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(54) Title: FUSED MORPHOLINOPYRIMIDINES AND METHODS OF USE THEREOF

(57) Abstract: The present disclosure relates to Fused Morpholinopyrimidines, pharmaceutical compositions comprising an effective amount of a Fused Morpholinopyrimidine and methods for using a Fused Morpholinopyrimidine in the treatment of a neurodegenerative disease, comprising administering to a subject in need thereof an effective amount of a Fused Morpholinopyrimidine.



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FUSED MORPHOLINOPYRIMIDINES AND METHODS OF USE THEREOF**1. RELATED APPLICATIONS**

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application Serial No. 61/952,704, filed on March 13, 2014 and to U.S. Provisional Application Serial No. 62/054,673, filed on September 24, 2014, the entire disclosures of which are incorporated by reference herein in their entirety.

2. FIELD

[0002] This disclosure relates generally to Fused Morpholinopyrimidine compounds. More specifically, the disclosure relates to the use of the Fused Morpholinopyrimidine compounds for the treatment of neurological disease.

3. BACKGROUND

[0003] Alzheimer's disease (AD) is the most prevalent form of dementia. It is a neurodegenerative disease that is associated (though not exclusively) with aging. The disease is clinically characterized by a progressive loss of memory, cognition, reasoning and judgment that leads to an extreme mental deterioration and ultimately death. The disease is pathologically characterized by the deposition of extracellular plaques and the presence of neurofibrillary tangles. The plaques are considered to play an important role in the pathogenesis of the disease. They mainly consist of fibrillar aggregates of β -amyloid peptide ($A\beta$), which are products of the amyloid precursor protein (APP). APP is initially processed by β -secretase forming a secreted peptide and a membrane bound C99 fragment. The C99 fragment is subsequently processed by the proteolytic activity of γ -secretase. Multiple sites of proteolysis on the C99 fragment lead to the production of a range of smaller peptides ($A\beta$ 37-42 amino acids). N-terminal truncations can also be found e.g., $A\beta$ (4-42). For convenience, notations $A\beta$ 40 and $A\beta$ 42, as used herein, include these N-terminal truncated peptides. Upon secretion, the $A\beta$ peptides initially form soluble aggregates which ultimately lead to the formation of insoluble deposits and plaques. $A\beta$ 42 is believed to be the most neurotoxic; the shorter peptides have less propensity to aggregate and form plaques. $A\beta$ plaques in the brain are also associated with cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, multi infarct dementia, dementia pugilistica and Down's Syndrome.

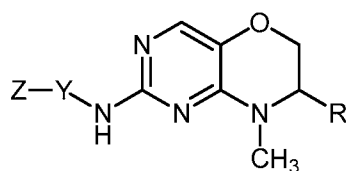
[0004] γ -secretase is an association of four proteins: Aph1, nicastrin, presenilin and Pen-2 (review De Strooper, *Neuron* 38:9-12 (2003)). Subjects carrying particular mutations in one of these components, presenilin, show increased A β 42/A β 40 ratio. These mutations are correlated with early onset familial AD. Inhibition of γ -secretase resulting in the lowering of A β 42 has been investigated by the pharmaceutical community, and numerous inhibitors have been found. See, e.g., Thompson *et al.* (*Bioorg. Med. Chem. Lett.* 2006, 16, 2357-63), Shaw *et al.* (*Bioorg. Med. Chem. Lett.* 2006, 17, 511-16) and Asberom *et al.* (*Bioorg. Med. Chem. Lett.* 2007, 15, 2219-2223). Inhibition of γ -secretase, though, is not without side-effects, some of which are due to the γ -secretase complex processing substrates other than C99, e.g., Notch. A more desirable approach is to modulate the proteolytic activity of the γ -secretase complex in a manner that lowers A β 42 in favor of shorter peptides without significantly affecting the activity of γ -secretase on substrates such as Notch.

[0005] Compounds that have shown modulation of γ -secretase include certain non-steroidal, anti-inflammatory drugs (NSAIDs), for example Flurbiprofen, (Stock *et al.*, *Bioorg. Med. Chem. Lett.* 2006, 16, 2219-2223). Other publications that disclose agents said to reduce A β 42 through the modulation of γ -secretase include: WO 2004/074232, WO 2005/054193, Perreto *et al.*, *Journal of Medicinal Chemistry* 2005, 48, 5705-20, WO 2005/108362, WO 2006/008558, WO 2006/021441, WO 2006/041874, WO 2006/045554, WO 2004/110350, WO 2006/043964, WO 2005/115990, EP 1847524, WO 2007/116228, WO 2007/110667, WO 2007/124394, EP 184752, EP 1849762, WO 2007/125364, WO 2009/086277.

4. SUMMARY

[0006] It is understood that any of the embodiments described below can be combined in any desired way, and that any embodiment or combination of embodiments can be applied to each of the aspects described below, unless the context indicates otherwise.

[0007] In one aspect, the invention provides a compound of Formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein: R is phenyl, C₁-C₄ alkylene-phenyl, -C₁-C₆ alkyl or 3- to 7-membered monocyclic heterocycle, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -OH,

-CN, -NH₂, -C₁-C₄ alkyl, halo-substituted C₁-C₄ alkyl, amino-substituted C₁-C₄ alkyl, -NH-C₁-C₄ alkyl, -NHC(O)-C₁-C₄ alkyl, -N(C₁-C₄ alkyl)(C(O)(C₁-C₄ alkyl)), -C(O)NH-C₁-C₄ alkyl, -C(O)N(C₁-C₄ alkyl)₂, hydroxy-substituted C₁-C₄ alkyl, -S(O)₂-C₁-C₄ alkyl, -S(O)₂-halo-substituted C₁-C₄ alkyl, -S(O)₂-NH-C₁-C₄ alkyl, -S(O)₂-N(C₁-C₄ alkyl)₂, -NH-S(O)₂-C₁-C₄ alkyl, -N(C₁-C₄ alkyl)-S(O)₂-C₁-C₄ alkyl, -C₁-C₄ alkoxy, halo-substituted C₁-C₄ alkoxy, 3- to 7-membered monocyclic heterocycle, C₃-C₈ monocyclic cycloalkyl and -C(O)NH₂; Y is 4- to 6-membered nonaromatic heterocycle, which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -C₁-C₄ alkoxy, halo-substituted C₁-C₄ alkoxy, -C₁-C₄ alkyl, halo-substituted C₁-C₄ alkyl, amino-substituted C₁-C₄ alkoxy, (C₁-C₄ alkyl)₂N-C₁-C₄ alkoxy, -NH-C₁-C₄ alkyl, -CN, -OH and -NH₂; and Z is nitrogen-containing 5- to 6-membered aromatic monocyclic heterocycle which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -NH₂, -OH, -C₁-C₄ alkyl, -C₁-C₄ alkoxy, halo-substituted C₁-C₄ alkyl, halo-substituted C₁-C₄ alkoxy and 3- to 7-membered monocyclic heterocycle.

[0008] In some embodiments, R is phenyl or C₁-C₄ alkylene-phenyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -NH₂, -C₁-C₄ alkyl, halo-substituted C₁-C₄ alkyl, amino-substituted C₁-C₄ alkyl, -NH-C₁-C₄ alkyl, -NHC(O)-C₁-C₄ alkyl, -N(C₁-C₄ alkyl)(C(O)(C₁-C₄ alkyl)), -C(O)NH-C₁-C₄ alkyl, -C(O)N(C₁-C₄ alkyl)₂, hydroxy-substituted C₁-C₄ alkyl, -S(O)₂-C₁-C₄ alkyl, -S(O)₂-halo-substituted C₁-C₄ alkyl, -S(O)₂-NH-C₁-C₄ alkyl, -S(O)₂-N(C₁-C₄ alkyl)₂, -NH-S(O)₂-C₁-C₄ alkyl, -N(C₁-C₄ alkyl)-S(O)₂-C₁-C₄ alkyl, -C₁-C₄ alkoxy, halo-substituted C₁-C₄ alkoxy, 3- to 7-membered monocyclic heterocycle, C₃-C₈ monocyclic cycloalkyl and -C(O)NH₂.

[0009] In some embodiments, R is phenyl or C₁-C₄ alkylene-phenyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -C₁-C₄ alkyl, -C₁-C₄ alkoxy, halo-substituted C₁-C₄ alkyl and halo-substituted C₁-C₄ alkoxy.

[0010] In some embodiments, Y is piperidinyl or azetidiny, each of which is unsubstituted.

[0011] In some embodiments, Z is pyridinyl or pyrimidinyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of -C₁-C₄ alkyl, halo-substituted C₁-C₄ alkyl and -C₁-C₄ alkoxy.

[0012] In some embodiments, R is phenyl or C₁-C₄ alkylene-phenyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen or -C₁-C₄ alkyl; Y is piperidinyl; and Z is pyridinyl or pyrimidinyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of -C₁-C₄ alkyl, halo-substituted C₁-C₄ alkyl and -C₁-C₄ alkoxy.

[0013] In some embodiments, R is phenyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen and -C₁-C₄ alkyl; and Z is pyridinyl which is unsubstituted or substituted with -C₁-C₄ alkoxy.

[0014] In some embodiments, R is phenyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen and -C₁-C₄ alkyl.

[0015] In some embodiments, R is phenyl which is unsubstituted. In some embodiments, R is phenyl substituted with two or three -F.

[0016] In some embodiments, each -C₁-C₄ alkyl is methyl and each C₁-C₄ alkylene is methylene.

[0017] In some embodiments, C₁-C₄ alkylene is methylene.

[0018] In some embodiments, C₁-C₄ alkylene-phenyl is benzyl.

[0019] In some embodiments, R is phenyl substituted with one methyl.

[0020] In some embodiments, R is C₁-C₄ alkylene-phenyl.

[0021] In some embodiments, R is -C₁-C₆ alkyl.

[0022] In some embodiments, R is 3- to 7-membered monocyclic heterocycle.

[0023] In some embodiments, Y is piperidinyl. In some embodiments, Y is azetidiny.

[0024] In some embodiments, Z is pyridinyl or pyrimidinyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of -C₁-C₄ alkyl, -CF₃ and -C₁-C₄ alkoxy.

[0025] In some embodiments, Z is pyridinyl substituted with one -CF₃. In some embodiments, Z is pyridinyl substituted with one methyl. In some embodiments, Z is pyridinyl substituted with one methoxy. In some embodiments, Z is pyrimidinyl which is

unsubstituted or substituted with one to three -C₁-C₄ alkyl. In some embodiments, Z is pyrimidinyl substituted with one methyl.

[0026] In one embodiment, the compound of Formula (I) is a compound selected from the list of compounds in Table I.

[0027] In one aspect, the compound of Formula (I) is selected from the group consisting of: N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; 8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; 7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; 8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-benzyl-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(3,5-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(4-fluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-benzyl-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-8-methyl-7-(o-tolyl)-N-(1-(2-(trifluoromethyl)

pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine; (+)-7-(4-fluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine; (+)-7-(2, 4-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine; (+)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine; (+)-7-(2, 4-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine; (-)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethoxy) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine; (+)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethoxy) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine ; (+)-7-(2, 4-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine; (+)-7-benzyl-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (-)-7-benzyl-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(2-chlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(2,4-dichlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(2-chloro-4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(4-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(5-chloro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(5-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(2-chloro-4,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(3,5-difluorophenyl)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-

amine; (+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (-)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; and (-)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine.

[0028] In one aspect, the compound of Formula (I) is selected from the group consisting of: 7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(2,4-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-benzyl-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(2-chlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(2,4-dichlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(2-chloro-4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(5-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(2-chloro-4,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-7-(3,5-difluorophenyl)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-

7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; (+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; and N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine.

[0029] In one aspect, the invention provides a compound selected from the group consisting of (+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine; (-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine; N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-7,7,8-trimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; and N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8'-methyl-6',8'-dihydrospiro[cyclopentane-1,7'-pyrimido[5,4-b][1,4]oxazin]-2'-amine, or a pharmaceutically acceptable salt thereof.

[0030] In one aspect, the invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier or vehicle and an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0031] In one aspect, the invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier or vehicle and an effective amount of a compound selected from the group consisting of (+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine; (-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine; N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-7,7,8-trimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; and N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8'-methyl-6',8'-dihydrospiro[cyclopentane-1,7'-pyrimido[5,4-b][1,4]oxazin]-2'-amine, or a pharmaceutically acceptable salt thereof.

[0032] In one aspect, the invention provides a method for treating a neurodegenerative disease, comprising administering to a subject in need thereof an effective amount of a compound or a pharmaceutically acceptable salt of a compound of Formula (I).

[0033] In one aspect, the invention provides a method for treating a neurodegenerative disease, comprising administering to a subject in need thereof an effective amount of a compound selected from the group consisting of (+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine; (-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-

b]pyrrolo[1,2-d][1,4]oxazin-2-amine; N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-7,7,8-trimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; and N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8'-methyl-6',8'-dihydrospiro[cyclopentane-1,7'-pyrimido[5,4-b][1,4]oxazin]-2'-amine, or a pharmaceutically acceptable salt thereof.

[0034] In some embodiments, the neurodegenerative disease is panic disorder, obsessive compulsive disorder, delusional disorder, drug-induced psychosis, post-traumatic stress disorder, age-related cognitive decline, attention deficit/hyperactivity disorder, personality disorder of the paranoid type, personality disorder of the schizoid type, dyskinesia, choreiform condition, psychosis associated with Parkinson's disease, psychotic symptoms associated with Alzheimer's disease, mood disorder, or dementia.

[0035] In one aspect, the invention provides a method for treating Alzheimer's disease, comprising administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0036] In one aspect, the invention provides a method for treating Alzheimer's disease, comprising administering to a subject in need thereof an effective amount of a compound selected from the group consisting of (+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine; (-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine; N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-7,7,8-trimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; and N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8'-methyl-6',8'-dihydrospiro[cyclopentane-1,7'-pyrimido[5,4-b][1,4]oxazin]-2'-amine, or a pharmaceutically acceptable salt thereof.

[0037] In one aspect, the invention provides a method for improving an impaired cognitive function, comprising administering to a subject having impaired cognitive function an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0038] In one aspect, the invention provides a method for improving an impaired cognitive function, comprising administering to a subject having impaired cognitive function an effective amount of a compound selected from the group consisting of (+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine; (-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine; N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-7,7,8-trimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; and

N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8'-methyl-6',8'-dihydrospiro[cyclopentane-1,7'-pyrimido[5,4-b][1,4]oxazin]-2'-amine, or a pharmaceutically acceptable salt thereof.

[0039] In one aspect, the invention provides a method for ameliorating a symptom of Alzheimer's disease, comprising administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0040] In one aspect, the invention provides a method for ameliorating a symptom of Alzheimer's disease, comprising administering to a subject in need thereof an effective amount of a compound selected from the group consisting of (+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine; (-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine; N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-7,7,8-trimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine; and N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8'-methyl-6',8'-dihydrospiro[cyclopentane-1,7'-pyrimido[5,4-b][1,4]oxazin]-2'-amine, or a pharmaceutically acceptable salt thereof.

[0041] In some embodiments, Alzheimer's disease is early onset Alzheimer's disease.

[0042] In some embodiments, the subject is a human.

[0043] In some embodiments, the symptom is progressive loss of memory, progressive loss of cognition, progressive loss of reasoning and/or progressive loss of judgment.

[0044] A compound of Formula (I), Table II, or a pharmaceutically acceptable salt thereof (also referred to herein as a "Fused Morpholinopyrimidine") is useful for treating, preventing or ameliorating one or more symptoms of a neurodegenerative disease.

[0045] Exemplary neurodegenerative diseases include, but are not limited to, Alzheimer's disease, early onset Alzheimer's disease, panic disorder, obsessive compulsive disorder, delusional disorder, drug-induced psychosis, post-traumatic stress disorder, age-related cognitive decline, attention deficit/hyperactivity disorder, personality disorder of the paranoid type, personality disorder of the schizoid type, dyskinesia, choreiform condition, psychosis associated with Parkinson's disease, psychotic symptoms associated with Alzheimer's disease, mood disorder, dementia, cognitive impairment, myoclonus, seizures, Parkinsonism, extrapyramidal signs (EPS), apraxia, dystonia, dementia with Lewy bodies (DLB), aphasia, visual agnosia, and ataxia.

[0046] In some embodiments, the cognitive function impaired is one or more of attention, learning, delayed memory, working memory, visual learning, speed of processing, vigilance,

verbal learning, visual motor function, social cognition, long term memory or executive function.

[0047] In some embodiments, the subject is 65 years old or older. In other embodiments, the subject is 55 years old or older. In still other embodiments, the subject is 55 years old or younger, or 50 years old or younger.

[0048] A pharmaceutical composition comprising an effective amount of a Fused Morpholinopyrimidine and a pharmaceutically acceptable carrier or vehicle is useful for treating or preventing a neurodegenerative disease.

[0049] The details of the invention are set forth in the accompanying description below.

[0050] All patents and publications cited in this specification are hereby incorporated by reference in their entirety.

5. DETAILED DESCRIPTION

5.1 Definitions and Abbreviations

[0051] The following are definitions of terms used in the present specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art.

[0052] The term “C₁-C₄ alkyl” as used herein, refers to a straight chain or branched non-cyclic hydrocarbon having from 1 to 4 carbon atoms, wherein one of the hydrocarbon's hydrogen atoms has been replaced by a single bond. Representative straight chain C₁-C₄ alkyls include -methyl, -ethyl, -*n*-propyl and -*n*-butyl. Representative branched C₁-C₄ alkyls include -isopropyl, -*sec*-butyl, -isobutyl and -*tert*-butyl.

[0053] The term “C₃-C₈ monocyclic cycloalkyl” as used herein, refers to a saturated cyclic hydrocarbon having from 3 to 8 carbon atoms. Representative C₃-C₈ monocyclic cycloalkyls include -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl and -cyclooctyl.

[0054] The term “C₁-C₄ alkylene” as used herein, refers to a straight or branched chain saturated hydrocarbon containing 1-4 carbon atoms, wherein two of the hydrocarbon's

hydrogen atoms have been replaced by a single a bond. Representative C₁-C₄ alkylene groups include, methylene, ethylene, n-propylene, isopropylene, n-butylene and isobutylene.

[0055] The term “C₁-C₄ alkoxy” as used herein, refers to a C₁-C₄ alkyl-O- group wherein the C₁-C₄ alkyl is as defined above. Examples of C₁-C₄ alkoxy include, but are not limited to, methoxy, trifluoromethoxy, ethoxy, propoxy or butoxy.

[0056] The term “halo-substituted C₁-C₄ alkoxy” as used herein, refers to a C₁-C₄ alkoxy group, as defined above, wherein one or more of the C₁-C₄ alkoxy group's hydrogen atoms have been replaced with -F, -Cl, -Br or -I. Examples of a halo-substituted C₁-C₄ alkoxy include, but are not limited to, -O-CH₂F, -O-CCl₃, -O-CF₃, -O-CH₂Cl, -O-CH₂CH₂Br, -O-CH₂CH₂I, -O-CF₂CF₃, -O-CH₂CH₂CH₂F, -O-CH₂CH₂CH₂Cl, -O-CH₂CH₂CH₂CH₂Br, -O-CH₂CH₂CH₂CH₂I, -O-CH₂CH(Br)CH₃, -O-CH₂CH(Cl)CH₂CH₃, -O-CH(F)CH₂CH₃, -OCH₂CF₃ and -O-C(CH₃)₂(CH₂Cl).

[0057] The term “amino-substituted C₁-C₄ alkoxy” as used herein, refers to a C₁-C₄ alkoxy group, as defined above, wherein one or more of the C₁-C₄ alkoxy group's hydrogen atoms have been replaced with -NH₂. Examples of amino-substituted C₁-C₄ alkoxy include, but are not limited to, -O-CH₂NH₂, -O-CH₂CH₂NH₂, -O-CH(NH₂)CH₃, -O-CH₂CH₂CH₂NH₂, -O-CH₂CH₂CH₂CH₂NH₂, -O-CH₂CH(NH₂)CH₃, -O-CH(NH₂)CH₂CH₃ and -O-C(CH₃)₂(CH₂NH₂).

[0058] A “nitrogen-containing 4- to 6-membered nonaromatic heterocycle” refers to a monocyclic 4- to 6-membered nonaromatic monocyclic cycloalkyl group in which one of the cycloalkyl group's ring carbon atoms has been replaced with a nitrogen atom and 0-3 of the cycloalkyl group's remaining ring carbon atoms are independently replaced with a N, O or S atom. The nitrogen-containing 4- to 6-membered nonaromatic heterocycles can be attached via a nitrogen or carbon atom. Representative examples of nitrogen-containing 4- to 6-membered nonaromatic heterocycles include, but are not limited to, azetidiny, piperidiny, oxazinyl, morpholinyl, imidazolidinyl, pyrazolidinyl and thiomorpholinyl.

[0059] A “4- to 6-membered nonaromatic heterocycle” refers to a monocyclic 4- to 6-membered nonaromatic monocyclic cycloalkyl group in which 1-3 of the cycloalkyl group's ring carbon atoms are independently replaced with a N, O or S atom. The 4- to 6-membered nonaromatic heterocycles can be attached via a nitrogen or carbon atom. Representative examples of nitrogen-containing 4- to 6-membered nonaromatic heterocycles include, but are not limited to, azetidiny, piperidiny, oxazinyl, morpholinyl, imidazolidinyl, pyrazolidinyl, thiomorpholinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl and dioxanyl.

[0060] The term “3- to 7-membered monocyclic heterocycle” as used herein, refers to a monocyclic 3- to 7-membered aromatic or non-aromatic monocyclic cycloalkyl in which 1-4 of the ring carbon atoms have been independently replaced with a N, O or S atom. The 3- to 7-membered monocyclic heterocycles can be attached via a nitrogen or carbon atom. Representative examples of a 3- to 7-membered monocyclic heterocycle group include, but are not limited to, nitrogen-containing 3- to 7-membered monocyclic heterocycles discussed above, tetrahydrofuranyl, dihydrofuranyl, pyranyl, dihydropyranyl, tetrahydropyranyl, thiopyranyl, dihydrothiopyranyl, tetrahydrothiopyranyl, dioxanyl, dithianyl, trithianyl, dioxolanyl, furanyl and thiophenyl. In one embodiment, the 3- to 7-membered monocyclic heterocycle is a nitrogen-containing 3- to 7-membered monocyclic heterocycle. In another embodiment, the 3- to 7-membered monocyclic heterocycle is fully saturated or partially saturated.

