (method A): ESI+ [M+H]⁺: m/z 497 tr (min) = 0.71

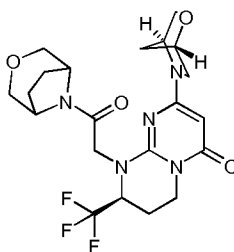
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.81-1.95 (m, 2H), 2.21 (m, 1H), 2.44 (m, 1H),

2.95-3.36 (m, 3H), 3.47-3.64 (m, 2H), 3.69 (m, 1H), 4.08 (m, 1H), 4.57-5.05 (m, 4H), 5.40 (m, 1H), 8.74 (m, 1H).

5

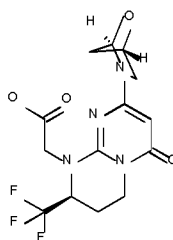
Example 49:

(8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 99)



10

Step 49.1: ((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetic acid



15

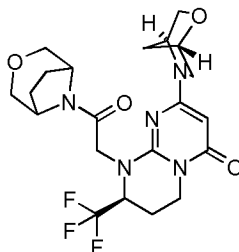
95 mg (2.22 mmol) of lithium hydroxide monohydrate are added to a solution of 720 mg (1.85 mmol) of methyl ((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetate (preparation described in Step 38.1) in 20 mL of THF/water (1/1: v/v). The reaction mixture is stirred at room temperature for 2 hours, after which the THF is evaporated off and the solution is acidified with 1 N HCl and extracted with EtOAc. The organic phase is washed with water and with saturated NaCl, dried over magnesium sulfate and then evaporated to dryness to give 690 mg of ((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetic acid, the characteristics of which are as follows:

25

LC/MS (method A): ESI+ [M+H]⁺: m/z 375 tr (min) = 1.63

¹H NMR (300 MHz, δ in ppm, DMSO- d_6): 1.81 (m, 2H), 2.02-2.18 (m, 1H), 2.32-2.43 (m, 1H), 3.10-3.32 (m, 3H), 3.49-3.59 (m, 1H), 3.68 (m, 1H), 3.98-4.08 (m, 1H), 4.24-4.35 (m, 1H), 4.37-4.47 (m, 1H), 4.57-4.86 (m, 4H), 12.71 (m, 1H).

Step 49.2: **(8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one**



98 μ L (0.881 mmol) of N-methylmorpholine, 86 mg (0.44 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 69 mg (0.44 mmol) of 1-hydroxybenzotriazole hydrate are added to a solution of 150 mg (0.4 mmol) of ((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetic acid in 10 mL of DMF. The reaction mixture is stirred for 10 minutes at room temperature, followed by addition of 66 mg (0.44 mmol) of (1R,5S)-3-oxa-8-azabicyclo[3.2.1]octane hydrochloride. The reaction is continued at room temperature for 5 hours. The DMF is evaporated off and the residue obtained is purified by chromatography on silica gel (eluent: 95/5 DCM/MeOH) to give 130 mg of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

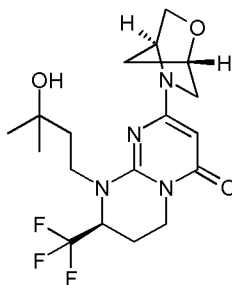
LC/MS (method A): ESI+ $[M+H]^+$: m/z 470 tr (min) = 0.5

^1H NMR (600 MHz, δ in ppm, DMSO- d_6) performed at 140°C: 1.77-1.95 (m, 6H), 2.21-2.43 (m, 2H), 3.14-3.38 (m, 3H), 3.53-3.72 (m, 6H), 3.98 (d, 1H), 4.27-4.48 (m, 4H), 4.62 (s, 1H), 4.71 (s, 1H), 4.76 (s, 1H), 5.11 (d, 1H).

Example 50:

(8S)-9-(3-hydroxy-3-methylbutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 50)

135



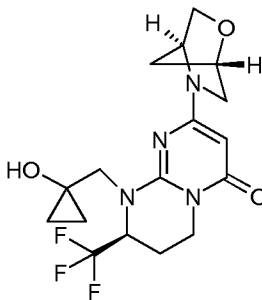
430 μ L (1.29 mmol) of a 3 M solution of methylmagnesium bromide in ethyl ether are added at 0°C to a solution of 173 mg (0.43 mmol) of methyl 3-((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)-propionate (preparation described in Step 39.1) in 10 mL of THF. The reaction medium is stirred at 0°C for 2 hours. 10 mL of saturated ammonium chloride solution are added to the reaction medium. The resulting mixture is extracted with ethyl acetate and the organic phase is dried over magnesium sulfate and evaporated to dryness. After purification by chromatography on silica gel (eluent: 95/5 DCM/MeOH), 128 mg of (8S)-9-(3-hydroxy-3-methylbutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, corresponding to the following characteristics:

LC/MS (method A): ESI+ $[M+H]^+$: m/z 403 tr (min) = 0.53

^1H NMR (600 MHz, δ in ppm, DMSO- d_6): 1.09 (s, 3H), 1.12 (s, 3H), 1.64-1.76 (m, 2H), 1.78-1.87 (m, 2H), 2.02 (m, 1H), 2.33 (m, 1H), 3.13 (m, 1H), 3.24-3.35 (m, 2H), 3.63 (m, 1H), 3.69 (m, 1H), 4.12 (m, 1H), 4.20 (m, 1H), 4.25 (s, 1H), 4.53 (m, 1H), 4.59-5.03 (m, 4H).

Example 51:

(8S)-9-(1-hydroxycyclopropylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 104)



146 mg (0.515 mmol) of titanium (IV) isopropoxide are added to a solution of

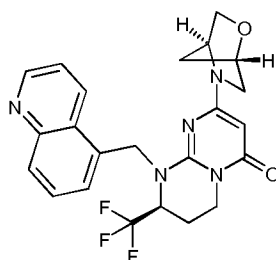
200 mg (0.515 mmol) of methyl ((2S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetate (preparation described in Step 38.1) in 3 mL of THF. The solution is cooled to 0°C, followed by dropwise addition of 858 µL (2.58 mmol) of 3 M ethylmagnesium bromide in ethyl ether. The reaction mixture is stirred for 30 minutes at room temperature. 10 mL of saturated ammonium chloride solution are added to the reaction medium. The resulting mixture is extracted with ethyl acetate and the organic phase is dried over magnesium sulfate and evaporated to dryness. After purification by chromatography on silica gel (eluent: 95/5 DCM/MeOH), 80 mg of (8S)-9-(1-hydroxycyclopropylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one are obtained, corresponding to the following characteristics:

LC/MS (method A): ESI+ [M+H]⁺: m/z 387 tr (min) = 0.52

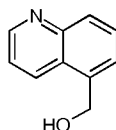
¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 0.52-0.71 (m, 4H), 1.77-1.86 (m, 2H), 2.27 (m, 1H), 2.40 (m, 1H), 3.20-3.29 (m, 3H), 3.45 (d, 1H), 3.59 (m, 1H), 3.72 (m, 1H), 4.18 (m, 1H), 4.37 (m, 1H), 4.59-5.01 (m, 4H), 5.54 (s, 1H).

Example 52:

(8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-quinolin-5-ylmethyl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 106)



Step 52.1: Quinolin-5-ylmethanol



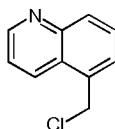
A suspension of 171 mg (4.49 mmol) of lithium aluminum hydride in 20 ml of THF is cooled to 0°C. A solution of 700 mg (3.74 mmol) of methyl quinoline-5-carboxylate in 5 ml of THF is then added dropwise. The reaction mixture is stirred at 0°C for 1 hour and then hydrolysed with, in this order, 0.17 ml of H₂O, 0.17 ml of NaOH and 3 × 0.17 ml of H₂O. The precipitate formed is filtered off and washed with THF and

then with EtOAc. The organic phase is washed with saturated NaCl solution, dried and evaporated. After purification by chromatography on silica gel (eluent: 95/5 DCM/MeOH), 190 mg of quinolin-5-ylmethanol are obtained, corresponding to the following characteristics:

5 LC/MS (method G): ESI+ [M+H]⁺: m/z 160 tr (min) = 0.43

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 4.97 (d, 2H), 5.40 (t, 1H), 7.51-7.65 (m, 2H), 7.72 (t, 1H), 7.93 (d, 1H), 8.53 (d, 1H), 8.88-8.93 (m, 1H).

Step 52.2: 5-chloromethylquinoline hydrochloride



10

A solution of 190 mg (1.19 mmol) of quinolin-5-ylmethanol in 5 ml of thionyl chloride is stirred for 10 minutes at room temperature and then refluxed for 2 hours. The reaction mixture is evaporated, the solid obtained is taken up in ethyl ether and the solution is filtered, washed with ethyl ether and dried to give 255 mg of 5-chloromethylquinoline hydrochloride, corresponding to the following characteristics:

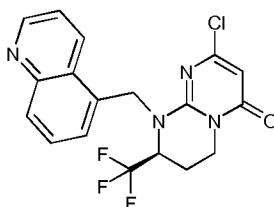
15

LC/MS (method G): ESI+ [M+H]⁺: m/z 178 tr (min) = 1.07

¹H NMR (300 MHz, δ in ppm, DMSO-d₆): 5.40 (s, 2H), 7.96-8.10 (m, 3H), 8.34 (m, 1H), 9.17 (m, 1H), 9.27 (m, 1H).

20

Step 52.3: (8S)-2-Chloro-9-quinolin-5-ylmethyl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



A suspension of 180 mg (0.709 mmol) of (8S)-2-chloro-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 693 mg (2.13 mmol) of cesium carbonate in 10 mL of acetonitrile is stirred for 15 minutes at room temperature. 182 mg (0.851 mmol) of 5-chloromethylquinoline hydrochloride are then added, along with a catalytic amount of sodium iodide.

25

The reaction mixture is stirred at room temperature for 5 hours. The crude product is evaporated and the residue is taken up in water and extracted with ethyl

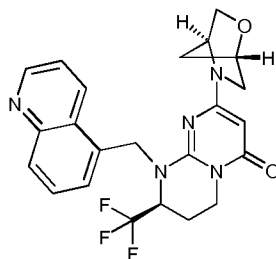
30

acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 DCM/MeOH) to give 160 mg of (8S)-2-chloro-9-quinolin-5-ylmethyl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 395 tr (min) = 2.00

¹H NMR spectrum (300 MHz, δ in ppm, DMSO-d₆): 2.24-2.46 (m, 2H), 3.35-3.47 (m, 1H), 4.26-4.36 (m, 1H), 4.66-4.80 (m, 1H), 5.04 (d, 1H), 5.83 (d, 1H), 5.98 (s, 1H), 7.42 (d, 1H), 7.61 (m, 1H), 7.73 (t, 1H), 7.97 (d, 1H), 8.57 (d, 1H), 8.95 (m, 1H).

Step 52.4: (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-quinolin-5-ylmethyl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



160 mg (0.40 mmol) of (8S)-2-chloro-9-quinolin-5-ylmethyl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one and 82 mg (0.60 mmol) of (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride are mixed together. The powder obtained is placed in a tube and 158 µL (1.13 mmol) of triethylamine are added. The tube is sealed and heated at 130°C in an oil bath for 7 hours. The crude product obtained is taken up in DCM and the organic phase is washed with water, dried over magnesium sulfate and then evaporated to dryness. The residue is purified by chromatography on silica gel (eluent: 95/5 DCM/MeOH) to give 125 mg of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-9-quinolin-5-ylmethyl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, the characteristics of which are as follows:

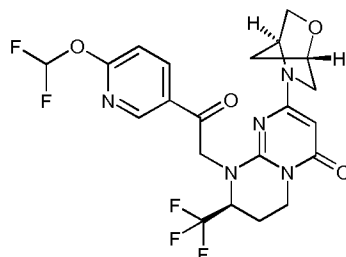
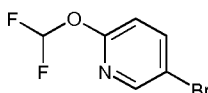
LC/MS (method A): ESI+ [M+H]⁺: m/z 458 tr (min) = 0.47

¹H NMR (600 MHz, δ in ppm, DMSO-d₆): 1.42-1.67 (bm, 2H), 2.29-2.46 (m, 2H), 2.74-3.20 (bm, 4H), 3.27-3.36 (m, 1H), 4.27 (m, 2H), 4.42 (m, 1H), 4.52-4.80 (bm, 2H), 4.85 (m, 1H), 5.91 (d, 1H), 7.39 (d, 1H), 7.56 (m, 1H), 7.71 (t, 1H), 7.93 (d, 1H), 8.62 (m, 1H), 8.92 (m, 1H).