[0061] The term “nitrogen-containing 5- to 6-membered aromatic monocyclic heterocycle” as used herein, refers to a 5- or 6-membered aromatic monocyclic heterocycle in which from 1 to 4 of the ring carbon atoms have been independently replaced with a nitrogen atom and 0-4 of the cycloalkyl group’s remaining ring carbon atoms have been independently replaced with an O or S atom. The nitrogen-containing 5- to 6-membered aromatic monocyclic heterocycle can be attached via a nitrogen or carbon atom. Representative examples of a 5- to 6-membered aromatic monocyclic heterocycles include, but are not limited to, imidazolyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyrimidinyl, pyrazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrrolyl, thiazolyl, thiadiazolyl, triazinyl, and triazolyl. Unless otherwise indicated, the nitrogen-containing 5- to 6-membered aromatic monocyclic heterocycle is unsubstituted.

[0062] The terms “halogen” or “halo” as used herein, refer to chlorine, bromine, fluorine or iodine.

[0063] The term “halo-substituted C₁-C₄ alkyl” as used herein, refers to a C₁-C₄ alkyl group, as defined above, wherein one or more of the C₁-C₄ alkyl group’s hydrogen atoms have been replaced with -F, -Cl, -Br or -I. Examples of a halo-substituted C₁-C₄ alkyl include, but are not limited to, -CH₂F, -CCl₃, -CF₃, -CH₂Cl, -CH₂CH₂Br, -CH₂CH₂I, -CF₂CF₃, -CH₂CH₂CH₂F, -CH₂CH₂CH₂Cl, -CH₂CH₂CH₂CH₂Br, -CH₂CH₂CH₂CH₂I, -CH₂CH(Br)CH₃, -CH₂CH(Cl)CH₂CH₃, -CH(F)CH₂CH₃, -CH₂CF₃ and -C(CH₃)₂(CH₂Cl).

[0064] The term “amino-substituted C₁-C₄ alkyl” as used herein, refers to a C₁-C₄ alkyl group, as defined above, wherein one or more of the C₁-C₄ alkyl group’s hydrogen atoms have been replaced with –NH₂. Examples of amino-substituted C₁-C₄ alkyl include, but are not

limited to, –CH₂NH₂, –CH₂CH₂NH₂, –CH(NH₂)CH₃, –CH₂CH₂CH₂NH₂, –CH₂CH(NH₂)CH₃, –CH₂CH(NH₂)CH₂CH₃, –CH(NH₂)CH₂CH₃ and –C(CH₃)₂(CH₂NH₂).

[0065] The term “C₁-C₄ alkylene-phenyl” as used herein, refers to a C₁-C₄ alkyl group, as defined above, wherein one of the C₁-C₄ alkyl group’s hydrogen atoms has been replaced with phenyl.

[0066] The term “hydroxy-substituted C₁-C₄ alkyl” as used herein, refers to a C₁-C₄ alkyl group, as defined above, wherein one or more of the C₁-C₄ alkyl group’s hydrogen atoms have been replaced with –OH. Representative examples of a hydroxy-substituted C₁-C₄ alkyl include, but are not limited to, –CH₂OH, –CH₂CH₂OH, –CH₂CH₂CH₂OH, –CH₂CH₂CH₂CH₂OH, –CH₂CH(OH)CH₃, –CH₂CH(OH)CH₂CH₃, –CH(OH)CH₂CH₃ and –C(CH₃)₂(CH₂OH).

[0067] Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

[0068] The phrase “pharmaceutically acceptable carrier or vehicle” as used herein, refers to a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the Fused Morpholinopyrimidine from one organ, or portion of the body, to another organ, or portion of the body. Each carrier or vehicle must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Some examples of materials which can serve as pharmaceutically acceptable carriers or vehicles include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as butylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution;

ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

[0069] The compounds described herein may form salts which are also within the scope of this invention. Reference to a compound described herein is understood to include reference to salts thereof, unless otherwise indicated. The term “salt(s)”, as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound described herein contains both a basic moiety, such as, but not limited to, amine, pyridine or imidazole and an acidic moiety, such as, but not limited to, a carboxylic acid, zwitterions (“inner salts”) may be formed and are included within the term “salt(s)” as used herein. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, *e.g.*, in isolation or purification steps which may be employed during preparation. Salts of the compounds described herein may be formed, for example, by reacting a compound with an amount of acid or base, such as an equivalent amount, in a medium, such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0070] The compounds described herein which contain a basic moiety, such as, but not limited to, an amine or a pyridine or imidazole ring, may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, hydroxyethanesulfonates (*e.g.*, 2-hydroxyethanesulfonates), lactates, maleates, methanesulfonates, naphthalenesulfonates (*e.g.*, 2-naphthalenesulfonates), nicotines, nitrates, oxalates, pectinates, persulfates, phenylpropionates (*e.g.*, 3-phenylpropionates), phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates, tartrates, thiocyanates, toluenesulfonates, such as tosylates, undecanoates and the like.

[0071] The compounds described herein which contain an acidic moiety, such as, but not limited to, a carboxylic acid, may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts, such as sodium, lithium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases (for example, organic amines), such as benzathines, dicyclohexylamines,

hydrabamines (formed with N,N-bis(dehydroabietyl) ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glycamides, t-butyl amines and salts with amino acids, such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents, such as lower alkyl halides (*e.g.*, methyl, ethyl, propyl and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, dibutyl and diamyl sulfates), long chain halides (*e.g.*, decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

[0072] Prodrugs and solvates of the compounds described herein are also contemplated herein. The term “prodrug” as employed herein denotes a compound that, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound described herein, or a salt and/or solvate thereof. Solvates of the compounds described herein include, for example, hydrates.

[0073] Compounds described herein are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 90%, for example, equal to or greater than 95%, equal to or greater than 97%, equal to or greater than 98%, or equal to or greater than 99% of the compounds (“substantially pure” compounds), which is then used or formulated as described herein. Such “substantially pure” compounds described herein are also contemplated herein as part of the present invention.

[0074] All stereoisomers of the present compounds (for example, those which may exist due to asymmetric carbons on various substituents), including enantiomeric forms and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds described herein may, for example, be substantially free of other isomers (*e.g.*, as a pure or substantially pure optical isomer having a specified activity), or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the compounds described herein may have the S or R configuration as defined by the International Union of Pure and Applied Chemistry (IUPAC) 1974 Recommendations. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by any suitable method, including without limitation, conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

[0075] If, for instance, a particular enantiomer of a compound described herein is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

[0076] All configurational isomers of the compounds described herein are contemplated, either in admixture or in pure or substantially pure form. Certain compounds described herein may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *cis* (*Z*) and *trans* (*E*) alkene isomers *R*- and *S*-enantiomers, diastereomers, (*D*)-isomers, (*L*)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent, such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[0077] Isomeric mixtures containing any of a variety of isomer ratios may be utilized in accordance with the present invention. For example, where only two isomers are combined, mixtures containing 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0 isomer ratios are all contemplated by the present invention. Those of ordinary skill in the art will readily appreciate that analogous ratios are contemplated for more complex isomer mixtures.

[0078] Throughout the specifications, groups and substituents thereof may be chosen to provide stable moieties and compounds. Compounds useful in the treatment, for example, are neurodegenerative disorders. The term “stable”, as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be detected and preferably for a sufficient period of time to be useful for the purposes detailed herein.

[0079] Definitions of specific functional groups and chemical terms are described in more detail above. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific

functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999, the entire contents of which are incorporated herein by reference.

[0080] In some embodiments, the present invention also includes isotopically labeled compounds, which are identical to the compounds disclosed herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{11}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Compounds described herein, or an enantiomer, diastereomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, which contain the aforementioned isotopes and/or other isotopes of other atoms, are within the scope of this invention. Certain isotopically labeled compounds described herein, for example those into which radioactive isotopes, such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, *i.e.*, ^3H , and carbon-14, *i.e.*, ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes, such as deuterium, *i.e.*, ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements, and hence, may be preferred in some circumstances. Isotopically labeled compounds can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[0081] When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position.

[0082] As used herein, “effective amount” refers to any amount that is necessary or sufficient for achieving or promoting a desired outcome, e.g., for treating, preventing, or ameliorating a symptom of a neurodegenerative disease. In some instances an effective amount is a therapeutically effective amount. A therapeutically effective amount is any amount that is necessary or sufficient for promoting or achieving a desired biological response in a subject. The effective amount for any particular application can vary depending on such factors as the disease or condition being treated, the particular agent being administered, the size of the subject, or the severity of the disease or condition.

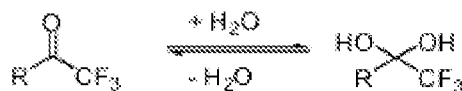
[0083] As used herein, “treat” or “treating” includes stopping the progression and/or reducing or ameliorating a symptom of a neurodegenerative disease, for example, improving cognitive function.

[0084] As used herein, the term “subject” refers to a vertebrate animal. In one embodiment the subject is a mammal. In one embodiment the subject is a human. In other embodiments the subject is a non-human vertebrate animal, including, without limitation, non-human primates, laboratory animals, livestock, domesticated animals and non-domesticated animals. Non-limiting examples of subject include a mammal, *e.g.*, a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, and non-human primate, such as a monkey, chimpanzee, baboon or rhesus. In one embodiment, the subject is a human.

[0085] Practitioners of the art will recognize that certain chemical groups may exist in multiple tautomeric forms (for example, as an amide or imino ether). The scope of this disclosure is meant to include all such tautomeric forms. For example, a tetrazole may exist in two tautomeric forms, 1-H tetrazole and a 2-H tetrazole. This is depicted in the figure below. This example is not meant to be limiting in the scope of tautomeric forms.



[0086] Practitioners of the art will recognize that certain electrophilic ketones, may exist in a hydrated form. The scope of this disclosure is to include all such hydrated forms. For example, a trifluoromethyl ketone may exist in a hydrated form via addition of water to the carbonyl group. This is depicted in the figure below. This example is not meant to be limiting in the scope of hydrated forms.



Abbreviations

[0087] Abbreviations used in the following examples and preparations include:

Aβ	Amyloid-beta
Ac	Acyl (Me-C(O)-)
ACN	Acetonitrile
AD	Alzheimer's Disease

APP	Amyloid Precursor Protein
Aq	Aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	Tert-butyloxycarbonyl
BSA	Bovine Serum Albumin
Bu	Butyl
BuLi	Butyllithium
c	Cyclo
cBu	Cylcobutyl
Conc.	Concentrated
cPr	Cyclopropyl
CSF	Cerebrospinal Fluid
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1, 2-Dichloroethane
DCM	Dichloromethane
DEA	Di-ethylamine
DIAD	Diisopropyl Azodicarboxylate
DIPEA	N, N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethyl Sulfoxide
DPPA	Diphenoxyphosphoryl Azide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
ELISA	Enzyme-Linked Immuno Sorbent Assay
ESI	Electrospray Ionization
Et	Ethyl
Et ₃ N	Triethylamine
Eq.	Equivalent
g	Grams(s)
HPLC	High Pressure Liquid Chromatography

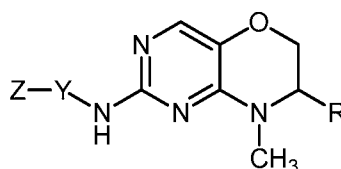
h	Hour(s)
IPA	Isopropyl Alcohol
ipc	Isopyropinocampheyl
iPr	Isopropyl
i.v or IV.	Intravenous
LAH	Lithium Aluminum Hydride
LC-MS	Liquid Chromatography-Mass Spectrometry
LC/MS	Liquid Chromatography Mass Spectrometry
LG	Leaving Group
LRMS	Low Resolution Mass Spectrometry
m	Multiplet
MeOH	Methanol
min	Minute(s)
mmol	Millimoles
μl	Microliter
ul	Microliter
μm	Micrometer
Ms	Mesylate
MS	Mass Spectrometry
MW	Molecular Weight (all values are ± 0.05)
n	Normal
N	Normal
NBS	N-Bromosuccinimide
NMP	1-Methylpyrrolidin-2-one
NMR	Nuclear Magnetic Resonance
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
o/n	Overnight
PMB	Para-methoxybenzyl
PBS	Phosphate Buffered Saline
Py	Pyridine
Ra-Ni	Raney Nickel
Rf	Retention Factor
RT (or rt)	Room Temperature (about 20-25°C) or Retention Time

RT	Retention Time
s	Singlet
sat.	Saturated
t	Triplet
t-Bu	Tertiary Butyl
tert	Tertiary
Tf	Triflate
TFA	Trifluoroacetic Acid
TFAA	Trifluoroacetic Anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TPP	Triphenylphosphine
Ts	Tosylate
UPLC	Ultra Performance Liquid Chromatography
v/v	Volume/volume
wt/v	Weight/volume

5.2 Fused Morpholinopyrimidines

[0088] Described below are Fused Morpholinopyrimidines, i.e., compounds according to Formula (I), the compounds in Table II, and pharmaceutically acceptable salts thereof, as well as methods for preparing the compounds and using the compounds to treat one or more neurodegenerative diseases, e.g., reducing a symptom of Alzheimer's disease (such as improving cognitive function). The compounds of the disclosure are believed to be gamma secretase modulators (GSMs), i.e., compounds that act to shift the relative levels of A β peptides produced by γ -secretase. In some embodiments, the compounds alter the relative levels of A β peptides produced by γ -secretase, for example the level of A β 42 peptide, without significantly changing the total level of A β peptides produced.

[0089] In one aspect, described herein are compounds according to Formula (I), below:



(I)

and pharmaceutically acceptable salts thereof,

wherein R, Y and Z are as defined above for the compounds of Formula (I).

[0090] In some embodiments, R is phenyl or C₁-C₄ alkylene-phenyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -NH₂, -C₁-C₄ alkyl, halo-substituted C₁-C₄ alkyl, amino-substituted C₁-C₄ alkyl, -NH-C₁-C₄ alkyl, -NHC(O)-C₁-C₄ alkyl, -N(C₁-C₄ alkyl)(C(O)(C₁-C₄ alkyl)), -C(O)NH-C₁-C₄ alkyl, -C(O)N(C₁-C₄ alkyl)₂, hydroxy-substituted C₁-C₄ alkyl, -S(O)₂-C₁-C₄ alkyl, -S(O)₂-halo-substituted C₁-C₄ alkyl, -S(O)₂-NH-C₁-C₄ alkyl, -S(O)₂-N(C₁-C₄ alkyl)₂, -NH-S(O)₂-C₁-C₄ alkyl, -N(C₁-C₄ alkyl)-S(O)₂-C₁-C₄ alkyl, -C₁-C₄ alkoxy, halo-substituted C₁-C₄ alkoxy, 3- to 7-membered monocyclic heterocycle, C₃-C₈ monocyclic cycloalkyl and -C(O)NH₂.

[0091] In some embodiments, R is phenyl or C₁-C₄ alkylene-phenyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -C₁-C₄ alkyl, -C₁-C₄ alkoxy, halo-substituted C₁-C₄ alkyl and halo-substituted C₁-C₄ alkoxy.

[0092] In some embodiments, Y is piperidinyl or azetidinyl, each of which is unsubstituted.

[0093] In some embodiments, Z is pyridinyl or pyrimidinyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of -C₁-C₄ alkyl, halo-substituted C₁-C₄ alkyl and -C₁-C₄ alkoxy.

[0094] In some embodiments, R is phenyl or C₁-C₄ alkylene-phenyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen or -C₁-C₄ alkyl; Y is piperidinyl; and Z is pyridinyl or pyrimidinyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of -C₁-C₄ alkyl, halo-substituted C₁-C₄ alkyl and -C₁-C₄ alkoxy.

[0095] In some embodiments, R is phenyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen and -C₁-C₄ alkyl; and Z is pyridinyl which is unsubstituted or substituted with -C₁-C₄ alkoxy.

[0096] In some embodiments, R is phenyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen and -C₁-C₄ alkyl.

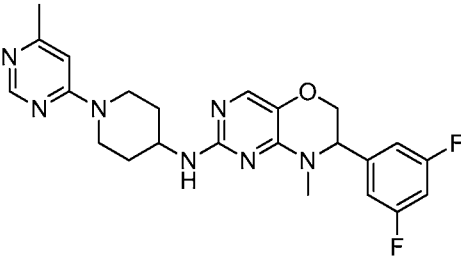
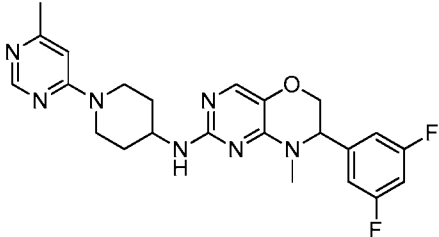
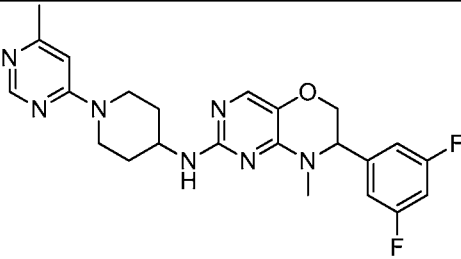
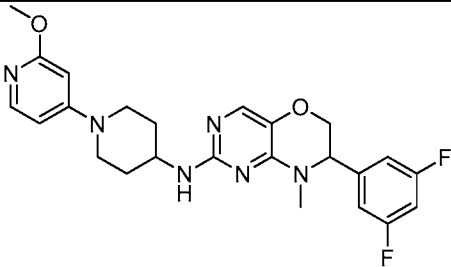
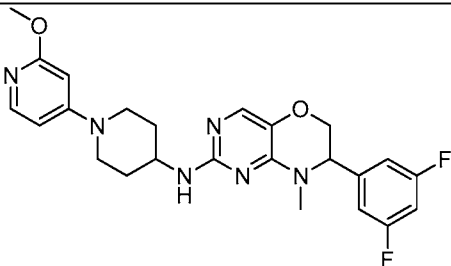
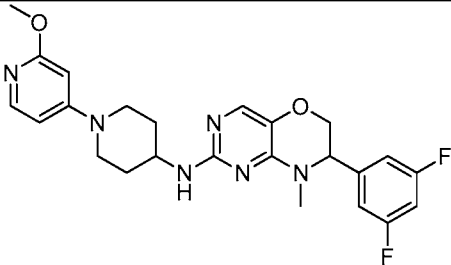
- [0097] In some embodiments, R is phenyl which is unsubstituted. In some embodiments, R is phenyl substituted with two or three -F.
- [0098] In some embodiments, each -C₁-C₄ alkyl is methyl and each C₁-C₄ alkylene is methylene.
- [0099] In some embodiments, C₁-C₄ alkylene is methylene.
- [0100] In some embodiments, C₁-C₄ alkylene-phenyl is benzyl.
- [0101] In some embodiments, R is phenyl substituted with one methyl.
- [0102] In some embodiments, R is C₁-C₄ alkylene-phenyl.
- [0103] In some embodiments, R is -C₁-C₆ alkyl.
- [0104] In some embodiments, R is 3- to 7-membered monocyclic heterocycle.
- [0105] In some embodiments, Y is piperidinyl. In some embodiments, Y is azetidiny.
- [0106] In some embodiments, Z is pyridinyl or pyrimidinyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of -C₁-C₄ alkyl, -CF₃ and -C₁-C₄ alkoxy.
- [0107] In some embodiments, Z is pyridinyl substituted with one -CF₃. In some embodiments, Z is pyridinyl substituted with one methyl. In some embodiments, Z is pyridinyl substituted with one methoxy. In some embodiments, Z is pyrimidinyl which is unsubstituted or substituted with one to three -C₁-C₄ alkyl. In some embodiments, Z is pyrimidinyl substituted with one methyl.
- [0108] In some embodiments, Z is attached to Y at the 4 position of Y. In some embodiments, Z is attached to Y at the 4 position of Z. In some embodiments, Z is attached to Y at the 1 position of Z.
- [0109] In some embodiments, halogen is -F. In some embodiments, halogen is -Cl.
- [0110] In some embodiments, the compound of Formula (I) is a compound selected from the compounds in Table I.

Table I. Exemplary Fused Morpholinopyrimidines of Formula (I)

Compound of Example	Structure	Name
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26		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)
26A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
26B		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
27		8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
28		N-(1-(2-methoxypyridin-4-yl)azetidin-3-yl)-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
29		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)

29A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
29B		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
30		N-(1-(2-methoxypyridin-4-yl)azetidin-3-yl)-8-methyl-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
31		8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)
31A		(-)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
31B		(+)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine

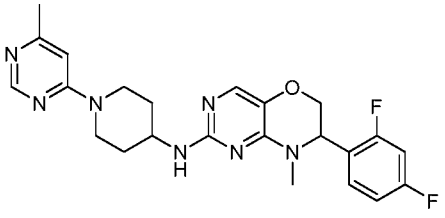
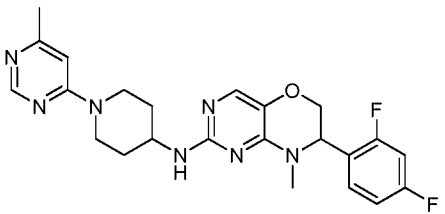
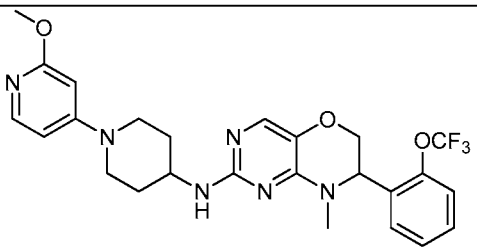
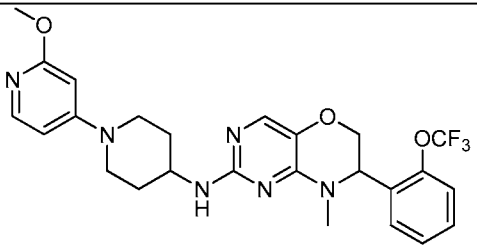
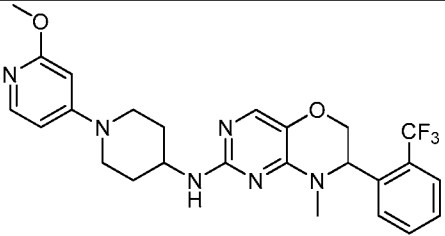
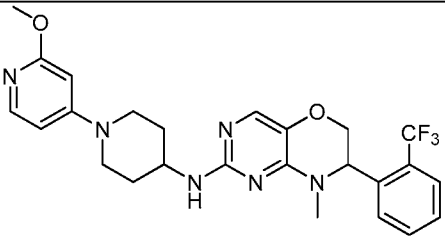
32		7-(3,5-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)
32A		(+)-7-(3,5-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
32B		(-)-7-(3,5-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
33		7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)
33A		(+)-7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
33B		(-)-7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine

34		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)
34A		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
34B		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
35		8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)
35A		(+)-8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
35B		(-)-8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine

36		N-(1-(6-methoxypyrimidin-4-yl) piperidin-4-yl)-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine
37A		(+)-7-benzyl-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine
37B		(-)-7-benzyl-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine
38A		(+)-7-(3, 5-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine
38B		(-)-7-(3, 5-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine
39A		(+)-7-(4-fluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

39B		(-)-7-(4-fluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine
40A		(+)-7-benzyl-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine
40B		(-)-7-benzyl-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine
41A		(+)-7-(4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine
41B		(-)-7-(4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine
42A		(+)-8-methyl-7-(o-tolyl)-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine
42B		(-)-8-methyl-7-(o-tolyl)-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

43A		(+)-7-(4-fluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
43B		(-)-7-(4-fluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
44A		(-)-7-(2,4-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
44B		(+)-7-(2,4-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
45A		(+)-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
45B		(-)-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine

46A		(-)-7-(2,4-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5,4-b] [1,4] oxazin-2-amine
46B		(+)-7-(2,4-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5,4-b] [1,4] oxazin-2-amine
47A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2-(trifluoromethoxy)phenyl)-7,8-dihydro-6H-pyrimido [5,4-b] [1,4] oxazin-2-amine
47B		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2-(trifluoromethoxy)phenyl)-7,8-dihydro-6H-pyrimido [5,4-b] [1,4] oxazin-2-amine
48A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrimido [5,4-b] [1,4] oxazin-2-amine
48B		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrimido [5,4-b] [1,4] oxazin-2-amine

49A		(-)-7-(2,4-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
49B		(+)-7-(2,4-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
60A		(+)-7-benzyl-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
60B		(-)-7-benzyl-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
61A		(-)-7-(2-chlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
61B		(+)-7-(2-chlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
62A		(-)-7-(2,4-dichlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine

62B		(+)-7-(2,4-dichlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
63A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
63B		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
64A		(-)-7-(2-chloro-4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
64B		(+)-7-(2-chloro-4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
65A		(-)-7-(4-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
65B		(+)-7-(4-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine

66A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(tetrahydro-2H-pyran-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
66B		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(tetrahydro-2H-pyran-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
67A		(-)-7-(5-chloro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
67B		(+)-7-(5-chloro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
68A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-7,8-dimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
68B		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-7,8-dimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
69A		(-)-7-(5-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine

69B		(+)-7-(5-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
70A		(-)-7-(2-chloro-4,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
70B		(+)-7-(2-chloro-4,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
71A		(-)-7-(4-chloro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
71B		(+)-7-(4-chloro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
72A		(+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
72B		(-)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine

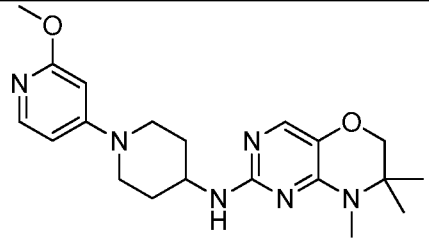
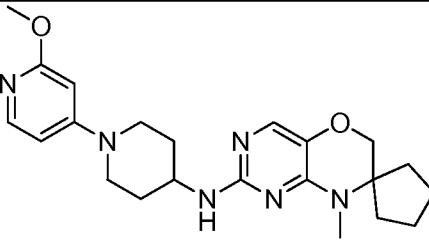
73A		(+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
73B		(-)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
74A		(+)-7-(3,5-difluorophenyl)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
74B		(-)-7-(3,5-difluorophenyl)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
75A		(+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
75B		(-)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
76A		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine

76B		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
77A		(-)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
77B		(+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine

[0111] In some embodiments, a Fused Morpholinopyrimidine is a compound selected from the compounds in Table II.

Table II. Exemplary Fused Morpholinopyrimidines

Compound of Example	Structure	Name
82A		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine
82B		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine

83		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-7,7,8-trimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine
84		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8'-methyl-6',8'-dihydrospiro[cyclopentane-1,7'-pyrimido[5,4-b][1,4]oxazin]-2'-amine

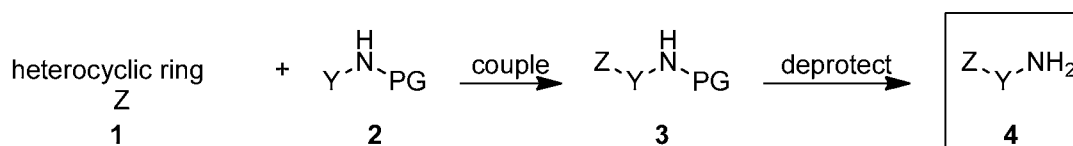
5.3 Methods for Making Fused Morpholinopyrimidines

[0112] Methods useful for making the Fused Morpholinopyrimidines are set forth in the Examples below and generalized in Schemes 1-3 for the compounds of Formula (I).

[0113] Schemes 1-3 represent general synthetic schemes for manufacturing Fused Morpholinopyrimidines. These schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to manufacture compounds disclosed herein. Different methods will be evident to those skilled in the art. Additionally, the various steps in the synthesis may be performed in an alternate sequence or order to give the desired compound(s).

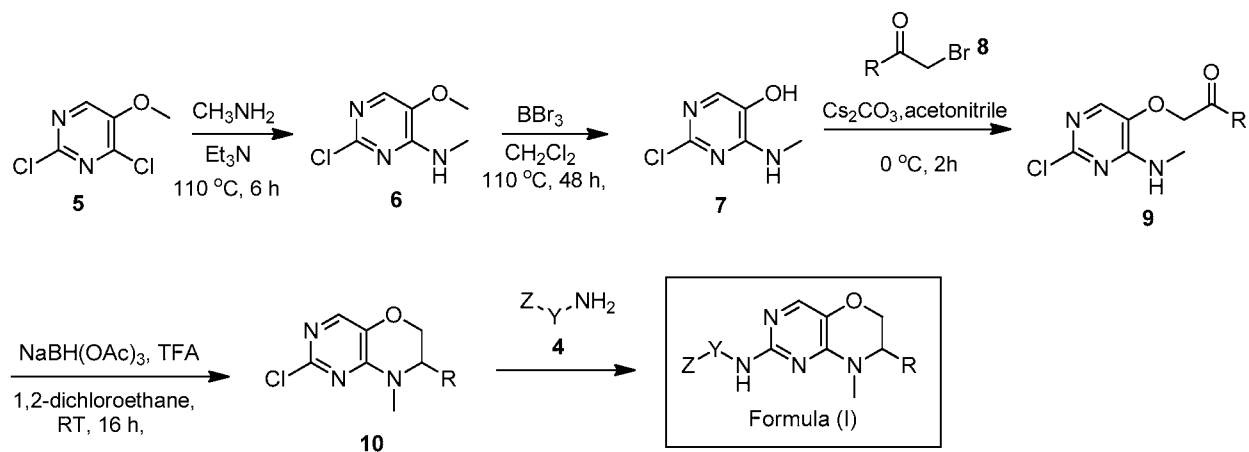
Various modifications to these methods may be envisioned by those skilled in the art to achieve similar results to that of the inventors provided below. For example, optional protecting groups can be used as described, for example, in Greene *et al.*, *Protective Groups in Organic Synthesis* (3rd ed. 1999).

Scheme 1



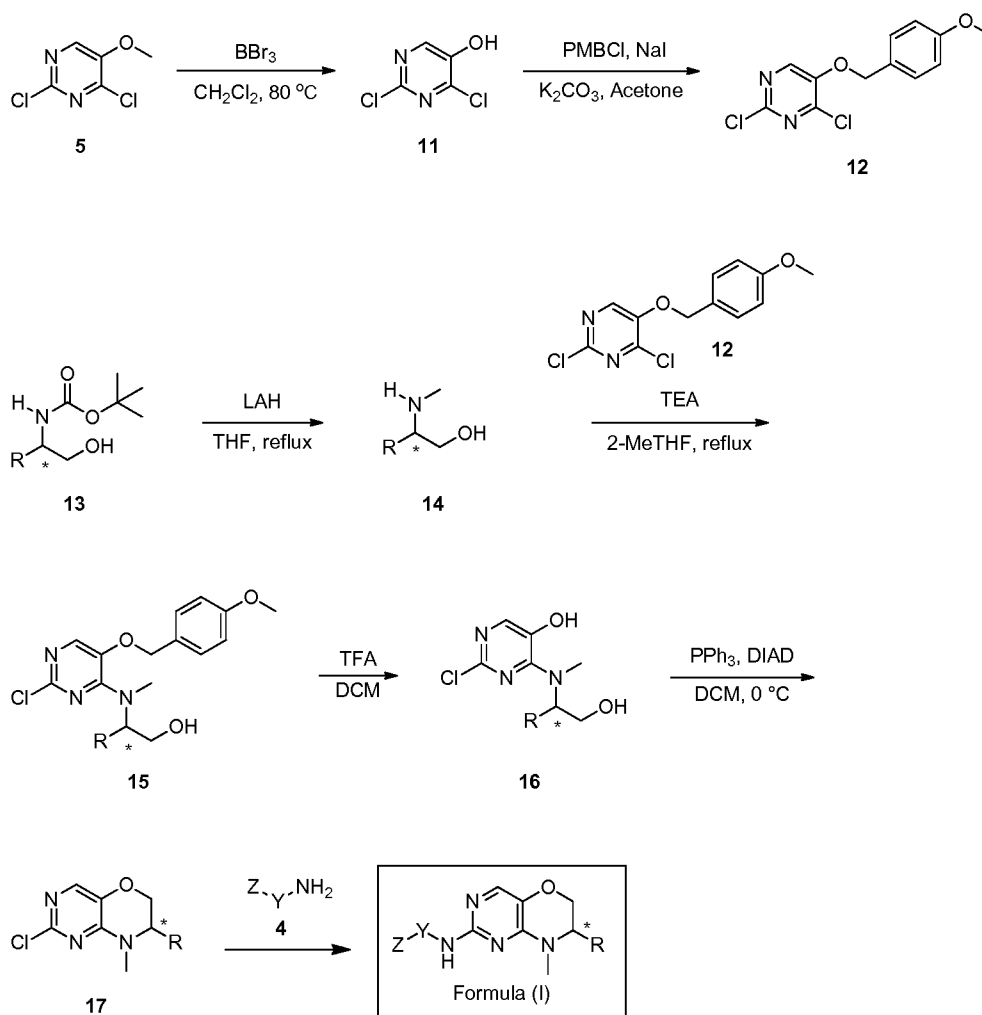
[0114] As shown in Scheme 1, a compound of formula 1 is coupled to the compound of formula 2 under standard coupling conditions to provide a compound of formula 3. The compound of formula 3 is deprotected to provide a compound of formula 4.

Scheme 2



[0115] As shown in Scheme 2, a compound of formula 5 is reacted with methyl amine under basic conditions to provide a compound of formula 6. The compound of formula 6 is then reacted with BBr_3 to provide a compound of formula 7. The compound of formula 7 is reacted using, for example, a compound of formula 8, to provide a compound of formula 9. The compound of formula 9 is then cyclized to form a compound of formula 10. The compound of formula 10 is reacted with a compound of formula 4 to provide a Fused Morpholinopyrimidine.

Scheme 3



[0116] As shown in Scheme 3, a compound of formula 5 is reacted with BBr_3 to provide a compound of formula 11. The compound of formula 11 is then protected to form compound 12. Enantio-pure compound of formula 13 is reduced with LAH to provide a compound of formula 14. The compound of formula 14 is then coupled with compound 12 to form compound 15. The compound of formula 15 is then deprotected under acidic conditions to provide a compound of formula 16. The compound of formula 16 is then cyclized to form a compound of formula 17. The compound of formula 17 is coupled to a compound of formula 4 to provide an enantiomerically-pure Fused Morpholinopyrimidine at the chiral carbon atom (marked with *).

5.4 Pharmaceutical Compositions Comprising a Fused Morpholinopyrimidine

[0117] In another aspect, the present disclosure provides pharmaceutical compositions for treating, preventing, or ameliorating a symptom of a neurodegenerative disease in a subject having a neurodegenerative disease, wherein the pharmaceutical composition comprises a therapeutically effective amount of a Fused Morpholinopyrimidine, and a pharmaceutically acceptable carrier or vehicle.

[0118] As set out above, in some embodiments, Fused Morpholinopyrimidines are provided in the form of pharmaceutically acceptable salts. These salts can be prepared *in situ* during the final isolation and purification of the compounds described herein, or by separately reacting a purified compound described herein in its free base or acid form with a suitable organic or inorganic acid or base, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, laurylsulphonate, ammonium, amine salts and the like. See, for example, Berge, *et al.*, (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19.

[0119] The pharmaceutically acceptable salts of Fused Morpholinopyrimidines include the conventional nontoxic salts or acid salts of the compounds, *e.g.*, from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids, such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids, such as acetic, butionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic and the like.

[0120] In general, a suitable dose of a Fused Morpholinopyrimidine will be in the range of 0.01 to 100 mg per kilogram body weight of the recipient per day or in the range of 0.2 to 10 mg per kilogram body weight per day. The desired dose can be administered once daily, but may be dosed as two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day.

[0121] The concentration of compounds included in compositions used in the methods described herein can range from about 1 nM to about 100 μ M. Effective doses are believed to range from about 10 picomole/kg to about 100 micromole/kg.

[0122] A Fused Morpholinopyrimidine can be administered as the sole active agent, or in combination with other known therapeutics to be beneficial in the treatment of neurodegenerative diseases. In any event, the administering physician can provide a method of treatment that is prophylactic or therapeutic by adjusting the amount and timing of drug administration on the basis of observations of one or more symptoms (e.g., motor or cognitive function as measured by standard clinical scales or assessments) of the disease being treated.

[0123] Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., Remington: The Science and Practice of Pharmacy (2 Volumes), (22nd Edition, 2012), Pharmaceutical Press ("Remington's"). After a pharmaceutical composition has been formulated in an acceptable carrier, it can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of a Fused Morpholinopyrimidine, such labeling would include, e.g., instructions concerning the amount, frequency, and method of administration.

[0124] The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, the particular mode of administration. The amount of active ingredient, which can be combined with a carrier or vehicle material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of 100%, this amount will range from about 1% to about 99% of active ingredient, preferably from about 5% to about 70%, most preferably from about 10% to about 30%.

[0125] The compounds and pharmaceutical compositions described herein can be employed in combination therapies, that is, the compounds and pharmaceutical compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved.

[0126] Methods of preparing these formulations or compositions include the step of bringing into association a compound described herein with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound described herein with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0127] When a Fused Morpholinopyrimidine is administered as pharmaceuticals to humans and animals, it can be given *per se* or as a pharmaceutical composition containing, for example, 0.1% to 99.5% (more preferably, 0.5% to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[0128] The pharmaceutical compositions described herein can be administered in a variety of dosage forms including, but not limited to, a solid dosage form, a liquid dosage form, an oral dosage form, a parenteral dosage form, an intranasal dosage form, a suppository, a lozenge, a troche, a buccal dosage form, a controlled release dosage form, a pulsed release dosage form, an immediate release dosage form, an intravenous solution, a suspension or combinations thereof.

Oral Formulations and Administration

[0129] Pharmaceutical formulations described herein suitable for oral administration can be in the form of capsules, cachets, pills, tablets, caplet, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouthwashes and the like, each containing a predetermined amount of a compound described herein as an active ingredient. The dosage can be an oral dosage form that is a controlled release dosage form. A Fused Morpholinopyrimidine can also be administered as a bolus, electuary or paste.

[0130] In solid dosage forms described herein for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium

carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium carbonate, and sodium starch glycolate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and polyethylene oxide-polybutylene oxide copolymer; absorbents, such as kaolin and bentonite clay; lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions can also comprise buffering agents. Solid compositions of a similar type can also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0131] A tablet can be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared using a binder (for example, gelatin or hydroxybutylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0132] Tablets, and other solid dosage forms of the pharmaceutical compositions described herein, such as dragees, capsules, pills and granules, can optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They can also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxybutylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They can be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions, which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions can also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0133] Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules, wherein the active ingredients is mixed with water or an oil, such as peanut oil, liquid paraffin or olive oil.

[0134] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0135] Liquid dosage forms for oral administration of the compounds described herein include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isobutyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, butylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Additionally, cyclodextrins, e.g., hydroxybutyl- β -cyclodextrin, may be used to solubilize compounds.

[0136] Suspensions, in addition to the active compounds, can contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar and tragacanth, and mixtures thereof.

[0137] Besides inert diluents, the oral compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0138] Pharmaceutical preparations for oral use can be obtained through combination of a Fused Morpholinopyrimidine with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable additional compounds, if desired, to obtain tablets or dragee cores. Suitable solid excipients in addition to those previously mentioned are carbohydrate or protein fillers that include, but are not limited to, sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose or sodium

carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

[0139] Pharmaceutical preparations for oral use can be presented as aqueous or liposome formulations. Aqueous suspensions can contain a Fused Morpholinopyrimidine in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents, such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (e.g., polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). The aqueous suspension can also contain one or more preservatives, such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolarity.

[0140] Oil suspensions can be formulated by suspending a Fused Morpholinopyrimidine in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil, such as liquid paraffin; or a mixture of these. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation, such as glycerol, sorbitol or sucrose. These formulations can be preserved by the addition of an antioxidant, such as ascorbic acid. As an example of an injectable oil vehicle, see Minto, *J. Pharmacol. Exp. Ther.* 281:93-102, 1997. The pharmaceutical formulations can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil, described above, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening agents and flavoring agents,

as in the formulation of syrups and elixirs. Such formulations can also contain a demulcent, a preservative, or a coloring agent.

Parenteral Formulations and Administration

[0141] In another embodiment, a Fused Morpholinopyrimidine can be administered parenterally, such as intravenous (IV) or intramuscular (IM) administration. The formulations for administration will commonly comprise a solution of a Fused Morpholinopyrimidine dissolved in a pharmaceutically acceptable carrier. Administration of a Fused Morpholinopyrimidine to any of the above mentioned sites can be achieved by direct injection of the pharmaceutical composition comprising the Fused Morpholinopyrimidine or by the use of infusion pumps. The pharmaceutical compositions can be formulated in solid form and re-dissolved or suspended immediately prior to use. Lyophilized forms are also included. The injection can be, for example, in the form of a bolus injection or continuous infusion (e.g., using infusion pumps) of pharmaceutical composition.

[0142] Pharmaceutical compositions suitable for parenteral administration comprise one or more compounds described herein in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0143] Among the acceptable vehicles and solvents that can be employed for formulation and/or reconstitution are water (e.g., water for injection) and Ringer's solution, an isotonic sodium chloride. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids, such as oleic acid can likewise be used in the preparation of injectables. These solutions are sterile and generally free of undesirable matter. These formulations may be sterilized by conventional, well known sterilization techniques such as gamma-radiation or electron beam sterilization. The formulations can contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, toxicity adjusting agents, e.g., sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like. The concentration of a Fused Morpholinopyrimidine in these

formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight, and the like, in accordance with the particular mode of administration selected and the subject's needs. For IV administration, the formulation can be a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or solvent, such as a solution of 1,3-butanediol.

[0144] In some embodiments, a Fused Morpholinopyrimidine can be administered by introduction into the central nervous system of the subject, e.g., into the cerebrospinal fluid of the subject. The formulations for administration will commonly comprise a solution of the Fused Morpholinopyrimidine dissolved in a pharmaceutically acceptable carrier. In certain aspects, the Fused Morpholinopyrimidine is introduced intrathecally, e.g., into a cerebral ventricle, the lumbar region, or the cisterna magna.

[0145] In some embodiments, the pharmaceutical composition comprising a Fused Morpholinopyrimidine is administered into a subject intrathecally. As used herein, the term "intrathecal administration" is intended to include delivering a pharmaceutical composition comprising a Fused Morpholinopyrimidine directly into the cerebrospinal fluid of a subject, by techniques including lateral cerebroventricular injection through a borehole or cisternal or lumbar puncture or the like (described in Lazorthes *et al.*, *Advances in Drug Delivery Systems and Applications in Neurosurgery*, 1991, 18:143-192 and Omayya *et al.*, *Cancer Drug Delivery*, 1984, 1:169-179, the contents of which are incorporated herein by reference). The term "lumbar region" is intended to include the area between the third and fourth lumbar (lower back) vertebrae. The term "cisterna magna" is intended to include the area where the skull ends and the spinal cord begins at the back of the head. The term "cerebral ventricle" is intended to include the cavities in the brain that are continuous with the central canal of the spinal cord. In some embodiments, the pharmaceutical composition is administered by injection into the cisterna magna, or lumbar area of a subject.

Depot Formulations and Administration

[0146] A Fused Morpholinopyrimidine can be formulated as a depot preparation. Such long acting formulations may be administered by implantation or transcutaneous delivery (e.g., subcutaneously or intramuscularly), intramuscular injection or a transdermal patch.

Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (e.g., as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0147] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. One strategy for depot injections includes the use of polyethylene oxide-polybutylene oxide copolymers, wherein the vehicle is fluid at room temperature and solidifies at body temperature.