Example 53:

(S)-9-[2-(6-difluoromethoxypyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one (compound 114)

5

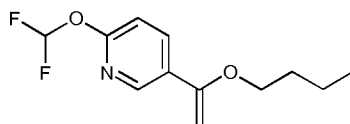
**Step 53.1: 5-bromo-2-difluoromethoxypyridine**

10 5.42 g (34.48 mmol) of sodium chlorodifluoroacetate are added to a solution of 5 g (28.74 mmol) of 5-bromo-1H-pyrid-2-one in 120 ml of acetonitrile, under argon.

The white suspension obtained is refluxed overnight and then evaporated to dryness. The residue is taken up in aqueous ammonium chloride solution and extracted with EtOAc. The organic phase is dried over magnesium sulfate and then
15 evaporated to dryness. The crude product is purified by chromatography on silica gel (eluent: 0/100 EtOAc/heptane to 20/80 EtOAc/heptane over 35 minutes) to give 2.2 g of 5-bromo-2-difluoromethoxypyridine, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 226 tr (min) = 2.08

¹H NMR spectrum (300 MHz, δ in ppm, DMSO-d₆): 7.12 (d, 1H), 7.67 (t, 1H), 8.15 (dd, 1H), 8.43 (d, 1H).
20

Step 53.2: 5-(1-butoxyvinyl)-2-difluoromethoxypyridine

25

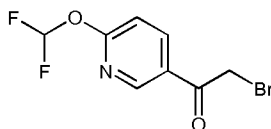
1 g (4.46 mmol) of 5-bromo-2-difluoromethoxypyridine in 20 mL of H₂O/DMF (1/4: v/v), 1.46 mL (11.16 mmol) of N-butyl vinyl ether, 30.68 mg (0.13 mmol) of palladium(II) acetate, 125 mg (0.29 mmol) of 1,3-bis(diphenylphosphino)propane and

746 mg (5.36 mmol) of potassium carbonate are placed in a microwave tube. After microwave irradiation for 1 hour at 120°C, the crude product is taken up in water and extracted with DCM. The organic phase is dried over magnesium sulfate and then evaporated to dryness. The crude product is purified by chromatography on silica gel (eluent: 0/100 EtOAc/heptane to 20/80 EtOAc/heptane over 35 minutes) to give 110 mg of 5-(1-butoxyvinyl)-2-difluoromethoxypyridine, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 244 tr (min) = 2.74

¹H NMR spectrum (300 MHz, δ in ppm, DMSO-d₆): 0.94 (t, 3H), 1.38-1.53 (m, 2H), 1.66-1.78 (m, 2H), 3.86 (t, 2H), 4.38 (d, 1H), 4.85 (d, 1H), 7.09 (d, 1H), 7.71 (t, 1H), 8.09 (dd, 1H), 8.49 (d, 1H).

Step 53.3: 2-bromo-1-(6-difluoromethoxypyrid-3-yl)ethanone

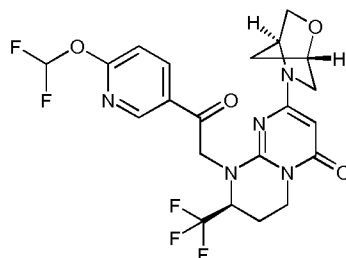


A solution of 100 mg (0.41 mmol) of 5-(1-butoxyvinyl)-2-difluoromethoxypyridine in 4 mL of THF/H₂O (3/1: v/v) is cooled to 0°C. 74 mg (0.41 mmol) of N-bromosuccinimide are then added in a single portion. The yellow solution is stirred at 0°C for 1 hour and then taken up in water and extracted with EtOAc. The organic phase is washed with saturated aqueous NaHCO₃ solution and then with saturated NaCl solution, dried over magnesium sulfate and then evaporated to dryness. The crude product is purified by chromatography on silica gel (eluent: 20/80 EtOAc/heptane to 40/60 EtOAc/heptane over 15 minutes) to give 82 mg of 2-bromo-1-(6-difluoromethoxypyrid-3-yl)ethanone, corresponding to the following characteristics:

LC/MS (method G): ESI+ [M+H]⁺: m/z 266 tr (min) = 1.84

¹H NMR spectrum (300 MHz, δ in ppm, DMSO-d₆): 4.91 (s, 2H), 7.19 (d, 1H), 7.75 (t, 1H), 8.36 (dd, 1H), 8.85 (d, 1H).

Step 53.4: (8S)-9-[2-(6-difluoromethoxypyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one



The procedure used is the same as that of step 12.3.

120 mg (0.38 mmol) of (8S)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one, 371 mg (1.42 mmol) of cesium carbonate, 121 mg (0.45 mmol) of 2-bromo-1-(6-difluoromethoxypyrid-3-yl)ethanone and 15 mL of acetonitrile were used in the reaction. After purification by chromatography on silica gel (eluent A/B: DCM/MeOH, gradient A/B: t 0 min 0% B, t 25 min 10% B, t 30 min 10% B), 38 mg of (8S)-9-[2-(6-difluoromethoxypyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one were obtained, corresponding to the following characteristics:

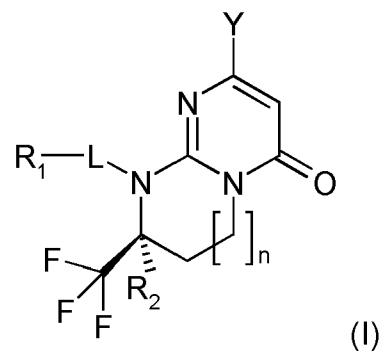
LC/MS (method A): ESI+ $[M+H]^+$: m/z 502 tr (min) = 0.67

^1H NMR (600 MHz, δ in ppm, DMSO- d_6): 1.56-1.74 (m, 2H), 2.21 (m, 1H), 2.44 (m, 1H), 2.78-3.09 (m, 3H), 3.23 (m, 1H), 3.47-3.85 (m, 1H), 4.37 (m, 1H), 4.41-4.53 (m, 2H), 4.53-4.71 (m, 3H), 5.66-5.78 (m, 1H), 7.26 (d, 1H), 7.82 (t, 1H), 8.48 (dd, 1H), 9.01 (m, 1H).

The table which follows illustrates the chemical structures and the physical properties of some examples of compounds according to the invention. In this table:

- in the "Salt" column, "-" represents a compound in free base form, whereas "HCl" represents a compound in hydrochloride form;

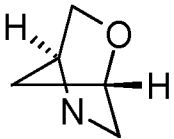
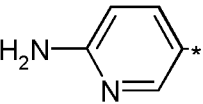
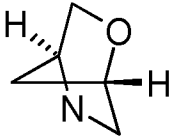
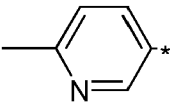
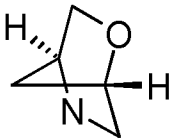
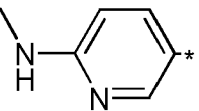
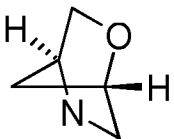
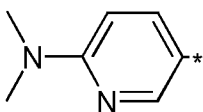
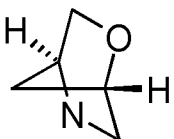
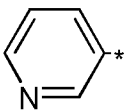
- the "Data" column successively indicates the LC/MS analytical method used (A, B, C or F) and detailed in the experimental section, the retention time (tr) of the compound expressed in minutes, and the peak $[M+H]^+$ identified by mass spectrometry.

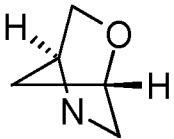
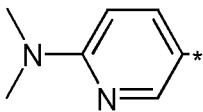
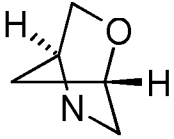
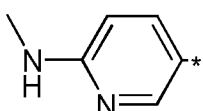
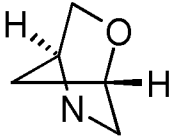
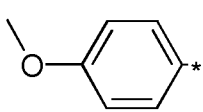
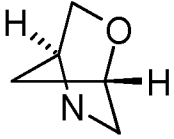
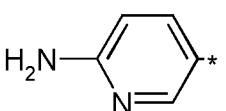
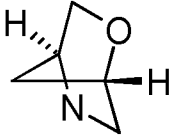
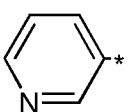
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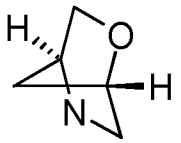
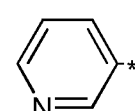
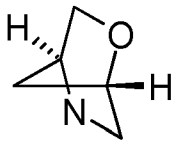
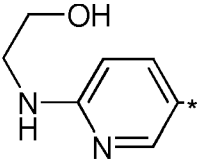
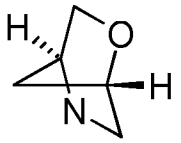
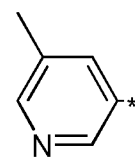
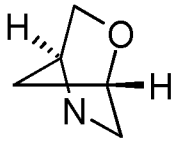
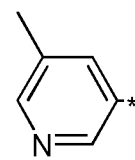
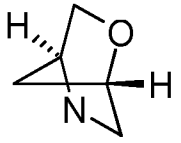
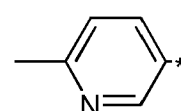
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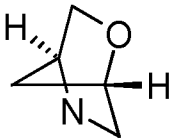
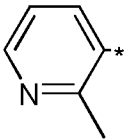
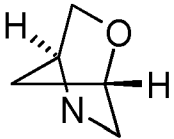
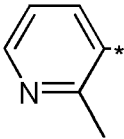
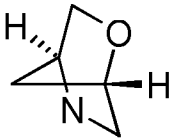
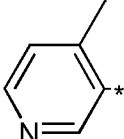
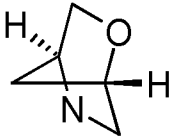
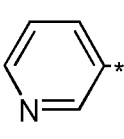
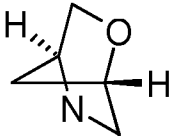
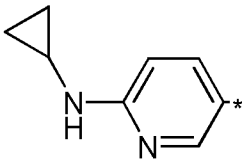
The asterisk * on R₁ and L indicates the atom of attachment of R₁ to L.

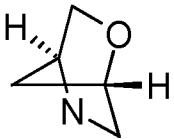
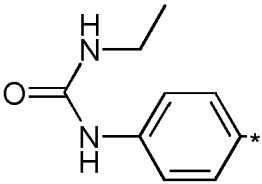
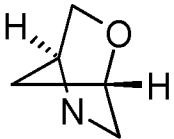
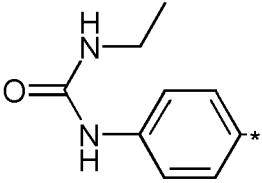
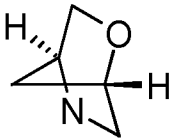
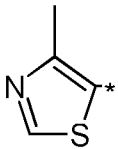
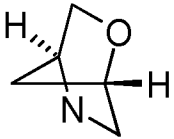
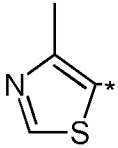
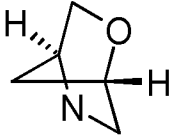
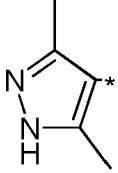
No.	n	Y	R ₁	L	Salt	Data
1 Ex. 13	1			*-C(CH ₃) ₂ -CH ₂ -	-	Method B: tr (min) = 0.53 [M+H] ⁺ : 450
2 Ex. 27	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.50 [M+H] ⁺ : 436

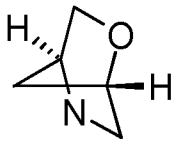
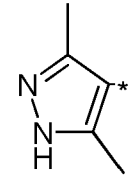
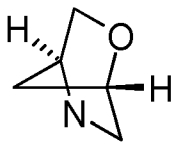
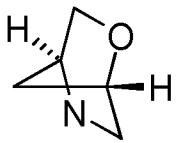
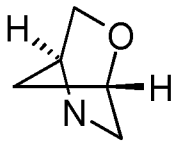
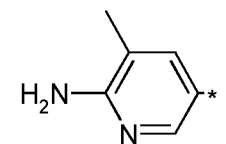
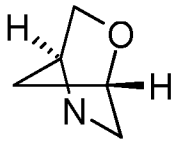
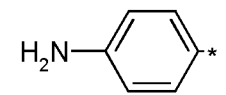
No.	n	Y	R ₁	L	Salt	Data
3	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.38 [M+H] ⁺ : 451
4 Ex. 28	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.49 [M+H] ⁺ : 450
5 Ex. 42	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.41 [M+H] ⁺ : 465
6 Ex. 25	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.48 [M+H] ⁺ : 479
7 Ex. 6	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.51 [M+H] ⁺ : 436