[0148] Injectable depot forms can be made by forming microencapsule matrices of the subject compounds in biodegradable polymers, such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly (orthoesters) and poly (anhydrides). Depot injectable formulations can also be prepared by entrapping the drug in liposomes or microemulsions, which are compatible with body tissue.

Intranasal Formulations and Administration

[0149] For administration by inhalation, the compounds are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base, such as lactose or starch.

Other Formulations and Modes of Administration

[0150] For transmucosal administration (e.g., buccal, rectal, nasal, ocular, etc.), penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0151] Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the compounds, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as poly(lactide-glycolide), copolyoxalates, polycaprolactones, polyesteramides, polyorthoesters, polyhydroxybutyric acid and polyanhydrides. Microcapsules of the foregoing polymers containing drugs are described in, for example, U.S. Pat. No. 5,075,109. Delivery systems also include non-polymer systems that are: lipids including sterols, such as cholesterol, cholesterol esters and fatty acids or neutral fats, such as mono-, di- and tri-glycerides; hydrogel release systems; silastic systems; peptide based systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to: (a) erosional systems in which an agent described herein is contained in a form within a matrix, such as those described in U.S. Pat. Nos. 4,452,775, 4,675,189, and 5,736,152, and (b) diffusional systems in which an active component permeates at a controlled rate from a polymer, such as described in U.S. Pat. Nos. 3,854,480, 5,133,974 and 5,407,686. In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

5.5 Treatment, Prevention or Amelioration of Symptoms of a Neurodegenerative Disease

[0152] In another aspect, a method for treating a neurodegenerative disease is described, comprising administering to a subject an effective amount a pharmaceutical composition comprising an effective amount of a Fused Morpholinopyrimidine.

[0153] In some embodiments, the method for treating a neurodegenerative disease is a method for reducing or ameliorating a symptom of the neurodegenerative disease.

[0154] In some embodiments, a method for reducing or ameliorating a symptom of a neurological disease is described, comprising administering to a subject in need thereof an effective amount of a Fused Morpholinopyrimidine. Ameliorating or reducing the symptoms can be manifested in a variety of ways, for example, by improvement in cognitive function.

Such improvement can be assessed relative to the cognitive function of the subject prior to being treated or being administered a Fused Morpholinopyrimidine or a pharmaceutical composition comprising an effective amount of a Fused Morpholinopyrimidine.

[0155] In some embodiments, a method for preventing a neurological disease is described, comprising administering to a subject in need thereof an effective amount of a Fused Morpholinopyrimidine.

[0156] In some embodiments, a method for stopping progression of a neurological disease is described, comprising administering to a subject in need thereof an effective amount of a Fused Morpholinopyrimidine.

[0157] Exemplary symptoms of neurological disease that can be reduced or ameliorated by administration of a Fused Morpholinopyrimidine include, but are not limited to, loss of memory, loss of cognition, loss of reasoning and/or loss of judgment. The loss of each of memory, cognition, reasoning and/or judgment can be progressive or sudden. Dementia is an exemplary symptom of neurodegenerative disease. Administration of a Fused Morpholinopyrimidine can reduce or improve one or more of these symptoms.

[0158] Exemplary cognitive functions that can be improved by administration of a Fused Morpholinopyrimidine are attention, learning, delayed memory, working memory, visual learning, speed of processing, vigilance, verbal learning, visual motor function, social cognition, long term memory or executive function.

[0159] In one embodiment, the neurodegenerative disease is Alzheimer's disease. In some embodiments, the neurodegenerative disease is early onset Alzheimer's disease. In some embodiments, the early onset Alzheimer's disease is autosomal dominant early onset Alzheimer's disease.

[0160] In some embodiments, the subject is 65 years or older. In some embodiments, the subject is 55 years old or younger, or 50 years old or younger. In some embodiments, the subject is older than 55 years and younger than 65 years. In some embodiments, the subject is older than 55 years.

[0161] In some embodiments, the neurodegenerative disease is panic disorder, obsessive compulsive disorder, delusional disorder, drug-induced psychosis, post-traumatic stress disorder, age-related cognitive decline, attention deficit/hyperactivity disorder, personality disorder of the paranoid type, personality disorder of the schizoid type, dyskinesia, choreiform condition, psychosis associated with Parkinson's disease, psychotic symptoms associated with Alzheimer's disease, mood disorder, or dementia.

[0162] In some embodiments, the neurodegenerative disease is cognitive impairment, myoclonus, seizures, Parkinsonism, extrapyramidal signs (EPS), apraxia, dystonia, dementia with Lewy bodies (DLB), aphasia, visual agnosia, or ataxia.

[0163] In some embodiments, the subject has impaired cognitive function including one or more of attention, learning, delayed memory, working memory, visual learning, speed of processing, vigilance, verbal learning, visual motor function, social cognition, long term memory or executive function.

[0164] In some embodiments, the subject has a mutation in at least one gene selected from PSEN1, PSEN2 and APP. In some embodiments, the mutation in PSEN1, PSEN2 or APP is a missense mutation.

[0165] In some embodiments, the invention provides a method for treating or ameliorating a symptom of neurodegenerative disease (e.g., Alzheimer's disease) in a subject with an increased level of A β 42 in cerebrospinal fluid, the method comprising administering to a subject in need thereof an effective amount of a Fused Morpholinopyrimidine. In such subject, the increased level of A β 42 in cerebrospinal fluid can be detected relative to the level of A β 42 in cerebrospinal fluid of a healthy subject.

[0166] In some embodiments, the invention provides a method for lowering A β 42 concentration in a subject, the method comprising administering to a subject in need thereof an effective amount of a Fused Morpholinopyrimidine. In some embodiments, the subject has an elevated A β 42 concentration relative to a healthy subject.

[0167] In some embodiments, the invention provides a method for preventing increase of A β 42 concentration in a subject, the method comprising administering to a subject in need thereof an effective amount of a Fused Morpholinopyrimidine.

5.6 Kits

[0168] Described herein are kits that can simplify the administration of an Fused Morpholinopyrimidine to a subject. The kit can comprise one or more containers filled with one or more of the ingredients of the pharmaceutical compositions described herein. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

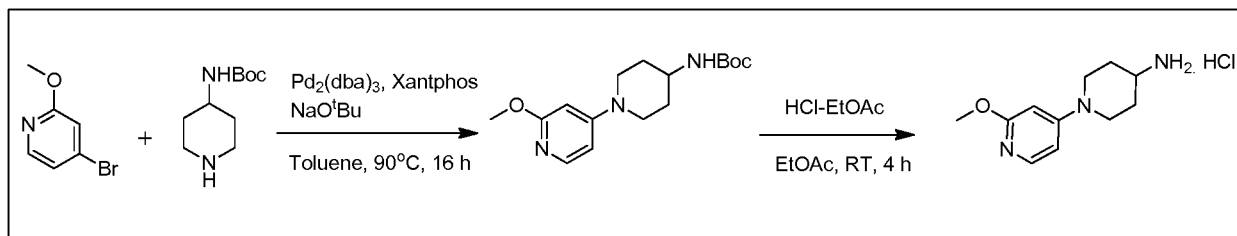
[0169] A typical kit comprises a unit dosage form of a Fused Morpholinopyrimidine. In one embodiment, the unit dosage form is a container, which can be sterile, containing an effective amount of a Fused Morpholinopyrimidine and a pharmaceutically acceptable carrier or vehicle. The kit can further comprise a label or printed instructions instructing the use of the Fused Morpholinopyrimidine to treat or prevent a neurodegenerative disease. The kit can also further comprise a unit dosage form of another prophylactic or therapeutic agent, for example, a container containing an effective amount of the other prophylactic or therapeutic agent. In one embodiment, the kit comprises a container containing an effective amount of a Fused Morpholinopyrimidine and an effective amount of another prophylactic or therapeutic agent. Examples of other prophylactic or therapeutic agents include, but are not limited to, those listed above.

[0170] The representative examples which follow are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples which follow and the references to the scientific and patent literature cited herein. It should further be appreciated that the contents of those cited references are incorporated herein by reference to help illustrate the state of the art. The following examples contain additional information, exemplification and guidance which can be adapted to the practice of this invention in its various embodiments and equivalents thereof. The examples do not limit the scope of the invention described in the claims.

6. EXAMPLES

Example 1

Synthesis of 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride



Synthesis of *tert*-Butyl (1-(2-methoxypyridin-4-yl) piperidin-4-yl) carbamate

[0171] To a stirred solution of *tert*-butyl piperidin-4-ylcarbamate (1.2 g, 6.38 mmol) in toluene (80 mL) was added 4-bromo-2-methoxypyridine (1.3 g, 6.38 mmol), sodium *tert*-butoxide (1.8 g, 19.14 mmol) and Xantphos (220 mg, 0.06 mmol). The mixture was purged under an argon atmosphere for 20 min, then $\text{Pd}_2(\text{dba})_3$ (73 mg, 0.12 mmol) was added. The reaction mixture was heated to 90°C and stirred for 16 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (30 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified through silica gel column chromatography using 30% EtOAc:hexanes to afford *tert*-butyl (1-(2-methoxypyridin-4-yl) piperidin-4-yl) carbamate (1 g, 53%) as an off-white solid. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ 7.77-7.75 (m, 1H), 6.83-6.82 (m, 1H), 6.52 (d, 1H), 6.08 (s, 1H), 3.80-3.75 (m, 5H), 3.47 (s, 1H), 2.86 (t, 2H), 1.75-1.73 (m, 2H), 1.38-1.30 (m, 11H); LC-MS: 308.3 (M+1); (column; X-Bridge C-18 (50 x 3.0 mm, 3.5 μ); RT 3.14 min. 0.05% aq TFA: ACN; 0.80 mL/min); TLC: 45% EtOAc:hexanes (R_f 0.3).

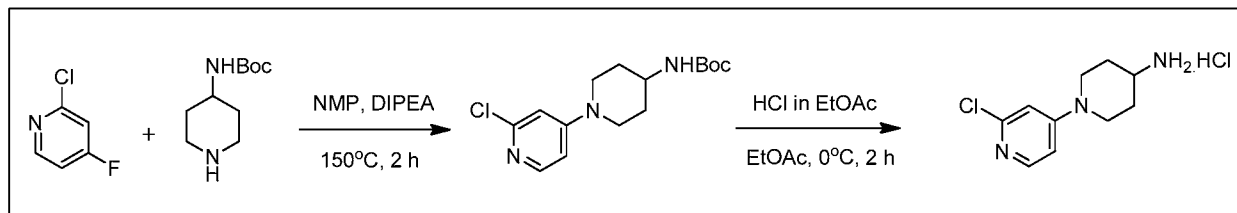
Synthesis of 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride

[0172] To a stirred solution of *tert*-Butyl (1-(2-methoxypyridin-4-yl) piperidin-4-yl) carbamate (1 g, 3.25 mmol) in EtOAc (15 mL) was added 4M HCl-EtOAc (2 mL) at 0°C . The reaction mixture was warmed to RT and stirred for 2 h. After consumption of the starting materials (monitored by TLC), the mixture was concentrated *in vacuo*. The crude material was washed with ether (2 x 20 mL) to afford 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (950 mg) as an off-white solid which was used for the next step without further purification. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ 8.34 (bs, 2H), 7.90-7.89 (m, 1H), 6.88-6.87 (m, 1H), 6.50 (s, 1H), 4.26 (d, 2H), 4.02 (s, 3H), 3.40-3.39 (m, 1H), 3.24-3.19 (m, 2H), 2.06-2.04 (m, 2H), 1.60-1.54 (m, 2H); LC-MS: 208.1 (M+1); (column; X-Bridge C-18 (50 x 3.0

mm, 3.5 μ); RT 0.52 min. 0.05% aq TFA: ACN; 0.80 mL/min) TLC: 5% MeOH:CH₂Cl₂ (R_f, 0.1).

Example 2

Synthesis of 1-(2-chloropyridin-4-yl) piperidin-4-amine hydrochloride



Synthesis of tert-Butyl (4-(2-chloropyridin-4-yl) cyclohexyl) carbamate

[0173] To a stirred solution of 2-chloro-4-fluoropyridine (1.5 g, 11.40 mmol) in NMP (15 mL) was added tert-Butyl piperidin-4-ylcarbamate (2.7 g, 13.68 mmol) and DIPEA (1.9 mL, 14.82 mmol) and purged under an argon atmosphere for 15 min. The reaction mixture was heated 150 °C and stirred for 2 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 50% EtOAc:hexanes to afford *tert*-butyl (4-(2-chloropyridin-4-yl) cyclohexyl) carbamate (2.3 g, 65%) as a brown solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.90-7.89 (m, 1H), 6.83-6.79 (m, 2H), 3.85 (d, 2H), 3.49 (br s, 1H), 2.94 (t, 2H), 1.76-1.73 (m, 2H), 1.37 (s, 9H), 1.33-1.30 (m, 3H); LC-MS: 312 (M+1); (column; X-Bridge C-18 (50 $\times$ 3.0 mm, 3.5 μ m); RT 2.55 min. 0.05% aq TFA in water: ACN; 0.80 mL/min); TLC: 30% EtOAc:hexanes (R_f, 0.2).

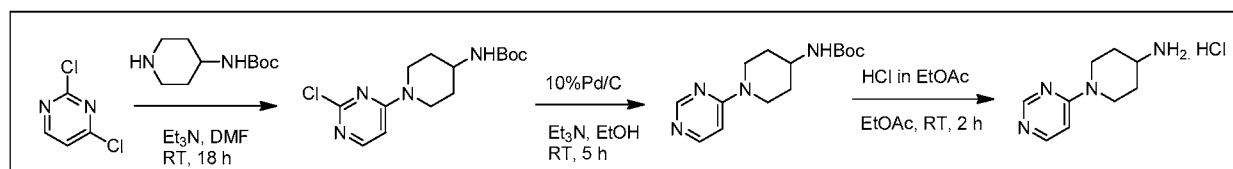
Synthesis of 1-(2-chloropyridin-4-yl) piperidin-4-amine hydrochloride

[0174] To a stirred solution of *tert*-Butyl (4-(2-chloropyridin-4-yl) cyclohexyl) carbamate (2.1 g, 3.20 mmol) in EtOAc (25 mL) was added 4M HCl-EtOAc (4 mL) at 0 °C. The reaction was warmed to RT and stirred for 2 h. After consumption of the starting materials (monitored by TLC), the mixture was neutralized with a saturated NaHCO₃ solution (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over

sodium sulfate, filtered and concentrated *in vacuo* to afford 1-(2-chloropyridin-4-yl) piperidin-4-amine hydrochloride (950 mg, 67%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.99-7.97 (m, 2H), 7.95-7.94 (m, 1H), 6.88 (s, 1H), 6.86-6.85 (m, 1H), 3.99 (d, 2H), 3.31-3.29 (m, 1H), 2.96 (t, 2H), 1.91 (d, 2H), 1.47-1.45 (m, 2H); LC-MS: 212.2 (M+1); (column; Eclipse XDB C18 (150 × 4.6 mm, 5 μm); RT 7.92 min. 0.05% aq TFA: ACN; 1.00 mL/min); TLC: 50% EtOAc:hexanes (*R*_f 0.1).

Example 3

Synthesis of 1-(pyrimidin-4-yl) piperidin-4-amine hydrochloride



Synthesis of *tert*-butyl (1-(2-chloropyrimidin-4-yl) piperidin-4-yl) carbamate

[0175] To a stirred solution of 2, 4-dichloropyrimidine (2 g, 13.42 mmol) in DMF (20 mL) was added triethyl amine (2.03 g, 20.13 mmol) and *tert*-butyl piperidin-4-ylcarbamate (2.9 g, 14.76 mmol). The reaction mixture was stirred for 18 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified through silica gel column chromatography using 50% EtOAc:hexanes to afford *tert*-butyl (1-(2-chloropyrimidin-4-yl) piperidin-4-yl) carbamate (2.2 g, 53%) as an off-white solid. ¹H-NMR (CDCl₃, 400 MHz): δ 8.03-8.02 (m, 1H), 6.40-6.39 (m, 1H), 4.49-4.29 (m, 3H), 3.74 (br s, 1H), 3.09-3.02 (m, 2H), 2.07-2.04 (m, 2H), 1.50 (s, 9H), 1.38-1.25 (m, 2H); LC-MS: 313.2 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 3.21 min. 5 mM NH₄OAc: ACN; 0.80 mL/min); TLC: 50% EtOAc:hexanes (*R*_f 0.6).

Synthesis of *tert*-butyl (1-(pyrimidin-4-yl) piperidin-4-yl) carbamate

[0176] To a stirred solution of *tert*-butyl (1-(2-chloropyrimidin-4-yl) piperidin-4-yl) carbamate (2 g, 6.39 mmol) in EtOH (300 mL) was added 10% Pd/C (300 mg) and

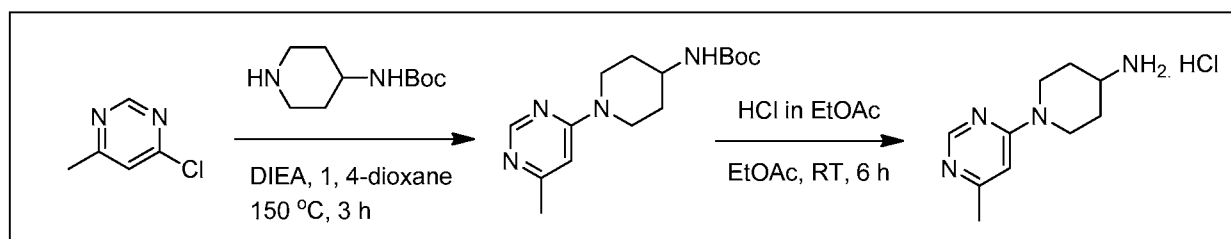
triethylamine (646 mg, 6.39 mmol). The reaction mixture was stirred for 5 h under a H₂ atmosphere (balloon pressure). After consumption of the starting materials (monitored by TLC), the mixture was filtered through celite and concentrated *in vacuo*. The crude material was purified through silica gel column chromatography using 50% EtOAc:hexanes to afford *tert*-butyl (1-(pyrimidin-4-yl) piperidin-4-yl) carbamate (1 g, 56%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.45 (s, 1H), 8.14-8.12 (m, 1H), 6.85-6.80 (m, 2H), 4.28-4.25 (m, 2H), 3.54 (br s, 1H), 3.02-2.95 (m, 2H), 1.79-1.76 (m, 2H), 1.35 (s, 9H), 1.32-1.23 (m, 2H); LC-MS: 279 (M+1); (column; X-Bridge C18 (50 × 3.0 mm, 3.5 μm); RT 2.83 min. 5 mM NH₄OAc: ACN; 0.80 mL/min); TLC: 50% EtOAc:hexanes (R_f 0.2).

Synthesis of 1-(pyrimidin-4-yl) piperidin-4-amine hydrochloride

[0177] To a stirred solution of *tert*-butyl (1-(pyrimidin-4-yl) piperidin-4-yl) carbamate (1 g, 3.59 mmol) in EtOAc (10 mL) was added 4M HCl in EtOAc (2 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. After consumption of the starting materials (monitored by TLC), the mixture was filtered through celite and concentrated *in vacuo* to afford 1-(pyrimidin-4-yl) piperidin-4-amine hydrochloride (700 mg, 94%) as a brown solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.8 (s, 1H), 8.35-8.33 (m, 2H), 7.24-7.22 (m, 1H), 4.14-4.12 (m, 2H), 3.40-3.30 (m, 3H), 2.11-2.06 (m, 2H), 1.62-1.54 (m, 2H); LC-MS: 179.2 (M+1); (column; Deltapak C-4 (150 × 3.9 mm, 5 μm); RT 2.02 min. 0.05% aq TFA: ACN; 1.00 mL/min). TLC: 10% MeOH:DCM (R_f 0.1).

Example 4

Synthesis of 1-(6-methylpyrimidin-4-yl) piperidin-4-amine hydrochloride



Synthesis of tert-butyl (1-(6-methylpyrimidin-4-yl) piperidin-4-yl) carbamate

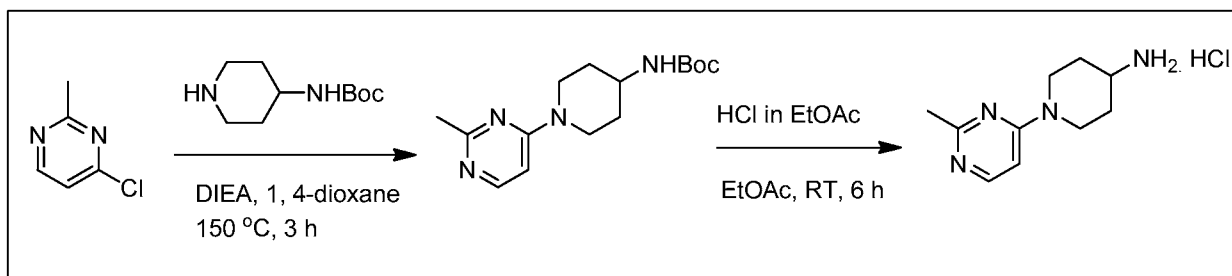
[0178] To a stirred solution of 4-chloro-6-methylpyrimidine (1 g, 7.77 mmol) in 1, 4-dioxane (30 mL) was added diisopropylethylamine (1.35 g, 10.50 mmol) and tert-butyl piperidin-4-ylcarbamate (1.7 g, 8.55 mmol). The reaction mixture was heated to 150 °C and stirred for 3 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified through silica gel column chromatography using 5% MeOH:DCM to afford *tert*-butyl (1-(6-methylpyrimidin-4-yl) piperidin-4-yl) carbamate (1.75 g, 77%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.34 (s, 1H), 6.69 (s, 1H), 4.28-4.24 (m, 2H), 3.54-3.52 (m, 1H), 3.00-2.93 (m, 2H), 2.23 (s, 3H), 1.77-1.75 (m, 2H), 1.38 (s, 9H), 1.30-1.22 (m, 3H); LC-MS: 293.3 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 3.32 min. 5 mM NH₄OAc: ACN; 0.80 mL/min); TLC: 50% EtOAc:hexanes (R_f 0.2).

Synthesis of 1-(6-methylpyrimidin-4-yl) piperidin-4-amine hydrochloride

[0179] To a stirred solution of *tert*-butyl (1-(6-methylpyrimidin-4-yl) piperidin-4-yl) carbamate (1.75 g, 5.13 mmol) in EtOAc (5 mL) was added 4M HCl in EtOAc (4.5 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 6 h. After consumption of the starting materials (monitored by TLC), the mixture was filtered through celite and concentrated *in vacuo* to afford 1-(6-methylpyrimidin-4-yl) piperidin-4-amine hydrochloride (1.1 g, 84%) as a brown solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.76 (s, 1H), 8.42 (bs, 2H), 7.19 (br s, 1H), 4.86-4.36 (m, 2H), 3.4-3.25 (m, 3H), 2.40 (s, 3H), 2.11-2.09 (m, 2H), 1.59-1.56 (m, 2H); LC-MS: 193.2 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 2.13 min. 5 mM NH₄OAc: ACN; 0.80 mL/min); TLC: 50% EtOAc:hexanes (R_f 0.1).

Example 5

Synthesis of 1-(2-methylpyrimidin-4-yl) piperidin-4-amine hydrochloride



Synthesis of tert-butyl (1-(2-methylpyrimidin-4-yl) piperidin-4-yl) carbamate

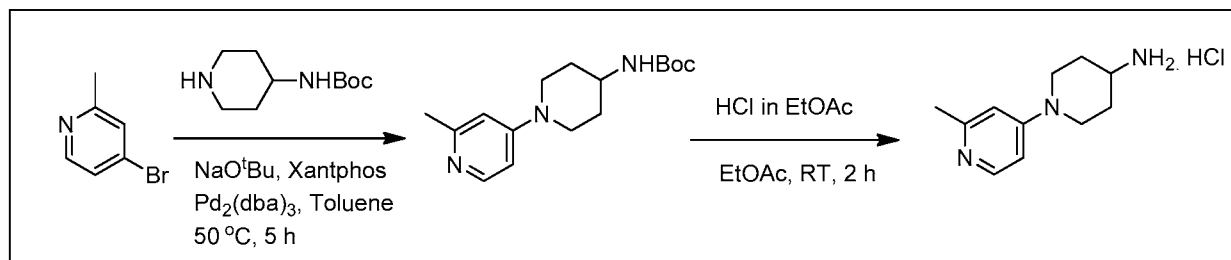
[0180] To a stirred solution of 4-chloro-2-methylpyrimidine (1 g, 7.77 mmol) in 1, 4-dioxane (30 mL) was added diisopropylethylamine (1.35 g, 10.50 mmol) and *tert*-butyl piperidin-4-ylcarbamate (1.7 g, 8.55 mmol). The reaction mixture was heated to 150 °C and stirred for 3 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified through silica gel column chromatography using 5% MeOH:DCM to afford *tert*-butyl (1-(2-methylpyrimidin-4-yl) piperidin-4-yl) carbamate (1.5 g, 66%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 8.04-8.02 (m, 1H), 6.83-6.82 (m, 1H), 6.61-6.60 (m, 1H), 4.27-4.25 (m, 2H), 3.51 (s, 1H), 2.96-2.91 (m, 2H), 2.33 (s, 3H), 1.77-1.74 (m, 2H), 1.37 (s, 9H), 1.28-1.22 (m, 2H); LC-MS: 293.3 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 2.90 min. 5 mM NH₄OAc: ACN; 0.80 mL/min); TLC: 50% EtOAc:hexanes (R_f 0.2).

Synthesis of 1-(2-methylpyrimidin-4-yl) piperidin-4-amine hydrochloride

[0181] To a stirred solution of *tert*-butyl (1-(2-methylpyrimidin-4-yl) piperidin-4-yl) carbamate (2.1 g, 7.18 mmol) in EtOAc (5 mL) was added 4M HCl in EtOAc (5 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 6 h. After consumption of the starting materials (monitored by TLC), the reaction was filtered through celite and concentrated *in vacuo* to afford 1-(2-methylpyrimidin-4-yl) piperidin-4-amine hydrochloride (1 g, 61%) as a brown solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 8.37 (bs, 2H), 8.29 -7.96 (d, 1H), 7.13-7.12 (d, 1H), 4.91-4.89 (m, 1H), 4.30-4.28m (m, 1H), 3.41-3.34 (m, 2H), 3.16-3.14 (m, 1H), 2.52 (s, 3H), 2.10-2.07 (m, 2H), 1.58-1.56 (m, 2H); LC-MS: 193.2 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 2.06 min. 5 mM NH₄OAc: ACN; 0.80 mL/min); TLC: 50% EtOAc:hexanes (R_f 0.1).

Example 6

Synthesis of 1-(2-methylpyridin-4-yl) piperidin-4-amine hydrochloride

*Synthesis of tert-butyl (1-(2-methylpyridin-4-yl) piperidin-4-yl) carbamate*

[0182] To a stirred solution of 4-bromo-2-methylpyridine (2 g, 11.62 mmol) in toluene (200 mL) was added tert-butyl piperidin-4-ylcarbamate (2.56 g, 12.79 mmol), sodium tertiary butoxide (3.35 mg, 34.86 mmol) and Xantphos (403 mg, 0.69 mmol) at 0 °C. The mixture was stirred while purging under an argon atmosphere for 20 min. To the mixture was added Pd₂(dba)₃ (212 mg, 0.23 mmol) and the mixture was purged under an argon atmosphere for 20 min. The reaction mixture was heated to 50 °C and stirred for 5 h. After consumption of the starting materials (monitored by TLC), the reaction was filtered through celite and concentrated *in vacuo*. The crude material was washed with hexane:ether: EtOAc (1: 1: 1, 2 x 30 mL) to afford *tert*-butyl (1-(2-methylpyridin-4-yl) piperidin-4-yl) carbamate (1.4 g, 41%) as a brown solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 8.01-7.99 (m, 1H), 6.83-6.80 (m, 1H), 6.67 (s, 1H), 6.64-6.60 (m, 1H), 3.87-3.79 (m, 2H), 3.53-3.48 (m, 1H), 2.88-2.83 (m, 2H), 2.30 (s, 3H), 1.79-1.73 (m, 2H), 1.40 (s, 9H), 1.29-1.26 (m, 2H); LC-MS: 292.1 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 2.49 min. 5 mM NH₄OAc: ACN; 0.80 mL/min); TLC: 40% EtOAc:hexanes (R_f 0.1).

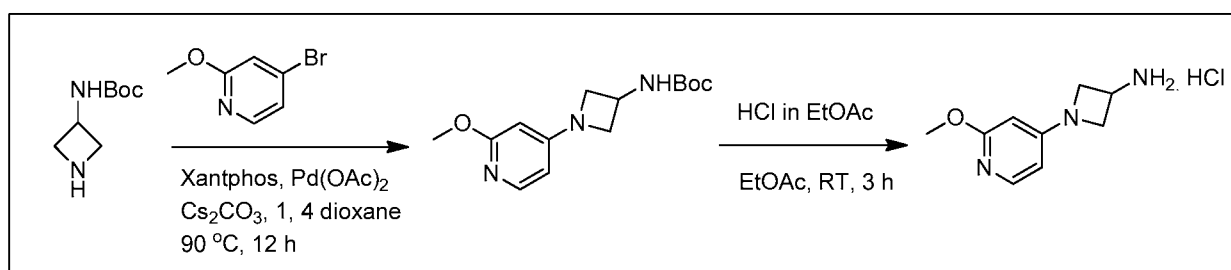
Synthesis of 1-(2-methylpyridin-4-yl) piperidin-4-amine hydrochloride

[0183] To a stirred solution of *tert*-butyl (1-(2-methylpyridin-4-yl) piperidin-4-yl) carbamate (800 mg, 2.74 mmol) in EtOAc (8 mL) was added 4M HCl in EtOAc (2 mL) at 0 °C. The reaction mixture was stirred for 1 h, then warmed to RT and continued to stir for 2 h. After consumption of the starting materials (monitored by TLC), the mixture was concentrated *in vacuo*. The crude material was washed with ether (2 x 20 mL) to afford 1-(2-

methylpyridin-4-yl) piperidin-4-amine hydrochloride (600 mg, 96%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 8.22-8.16 (m, 3H), 7.10-7.07 (m, 2H), 4.21-4.20 (m, 2H), 3.23-2.19 (m, 3H), 2.43 (s, 3H), 2.07-2.02 (m, 2H), 1.57-1.50 (m, 2H); LC-MS: 192.3 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 0.38 min. 5 mM NH₄OAc: ACN; 0.80 mL/min); TLC: 10% MeOH:CH₂Cl₂ (R_f 0.1).

Example 7

Synthesis of 1-(2-methoxypyridin-4-yl)azetidin-3-amine hydrochloride



Synthesis of tert-butyl (1-(2-methoxypyridin-4-yl) azetidin-3-yl) carbamate

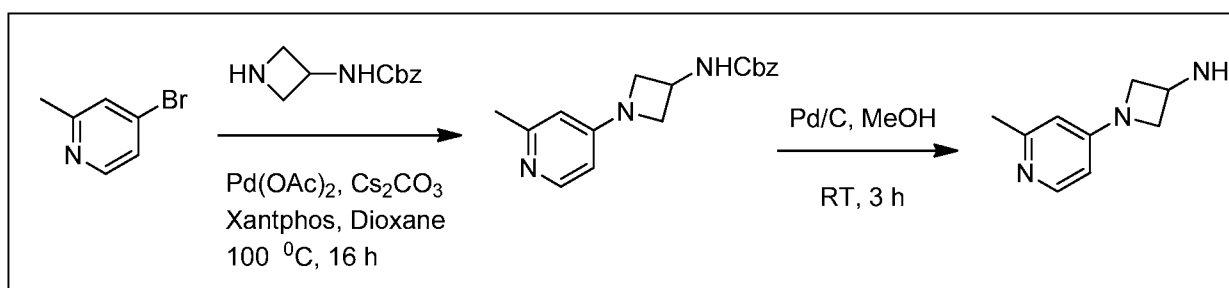
[0184] To a stirred solution of tert-butyl azetidin-3-ylcarbamate (50 mg, 0.29 mmol) in 1,4-dioxane (5 mL) was added 4-bromo-2-methoxypyridine (50 mg, 0.29 mmol), Xantphos (11.7 mg, 0.02 mmol), and cesium carbonate (236 mg, 0.72 mmol). The mixture was purged under an argon atmosphere for 15 min. To the mixture was added Pd(OAc)₂ (1.95 mg, 0.08 mmol) and the reaction mixture was heated to 90 °C and stirred for 12 h. After consumption of the starting materials (monitored by TLC), the mixture was concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 40% EtOAc:hexanes to afford tert-butyl (1-(2-methoxypyridin-4-yl) azetidin-3-yl) carbamate (40 mg, 50%) as an off-white solid. ¹H-NMR (CD₃OD, 400 MHz): δ 7.69-7.67 (m, 1H), 6.09-6.05 (m, 1H), 5.70 (s, 1H), 4.50 (br s, 1H), 4.21-4.19 (m, 2H), 3.80 (s, 3H), 3.75-3.69 (m, 2H), 1.43 (s, 9H); LC-MS: 280.3 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 3.88 min. 5 mM NH₄OAc: ACN; 0.80 mL/min); TLC: 50% EtOAc:hexanes (R_f 0.4).

Synthesis of 1-(2-methoxypyridin-4-yl)azetidin-3-amine hydrochloride

[0185] To a stirred solution of tert-butyl (1-(2-methoxypyridin-4-yl) azetidin-3-yl) carbamate 210 mg, 0.75 mmol) in EtOAc (3 mL) was added 4M HCl in EtOAc (0.2 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 3 h. After consumption of the starting materials (monitored by TLC), the mixture was concentrated *in vacuo* to afford 1-(2-methoxypyridin-4-yl)azetidin-3-amine hydrochloride (200 mg) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 8.99-8.97 (m, 2H), 7.84 (d, 1H), 6.42-6.40 (d, 1H), 6.18 (s, 1H), 4.46-4.40 (m, 2H), 4.29-4.24 (m, 2H), 4.20 (br s, 1H), 4.03 (s, 3H); LC-MS: 180 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 0.49 min. 0.05% TFA in water: ACN; 0.80 mL/min); TLC: 5% MeOH:CH₂Cl₂ (R_f 0.1).

Example 8

Synthesis of 1-(2-methylpyridin-4-yl) azetidin-3-amine



Synthesis of benzyl (1-(2-methylpyridin-4-yl) azetidin-3-yl) carbamate

[0186] To a solution of 4-bromo-2-methylpyridine (598 mg, 2.90 mmol) in 1, 4-dioxane (15 mL) was added benzyl azetidin-3-ylcarbamate (500 mg, 2.90 mmol), Xantphos (132 mg, 0.22 mmol), Pd(OAc)₂ (25.3 mg, 0.11 mmol) and Cs₂CO₃ (2.3 g, 7.26 mmol). The reaction mixture was heated to 100 °C and stirred for 16 h. After consumption of the starting materials (monitored by TLC), the mixture was cooled to RT and concentrated *in vacuo*. The crude material was diluted with water and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed successively with water (10 mL), brine (10 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography to afford benzyl (1-(2-methylpyridin-4-yl) azetidin-3-yl) carbamate (0.35 g, 40%) as a white solid. ¹H-NMR (DMSO *d*₆, 400 MHz): δ 7.96 (d, 2H),

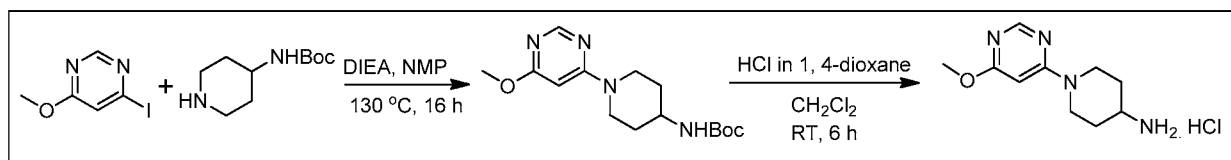
7.38-7.31 (m, 5H), 6.21 (s, 1H), 6.14 (d, 1H), 5.04 (s, 2H), 4.44-4.41 (m, 1H), 4.14 (t, 2H), 3.64 (m, 2H), 2.26 (s, 3H); Mass (ESI): 298 [M+1]; TLC: 30% MeOH:DCM (R_f 0.3).

Synthesis of 1-(2-methylpyridin-4-yl) azetidin-3-amine

[0187] To a stirred solution of benzyl (1-(2-methylpyridin-4-yl) azetidin-3-yl) carbamate (0.35 g, 1.17 mmol) in MeOH (20 mL) was added 10% Pd-C (75 mg). The suspension was stirred for 3 h under H₂ atmosphere (balloon pressure). After consumption of the starting materials (monitored by TLC), the mixture was filtered through celite and washed with MeOH (10 mL). The filtrate was concentrated *in vacuo* to afford 1-(2-methylpyridin-4-yl) azetidin-3-amine (200 mg) as a white solid which was used for the next step without further purification. ¹H-NMR (DMSO d₆, 400 MHz): δ 7.96 (d, 1H), 6.19 (s, 1H), 6.12 (d, 1H), 4.12-4.04 (m, 2H), 3.84-3.81 (m, 1H), 3.48-3.42 (m, 2H), 2.31 (s, 3H); Mass (ESI): 164 [M+1]; TLC: 30% MeOH/DCM (R_f 0.2).

Example 9

Synthesis of 1-(6-methoxypyrimidin-4-yl) piperidin-4-amine hydrochloride



Synthesis of tert-butyl (1-(6-methoxypyrimidin-4-yl) piperidin-4-yl) carbamate

[0188] To a stirred solution of 4-iodo-6-methoxypyrimidine (500 mg, 2.12 mmol) in NMP (5 mL) was added diisopropylethylamine (383 mg, 2.96 mmol) and tert-butyl piperidin-4-ylcarbamate (550 mg, 2.75 mmol) and purged with argon for 15 min. The reaction mixture was heated to 130 °C and stirred for 16 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with ice cold water (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 10-30% EtOAc:hexanes to afford tert-butyl (1-(6-methoxypyrimidin-4-yl) piperidin-4-yl) carbamate (400 mg, 61%) as an off-white solid. ¹H-NMR (DMSO-*d*₆,

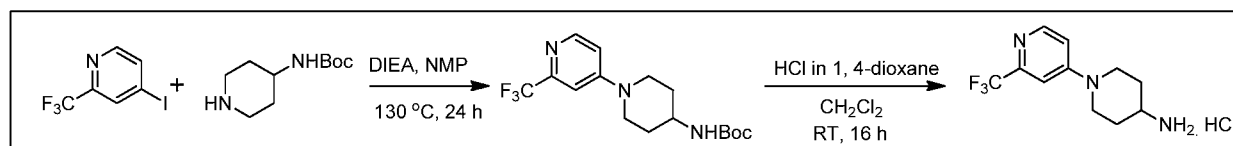
500 MHz): δ 8.22 (s, 1H), 6.84-6.82 (m, 1H), 6.06 (s, 1H), 4.24-4.21 (m, 2H), 3.81 (s, 3H), 3.51 (br s, 1H), 2.94 (t, 2H), 1.75-1.73 (m, 2H), 1.38 (s, 9H), 1.30-1.22 (m, 2H); LC-MS: 308.9 (M+1); (column; X-Select CSH C-18 (50 $\times$ 3.0 mm, 3.5 μ m); RT 2.45 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity BEH C-18 50 X 2.1 mm, 1.7 μ m); RT 1.67 min. ACN: 0.025% Aq TFA; 0.5 mL/min; TLC: 30% EtOAc:hexanes (R_f 0.2).

Synthesis of 1-(6-methoxypyrimidin-4-yl) piperidin-4-amine hydrochloride

[0189] To a stirred solution of tert-butyl (1-(6-methoxypyrimidin-4-yl) piperidin-4-yl) carbamate (300 mg, 0.97 mmol) in CH_2Cl_2 (6 mL) was added 4N HCl in 1, 4-dioxane (10 mL) and the reaction mixture was stirred for 6 h. After consumption of the starting materials (monitored by TLC), the mixture was filtered and the solid was washed successively with CH_2Cl_2 (50 mL) and ether (50 mL) to afford 1-(6-methoxypyrimidin-4-yl) piperidin-4-amine hydrochloride (290 mg, 92%) as a yellow solid. ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ 8.35 (s, 1H), 8.30-8.28 (m, 3H), 6.29 (s, 1H), 4.45-4.42 (m, 2H), 3.90 (s, 3H), 3.35-3.31 (m, 1H), 3.04 (t, 2H), 2.01-1.98 (m, 2H), 1.53-1.43 (m, 2H); LC-MS: 209.2 (M+1); (column; Eclipse XDB C-18 (150 $\times$ 4.6 mm, 5 μ m); RT 4.03 min 0.05% Aq TFA: ACN; 1.0 mL/min); TLC: 30% EtOAc:hexanes (R_f 0.1).

Example 10

Synthesis of 1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-amine hydrochloride



Synthesis of tert-butyl (1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl) carbamate

[0190] To a stirred solution of 4-iodo-2-(trifluoromethyl) pyridine (2 g, 7.32 mmol) in NMP (20 mL) was added diisopropylethylamine (1.32 g, 10.23 mmol) and tert-butyl piperidin-4-ylcarbamate (1.90 g, 9.50 mmol) and purged with argon for 15 min. The reaction mixture was heated to 130 °C and stirred for 24 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with ice cold water (100 mL) and extracted with EtOAc (2 $\times$ 50 mL). The combined organic extracts were dried over sodium sulfate,

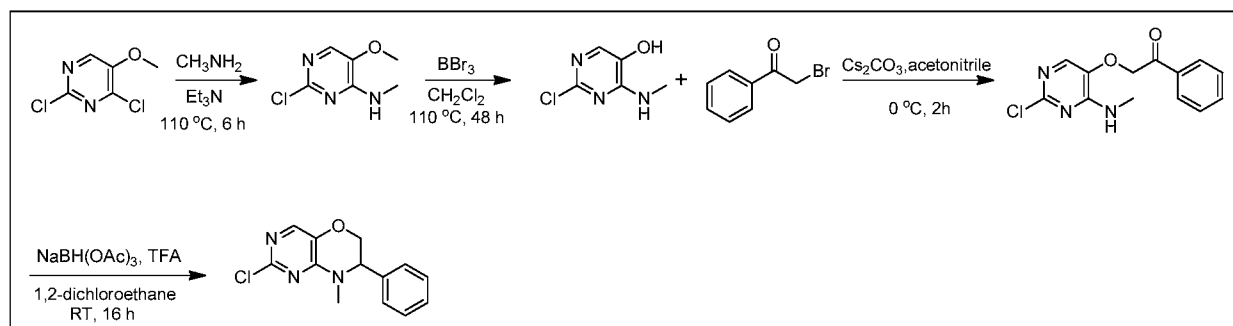
filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 25% EtOAc:hexanes to afford *tert*-butyl (1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl) carbamate (1.7 g, 67%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.23 (d, 1H), 7.18 (s, 1H), 7.02-7.00 (m, 1H), 6.85 (d, 1H), 3.97-3.93 (m, 2H), 3.57-3.50 (m, 1H), 3.00 (t, 2H), 1.80-1.77 (m, 2H), 1.34 (s, 9H), 1.31-1.30 (m, 2H); LC-MS: 346.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.25 min 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 30% EtOAc:hexanes (R_f 0.2).

Synthesis of 1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-amine hydrochloride

[0191] To a stirred solution of *tert*-butyl (1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl) carbamate (1.7 g, 4.92 mmol) in CH₂Cl₂ (20 mL) was added 2M HCl in 1, 4-dioxane (10 mL) and the reaction mixture was stirred for 16 h. After consumption of the starting materials (monitored by TLC), the mixture was concentrated *in vacuo*. The crude material was washed successively with *n*-pentane (2 x 10 mL) and ether (2 x 10 mL) to afford 1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-amine hydrochloride (1 g, 90%) as a yellow solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 8.32-8.30 (m, 3H), 7.35 (s, 1H), 7.16-7.14 (m, 1H), 4.18-4.15 (m, 2H), 3.36-3.32 (m, 1H), 3.10 (t, 2H), 2.02-2.00 (m, 2H), 1.59-1.51 (m, 2H); LC-MS: 246.1 (M+1); (column; Eclipse XDB C-18 (150 × 4.6 mm, 5 μm); RT 5.02, 43.20 min 0.05% Aq TFA: ACN; 1.0 mL/min); TLC: 5% MeOH:CH₂Cl₂ (R_f 0.1).