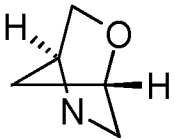
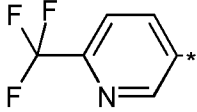
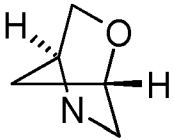
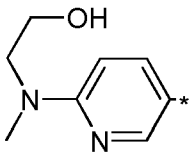
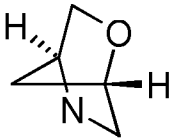
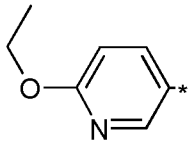
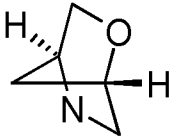
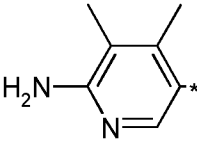
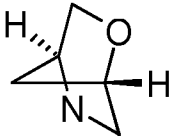
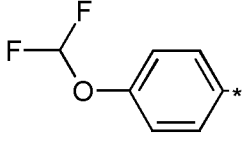
No.	n	Y	R ₁	L	Salt	Data
8	0			*-CO-CH ₂ -	-	Method A: tr (min) = 0.49 [M+H] ⁺ : 479
9 Ex. 43	0			*-CO-CH ₂ -	-	Method A: tr (min) = 0.42 [M+H] ⁺ : 465
10	0			*-CH ₂ -CH ₂ -	-	* Method C tr (min) = 1.19 [M+H] ⁺ : 451
11	0			*-CO-CH ₂ -	-	Method A: tr (min) = 0.38 [M+H] ⁺ : 451
12 Ex. 31	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.39 [M+H] ⁺ : 422

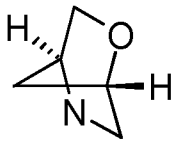
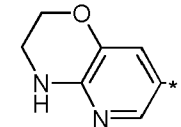
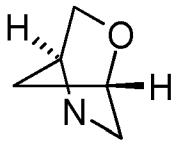
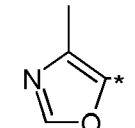
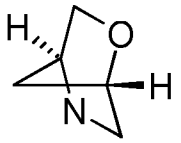
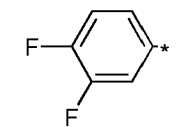
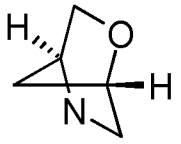
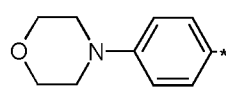
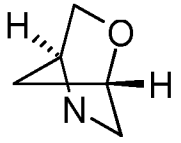
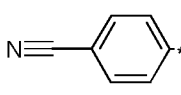
No.	n	Y	R ₁	L	Salt	Data
13	0			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.39 [M+H] ⁺ : 422
14 Ex. 41	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.40 [M+H] ⁺ : 495
15 Ex. 3	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.51 [M+H] ⁺ : 450
16 Ex. 7	0			*-CO-CH ₂ -	-	Method A: tr (min) = 0.52 [M+H] ⁺ : 450
17 Ex. 29	0			*-CO-CH ₂ -	-	Method A: tr (min) = 0.49 [M+H] ⁺ : 450

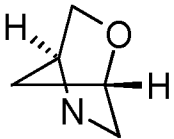
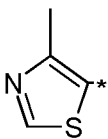
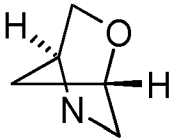
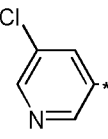
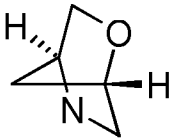
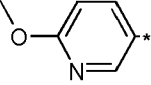
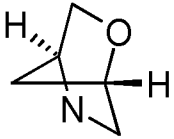
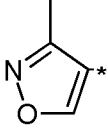
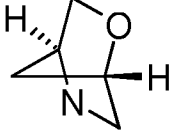
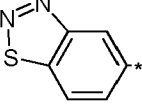
No.	n	Y	R ₁	L	Salt	Data
18	0			*-CO-CH ₂ -	-	Method A: tr (min) = 0.48 [M+H] ⁺ : 450
19 Ex. 9	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.48 [M+H] ⁺ : 450
20 Ex. 12	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.50 [M+H] ⁺ : 450
21 Ex. 30	0			*-CO-CH ₂ -	-	Method A: tr (min) = 0.51 [M+H] ⁺ : 436
22	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.45 [M+H] ⁺ : 491

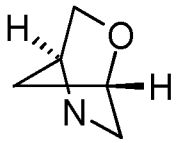
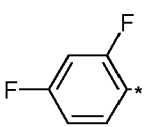
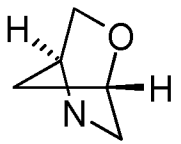
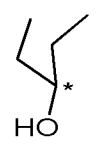
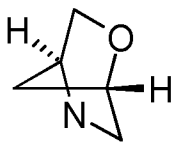
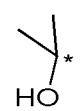
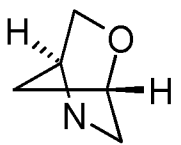
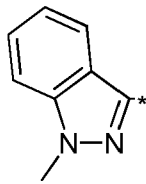
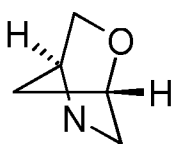
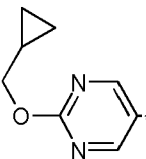
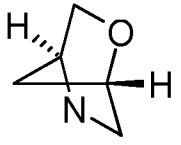
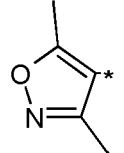
No.	n	Y	R ₁	L	Salt	Data
23 Ex. 14	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.60 [M+H] ⁺ : 507
24 Ex. 15	0			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.60 [M+H] ⁺ : 507
25 Ex. 2	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.55 [M+H] ⁺ : 442
26 Ex. 8	0			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.56 [M+H] ⁺ : 442
27	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.46 [M+H] ⁺ : 439

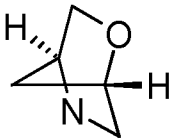
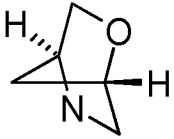
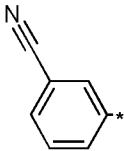
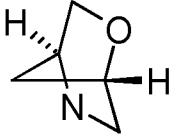
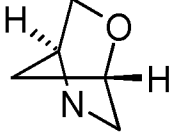
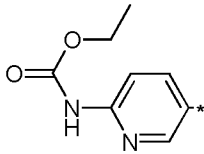
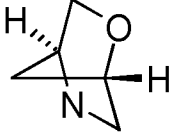
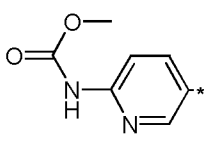
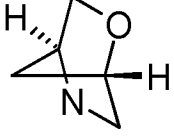
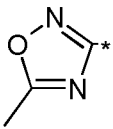
No.	n	Y	R ₁	L	Salt	Data
28	0			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.45 [M+H] ⁺ : 439
29 Ex. 26	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.67 [M+H] ⁺ : 415
30	0			*-CO-CH ₂ -	-	Method A: tr (min) = 0.67 [M+H] ⁺ : 415
31	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.42 [M+H] ⁺ : 465
32	0			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.48 [M+H] ⁺ : 436

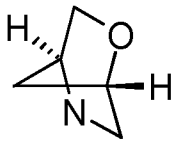
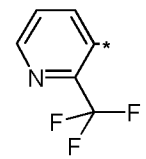
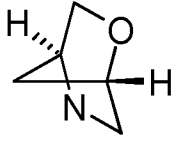
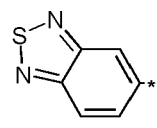
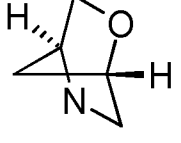
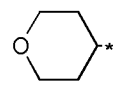
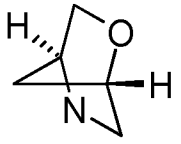
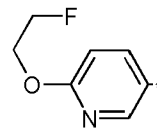
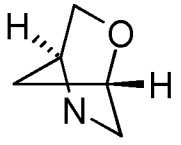
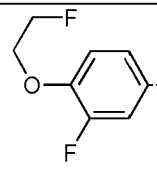
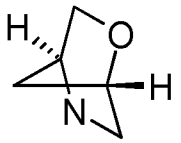
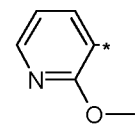
No.	n	Y	R ₁	L	Salt	Data
33	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.67 [M+H] ⁺ : 504
34	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.47 [M+H] ⁺ : 509
35	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.67 [M+H] ⁺ : 480
36	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.43 [M+H] ⁺ : 479
37	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.69 [M+H] ⁺ : 501

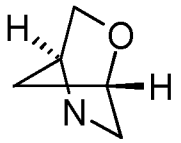
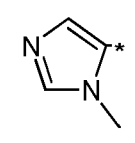
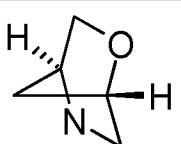
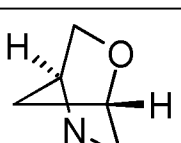
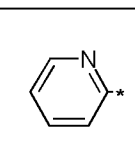
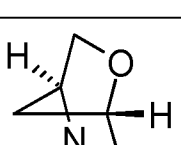
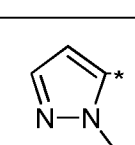
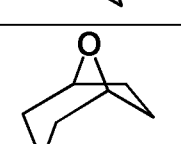
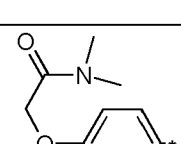
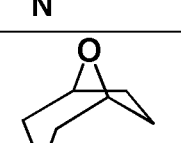
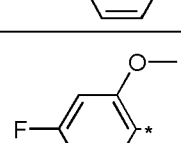
No.	n	Y	R ₁	L	Salt	Data
38 Ex. 16	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.49 [M+H] ⁺ : 439
39	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.52 [M+H] ⁺ : 440
40	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.68 [M+H] ⁺ : 471
41	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.64 [M+H] ⁺ : 520
42	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.62 [M+H] ⁺ : 460

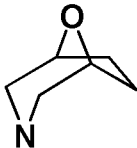
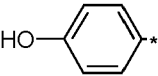
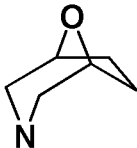
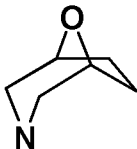
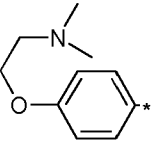
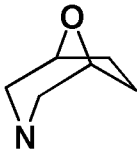
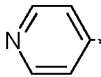
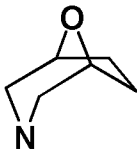
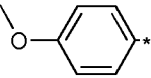
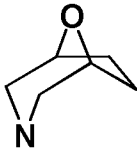
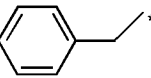
No.	n	Y	R ₁	L	Salt	Data
43 Ex. 10	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.55 [M+H] ⁺ : 456
44	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.61 [M+H] ⁺ : 470
45 Ex. 32	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.61 [M+H] ⁺ : 466
46	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.55 [M+H] ⁺ : 440
47 Ex. 17	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.64 [M+H] ⁺ : 493

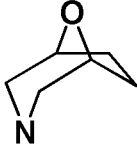
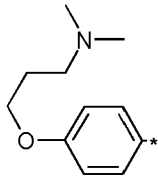
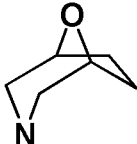
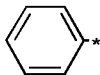
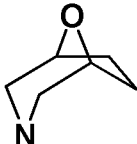
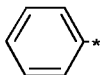
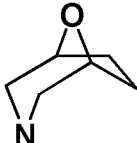
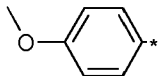
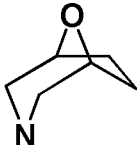
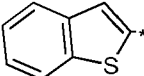
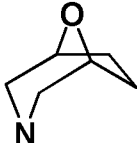
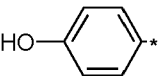
No.	n	Y	R ₁	L	Salt	Data
48 Ex. 1	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.68 [M+H] ⁺ : 471
49 Ex. 39	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.63 [M+H] ⁺ : 431
50 Ex. 50	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.53 [M+H] ⁺ : 403
51 Ex. 18	1			*-CH ₂ -	-	Method A: tr (min) = 0.68 [M+H] ⁺ : 461
52 Ex. 19	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.65 [M+H] ⁺ : 507
53 Ex. 4	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.58 [M+H] ⁺ : 454