Example 11

Synthesis of 2-chloro-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine



Synthesis of 2-chloro-5-methoxy-N-methylpyrimidin-4-amine

[0192] To a stirred solution of 2,4-dichloro-5-methoxypyrimidine (5 g, 28.0 mmol) in triethylamine (7.8 mL) under an argon atmosphere was added methyl amine (33% in ethanol, 3.9 mL, 42.1 mmol) in a sealed tube at RT and heated to 110 °C for 6 h. After completion of the reaction (monitored by TLC), the reaction was diluted with water. The resultant solid was filtered, washed with cold water and dried to afford 2-chloro-5-methoxy-N-methylpyrimidin-4-amine (3.85 g, 79%) as a white crystalline solid. LC-MS: 173.8 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 µm); RT 1.51 min. 0.05% Aq TFA: ACN; 0.80 ml/min); TLC: 80% EtOAc:hexanes (R_f 0.3).

Synthesis of 2-chloro-4-(methylamino) pyrimidin-5-ol

[0193] To a stirred solution of 2-chloro-5-methoxy-N-methylpyrimidin-4-amine (6 g, 34.68 mmol) in CH₂Cl₂ (600 mL) under an argon atmosphere at 0 °C was added 1M BBr₃ in CH₂Cl₂ (49.2 mL, 520 mmol). The reaction mixture was warmed to RT and stirred for 48 h. After completion of the reaction (monitored by TLC), the reaction was quenched with methanol (100 mL) and volatile components were concentrated *in vacuo*. To the resultant residue a saturated sodium bicarbonate solution (100 mL) was added and extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-chloro-4-(methylamino) pyrimidin-5-ol (5 g, 92%) as an off-white solid which was used for the next step without further purification. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 10.2 (brs, 1H), 7.39 (s, 1H), 7.21 (br s, 1H), 2.80 (s, 3H); LC-MS: 159.8 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 µm); RT 0.93 min. 0.05% Aq TFA: ACN; 0.80 ml/min); TLC: 90% EtOAc:hexanes (R_f 0.3).

Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-phenylethan-1-one

[0194] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (2.0 g, 12.57 mmol) in acetonitrile (35 mL) under an argon atmosphere at 0 °C were added cesium carbonate (8.2 g, 25.14 mmol) and 2-bromo-1-phenylethan-1-one (2.75 g, 13.8 mmol) and stirred for 2 h. After completion of the reaction (monitored by TLC), the reaction was diluted with water (100 mL) and extracted with EtOAc (2 x 150 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 20-30% EtOAc:hexanes to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-phenylethan-1-one (2.3 g, 66%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.81 (s, 1H), 7.41-7.36 (m, 5H), 7.09 (s, 1H),

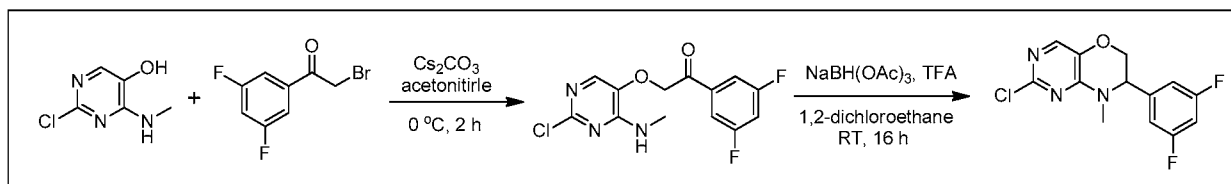
4.13 (d, 1H), 4.00 (d, 1H), 2.78 (s, 3H); LC-MS: 277.9 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 3.25 min. 0.05% TFA in water: ACN; 0.80 ml/min); TLC: 80% EtOAc:hexanes (R_f 0.5).

Synthesis of 2-chloro-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine

[0195] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-phenylethan-1-one (2.0 g, 7.22 mmol) in 1, 2-dichloroethane (40 mL) under an argon atmosphere were added $\text{NaBH}(\text{OAc})_3$ (3.06 g, 14.44 mmol) and trifluoroacetic acid (0.55 mL, 7.22 mmol) at RT and stirred for 16 h. After completion of the reaction (monitored by TLC), the reaction was diluted with a 1N sodium hydroxide solution (50 mL) and extracted with CH_2Cl_2 (2 x 75 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 20-30% EtOAc:hexanes to afford 2-chloro-7-(phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.70 (s, 1H), 7.40-7.36 (m, 3H), 7.19 (d, 2H), 4.60-4.58 (m, 1H), 4.23 (d, 1H), 4.19 (d, 1H), 3.08 (s, 3H); LC-MS: 262.3 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 4.02 min. 0.05% Aq TFA: ACN; 0.80 ml/min); TLC: 60% EtOAc:hexanes (R_f 0.4).

Example 12

Synthesis of 2-chloro-7-(3, 5-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(3, 5-difluorophenyl) ethan-1-one

[0196] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (400 mg, 2.51 mmol) in acetonitrile (8 mL) under an argon atmosphere at 0 °C was added cesium carbonate

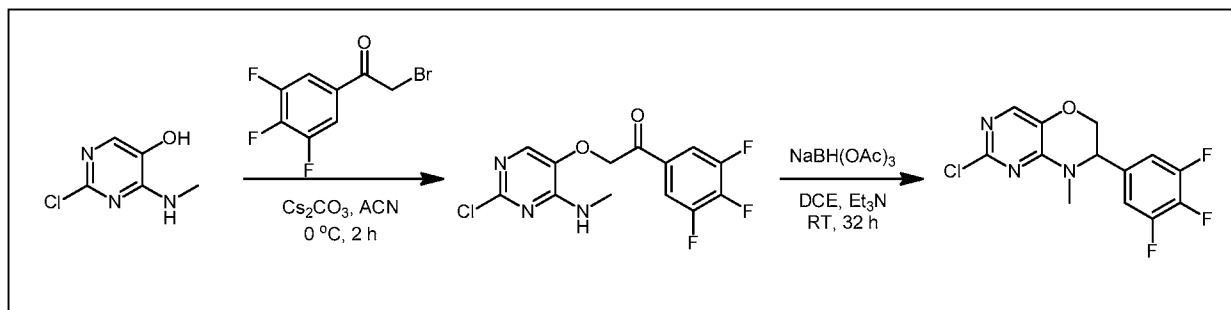
(1.64 g, 5.02 mmol) and 2-bromo-1-(3, 5-difluorophenyl) ethan-1-one (650 mg, 2.76 mmol) and stirred for 2 h. After completion of the reaction (monitored by TLC), the reaction was diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 20-30% EtOAc:hexanes to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(3, 5-difluorophenyl) ethan-1-one (420 mg, 54%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.83 (s, 1H), 7.30-7.27 (m, 2H), 7.19-7.17 (m, 2H), 4.20 (d, 1H), 4.00 (d, 1H), 2.78 (s, 3H). LC-MS: 314.3 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 4.17 min. 0.05% Aq TFA: ACN; 0.80 ml/min); TLC: 60% EtOAc:hexanes (R_f 0.5).

Synthesis of 2-chloro-7-(3, 5-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0197] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(3, 5-difluorophenyl) ethan-1-one (500 mg, 1.59 mmol) in 1, 2-dichloroethane (10 mL) under an argon atmosphere was added NaBH(OAc)₃ (684 mg, 3.18 mmol) and trifluoroacetic acid (0.122 mL, 1.59 mmol) at RT and stirred for 16 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with a 1N sodium hydroxide solution (50 mL) and extracted with CH₂Cl₂ (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-chloro-7-(3, 5-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (370 mg, 78%) as a pale yellow solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.71 (s, 1H), 6.81 (t, 1H), 6.70 (d, 2H), 4.55-4.54 (m, 1H), 4.25-4.19 (m, 2H), 3.10 (s, 3H); LC-MS: 298 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.13 min. 0.05% Aq TFA: ACN; 0.80 ml/min); TLC: 60% EtOAc:hexanes (R_f 0.4).

Example 13

Synthesis of 2-chloro-8-methyl-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(3, 4, 5-trifluorophenyl) ethan-1-one

[0198] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (630 mg, 3.95 mmol) in acetonitrile (5 mL) under an argon atmosphere at 0 °C were added cesium carbonate (1.4 g, 4.13 mmol) and 2-bromo-1-(3, 4, 5-trifluorophenyl) ethan-1-one (1.1 g, 4.3 mmol) and stirred for 2 h. After completion of the reaction (monitored by TLC), the reaction was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with water (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 15% EtOAc:hexanes to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(3, 4, 5-trifluorophenyl) ethan-1-one (430 mg, 66%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.82 (s, 1H), 7.42-7.35 (m, 2H), 7.30 (s, 1H), 4.20 (d, 1H), 4.01 (d, 1H), 2.70 (s, 3H); TLC: 30% EtOAc:hexanes (*R_f* 0.5).

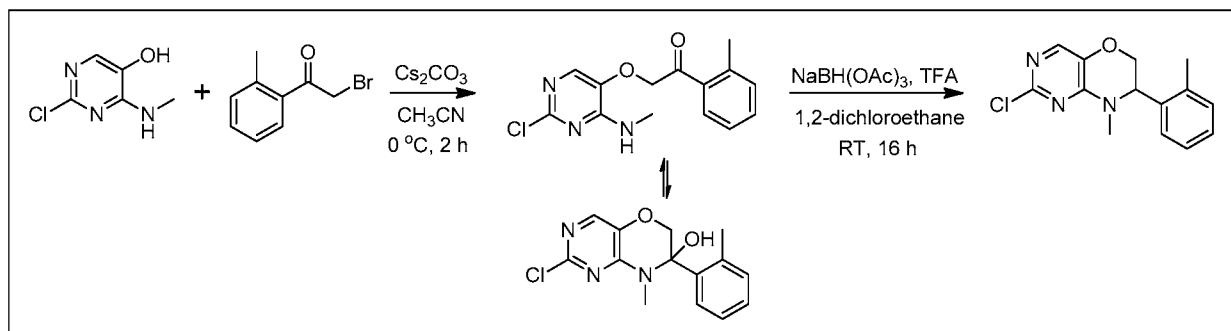
Synthesis of 2-chloro-8-methyl-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0199] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(3, 4, 5-trifluorophenyl) ethan-1-one (480 mg, 1.45 mmol) in 1,2-dichloroethane (8 mL) under an argon atmosphere was added NaBH(OAc)₃ (614 mg, 2.90 mmol) and trifluoroacetic acid (0.11 mL, 1.45 mol) at 0 °C. The reaction mixture was warmed to RT and stirred for 32 h. After completion of the reaction (monitored by TLC), the reaction was quenched with a 1N sodium hydroxide solution (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was washed with ether (2 x 10 mL) to afford 2-chloro-8-methyl-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (300 mg, 66%) as an off-

white solid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.74 (s, 1H), 6.84-6.80 (m, 2H), 4.52-4.51 (m, 1H), 4.25-4.16 (m, 2H), 3.12 (s, 3H); LC-MS: 316.2 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 4.31 min. 0.05% Aq TFA: ACN; 0.80 ml/min); TLC: 30% EtOAc:hexanes (R_f 0.3).

Example 14

Synthesis of 2-chloro-8-methyl-7-(*o*-tolyl)-7,8-dihydro-6H-pyrimido[5,4-*b*][1,4]oxazine



Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(*o*-tolyl) ethan-1-one

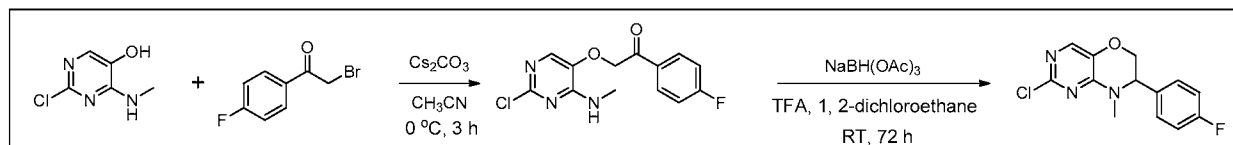
[0200] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (100 mg, 0.62 mmol) in CH_3CN (2 mL) under an argon atmosphere at 0°C were added cesium carbonate (409 mg, 1.25 mmol) and 2-bromo-1-(*o*-tolyl) ethan-1-one (120 mg, 0.69 mmol) and stirred for 2 h. After completion of reaction (monitored by TLC), the reaction was diluted with a saturated sodium bicarbonate solution (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 20-50% EtOAc:hexanes to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(*o*-tolyl) ethan-1-one (120 mg, 66%) as an off-white solid. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 7.87 (s, 1H), 7.52 (d, 1H), 7.30-7.19 (m, 3H), 7.08 (s, 1H), 4.25 (d, 1H), 3.95 (d, 1H), 2.79 (s, 3H), 2.30 (s, 3H); TLC: 60% EtOAc:hexanes (R_f 0.4).

Synthesis of 2-chloro-8-methyl-7-(*o*-tolyl)-7,8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazine

[0201] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(*o*-tolyl) ethan-1-one (1 g, 3.43 mmol) in 1, 2-dichloroethane (20 mL) under an argon atmosphere was added NaBH(OAc)₃ (1.45 g, 6.87 mmol) and trifluoroacetic acid (0.26 mL, 3.43 mmol) at RT and stirred for 16 h. After completion of reaction (monitored by TLC), the mixture was diluted with a 1N sodium hydroxide solution (100 mL) and extracted with CH₂Cl₂ (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 10-20% EtOAc:hexanes to afford 2-chloro-8-methyl-7-(*o*-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (700 mg, 74%) as a pale yellow solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.80 (s, 1H), 7.25-7.19 (m, 3H), 6.97 (d, 1H), 4.88-4.86 (m, 1H), 4.27-4.23 (m, 1H), 4.12-4.09 (m, 1H), 3.03 (s, 3H), 2.40 (s, 3H); LC-MS: 276.3 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 4.28 min. 0.05% Aq TFA:ACN; 0.80 ml/min); TLC: 60% EtOAc:hexanes (R_f 0.5).

Example 15

Synthesis of 2-chloro-7-(4-fluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluorophenyl) ethan-1-one

[0202] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (1.5 g, 9.43 mmol) in CH₃CN (20 mL) was added cesium carbonate (6.1 g, 18.86 mmol) and stirred for 10 min at 0 °C. 2-Bromo-1-(4-fluorophenyl) ethan-1-one (2.25 g, 10.37 mmol) was added and the reaction mixture was stirred for 3 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with water (30 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was washed with ether: *n*-

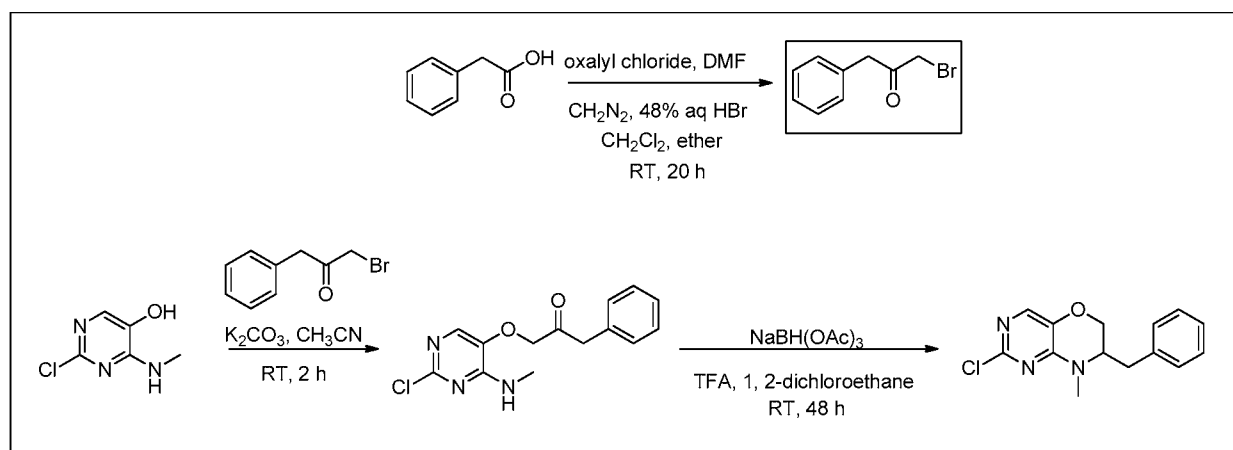
hexane (1: 1, 2 x 5 mL) to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluorophenyl) ethan-1-one (2 g, 71%) as an off-white solid. TLC: 40% EtOAc:hexanes (R_f 0.6).

Synthesis of 2-chloro-7-(4-fluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0203] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluorophenyl) ethan-1-one (2 g, 6.75 mmol) in 1, 2-dichloroethane (20 mL) was added trifluoroacetic acid (770 mg, 6.75 mmol) and stirred for 10 min. Sodium triacetoxymethylborohydride (2.86 g, 13.51 mmol) was added and the reaction mixture was stirred for 72 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with a 1N sodium hydroxide solution (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 20% EtOAc:hexanes to afford 2-chloro-7-(4-fluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (1.8 g, 96%) as a pale yellow oil. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.70 (s, 1H), 7.18-7.02 (m, 4H), 4.53-4.51 (m, 1H), 4.22-4.20 (m, 1H), 4.12-4.08 (m, 1H), 3.08 (s, 3H); LC-MS: 279.8 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 3.53 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 40% EtOAc:hexanes (R_f 0.6).

Example 16

Synthesis of 7-benzyl-2-chloro-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 1-bromo-3-phenylpropan-2-one

[0204] To a stirred solution of 2-phenylacetic acid (5 g, 36.76 mmol) in CH₂Cl₂ (50 mL) was added oxalyl chloride (4.6 g, 36.76 mmol) and DMF (2 drops) at 0 °C. The reaction mixture was warmed to RT and continued to stir for 2 h. After consumption of acid (monitored by TLC), the mixture was concentrated *in vacuo*. The crude material was dissolved in ether and cooled to 0 °C. A solution of CH₂N₂ in ether was added and the reaction mixture was warmed to RT and stirred for 2 h. After consumption of the starting materials (monitored by TLC), the mixture was concentrated *in vacuo*. To a stirred solution of the crude material in THF (20 mL) was added a solution of 48% aq HBr (5 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 20 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with a sodium bicarbonate solution (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed successively with a sodium bicarbonate solution (50 mL) and water (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 1-bromo-3-phenylpropan-2-one (6 g, 76%) as a viscous oil. ¹H-NMR (CDCl₃, 400 MHz): δ 7.38-7.30 (m, 3H), 7.27-7.20 (m, 2H), 3.92 (s, 2H), 3.89 (s, 2H); TLC: 10% EtOAc:hexanes (R_f 0.6).

Synthesis of 1-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-3-phenylpropan-2-one

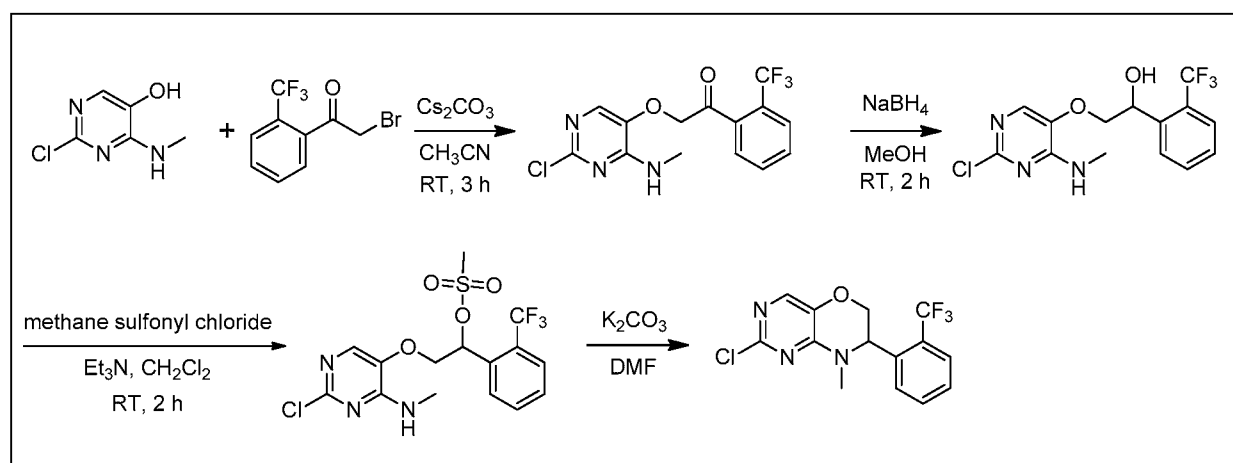
[0205] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (3 g, 18.8 mmol) in acetonitrile (30 mL) was added potassium carbonate (12.2 g, 37.60 mmol) followed by 1-bromo-3-phenylpropan-2-one (4.4 g 20.70 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with ice cold water (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was triturated with n-hexane:CH₂Cl₂ (1:1, 2 x 50 mL) to afford 1-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-3-phenylpropan-2-one (3 g, 55%) as a pale brown solid. ¹H-NMR (CDCl₃, 500 MHz): δ 7.70 (s, 1H), 7.39-7.30 (m, 3H), 7.29-7.27 (m, 2H), 4.02 (d, 1H), 2.62 (d, 1H), 3.21 (d, 1H), 3.19 (s, 3H), 2.96 (d, 1H); LC-MS: 291.9 (M⁺); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.37 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 30% EtOAc:hexanes (R_f 0.8).