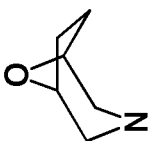
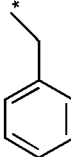
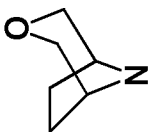
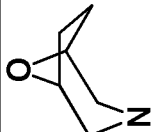
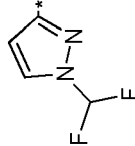
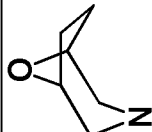
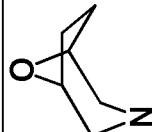
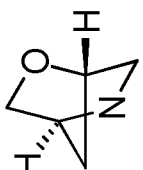
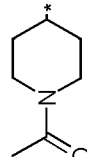
No.	n	Y	R ₁	L	Salt	Data
54 Ex. 38	1			*-CH ₂ -	-	Method A: tr (min) = 0.63 [M+H] ⁺ : 417
55	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.61 [M+H] ⁺ : 460
56 Ex. 5	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.60 [M+H] ⁺ : 401
57 Ex. 21	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.60 [M+H] ⁺ : 523
58	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.55 [M+H] ⁺ : 509
59	1			*-CH ₂ -	-	Method C tr (min) = 0.85 [M+H] ⁺ : 413

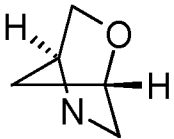
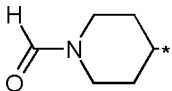
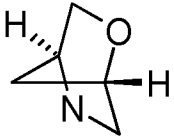
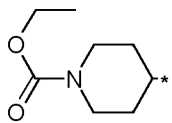
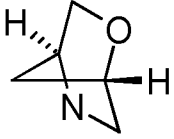
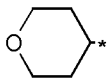
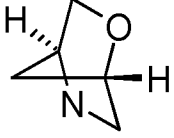
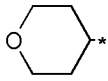
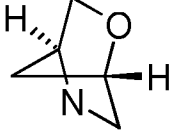
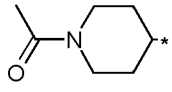
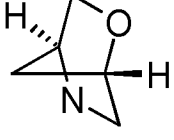
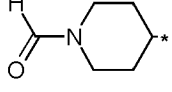
No.	n	Y	R ₁	L	Salt	Data
60	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.62 [M+H] ⁺ : 504
61	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.64 [M+H] ⁺ : 493
62 Ex. 11	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.52 [M+H] ⁺ : 443
63 Ex. 33	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.62 [M+H] ⁺ : 498
64	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.65 [M+H] ⁺ : 515
65	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.63 [M+H] ⁺ : 466

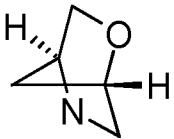
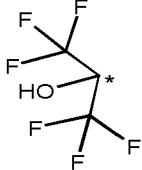
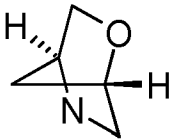
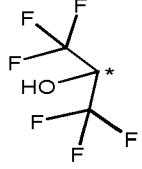
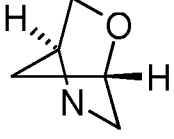
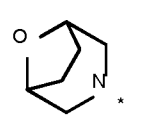
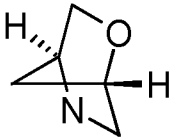
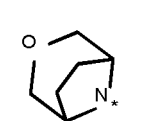
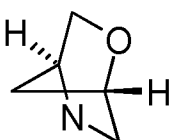
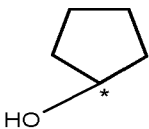
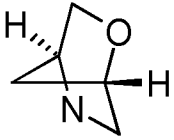
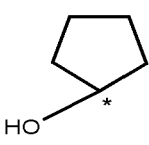
No.	n	Y	R ₁	L	Salt	Data
66	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.40 [M+H] ⁺ : 439
67	1			*-CO-CH ₂ -	-	Method C tr (min) = 0.88 [M+H] ⁺ : 399
68 Ex. 40	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.59 [M+H] ⁺ : 436
69 Ex. 20	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.54 [M+H] ⁺ : 439
70 Ex. 37	0			*-CH ₂ -CH ₂ -	-	Method B: tr (min) = 0.69 [M+H] ⁺ : 536
71 Ex. 34	1			*-CHOH-CH ₂ - OH abs. conf. (S)	-	Method B: tr (min) = 0.71 [M+H] ⁺ : 499

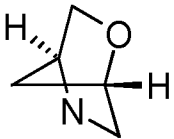
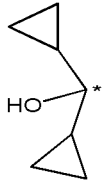
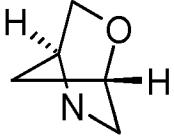
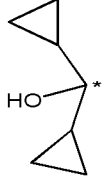
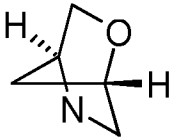
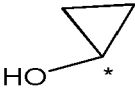
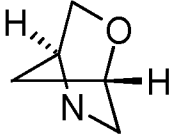
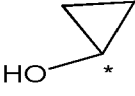
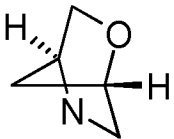
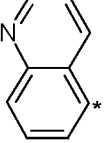
No.	n	Y	R ₁	L	Salt	Data
72 Ex. 35	0			*-CH ₂ -CH ₂ -	-	Method B: tr (min) = 0.68 [M+H] ⁺ : 451
73	1			*-CO-CH ₂ -	-	Method F tr (min) = 0.84 [M+H] ⁺ : 449
74 Ex. 36	0			*-CH ₂ -CH ₂ -	HCl	Method B: tr (min) = 0.56 [M+H] ⁺ : 522
75 Ex. 23	1			*-CO-CH ₂ -	-	Method B: tr (min) = 0.55 [M+H] ⁺ : 450
76	0			*-CH ₂ -CH ₂ -	-	Method C tr (min) = 1.26 [M+H] ⁺ : 465
77	0			*-CH ₂ -CH ₂ -	-	Method B: tr (min) = 82 [M+H] ⁺ : 449

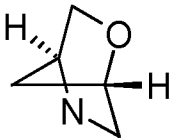
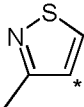
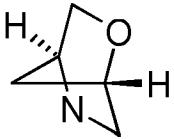
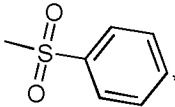
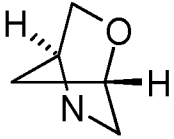
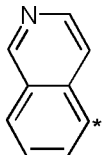
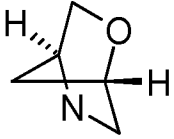
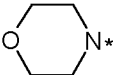
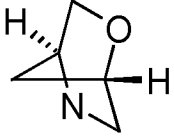
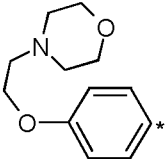
No.	n	Y	R ₁	L	Salt	Data
78	0			*-CH ₂ -CH ₂ -	HCl	Method B: tr (min) = 0.58 [M+H] ⁺ : 536
79	0			*-CHOH-CH ₂ - OH abs. conf. (S)	-	Method B: tr (min) = 0.65 [M+H] ⁺ : 451
80 Ex. 24	1			*-CHOH-CH ₂ - OH abs. conf. (S)	-	Method B: tr (min) = 0.68 [M+H] ⁺ : 451
81	1			*-CH ₂ -CH ₂ -	-	Method B: tr (min) = 0.81 [M+H] ⁺ : 465
82	1			*-CHOH-CH ₂ - OH abs. conf. (R)	-	Method B: tr (min) = 0.85 [M+H] ⁺ : 507
83	1			*-CH ₂ -CH ₂ -	-	Method B: tr (min) = 0.68 [M+H] ⁺ : 451

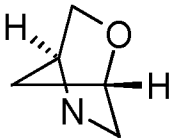
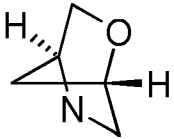
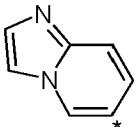
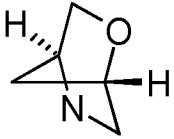
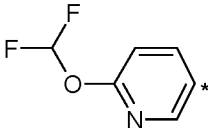
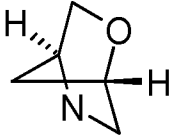
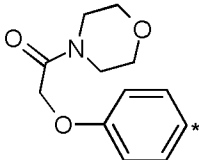
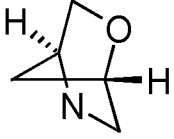
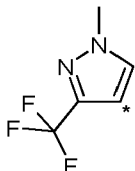
No.	n	Y	R ₁	L	Salt	Data
84 Ex. 22	1			*-CH ₂ -CH ₂ -	-	Method B: tr (min) = 0.85 [M+H] ⁺ : 449
85	1			*-CO-CH ₂ -	-	Method B: tr (min) = 0.52 [M+H] ⁺ : 450
86	1			*-CH ₂ -	-	Method F tr (min) = 0.83 [M+H] ⁺ : 461
87	1			*-CO-CH ₂ -	-	Method F tr (min) = 0.83 [M+H] ⁺ : 450
88	1			*-CO-CH ₂ -	-	Method F tr (min) = 1.01 [M+H] ⁺ : 450
89	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.55 [M+H] ⁺ : 470

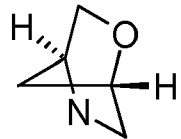
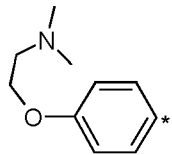
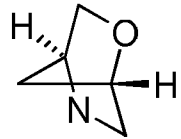
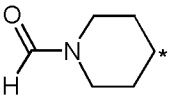
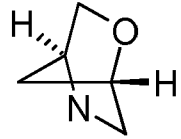
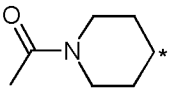
No.	n	Y	R ₁	L	Salt	Data
90 Ex. 44	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.54 [M+H] ⁺ : 456
91	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.62 [M+H] ⁺ : 514
92 Ex. 45	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.61 [M+H] ⁺ : 429
93 Ex. 46	1			*-CH ₂ -	-	Method A: tr (min) = 0.57 [M+H] ⁺ : 415
94	1			*-CH ₂ -	-	Method D tr (min) = 0.84 [M+H] ⁺ : 456
95 Ex. 47	1			*-CH ₂ -	-	Method D tr (min) = 1.01 [M+H] ⁺ : 450

No.	n	Y	R ₁	L	Salt	Data
96 Ex. 48	1			*-CH ₂ -	-	Method A: tr (min) = 0.71 [M+H] ⁺ : 497
97	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.68 [M+H] ⁺ : 511
98	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.51 [M+H] ⁺ : 470
99 Ex. 49	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.5 [M+H] ⁺ : 470
100	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.6 [M+H] ⁺ : 429
101	1			*-CH ₂ -	-	Method D tr (min) = 0.95 [M+H] ⁺ : 415

No.	n	Y	R ₁	L	Salt	Data
102	1			$^{**}\text{CH}_2\text{-CH}_2\text{-}$	-	Method A: tr (min) = 0.68 [M+H] ⁺ : 455
103	1			$^{**}\text{CH}_2\text{-}$	-	Method D tr (min) = 1.13 [M+H] ⁺ : 441
104 Ex. 51	1			$^{**}\text{CH}_2\text{-}$	-	Method A: tr (min) = 0.52 [M+H] ⁺ : 387
105	1			$^{**}\text{CH}_2\text{-CH}_2\text{-}$	-	Method A: tr (min) = 0.53 [M+H] ⁺ : 401
106 Ex. 52	1			$^{**}\text{CH}_2\text{-}$	-	Method A: tr (min) = 0.47 [M+H] ⁺ : 458

No.	n	Y	R ₁	L	Salt	Data
107	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.57 [M+H] ⁺ : 456
108	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.54 [M+H] ⁺ : 513
109	1			*-CH ₂ -	-	Method A: tr (min) = 0.53 [M+H] ⁺ : 458
110	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.56 [M+H] ⁺ : 444
111	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.49 [M+H] ⁺ : 550

No.	n	Y	R ₁	L	Salt	Data
112	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.53 [M+H] ⁺ : 418
113	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.38 [M+H] ⁺ : 475
114 Ex. 53	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.67 [M+H] ⁺ : 502
115	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.61 [M+H] ⁺ : 564
116	1			*-CH ₂ -	-	Method A: tr (min) = 0.67 [M+H] ⁺ : 479

No.	n	Y	R ₁	L	Salt	Data
117	1			*-CH ₂ -CH ₂ -	-	Method A: tr (min) = 0.49 [M+H] ⁺ : 508
118	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.79 [M+H] ⁺ : 567
119	1			*-CO-CH ₂ -	-	Method A: tr (min) = 0.48 [M+H] ⁺ : 484

The compounds according to the invention underwent pharmacological trials to determine their inhibitory effect on the growth of *Plasmodium falciparum*.