Synthesis of 7-benzyl-2-chloro-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0206] To a stirred solution of 1-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-3-phenylpropan-2-one (3 g, 10.3 mmol) in 1, 2-dichloroethane (30 mL) under argon was added trifluoroacetic acid (1.1 g, 10.31 mmol) at 0 °C and stirred for 10 min. Sodium triacetoxymethylborohydride (4.3 g, 20.62 mmol) was added and the reaction mixture was stirred for 48 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with 1 N sodium hydroxide (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 20% EtOAc:hexanes to afford 7-benzyl-2-chloro-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (1.6 g, 57%) as a white solid. ¹H-NMR (CDCl₃, 500 MHz): δ 7.70 (s, 1H), 7.38-7.34 (m, 2H), 7.32-7.28 (m, 1H), 7.28 (d, 2H), 4.10 (d, 1H), 3.81 (d, 1H), 3.60-3.58 (m, 1H), 3.14 (s, 3H), 3.10-3.07 (m, 1H), 2.81-2.78 (m, 1H); LC-MS: 275.8 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.61 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 30% EtOAc:hexanes (R_f 0.5).

Example 17

Synthesis of 2-chloro-8-methyl-7-(2-(trifluoromethyl) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-(trifluoromethyl) phenyl) ethan-1-one

[0207] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (100 mg, 0.62 mmol) in CH₃CN (2 mL) was added cesium carbonate (409 mg, 1.25 mmol) and 2-bromo-1-(2-(trifluoromethyl) phenyl) ethan-1-one (184 mg, 0.69 mmol) and the reaction mixture was stirred for 3 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 10% EtOAc:hexanes to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-(trifluoromethyl) phenyl) ethan-1-one (100 mg, 46%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.03 (d, 1H), 7.90 (d, 1H), 7.89-7.79 (m, 2H), 7.69 (s, 1H), 7.48-7.40 (m, 1H), 5.55 (s, 2H), 2.83 (d, 3H); LC-MS: 345.8 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.41 min. 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 50% EtOAc: hexanes (R_f 0.7).

Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-(trifluoromethyl) phenyl) ethan-1-ol

[0208] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-(trifluoromethyl) phenyl) ethan-1-one (400 mg, 1.15 mmol) in MeOH (4 mL) was added sodium borohydride (64 mg, 1.73 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 10% EtOAc:hexanes to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-(trifluoromethyl) phenyl) ethan-1-ol (250 mg, 62%) as an off-white solid. LC-MS: 347.8 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.30 min. 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 30% EtOAc:hexanes (R_f 0.6).

Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-(trifluoromethyl) phenyl) ethyl methanesulfonate

[0209] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-(trifluoromethyl) phenyl) ethan-1-ol (550 mg, 1.58 mmol) in CH₂Cl₂ (6 mL) was added successively triethyl amine (0.26 mL, 1.90 mmol) and methane sulfonyl chloride (180 mg, 1.58 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h.

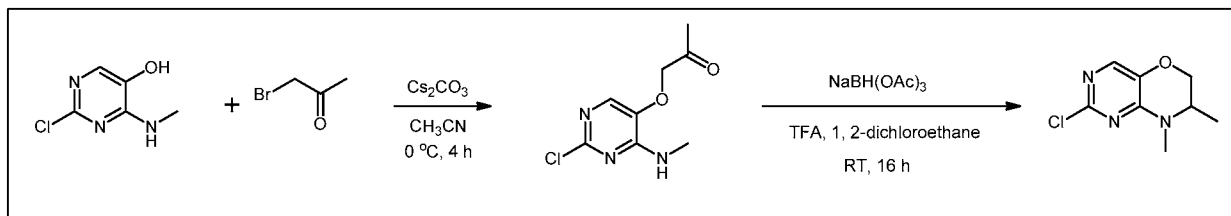
After consumption of the starting materials (monitored by TLC), the mixture was filtered. The filtrate was diluted with water (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was recrystallized from diisopropylether (2 x 5 mL) to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-(trifluoromethyl) phenyl) ethyl methanesulfonate (500 mg, 74%) as an off-white solid. LC-MS: 425.7 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.63 min. 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 40% EtOAc:hexanes (R_f 0.6).

Synthesis of 2-chloro-8-methyl-7-(2-(trifluoromethyl) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0210] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-(trifluoromethyl) phenyl) ethyl methanesulfonate (650 mg, 1.52 mmol) in DMF (6 mL) was added potassium carbonate (316 mg, 2.29 mmol). The reaction mixture was heated to 80 °C and stirred for 2 h. After consumption of the starting materials (monitored by TLC), the mixture was concentrated *in vacuo*. The crude material was dissolved in water (50 mL) and extracted with ether (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 10% EtOAc:hexanes to afford 2-chloro-8-methyl-7-(2-(trifluoromethyl) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (100 mg, 19%) as an off-white solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.77-7.71 (m, 2H), 7.59-7.51 (m, 1H), 7.49-7.45 (m, 1H), 7.19 (d, 1H), 5.02-5.00 (m, 1H), 4.30-4.25 (m, 1H), 4.18-4.12 (m, 1H), 3.02 (s, 3H); LC-MS: 330.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.55 min. 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 40% EtOAc:hexanes (R_f 0.7).

Example 18

Synthesis of 2-chloro-7, 8-dimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 1-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) propan-2-one

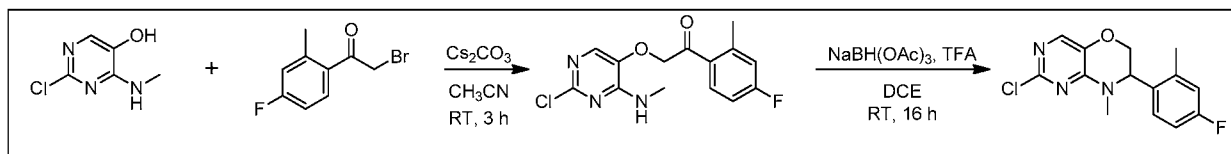
[0211] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (200 mg, 1.25 mmol) in CH₃CN (4 mL) was added successively 1-bromopropan-2-one (243 mg, 1.38 mmol) and cesium carbonate (815 mg, 2.50 mmol) at 0 °C and stirred for 4 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with a saturated sodium carbonate solution (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 15-20% EtOAc:hexanes to afford 1-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) propan-2-one (220 mg, 82%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.70 (s, 1H), 6.41 (s, 1H), 4.01 (d, 1H), 3.89 (d, 1H), 3.00 (s, 3H), 1.38 (s, 3H); LC-MS: 216(M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.18 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 60% EtOAc:hexanes (R_f 0.2).

Synthesis of 2-chloro-7, 8-dimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0212] To a stirred solution of 1-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) propan-2-one (200 mg, 0.93 mmol) in 1, 2-dichloroethane (4 mL) was added sodium triacetoxymethylborohydride (395 mg, 1.86 mmol) followed by trifluoroacetic acid (0.07 mL, 0.93 mmol) and stirred for 16 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with 1 N sodium hydroxide (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 10-15% EtOAc:hexanes to afford 2-chloro-7, 8-dimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (110 mg, 59%) as an off-white solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.63 (s, 1H), 4.01 (s, 2H), 3.61-3.58 (m, 1H), 3.14 (s, 3H), 1.31 (d, 3H); LC-MS: 200 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.49 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 60% EtOAc:hexanes (R_f 0.4).

Example 19

Synthesis of 2-chloro-7-(4-fluoro-2-methylphenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluoro-2-methylphenyl) ethan-1-one

[0213] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (100 mg, 0.62 mmol) in CH₃CN (2 mL) was added cesium carbonate (409 mg, 1.25 mmol) followed by 2-bromo-1-(4-fluoro-2-methylphenyl) ethan-1-one (159 mg, 0.69 mmol) and stirred for 3 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluoro-2-methylphenyl) ethan-1-one (120 mg, 62%) as an off-white solid. LC-MS: 309.8 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.35 min. 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 30% EtOAc:hexanes (R_f 0.7).

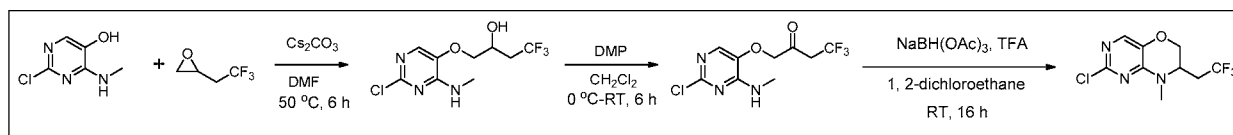
Synthesis of 2-chloro-7-(4-fluoro-2-methylphenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0214] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluoro-2-methylphenyl) ethan-1-one (150 mg, 0.48 mmol) in 1, 2-dichloroethane (2 mL) was added sodium triacetoxyborohydride (205 mg, 0.97 mmol) followed by trifluoroacetic acid (0.1 mL, 0.48 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 16 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with a 1N sodium hydroxide (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-chloro-7-(4-fluoro-2-methylphenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4]

oxazine and used without further purification. LC-MS: 294 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.31 min. 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 30% EtOAc:hexanes (R_f 0.3).

Example 20

Synthesis of 7-chloro-1-methyl-2-(2, 2, 2-trifluoroethyl)-2, 3-dihydro-1H-pyrido [3, 4-b] [1, 4] oxazine



Synthesis of 1-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-4, 4, 4-trifluorobutan-2-ol

[0215] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (200 mg, 1.25 mmol) in DMF (5 mL) was added cesium carbonate (810 mg, 0.50 mmol) followed by 2-(2, 2, 2-trifluoroethyl) oxirane (160 mg, 1.25 mmol). The reaction mixture was heated to 50 °C and stirred for 6 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 20-30% EtOAc:hexanes to afford 1-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-4, 4, 4-trifluorobutan-2-ol (220 mg, 62%) as an off-white solid. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.53 (s, 1H), 5.68 (br s, 1H), 4.43-4.39 (m, 1H), 4.02-3.99 (m, 2H), 3.04 (s, 3H), 2.90 (br s, 1H), 2.54-2.38 (m, 2H); LC-MS: 285.8 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.63 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 20% EtOAc:hexanes (R_f 0.6).

Synthesis of 1-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-4, 4, 4-trifluorobutan-2-one

[0216] To a stirred solution of 1-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-4, 4, 4-trifluorobutan-2-ol (400 mg, 1.40 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinone (893 mg, 2.10 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 6 h. After consumption of the starting materials (monitored by TLC), the mixture

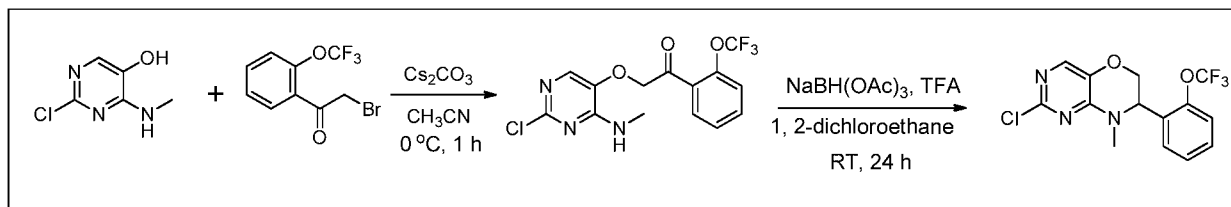
was diluted with a saturated sodium bicarbonate solution (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were washed with a sodium thiosulfate solution (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 30% EtOAc:hexanes to afford 1-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-4, 4, 4-trifluorobutan-2-one (220 mg, 55%) as a pale yellow solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.70 (s, 1H), 4.31 (d, 1H), 4.00 (d, 1H), 3.18 (s, 3H), 2.78-2.63 (m, 2H); LC-MS: 284.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.60 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 40% EtOAc:hexanes (R_f 0.4).

Synthesis of 7-chloro-1-methyl-2-(2, 2, 2-trifluoroethyl)-2, 3-dihydro-1H-pyrido [3, 4-b] [1, 4] oxazine

[0217] To a stirred solution of 1-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-4, 4, 4-trifluorobutan-2-one (200 mg, 0.70 mmol) in 1, 2-dichloroethane (4 mL) was added sodium triacetoxymethylborohydride (300 mg, 1.41 mmol) followed by trifluoroacetic acid (80 mg, 0.70 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 16 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with a 1N sodium hydroxide solution (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 15-20% EtOAc:hexanes to afford 7-chloro-1-methyl-2-(2, 2, 2-trifluoroethyl)-2, 3-dihydro-1H-pyrido [3, 4-b] [1, 4] oxazine (90 mg, 48%) as an off-white solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.72 (s, 1H), 4.32 (d, 1H), 4.02 (d, 1H), 3.83-3.79 (m, 1H), 3.21 (s, 3H), 2.60-2.40 (m, 2H); LC-MS: 268 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.77 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 50% EtOAc:hexanes (R_f 0.4).

Example 21

Synthesis of 2-chloro-8-methyl-7-(2-(trifluoromethoxy) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-(trifluoromethoxy) phenyl) ethan-1-one

[0218] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (300 mg, 1.88 mmol) in CH₃CN (10 mL) was added cesium carbonate (1.22 g, 0.37 mmol) followed by 2-bromo-1-(2-(trifluoromethoxy) phenyl) ethan-1-one (580 mg, 0.20 mmol) at 0 °C and stirred for 1 h. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 10% EtOAc:hexanes to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-(trifluoromethoxy) phenyl) ethan-1-one (350 mg, 51%) as an off white solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.88 (s, 1H), 7.77 (d, 1H), 7.58 (d, 1H), 7.46 (t, 1H), 7.41 (d, 1H), 7.50 (s, 1H), 4.21 (d, 1H), 4.11 (d, 1H), 2.79 (s, 3H); LC-MS: 362.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.25 min. 0.05% Aq TFA: ACN; 0.80 ml/min); TLC: 40% EtOAc:hexanes (*R_f* 0.7).

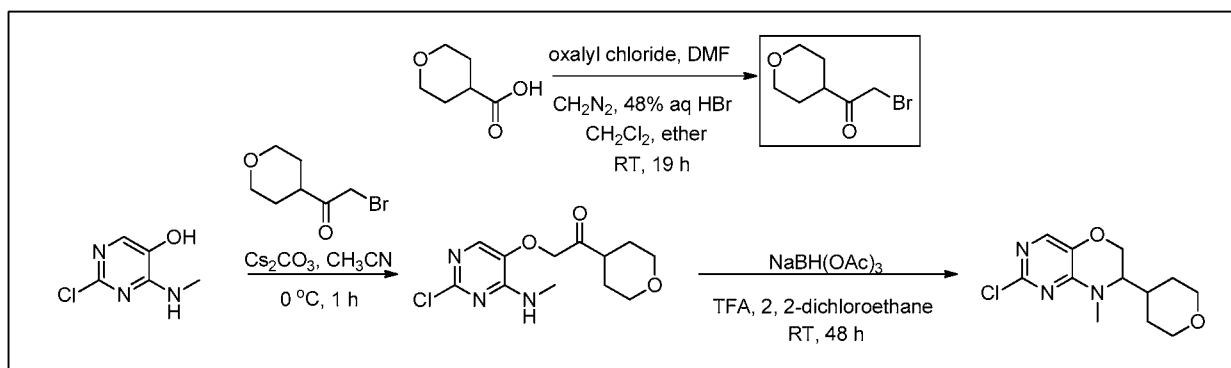
Synthesis of 2-chloro-8-methyl-7-(2-(trifluoromethoxy) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0219] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-(trifluoromethoxy) phenyl) ethan-1-one (350 mg, 0.96 mmol) in 1,2-dichloroethane (10 mL) under an argon atmosphere was added sodium triacetoxyborohydride (400 mg, 1.93 mmol) followed by trifluoroacetic acid (0.1 mL, 0.96 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 24 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with 1N sodium hydroxide (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was triturated with EtOAc (2 x 10 mL) to afford 2-chloro-8-methyl-7-(2-(trifluoromethoxy) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (220 mg, 66%) as an off white solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.71 (s,

1H), 7.45-7.30 (m, 3H), 7.08-7.03 (m, 1H), 5.00 (s, 1H), 4.24 (s, 2H), 3.11 (s, 3H); LC-MS: 346.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.51 min. 0.05% Aq TFA: ACN; 0.80 ml/min); TLC: 30% EtOAc:hexanes (R_f 0.7).

Example 22

Synthesis of 2-chloro-8-methyl-7-(tetrahydro-2H-pyran-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-bromo-1-(tetrahydro-2H-pyran-4-yl) ethan-1-one

[0220] To a stirred solution of tetrahydro-2H-pyran-4-carboxylic acid (1.5 g, 0.01 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (1.6 g, 0.01 mmol) and DMF (1 drop) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. After consumption of acid (monitored by TLC), the mixture was concentrated *in vacuo*. The crude material was dissolved in ether and cooled to -10 °C. A solution of CH_2N_2 in ether (20 mL) was added and the reaction mixture was warmed to RT and stirred for 19 h. After consumption of the starting materials (monitored by TLC), the mixture was concentrated *in vacuo*. To a stirred solution of the crude material in CH_2Cl_2 (20 mL) was added a solution of 48% aq HBr (5 mL) at -10 °C. The reaction mixture was warmed to RT and stirred for 1 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with a sodium bicarbonate solution (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were washed successively with a sodium bicarbonate solution (20 mL) and water (20 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-bromo-1-(tetrahydro-2H-pyran-4-yl) ethan-1-one (2 g, crude) as a yellow solid. ^1H -

NMR (DMSO-*d*₆, 500 MHz): δ 4.49 (s, 2H), 3.83 (d, 2H), 3.33 (t, 2H), 2.90-2.80 (m, 1H), 1.80-1.70 (m, 2H), 1.57-1.44 (m, 2H); TLC: 30% EtOAc:hexanes (*R*_f 0.7).

Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl)oxy)-1-(tetrahydro-2H-pyran-4-yl) ethan-1-one

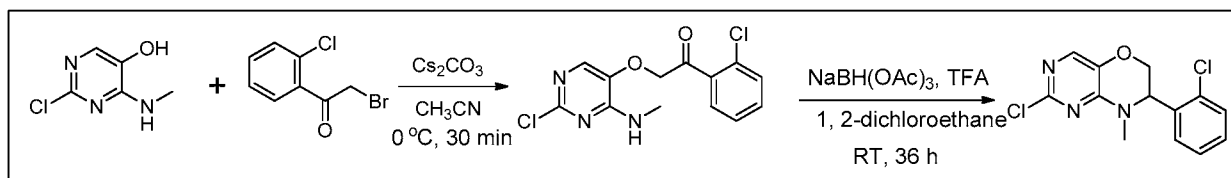
[0221] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (3 g, 18.8 mmol) in CH₃CN (60 mL) was added cesium carbonate (12.2 g, 37.70 mmol) followed by 2-bromo-1-(tetrahydro-2H-pyran-4-yl) ethan-1-one (3.9 g 18.8 mmol) at 0 °C and stirred for 1 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with a sodium carbonate solution (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(tetrahydro-2H-pyran-4-yl) ethan-1-one (2.5 g) as a yellow solid and used without further purification. LC-MS: 286.1 (M⁺); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μ m); RT 2.86 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 30% EtOAc:hexanes (*R*_f 0.5).

Synthesis of 2-chloro-8-methyl-7-(tetrahydro-2H-pyran-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0222] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(tetrahydro-2H-pyran-4-yl) ethan-1-one (2.5 g, 8.70 mmol) in 1, 2-dichloroethane (50 mL) was added trifluoroacetic acid (1 mL) followed by sodium triacetoxymethylborohydride (3.7 g, 17.50 mmol) and stirred for 48 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with 1N sodium hydroxide (50 mL) (pH>9) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 20-30% EtOAc:hexanes to afford 2-chloro-8-methyl-7-(tetrahydro-2H-pyran-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (2 g, 86%) as a pale yellow solid. LC-MS: 270.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μ m); RT 3.10 min. 0.05% Aq TFA: ACN; 0.8 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μ m); RT 1.63 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; TLC: 50% EtOAc:hexanes (*R*_f 0.3).

Example 23

Synthesis of 2-chloro-7-(2-chlorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-chlorophenyl) ethan-1-one

[0223] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (4 g, 25.15 mmol) in CH₃CN (100 mL) was added cesium carbonate (16.25 g, 50.31 mmol) followed by 2-bromo-1-(2-chlorophenyl) ethan-1-one (12 g, 37.7 mmol) at 0 °C and stirred for 30 min. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 6% EtOAc:hexanes to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-chlorophenyl) ethan-1-one (4.3 g, 55%) as a white solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.95-7.88 (m, 2H), 7.59-7.41 (m, 3H), 7.38 (s, 1H), 4.37 (d, 1H), 4.05 (d, 1H), 2.78 (s, 3H); TLC: 20% EtOAc:hexanes (R_f 0.7).

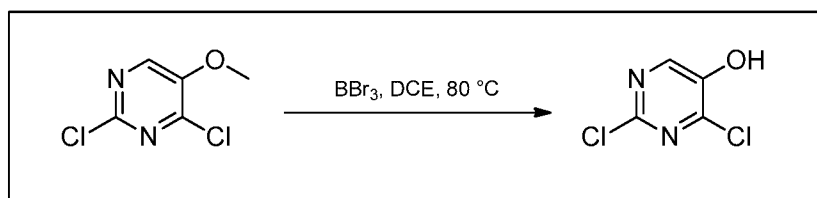
Synthesis of 2-chloro-7-(2-chlorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0224] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-chlorophenyl) ethan-1-one (4.3 g, 13.78 mmol) in 1, 2-dichloroethane (100 mL) was added sodium triacetoxyborohydride (6.1 g, 28.94 mmol) followed by trifluoroacetic acid (1.1 mL, 13.78 mmol) and stirred for 36 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with a 5% sodium bicarbonate solution (100 mL) and extracted with CH₂Cl₂ (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 12% EtOAc:hexanes to afford 2-chloro-7-(2-chlorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (1.8 g, 45%) as an off white solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.77 (s, 1H), 7.55 (d, 1H), 7.40 (t, 1H), 7.36 (t, 1H), 6.98

(d, 1H), 5.23 (s, 1H), 4.34 (s, 2H), 3.01 (s, 3H); LC-MS: 296.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.30 min. 0.05% Aq TFA: ACN; 0.80 ml/min); TLC: 20% EtOAc:hexanes (R_f 0.7).