Antimalarial activity test

5 The compounds according to the invention underwent pharmacological trials to determine their inhibitory effect on the growth of *Plasmodium falciparum* (strain NF54 sensitive to inhibition with chloroquine) in an *in vitro* test using infected human erythrocytes. The growth of the parasites is measured via the incorporation of tritiated hypoxanthine compared with the incorporation in the absence of drug. The tests are
10 performed in 96-well microplates (Falcon™ 96-well microtiter plates, ref. No. 353072) in RPMI 1640 solutions (10.44 g/l) (without hypoxanthine) with HEPES (5.94 g/l), NaHCO₃ (2.1 g/l), neomycin (100 g/mL)+ AlbumaxR II (5 g/l) supplemented with human erythrocytes with a final hematocrit of 1.25% and a final parasitemia of 0.15%.

15 The stock solution of the compounds is prepared at 10 mg/mL in DMSO. For the test, fresh solutions at the desired concentrations are prepared in RPMI medium. For the test, 100 µl of compound are mixed with 100 µl of infected blood. For the determination of the IC₅₀ values, the compounds are tested in twofold serial dilution.

20 The plates are incubated at 37°C under a humid atmosphere with 93% N₂, 4% CO₂ and 3% O₂. After 48 hours, 50 µl of ³H-hypoxanthine (= 0.5 µCi) in RPMI medium are added to each well and incubation is continued for a further 24 hours. Next, the plates are washed with distilled water and the cell lysate is transferred onto fiberglass filters. The filters are dried and the radioactivity is determined by liquid scintillation. The results in cpm are converted into percentages of inhibition. The inhibitory activity is given by the concentration that inhibits 50% of the growth of the parasite relative to a
25 control without compound.

 The IC₅₀ values are between 3 nM and 4000 nM, in particular between 3 nM and 384 nM and even more particularly less than or equal to 200 nM.

The table of results for the antimalarial activity test is given below:

Compound No.	IC ₅₀ <i>Plasmodium falciparum</i> NF54
1	20 nM
2	15 nM
3	13 nM
4	58 nM
5	95 nM
6	>200 nM
7	10 nM
8	>200 nM
9	>200 nM
10	11 nM
11	40 nM
12	9 nM
13	21 nM
14	70 nM
15	150 nM
16	>200 nM
17	160 nM
18	93 nM
19	24 nM
20	35 nM
21	82 nM
22	>200 nM
23	3 nM
24	8 nM
25	<3.4 nM
26	10 nM
27	<4.5 nM
28	9 nM
29	46 nM
30	>240 nM
31	75 nM
32	4 nM
33	4000 nM
34	>200 nM
35	>210 nM
36	240 nM
37	230 nM
38	140 nM
39	98 nM
40	80 nM

Compound No.	IC ₅₀ <i>Plasmodium falciparum</i> NF54
41	930 nM
42	80 nM
43	42 nM
44	106 nM
45	112 nM
46	398 nM
47	13 nM
48	27 nM
49	6 nM
50	8 nM
51	65 nM
52	130 nM
53	870 nM
54	10 nM
55	28 nM
56	45 nM
57	65 nM
58	53 nM
59	87 nM
60	19 nM
61	130 nM
62	11 nM
63	384 nM
64	39 nM
65	21 nM
66	73 nM
67	43 nM
68	27 nM
69	96 nM
70	12 nM
71	23 nM
72	37 nM
73	44 nM
74	68 nM
75	80 nM
76	93 nM
77	160 nM
78	360 nM
79	640 nM
82	9 nM

Compound No.	IC ₅₀ <i>Plasmodium falciparum</i> NF54
83	10 nM
84	110 nM
85	150 nM
86	170 nM
88	140 nM
89	3.4 nM
90	2 nM
91	25 nM
92	4 nM
93	4 nM
94	9 nM
95	7 nM
96	170 nM
97	30 nM
98	140 nM
99	170 nM
100	9 nM
101	10 nM

Compound No.	IC ₅₀ <i>Plasmodium falciparum</i> NF54
102	5 nM
103	75 nM
104	12 nM
105	24 nM
106	13 nM
107	100 nM
108	86 nM
109	79 nM
110	330 nM
111	5 nM
112	200 nM
113	430 nM
114	245 nM
115	3 nM
116	117 nM
117	6 nM
118	15 nM
119	30 nM

Human PI3K α activity test

5 The compounds according to the invention underwent pharmacological trials to measure the selectivity toward human lipid kinases and especially human PI3K α . The test uses a luciferin/luciferase system to measure the concentration of ATP and its consumption during the enzymatic reaction. The test is performed in 96-well format (Corning/Costar 96 black flat-bottomed half-wells plate, ref. 3694) in a total volume of
10 30 μ l.

To 1 μ l of inhibitor in 100% DMSO are added (final concentrations) 50 μ M of the substrate PIP2 ((L- α -phosphatidyl-D-myoinositol 4,5-bisphosphate, Calbiochem 524644), 2 μ M of ATP and 1.7 μ g/mL of PI3K α (p110 α /p85 α , Invitrogen PV4788) in a buffer of Tris/HCl 50 mM pH 7.5, EGTA 1 mM, MgCl₂ 10 mM, Chaps 0.03%, 1 mM
15 DTT). After 90 minutes, the reaction is quenched by adding 20 μ l/well of KinaseGlo reagent (Promega V6713). After 10 minutes in the dark, the luminescence is read using a PHERASstar microplate reader (reading at 0.8 sec/well).

The IC₅₀ values are determined by the preparation of successive threefold dilutions on at least a scale of more than 10 000. The IC₅₀ values are between 190 nM

and more than 10 000 nM, in particular between 1040 nM and more than 10 000 nM and even more particularly greater than 2000 nM.

The activity of the other isoforms of human PI3K may be measured in the same manner.

5 The table of results for the activity of human PI3K α test is given below:

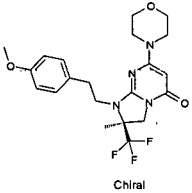
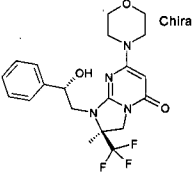
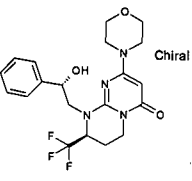
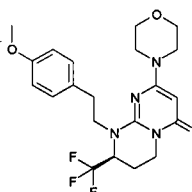
No.	IC ₅₀ Human PI3K α
1	3130 nM
2	10000 nM
3	7200 nM
4	>10000 nM
5	8200 nM
6	>10000 nM
7	10000 nM
8	>10000 nM
9	>10000 nM
10	7200 nM
11	10000 nM
12	2900 nM
13	5750 nM
14	>10000 nM
15	>7200 nM
16	>7200 nM
17	10000 nM
18	>10000 nM
19	>10000 nM
20	>10000 nM
21	>10000 nM
22	>10000 nM
23	1040 nM
24	2440 nM
25	1000 nM
26	2000 nM
27	1530 nM
28	2260 nM
29	7930 nM
30	>10000 nM
31	6350 nM
32	3700 nM
33	>10000 nM

No.	IC ₅₀ Human PI3K α
34	>10000 nM
35	>10000 nM
36	>10000 nM
37	>10000 nM
38	5770 nM
39	>10000 nM
40	>10000 nM
41	4200 nM
42	>10000 nM
43	>10000 nM
44	>10000 nM
45	>10000 nM
46	>10000 nM
47	>10000 nM
48	>10000 nM
49	2740 nM
50	4300 nM
51	>10000 nM
52	>10000 nM
53	>10000 nM
54	2210 nM
55	>10000 nM
56	>10000 nM
57	>10000 nM
58	6400 nM
59	>10000 nM
60	>10000 nM
61	>10000 nM
62	>10000 nM
63	>7200 nM
64	>10000 nM
65	>10000 nM
66	>10000 nM

No.	IC ₅₀ Human PI3K α
67	4000 nM
68	6600 nM
69	>10000 nM
70	1000 nM
71	810 nM
72	730 nM
73	2500 nM
74	820 nM
75	10000 nM
76	950 nM
77	820 nM
78	250 nM
79	1600 nM
80	1600 nM
81	2000 nM
82	340 nM
83	190 nM
84	200 nM
85	>10000 nM
86	7300 nM
87	10000 nM
88	1300 nM
89	2800 nM
90	2400 nM
91	>10000 nM
92	450 nM
93	780 nM
94	130 nM
95	180 nM
96	8500 nM
97	440 nM
98	>10000 nM
99	>10000 nM
100	1980 nM
101	450 nM
102	2500 nM
103	840 nM
104	930 nM
105	1900 nM

No.	IC ₅₀ Human PI3K α
106	>10000 nM
107	>10000 nM
108	>10000 nM
109	7800 nM
110	>10000 nM
111	330 nM
112	>10000 nM
113	>10000 nM
114	>10000 nM
115	590 nM
116	>10000 nM
117	380 nM
118	>10000 nM
119	>10000 nM

The table below shows the human PI3K α activity test results for known compounds derived from the applications mentioned above WO 2011/001 112 and WO 2011/001 113.

COMPOUNDS	STRUCTURE	IC ₅₀ Human PI3K α
Example 1 (p. 39, WO 2011/001 112)		15 nM
Example 10 (p. 61, WO 2011/001 112)		17 nM
Example 5 (p. 54, WO 2011/001 113)		6 nM
Example 1 (p. 44, WO 2011/001 113)		9 nM

5

It may be seen that although the compounds of the present invention are derived from inhibitors of human PI3K and in particular PI3K, such compounds no longer inhibit, or only sparingly inhibit, this class of human kinases. Thus, they are clearly distinguished from the already-known CF3 pyrimidinones, described in patent applications WO 2011/001 112 and WO 2011/001 113, which are powerful inhibitors of human PI3K α , which may be used for the treatment of malaria but above all for various cancers in man.

Similar kinomes are present in all species of *Plasmodium*, such as *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. The compounds of the

15

invention may thus be useful in the treatment of malaria induced by all the parasites mentioned above. In addition, these kinases are found in other parasites, such as *Trypanosoma* (for example *T. brucei*, *T. cruzi*) and *Leishmania* (for example *L. major*, *L. donovani*). The compounds of the invention may thus be used in the treatment of
5 sleeping sickness, Chagas disease, the various forms of leishmaniasis and other parasitic infections.

The compounds according to the invention may thus be used for the preparation of medicaments, in particular medicaments for inhibiting parasite growth.
10

Thus, according to another of its aspects, a subject of the invention is medicaments that comprise a compound of formula (I), or an addition salt of the compound of formula (I) with a pharmaceutically acceptable acid or base.

15 These medicaments find their use in therapeutics, especially in the treatment of malaria induced by all species of *Plasmodium* such as *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*, but also induced by other species of parasites, for instance *Trypanosoma* such as *T. brucei*, *T. cruzi* and *Leishmania*, for instance *L. major*, *L. donovani*.

20 These medicaments also find their use in therapeutics in the treatment of sleeping sickness, Chagas disease, the various forms of leishmaniasis and infections such as schistosomiasis (bilharzia), toxoplasmosis and coccidiosis which are caused by other parasites, respectively schistosomes, toxoplasma and Eimeria.

25 According to another of its aspects, the present invention relates to pharmaceutical compositions comprising, as active ingredient, a compound according to the invention. These pharmaceutical compositions contain an effective dose of at least one compound according to the invention, or a pharmaceutically acceptable salt
30 of said compound, and also at least one pharmaceutically acceptable excipient.

Said excipients are chosen, according to the pharmaceutical form and the mode of administration desired, from the usual excipients which are known to those skilled in the art.

35 In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, local, intratracheal, intranasal,

transdermal or rectal administration, the active ingredient of formula (I) above, or its salt, can be administered in unit administration form, as a mixture with conventional pharmaceutical excipients, to animals or to human beings for the treatment of the above disorders or diseases.

5

The appropriate unit administration forms include oral-route forms such as tablets, soft or hard gel capsules, powders, granules and oral solutions or suspensions, sublingual, buccal, intratracheal, intraocular and intranasal administration forms, inhalation forms, topical, transdermal, subcutaneous, intramuscular or intravenous
10 administration forms, rectal administration forms and implants. For topical application, the compounds according to the invention can be used in creams, gels, ointments or lotions.

By way of example, a unit administration form of a compound according to the
15 invention in tablet form may comprise the following components:

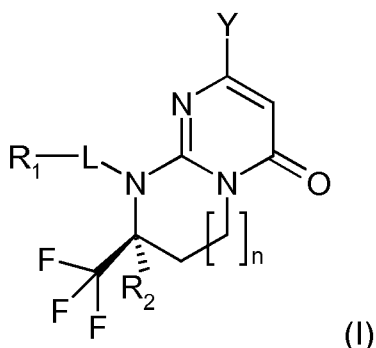
	Compound according to the invention	50.0 mg
	Mannitol	223.75 mg
	Croscarmellose sodium	6.0 mg
	Corn starch	15.0 mg
20	Hydroxypropylmethylcellulose	2.25 mg
	Magnesium stearate	3.0 mg

There may be particular cases where higher or lower dosages are appropriate; such dosages do not depart from the context of the invention. According to the usual
25 practice, the dosage appropriate for each patient is determined by the physician according to the method of administration and the weight and response of said patient.

According to another of its aspects, the present invention also relates to a
30 method for treating the pathological conditions indicated above, which comprises the administration, to a patient, of an effective dose of a compound according to the invention, or a pharmaceutically acceptable salt thereof.

CLAIMS

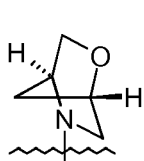
1. A compound corresponding to formula (I):



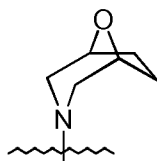
5

in which:

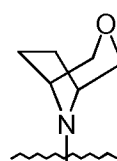
- n represents 0 or 1;
- Y represents a bridged morpholine chosen from



(a)



(b)



(c)

10

➤ L represents a linker $-\text{CH}_2-\text{CO}-$ such that the carbonyl function is attached to the substituent R_1 , or a (C_1-C_2) alkyl, said alkyl being optionally substituted with one or more substituents chosen from a (C_1-C_3) alkyl group and a hydroxyl group;

15

➤ R_1 represents:

- a linear, branched, cyclic or partially cyclic (C_1-C_5) alkyl group, optionally substituted with one or more substituents chosen from a hydroxyl group, an aryl group and a trifluoromethyl group,
- a (C_3-C_6) cycloalkyl group, optionally substituted with a hydroxyl group,
- an aryl group, optionally substituted with one or more substituents chosen from a halogen atom, a hydroxyl group, a cyano group, an $-\text{NH}_2$ group, a urea group of formula $-\text{NH}-\text{CO}-\text{NH}-(\text{C}_1-\text{C}_4)$ alkyl, a morpholine group, a group of formula $-\text{SO}_2-(\text{C}_1-\text{C}_5)$ alkyl, a (C_1-C_5) alkoxy group, said alkoxy being optionally substituted with one or more substituents chosen from:

25

- a halogen atom,

- a hydroxyl group or a (C₁-C₅)alkoxy group,
 - a group -COR₃, in which R₃ represents a substituent chosen from a heterocycloalkyl group and a hydroxyl group,
 - a group -CONR₄R_{4'} in which R₄ and R_{4'} are as defined below,
 - 5 ○ a group -NR₄R_{4'} in which R₄ and R_{4'} are as defined below,
 - a heterocycloalkyl group comprising one or two heteroelements chosen from a nitrogen atom and an oxygen atom,
 - a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group;
- 10 - a heteroaryl group, comprising one or more heteroatoms chosen from a nitrogen atom, a sulfur atom and an oxygen atom, optionally substituted with one or more substituents chosen from:
 - a halogen atom,
 - 15 ○ a (C₁-C₃)alkyl group optionally substituted with one or more halogen atoms,
 - a (C₁-C₅)alkoxy group, optionally substituted with one or more substituents chosen from a halogen atom, a (C₃-C₅)cycloalkyl group, a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group,
 - 20 ○ a group -NR₅R_{5'} in which R₅ and R_{5'}, independently, which may be identical or different, represent a substituent chosen from a hydrogen atom, a -CO₂-(C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group and a linear or branched (C₁-C₃)alkyl group, said alkyl group being optionally substituted with one or more hydroxyl groups,
 - 25 - a pyridine group bearing two linked adjacent groups forming, together with the two carbons that bear them, a heterocycle comprising a nitrogen atom and an oxygen atom,
 - 30 - a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group, an acetyl group and a -CO₂-(C₁-C₄)alkyl group,
 - 35 - a group -NR₆R_{6'} in which R₆ and R_{6'}, which are different, represent a (C₁-C₅)alkyl group and a (C₁-C₅)alkoxy group,
- R₂ represents a hydrogen atom when n represents 1 and a methyl group when

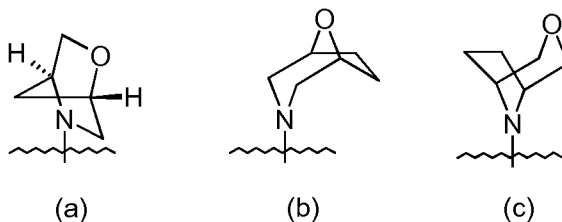
n represents 0;

➤ R_4 and $R_{4'}$, independently, which may be identical or different, represent a hydrogen atom or a (C_1-C_3) alkyl group, in the form of the base or of an addition salt with an acid or with a base.

5

2. The compound of formula (I) as claimed in claim 1, characterized in that:

- n represents 0 or 1;
- Y represents a bridged morpholine chosen from



10

➤ L represents a linker $-CH_2-CO-$ such that the carbonyl function is attached to the substituent R_1 , or a (C_1-C_2) alkyl, said alkyl being optionally substituted with one or more substituents chosen from a (C_1-C_3) alkyl group and a hydroxyl group;

15

➤ R_1 represents:

- a linear or branched (C_1-C_5) alkyl group, optionally substituted with one or more substituents chosen from a hydroxyl group and an aryl group,
- a (C_3-C_6) cycloalkyl group,
- an aryl group, optionally substituted with one or more substituents chosen from a halogen atom, a hydroxyl group, a cyano group, an $-NH_2$ group, a urea group of formula $-NH-CO-NH-(C_1-C_4)$ alkyl, a morpholine group, a group of formula $-SO_2-(C_1-C_5)$ alkyl, a (C_1-C_5) alkoxy group, said alkoxy being optionally substituted with one or more substituents chosen from:

20

25

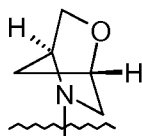
30

- a halogen atom,
- a hydroxyl group or a (C_1-C_5) alkoxy group,
- a group $-COR_3$, in which R_3 represents a substituent chosen from a heterocycloalkyl group and a hydroxyl group,
- a group $-CONR_4R_{4'}$ in which R_4 and $R_{4'}$ are as defined below,
- a group $-NR_4R_{4'}$ in which R_4 and $R_{4'}$ are as defined below,
- a heterocycloalkyl group comprising one or two heteroelements chosen from a nitrogen atom and an oxygen atom,

- a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group;
 - a heteroaryl group, comprising one or more heteroatoms chosen from a nitrogen atom, a sulfur atom and an oxygen atom, optionally substituted with one or more substituents chosen from:
 - a halogen atom,
 - a (C₁-C₃)alkyl group optionally substituted with one or more halogen atoms,
 - a (C₁-C₅)alkoxy group, optionally substituted with one or more substituents chosen from a halogen atom, a (C₃-C₅)cycloalkyl group, a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group,
 - a group -NR₅R_{5'} in which R₅ and R_{5'}, independently, which may be identical or different, represent a substituent chosen from a hydrogen atom, a -CO₂-(C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group and a linear or branched (C₁-C₃)alkyl group, said alkyl group being optionally substituted with one or more hydroxyl groups,
 - a pyridine group bearing two linked adjacent groups forming, together with the two carbons that bear them, a heterocycle comprising a nitrogen atom and an oxygen atom,
 - a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group and an acetyl group,
 - a group -NR₆R_{6'} in which R₆ and R_{6'}, which are different, represent a (C₁-C₅)alkyl group and a (C₁-C₅)alkoxy group,
 - R₂ represents a hydrogen atom when n represents 1 and a methyl group when n represents 0;
 - R₄ and R_{4'}, independently, which may be identical or different, represent a hydrogen atom or a (C₁-C₃)alkyl group,
- in the form of the base or of an addition salt with an acid or with a base.

3. The compound of formula (I) as claimed in claim 1 or 2, characterized in that:

- Y represents a bridged morpholine (a)

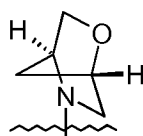


(a)

in the form of the base or of an addition salt with an acid or with a base.

4. The compound of formula (I) as claimed in claim 1 or 2, characterized in that:

- 5 ➤ n represents 0 or 1;
 ➤ Y represents a bridged morpholine (a)



(a)

- 10 ➤ L represents a linker $-\text{CH}_2\text{-CO}-$ such that the carbonyl function is attached to the substituent R_1 , or $(\text{C}_1\text{-C}_2)\text{alkyl}$, said alkyl being optionally substituted with one or more substituents chosen from a $(\text{C}_1\text{-C}_3)\text{alkyl}$ group;

- 15 ➤ R_1 represents:
- a linear, branched, cyclic or partially cyclic $(\text{C}_1\text{-C}_5)\text{alkyl}$ group, optionally substituted with one or more substituents chosen from a hydroxyl group, an aryl group, a trifluoromethyl group and a $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$ group,
 - a $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$ group, optionally substituted with a hydroxyl group,
 - an aryl group, optionally substituted with one or more substituents chosen from a halogen atom, a hydroxyl group, an $-\text{NH}_2$ group, a urea group of formula $-\text{NH-CO-NH-}(\text{C}_1\text{-C}_4)\text{alkyl}$, a morpholinyl group, a group of formula $-\text{SO}_2\text{-(C}_1\text{-C}_5)\text{alkyl}$,

20 a $(\text{C}_1\text{-C}_5)\text{alkoxy}$ group, said alkoxy being optionally substituted with one or more substituents chosen from:

 - a halogen atom,
 - a hydroxyl group or a $(\text{C}_1\text{-C}_5)\text{alkoxy}$,
 - a group $-\text{COR}_3$, in which R_3 represents a substituent chosen from a heterocycloalkyl group and a hydroxyl group,

25 ○ a heterocycloalkyl group comprising one or two heteroelements chosen from a nitrogen atom and an oxygen atom,

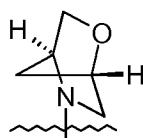
 - a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a $(\text{C}_1\text{-C}_3)\text{alkyl}$ group, a hydroxyl group and

an -NH₂ group;

- a heteroaryl group, comprising one or more heteroatoms chosen from a nitrogen atom, a sulfur atom and an oxygen atom, optionally substituted with one or more substituents chosen from:
 - 5 ○ a halogen atom,
 - a (C₁-C₃)alkyl group optionally substituted with one or more halogen atoms,
 - a (C₁-C₅)alkoxy group, optionally substituted with one or more substituents chosen from a halogen atom, a (C₃-C₅)cycloalkyl group, a
 - 10 heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group,
 - a group -NR₅R_{5'} in which R₅ and R_{5'}, independently, which may be identical or different, represent a substituent chosen from a hydrogen
 - 15 atom, a -CO₂-(C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group and a linear or branched (C₁-C₃)alkyl group, said alkyl group being optionally substituted with one or more hydroxyl groups,
- a pyridine group bearing two linked adjacent groups forming, together with the two carbons that bear them, a heterocycle comprising a nitrogen atom and an
- 20 oxygen atom,
- a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group, an acetyl group and a -CO₂-(C₁-C₄)alkyl group,
- 25 - a group -NR₆R_{6'} in which R₆ and R_{6'}, which are different, represent a (C₁-C₅)alkyl group and a (C₁-C₅)alkoxy group,
 - R₂ represents a hydrogen atom when n represents 1 and a methyl group when n represents 0;
 - R₄ and R_{4'}, independently, which may be identical or different, represent a
 - 30 hydrogen atom or a (C₁-C₃)alkyl group,
 - in the form of the base or of an addition salt with an acid or with a base.

5. The compound of formula (I) as claimed in any one of claims 1 to 4, characterized in that:

- 35 ➤ n represents 0 or 1;
- Y represents a bridged morpholine (a)



(a)

➤ L represents a linker $-\text{CH}_2\text{-CO}-$ such that the carbonyl function is attached to the substituent R_1 , or $(\text{C}_1\text{-C}_2)$ alkyl, said alkyl being optionally substituted with one or more substituents chosen from a $(\text{C}_1\text{-C}_3)$ alkyl group;

➤ R_1 represents:

- a linear, branched, cyclic or partially cyclic $(\text{C}_1\text{-C}_5)$ alkyl group, optionally substituted with one or more substituents chosen from a hydroxyl group and an aryl group,
- a $(\text{C}_3\text{-C}_6)$ cycloalkyl group,
- an aryl group, optionally substituted with one or more substituents chosen from a halogen atom, a hydroxyl group, an $-\text{NH}_2$ group, a urea group of formula $-\text{NH-CO-NH-}(\text{C}_1\text{-C}_4)\text{alkyl}$, a morpholinyl group, a group of formula $-\text{SO}_2\text{-(C}_1\text{-C}_5)\text{alkyl}$, a $(\text{C}_1\text{-C}_5)$ alkoxy group, said alkoxy being optionally substituted with one or more substituents chosen from:
 - a halogen atom,
 - a hydroxyl group or a $(\text{C}_1\text{-C}_5)$ alkoxy,
 - a group $-\text{COR}_3$, in which R_3 represents a substituent chosen from a heterocycloalkyl group and a hydroxyl group,
 - a heterocycloalkyl group comprising one or two heteroelements chosen from a nitrogen atom and an oxygen atom,
 - a heteroaryl group optionally substituted with one or more substituents chosen from a halogen atom, a $(\text{C}_1\text{-C}_3)$ alkyl group, a hydroxyl group and an $-\text{NH}_2$ group,
- a heteroaryl group, comprising one or more heteroatoms chosen from a nitrogen atom, a sulfur atom and an oxygen atom, optionally substituted with one or more substituents chosen from:
 - a halogen atom,
 - a $(\text{C}_1\text{-C}_3)$ alkyl group optionally substituted with one or more halogen atoms,
 - a $(\text{C}_1\text{-C}_5)$ alkoxy group, optionally substituted with one or more substituents chosen from a halogen atom, a $(\text{C}_3\text{-C}_5)$ cycloalkyl group, a heteroaryl group optionally substituted with one or more substituents

chosen from a halogen atom, a (C₁-C₃)alkyl group, a hydroxyl group and an -NH₂ group,

- a group -NR₅R_{5'} in which R₅ and R_{5'}, independently, which may be identical or different, represent a substituent chosen from a hydrogen atom, a -CO₂-(C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group and a linear or branched (C₁-C₃)alkyl group, said alkyl group being optionally substituted with one or more hydroxyl groups,

- a pyridine group bearing two linked adjacent groups forming, together with the two carbons that bear them, a heterocycle comprising a nitrogen atom and an oxygen atom,

- a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group and an acetyl group,

- a group -NR₆R_{6'} in which R₆ and R_{6'}, which are different, represent a (C₁-C₅)alkyl group and a (C₁-C₅)alkoxy group,

➤ R₂ represents a hydrogen atom when n represents 1 and a methyl group when n represents 0;

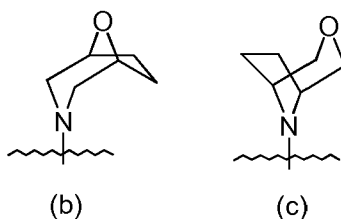
➤ R₄ and R_{4'}, independently, which may be identical or different, represent a hydrogen atom or a (C₁-C₃)alkyl group,

in the form of the base or of an addition salt with an acid or with a base.

6. The compound of formula (I) as claimed in claim 1 or 2, characterized in that:

➤ n represents 0 or 1;

➤ Y represents a bridged morpholine chosen from (b) and (c)



➤ L represents a linker -CH₂-CO- such that the carbonyl function is attached to the substituent R₁, or (C₁-C₂)alkyl, said alkyl being optionally substituted with a hydroxyl group;

➤ R₁ represents:

- a linear or branched (C₁-C₅)alkyl group, optionally substituted with an aryl group,
 - an aryl group, optionally substituted with one or more substituents chosen from a halogen atom, a hydroxyl group and a (C₁-C₅)alkoxy group, said alkoxy being optionally substituted with one or more substituents chosen from:
 - a group -CONR₄R_{4'} in which R₄ and R_{4'} are as defined below,
 - a group -NR₄R_{4'} in which R₄ and R_{4'} are as defined below,
 - a heteroaryl group comprising one or more heteroatoms chosen from a nitrogen atom, a sulfur atom and an oxygen atom, optionally substituted with one or more (C₁-C₃)alkyl groups, optionally substituted with one or more halogen atoms,
 - R₂ represents a hydrogen atom when n represents 1 and a methyl group when n represents 0;
 - R₄ and R_{4'}, independently, which may be identical or different, represent a hydrogen atom or a (C₁-C₃)alkyl group, in the form of the base or of an addition salt with an acid or with a base.
7. The compound as claimed in any one of claims 1 to 6, characterized in that the linker L represents -CH₂-CO, in the form of the base or of an addition salt with an acid or with a base.
8. The compound as claimed in any one of claims 1 to 7, characterized in that n represents 1, in the form of the base or of an addition salt with an acid or with a base.
9. The compound as claimed in any one of claims 1 to 7, characterized in that n represents 0, in the form of the base or of an addition salt with an acid or with a base.
10. The compound as claimed in any one of claims 1 to 9, characterized in that R₁ represents a heteroaryl group, in the form of the base or of an addition salt with an acid or with a base.
11. The compound as claimed in any one of claims 1 to 9, characterized in that R₁ represents a heterocycloalkyl group comprising one or more heteroatoms chosen from oxygen and nitrogen atoms, said nitrogen atom being optionally substituted with a substituent chosen from a formyl group, an acetyl group and a -CO₂-(C₁-C₄)alkyl group, in the form of the base or of an addition salt with an acid or with a base.

12. The compound as claimed in any one of the preceding claims 1 to 11, characterized in that it is chosen from:

- 1 (8S)-9-(2-Methyl-2-pyrid-4-ylpropyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 2 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 3 (8S)-9-[2-(6-Aminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 4 (8S)-9-[2-(6-Methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 5 (8S)-9-[2-(6-Methylaminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 6 (8S)-9-[2-(6-Dimethylaminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 7 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 8 1-[2-(6-Dimethylaminopyrid-3-yl)-2-oxoethyl]-2-(S)-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 9 2-(S)-Methyl-1-[2-(6-methylaminopyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 10 (8S)-1-[2-(4-Methoxyphenyl)ethyl]-2-methyl-7-(1S,4S)-2-oxa-5-

- azabicyclo[2.2.1]hept-5-yl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 11 (S)-1-[2-(6-Aminopyrid-3-yl)-2-oxoethyl]-2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 5
- 12 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 13 2-Methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-1-(2-pyrid-3-ylethyl)-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 10 14 (8S)-9-{2-[6-(2-Hydroxyethylamino)pyrid-3-yl]-2-oxoethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 15 15 (8S)-9-[2-(5-Methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 16 2-Methyl-1-[2-(5-methylpyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 17 2-Methyl-1-[2-(6-methylpyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 20
- 18 2-Methyl-1-[2-(2-methylpyrid-3-yl)-2-oxoethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 25 19 (8S)-9-[2-(2-Methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 20 (8S)-9-[2-(4-Methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-

4-one

- 21 2-Methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-1-(2-oxo-2-pyrid-3-ylethyl)-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 22 (8S)-9-[2-(6-Cyclopropylaminopyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 23 1-Ethyl-3-{4-[2-((S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]phenyl}urea
- 24 1-Ethyl-3-{4-[2-((S)-2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-5-oxo-2-trifluoromethyl-2,3-dihydro-5H-imidazo[1,2-a]pyrimidin-1-yl)ethyl]phenyl}urea
- 10
- 25 (8S)-9-[2-(4-Methylthiazol-5-yl)ethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 26 2-Methyl-1-[2-(4-methylthiazol-5-yl)ethyl]-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 15
- 27 (8S)-9-[2-(3,5-Dimethyl-1H-pyrazol-4-yl)ethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 28 1-[2-(3,5-Dimethyl-1H-pyrazol-4-yl)ethyl]-2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 20
- 29 (8S)-9-(3,3-Dimethyl-2-oxobutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 30 1-(3,3-Dimethyl-2-oxobutyl)-2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 25
- 31 (8S)-9-[2-(6-Amino-5-methylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

- 32 1-[2-(4-Aminophenyl)ethyl]-2-methyl-7-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-2-((S)-trifluoromethyl)-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 33 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-oxo-2-(6-trifluoromethylpyrid-3-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 5
- 34 (8S)-9-(2-{6-[(2-Hydroxyethyl)methylamino]pyrid-3-yl}-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 35 (8S)-9-[2-(6-Ethoxypyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 10
- 36 (8S)-9-[2-(6-Amino-4,5-dimethylpyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 37 (S)-9-[2-(4-Difluoromethoxyphenyl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 15
- 38 (8S)-9-[2-(3,4-Dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 20
- 39 (8S)-9-[2-(4-Methyloxazol-5-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 40 (S)-9-[2-(3,4-Difluorophenyl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 25
- 41 (8S)-9-[2-(4-Morpholin-4-ylphenyl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

- 42 4-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]benzonitrile
- 43 (8S)-9-[2-(4-Methylthiazol-5-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 5 4-one
- 44 (8S)-9-[2-(5-Chloropyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 45 (8S)-9-[2-(6-Methoxypyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 10 4-one
- 46 (8S)-9-[2-(3-Methylisoxazol-4-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 47 (8S)-9-(2-Benzo[1,2,3]thiadiazol-5-yl-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 15 4-one
- 48 (8S)-9-[2-(2,4-Difluorophenyl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 20 4-one
- 49 (8S)-9-(3-Ethyl-3-hydroxypentyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 50 (8S)-9-(3-Hydroxy-3-methylbutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 51 (8S)-9-(1-Methyl-1H-indazol-3-ylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 25 4-one
- 52 (8S)-9-[2-(2-Cyclopropylmethoxypyrimidin-5-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

- 53 (8S)-9-[2-(3,5-Dimethylisoxazol-4-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 54 (8S)-9-(2-Ethyl-2-hydroxybutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 55 3-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]benzonitrile
- 56 (8S)-9-(3-Methyl-2-oxobutyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 10 57 {5-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]pyrid-2-yl}carbamic acid ethyl ester
- 58 {5-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]pyrid-2-yl}carbamic acid methyl ester
- 15
- 59 (8S)-9-(5-Methyl-[1,2,4]oxadiazol-3-ylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 60 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-oxo-2-(2-trifluoromethylpyrid-3-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 20
- 61 (8S)-9-(2-Benzo[1,2,5]thiadiazol-5-yl-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 62 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-oxo-2-(tetrahydropyran-4-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 25
- 63 (8S)-9-{2-[6-(2-Fluoroethoxy)pyrid-3-yl]-2-oxoethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

- 64 (8S)-9-{2-[3-Fluoro-4-(2-fluoroethoxy)phenyl]-2-oxoethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 65 (8S)-9-[2-(2-Methoxypyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 66 (8S)-9-[2-(3-Methyl-3H-imidazol-4-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 10 67 (8S)-9-(2-Cyclopropyl-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 68 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(2-oxo-2-pyrid-2-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 69 (8S)-9-[2-(2-Methyl-2H-pyrazol-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 15 70 N,N-Dimethyl-2-(4-{2-[(S)-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-5-oxo-2-trifluoromethyl-2,3-dihydro-5H-imidazo[1,2-a]pyrimidin-1-yl]ethyl}phenoxy)acetamide
- 71 (8S)-9-[(S)-2-(4-Fluoro-2-methoxyphenyl)-2-hydroxyethyl]-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 20 72 (2S)-1-[2-(4-Hydroxyphenyl)ethyl]-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 73 (8S)-2-(8-Oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(2-oxo-2-phenylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 25 74 (2S)-1-{2-[4-(2-Dimethylaminoethoxy)phenyl]ethyl}-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one

- 75 (8S)-2-(8-Oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(2-oxo-2-pyrid-4-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 76 (S)-1-[2-(4-Methoxyphenyl)ethyl]-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 5 77 (S)-2-Methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-1-(3-phenylpropyl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 78 (S)-1-{2-[4-(3-Dimethylaminopropoxy)phenyl]ethyl}-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 10 79 (2S)-1-((S)-2-Hydroxy-2-phenylethyl)-2-methyl-7-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-trifluoromethyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-5-one
- 80 (8S)-9-((S)-2-Hydroxy-2-phenylethyl)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 81 (8S)-9-[2-(4-Methoxyphenyl)ethyl]-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 15 82 (8S)-9-((R)-2-Benzo[b]thiophen-2-yl-2-hydroxyethyl)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 83 (8S)-9-[2-(4-Hydroxyphenyl)ethyl]-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 20 84 (8S)-2-(8-Oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(3-phenylpropyl)-8-trifluoromethylmethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 85 (8S)-2-(3-Oxa-8-azabicyclo[3.2.1]oct-8-yl)-9-(2-oxo-2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 25 86 (8S)-9-(1-Difluoromethyl-1H-pyrazol-3-ylmethyl)-2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

- 87 (8S)-2-(8-Oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(2-oxo-2-pyrid-3-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 88 (8S)-2-(8-Oxa-3-azabicyclo[3.2.1]oct-3-yl)-9-(2-oxo-2-pyrid-2-ylethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 5 89 (S)-9-[2-(1-Acetylpiperid-4-yl)ethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 90 4-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)ethyl]piperidine-1-carbaldehyde
- 91 4-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]piperidine-1-carboxylic acid
10 ethyl ester
- 92 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-(tetrahydropyran-4-yl)ethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 93 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(tetrahydropyran-4-ylmethyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
15
- 94 (8S)-9-(1-Acetylpiperid-4-ylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 95 4-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-ylmethyl)piperidine-1-carbaldehyde
- 20 96 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(3,3,3-trifluoro-2-hydroxy-2-trifluoromethylpropyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 97 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-(4,4,4-trifluoro-3-hydroxy-3-trifluoromethylbutyl)-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
25
- 98 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

- 99 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-[2-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)-2-oxoethyl]-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 100 (8S)-9-[2-(1-Hydroxycyclopentyl)ethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 5
- 101 (8S)-9-(1-Hydroxycyclopentylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 102 (8S)-9-(3,3-Dicyclopropyl-3-hydroxypropyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 10
- 103 (8S)-9-(2,2-Dicyclopropyl-2-hydroxyethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 104 (8S)-9-(1-Hydroxycyclopropylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 15
- 105 (8S)-9-[2-(1-Hydroxycyclopropyl)ethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 106 (8S)-2-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-9-quinolin-5-ylmethyl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 20
- 107 (8S)-9-[2-(3-Methylisothiazol-4-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 108 (8S)-9-[2-(4-Methanesulfonylphenyl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 25
- 109 (8S)-9-Isoquinolin-5-ylmethyl-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 110 (8S)-9-(2-Morpholin-4-yl-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-

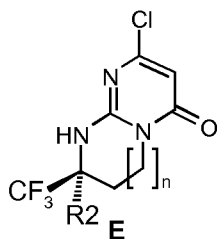
yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

- 111 (8S)-9-{2-[4-(2-Morpholin-4-ylethoxy)phenyl]ethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 5 112 N-Methoxy-N-methyl-2-((S)-8-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetamide
- 113 (8S)-9-(2-Imidazo[1,2-a]pyrid-6-yl-2-oxoethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 10 114 (8S)-9-[2-(6-Difluoromethoxypyrid-3-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 15 115 (S)-9-{2-[4-(2-Morpholin-4-yl-2-oxoethoxy)phenyl]ethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 116 (8S)-9-(1-Methyl-3-trifluoromethyl-1H-pyrazol-4-ylmethyl)-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 20 117 (8S)-9-{2-[4-(2-Dimethylaminoethoxy)phenyl]ethyl}-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one
- 118 4-[2-((S)-8-(1S,4S)-2-Oxa-5-azabicyclo[2.2.1]hept-5-yl-6-oxo-2-trifluoromethyl-3,4-dihydro-2H,6H-pyrimido[1,2-a]pyrimidin-1-yl)acetyl]piperidine-1-carbaldehyde
- 25 119 (8S)-9-[2-(1-Acetylpiperid-4-yl)-2-oxoethyl]-2-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl-8-trifluoromethyl-6,7,8,9-tetrahydropyrimido[1,2-a]pyrimidin-4-one

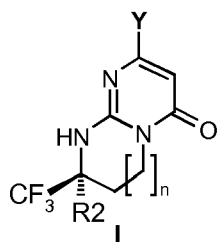
in the form of the base or of an addition salt with an acid or with a base.

13. A process for preparing a compound of formula (I) as claimed in any one of claims

1 to 12, comprising the reaction of a compound of formula E

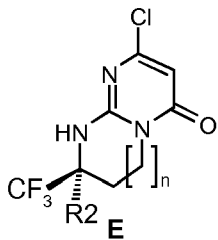


in which n represents 0 or 1 and R₂ represents a hydrogen atom when n = 1 or a methyl group when n = 0, with a bridged morpholine Y, chosen from (a), (b) and (c) as defined in claim 1, to obtain a compound of formula I

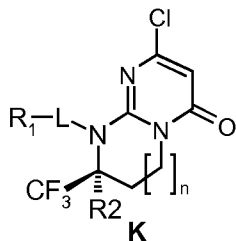


and the alkylation reaction by addition to I of a compound of formula J = R₁-L-Lg in which R₁ and L are as defined in any one of the preceding claims and Lg is a leaving group.

14. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 12, comprising the alkylation reaction of a compound of formula E



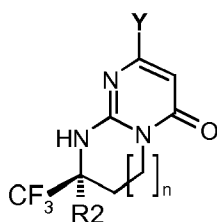
in which n represents 0 or 1 and R₂ represents a hydrogen atom when n = 1 or a methyl group when n = 0, by addition of a compound of formula J = R₁-L-Lg in which R₁ and L are as defined in any one of claims 1 to 8 and Lg is a leaving group, to obtain a compound of formula K



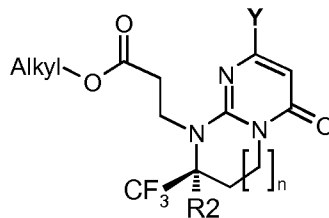
in which R₁, R₂, L and n are as defined in one of claims 1 to 8, and a reaction on a

compound K with a compound of formula Y being a bridged morpholine chosen from (a), (b) and (c) as defined in claim 1.

15. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 12, in which the linker L is an ethyl group, R₁ is a linear or branched (C₁-C₅)alkyl group substituted with a hydroxyl group, Y represents a bridged morpholine chosen from (a), (b) and (c) as defined in claim 1, n represents 1 or 0, and R₂ represents a hydrogen atom when n = 1 and a methyl group when n = 0, comprising a Michael addition reaction of a compound of formula E

**E**

in which n represents 0 or 1 and R₂ represents a hydrogen atom when n = 1 or a methyl group when n = 0, on a compound of formula M = CH₂=CH₂-CO₂Alkyl, to obtain a compound of formula N,

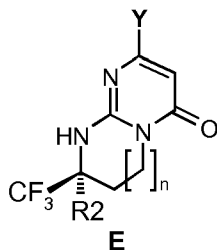
**N**

- 15 in which n represents 0 or 1 and R₂ represents a hydrogen atom when n = 1 or a methyl group when n = 0, and Y is a bridged morpholine chosen from (a), (b) and (c) as defined in claim 1,
and a reaction of alkyl on a compound of formula N with a compound of formula O = Z-Mg-X in which Z represents a linear or branched alkyl radical and X is a halogen atom.

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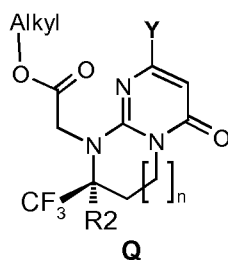
16. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 12, in which the linker L is a methyl group, R₁ is a linear or branched (C₁-C₅)alkyl group substituted with a hydroxyl group, Y represents a bridged morpholine chosen from (a), (b) and (c) as defined in claim 1, n represents 1 or 0, and R₂ represents a hydrogen atom when n = 1 and a methyl group when n = 0, comprising an addition reaction of a compound of formula E

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in which n represents 0 or 1 and R_2 represents a hydrogen atom when $n = 1$ or a methyl group when $n = 0$, with a compound of formula $P = X-CH_2-CO_2\text{Alkyl}$ with X being a halogen atom, to obtain a compound of formula Q

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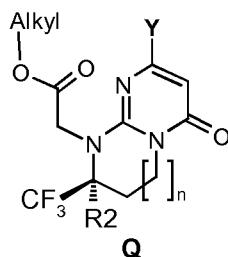


in which Y is a bridged morpholine chosen from (a), (b) and (c), n represents 0 or 1 and R_2 represents a hydrogen atom when $n = 1$ or a methyl group when $n = 0$,

and an alkylation reaction on a compound of formula Q with a compound of formula $O = Z-Mg-X$ in which Z represents a linear or branched alkyl radical and X is a halogen atom.

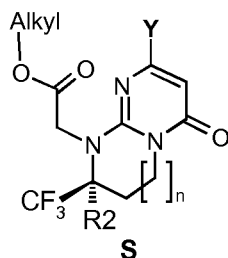
17. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 12, in which the linker L is a methyl group, R_1 is a group $-NR_6R_{6'}$ with R_6 et $R_{6'}$ being either different and representing an alkyl group and an alkoxy group, or R_6 and $R_{6'}$ together forming a monocyclic or bicyclic heterocycloalkyl, Y represents a bridged morpholine chosen from (a), (b) and (c) as defined in claim 1, n represents 1 or 0, and R_2 represents a hydrogen atom when $n = 1$ and a methyl group when $n = 0$, comprising a hydrolysis reaction of a compound of formula Q

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in which Y is a bridged morpholine chosen from (a), (b) and (c), n represents 0 or 1 and

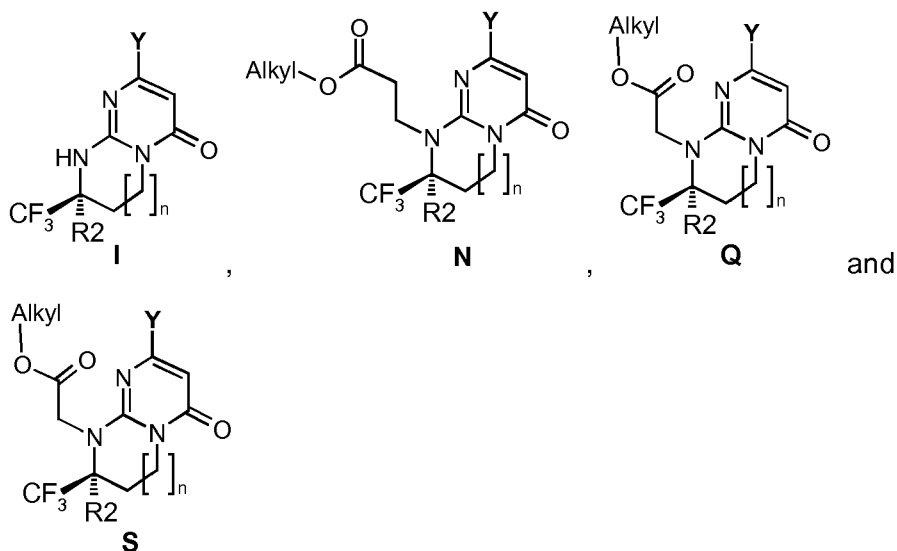
R_2 represents a hydrogen atom when $n = 1$ or a methyl group when $n = 0$, to obtain a compound of formula S



in which Y represents a bridged morpholine chosen from (a), (b) and (c) as defined in claim 1, n represents 1 or 0 and R_2 represents a hydrogen atom when $n = 1$ or a methyl group when $n = 0$,

and a coupling reaction between a compound of formula S and a compound of formula $HNR_6R_{6'}$ with R_6 and $R_{6'}$ being either different and representing an alkyl group and an alkoxy group, or R_6 and $R_{6'}$ together forming a monocyclic or bicyclic heterocycloalkyl.

18. Compounds of formulae I, N, Q and S:



in which n , R_2 and Y are as defined in claim 1.

19. A medicament, characterized in that it comprises a compound as claimed in any one of claims 1 to 12, or an addition salt of this compound with a pharmaceutically acceptable acid or base.

20. The compound as claimed in any one of claims 1 to 12, as a medicament.

21. A pharmaceutical composition, characterized in that it comprises a compound as claimed in any one of claims 1 to 12, or a pharmaceutically acceptable salt of this compound, and also at least one pharmaceutically acceptable excipient.

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22. The use of a compound as claimed in any one of claims 1 to 12, for the preparation of a medicament for treating parasite-induced malaria.

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23. The compound as claimed in any one of claims 1 to 12, for its use in the treatment of malaria induced by all species of *Plasmodium*, such as *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*, by all species of *Trypanosoma* and by all species of *Leishmania*, in the treatment of sleeping sickness, the treatment of Chagas disease, the various forms of leishmaniasis and the treatment of other parasitic infections, such as schistosomiasis (bilharzia), toxoplasmosis and coccidiosis.

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