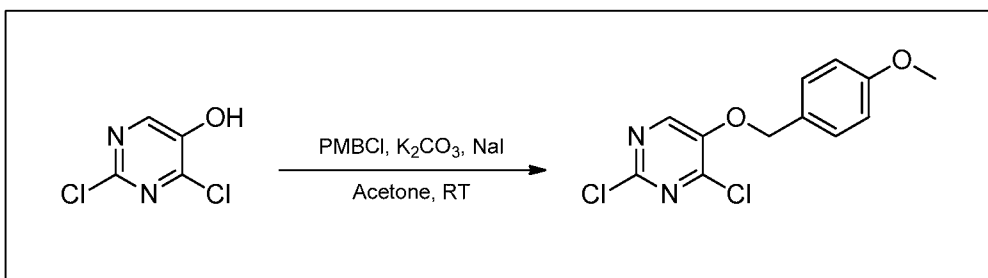
Example 24

Synthesis of (S)-2-chloro-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine



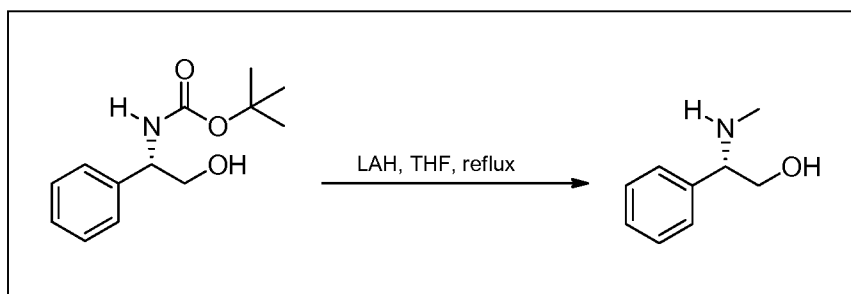
Synthesis of 2,4-Dichloropyrimidin-5-ol

[0225] To a solution of 2,4-dichloro-5-methoxypyrimidine (5.30 g, 29.6 mmol) in 1,2-dichloroethane (75 mL) at 0°C was slowly added BBr₃ (14 mL, 148 mmol). The reaction mixture was heated to 80 °C for 16 h and monitored by LC/MS until completion of the reaction. The reaction mixture was cooled to 0°C and basified with a 1N NaOH solution. The mixture was stirred for 1 h at RT and then acidified with NH₄Cl. The pH was adjusted between pH 6-7 using AcOH. The layers were separated and the aqueous layer was extracted 3 times with ethyl acetate. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was triturated with DCM:hexanes and filtered to afford pure 2,4-dichloropyrimidin-5-ol (2.03 g, 73 %) as a solid. ¹H NMR (CDCl₃, 400 MHz): δ 8.35 (s, 1H), 5.73 (s, 1H); LRMS (ESpos) calcd for C₄H₂Cl₂N₂O [M+H]⁺: 164.95. found: 165.13.



Synthesis of 2,4-dichloro-5-(4-methoxybenzyloxy)pyrimidine

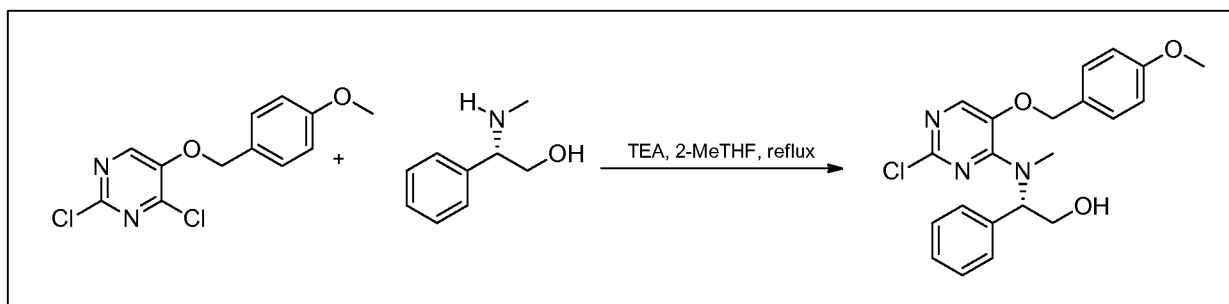
[0226] To a solution of 2,4-dichloropyrimidin-5-ol (3.58 g, 21.7 mmol), K₂CO₃ (7.5 g, 54.3 mmol) and NaI (325 mg, 2.2 mmol) in acetone (45 mL) at RT was added PMBCl (4.41 mL, 32.5 mmol). The reaction was stirred for 16 h. When the reaction was complete (by LC/MS), the mixture was partitioned between ethyl acetate and water. The layers were separated and the aqueous was extracted 3 times with ethyl acetate. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (gradient 0-30% EtOAc:hexanes) to afford pure 2,4-dichloro-5-(4-methoxybenzyloxy)pyrimidine (4.48 g, 72 %) as a white solid. ¹H NMR (CDCl₃, 400 MHz): δ 8.18 (s, 1H), 7.34 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 5.17 (s, 2H), 3.82 (s, 3H).



Synthesis of (S)-2-(methylamino)-2-phenylethanol

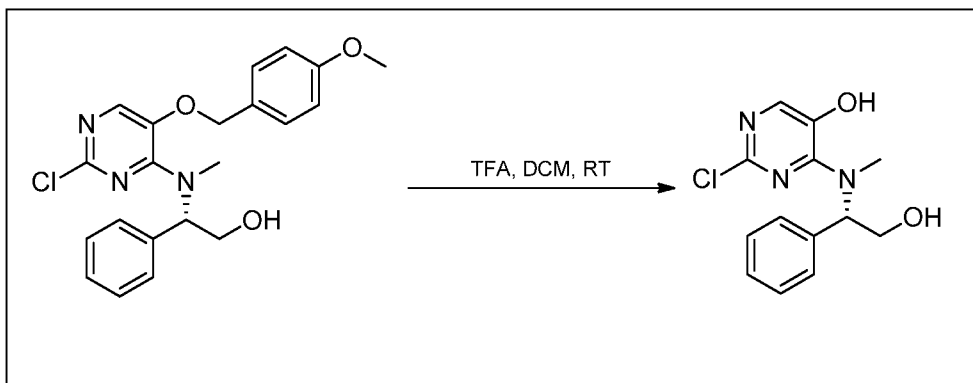
[0227] To a dry flask under N₂ atmosphere was added LAH (956 mg, 25.2 mmol), followed by THF (42 mL) and (S)-tert-butyl 2-hydroxy-1-phenylethylcarbamate (3.0 g, 12.6 mmol). The reaction mixture was heated to reflux for 16 h. When the reaction was complete (by LC/MS), a 10 % NaOH aqueous solution was added slowly at 0 °C until no gas evolution was observed. The reaction mixture was stirred at RT for 15 minutes and Na₂SO₄ was added.

The reaction mixture was stirred vigorously for 15 min, filtered and washed with THF. The filtrate was concentrated *in vacuo* to afford (S)-2-(methylamino)-2-phenylethanol (1.91 g) as a light yellow gum which solidified upon standing. ^1H NMR (CDCl_3 , 400 MHz): δ 7.38 – 7.33 (m, 2H), 7.31 – 7.26 (m, 3H), 3.72 (dd, J = 10.4, 4.4 Hz, 1H), 3.65 (dd, J = 8.3, 4.4 Hz, 1H), 3.55 (dd, J = 10.4, 8.3 Hz, 1H), 2.35 (s, 3H).



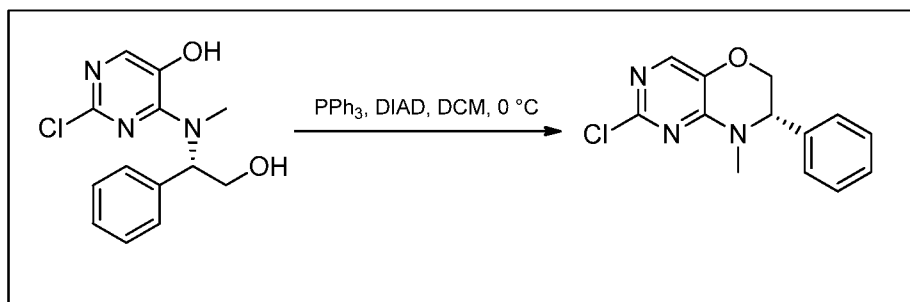
Synthesis of (S)-2-((2-chloro-5-(4-methoxybenzyloxy)pyrimidin-4-yl)(methyl)amino)-2-phenylethanol

[0228] To a mixture of 2,4-dichloro-5-(4-methoxybenzyloxy)pyrimidine (2.04 g, 7.15 mmol) and (S)-2-(methylamino)-2-phenylethanol (1.91 g, 7.49 mmol) in 2-methyl tetrahydrofuran (18 mL) was added triethylamine (2.5 mL, 17.9 mmol). The reaction mixture was stirred at reflux for 16 h. When the reaction was complete (by LC/MS), the mixture was diluted with ethyl acetate. The solution was washed twice with water, brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (gradient 10-80% EtOAc:hexanes) to afford of (S)-2-((2-chloro-5-(4-methoxybenzyloxy)pyrimidin-4-yl)(methyl)amino)-2-phenylethanol (2.14 g, 75 %) as a yellow gummy solid. ^1H NMR (CDCl_3 , 400 MHz): δ 7.80 (s, 1H), 7.35 – 7.27 (m, 3H), 7.22 (dd, J = 14.3, 7.9 Hz, 4H), 6.88 – 6.84 (m, 2H), 6.09 (dd, J = 8.9, 5.6 Hz, 1H), 4.96 (s, J = 11.1 Hz, 2H), 4.22 – 4.15 (m, 2H), 3.80 (s, 3H), 2.93 (s, 3H), 2.15 (s, 1H); LRMS (ESpos) calcd for $\text{C}_{21}\text{H}_{22}\text{ClN}_3\text{O}_3$ $[\text{M}+\text{H}]^+$: 400.13. found: 400.53.



Synthesis of (S)-2-chloro-4-((2-hydroxy-1-phenylethyl)(methyl)amino)pyrimidin-5-ol

[0229] To a mixture of (S)-2-((2-chloro-5-(4-methoxybenzyloxy)pyrimidin-4-yl)(methyl)amino)-2-phenylethanol (2.14 g, 5.35 mmol) at 0 °C in DCM (35 mL) was added trifluoroacetic acid (15mL). When the reaction was complete (by LC/MS), the reaction was concentrated to dryness and co-evaporated several times with toluene. The crude material was partitioned between ethyl acetate and a sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by normal phase chromatography on silica gel (gradient 0-10% MeOH:DCM) to afford (S)-2-chloro-4-((2-hydroxy-1-phenylethyl)(methyl)amino)pyrimidin-5-ol as a white foam (1.19 g, 80 %). ¹H NMR (CDCl₃, 400 MHz): δ 7.83 (s, 1H), 7.33 (dq, J = 14.2, 7.0 Hz, 4H), 7.11 (d, J = 7.1 Hz, 2H), 5.71 (d, J = 10.9 Hz, 1H), 4.36 (t, J = 10.7 Hz, 1H), 4.27 (dd, J = 10.7, 3.8 Hz, 1H), 3.42 (s, 1H), 2.72 (s, 3H); LRMS (ESpos) calcd for C₁₃H₁₄ClN₃O₂ [M+H]⁺: 280.08. found: 280.46.

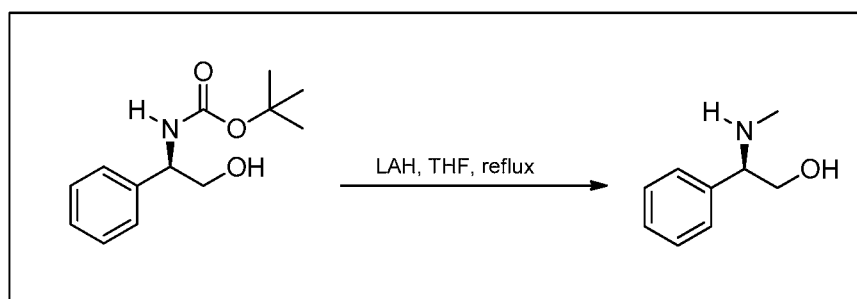


Synthesis of (S)-2-chloro-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine

[0230] To a mixture of (S)-2-chloro-4-((2-hydroxy-1-phenylethyl)(methyl)amino)pyrimidin-5-ol (600 mg, 2.14 mmol) and triphenylphosphine (616 mg, 2.35 mmol) at 0 °C in DCM (11 mL) was added DIAD (0.46 mL, 2.35 mmol) dropwise. The reaction was shown to be complete after 30 min (by LC/MS). The mixture was concentrated to dryness and purified by silica gel column chromatography (gradient 0-70% methyl *tert*-butylether (MTBE):hexanes) to afford (S)-2-chloro-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine (0.2 g, 36 %) as a colourless oil. ¹H NMR (CDCl₃, 400 MHz): δ 7.71 (s, 1H), 7.41 – 7.34 (m, 3H), 7.17 (dd, J = 7.7, 1.6 Hz, 2H), 4.57 (t, J = 3.6 Hz, 1H), 4.27 (dd, J = 11.2, 3.3 Hz, 1H), 4.18 (dd, J = 11.2, 4.0 Hz, 1H), 3.08 (s, 3H); LRMS (ESpos) calcd for C₁₃H₁₂ClN₃O [M+H]⁺: 262.07. found: 262.42.

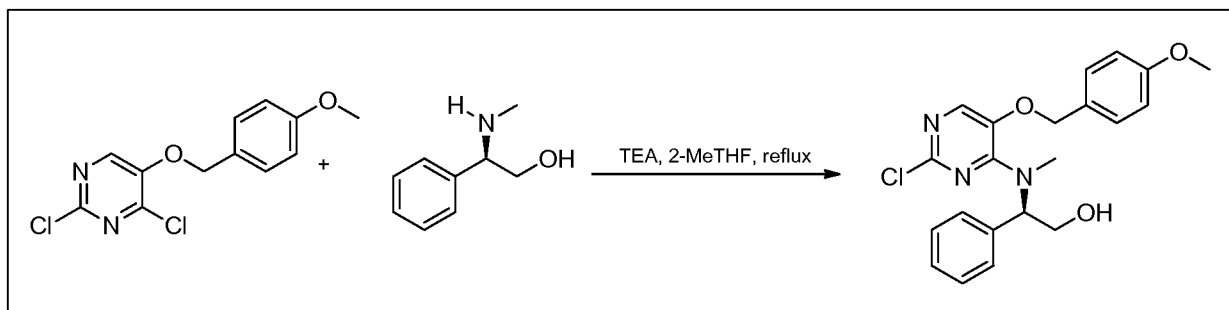
Example 25

Synthesis of (R)-2-chloro-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine



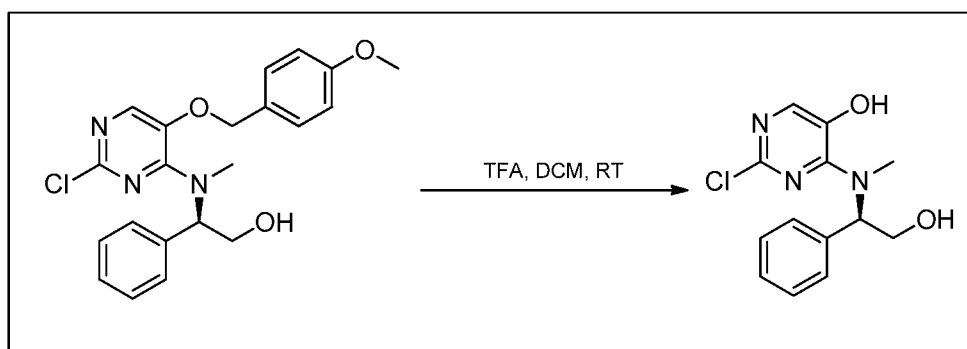
Synthesis of (R)-2-(methylamino)-2-phenylethanol

[0231] To a dry flask under nitrogen was charged with LAH (943 mg, 24.9 mmol) then tetrahydrofuran (THF) (40 mL) and (R)-tert-butyl 2-hydroxy-1-phenylethylcarbamate (2.95 g, 12.4 mmol). The reaction mixture was heated to reflux for 16 h. When the reaction was shown to be complete by LC/MS, a 10 % NaOH aqueous solution was added slowly at 0 °C until no more gas evolution was observed. The reaction mixture was stirred at RT for 15 minutes and Na₂SO₄ was added. The reaction mixture was vigorously stirred for 15 min, filtered and washed with THF. The volatile components were evaporated to afford (R)-2-(methylamino)-2-phenylethanol as a light yellow gum which solidifies upon standing (1.85 g, 98 %). ¹H NMR (CDCl₃, 400 MHz): δ 7.38 – 7.33 (m, 2H), 7.31 – 7.26 (m, 3H), 3.72 (dd, J = 10.4, 4.4 Hz, 1H), 3.65 (dd, J = 8.3, 4.4 Hz, 1H), 3.55 (dd, J = 10.4, 8.3 Hz, 1H), 2.35 (s, 3H).



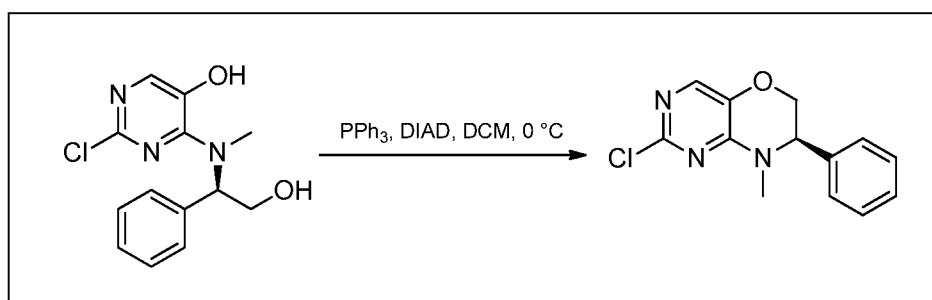
Synthesis of (R)-2-((2-chloro-5-(4-methoxybenzyloxy)pyrimidin-4-yl)(methyl)amino)-2-phenylethanol

[0232] To a mixture of 2,4-dichloro-5-(4-methoxybenzyloxy)pyrimidine (1.2 g, 4.21 mmol) and (R)-2-(methylamino)-2-phenylethanol (0.67 g, 4.42 mmol) in 2-methyl tetrahydrofuran (10 mL) was added triethylamine (1.5 mL, 10.5 mmol). The reaction mixture was stirred at reflux for 16 h. The reaction was diluted with ethyl acetate, washed twice with water, brine, dried over Na₂SO₄, filtered and concentrated. The crude material was purified by silica gel column chromatography (gradient 10-80% EtOAc:hexanes) to afford (R)-2-((2-chloro-5-(4-methoxybenzyloxy)pyrimidin-4-yl)(methyl)amino)-2-phenylethanol as a yellow gummy solid (852 mg, 51 %). ¹H NMR (CDCl₃, 400 MHz): δ 7.80 (s, 1H), 7.35 – 7.27 (m, 3H), 7.22 (dd, J = 14.3, 7.9 Hz, 4H), 6.88 – 6.84 (m, 2H), 6.09 (dd, J = 8.9, 5.6 Hz, 1H), 4.96 (s, J = 11.1 Hz, 2H), 4.22 – 4.15 (m, 2H), 3.80 (s, 3H), 2.93 (s, 3H), 2.15 (s, 1H); LRMS (ESpos) calcd for C₂₁H₂₂ClN₃O₃ [M+H]⁺: 400.13. found: 400.53.



Synthesis of (R)-2-chloro-4-((2-hydroxy-1-phenylethyl)(methyl)amino)pyrimidin-5-ol

[0233] To a mixture of (R)-2-((2-chloro-5-(4-methoxybenzyloxy)pyrimidin-4-yl)(methyl)amino)-2-phenylethanol (850 mg, 2.13 mmol) at 0 °C in dichloromethane (13.5 mL) was added trifluoroacetic acid (6.5 mL). When the reaction was shown to be complete by LC/MS, the mixture was concentrated to dryness and co-evaporated several times with toluene. The crude material was partitioned between ethyl acetate and a NaHCO₃ solution. The layers were separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was triturated in DCM:hexanes mixture, filtered and dried *in vacuo* to afford (R)-2-chloro-4-((2-hydroxy-1-phenylethyl)(methyl)amino)pyrimidin-5-ol as a white solid (327 mg, 55 %). ¹H NMR (CDCl₃, 400 MHz): δ 7.83 (s, 1H), 7.33 (dq, J = 14.2, 7.0 Hz, 4H), 7.11 (d, J = 7.1 Hz, 2H), 5.71 (d, J = 10.9 Hz, 1H), 4.36 (t, J = 10.7 Hz, 1H), 4.27 (dd, J = 10.7, 3.8 Hz, 1H), 3.42 (s, 1H), 2.72 (s, 3H); LRMS (ESpos) calcd for C₁₃H₁₄ClN₃O₂ [M+H]⁺: 280.08. found: 280.46.



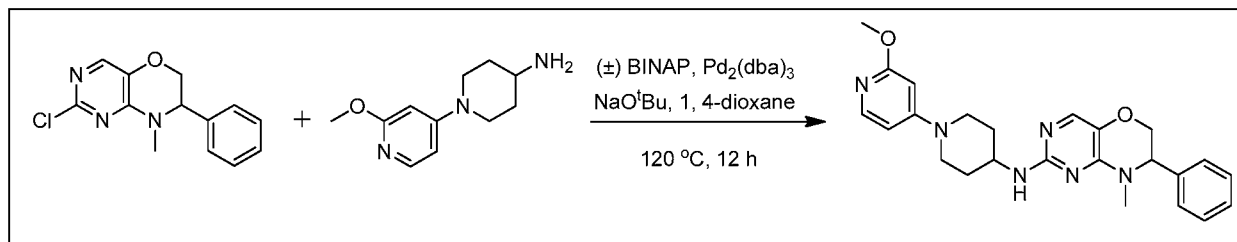
Synthesis of (R)-2-chloro-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine

[0234] To a mixture of (R)-2-chloro-4-((2-hydroxy-1-phenylethyl)(methyl)amino)pyrimidin-5-ol (325 mg, 1.16 mmol) and triphenylphosphine (335 mg, 1.28 mmol) at 0 °C in dichloromethane (11 mL) was added DIAD (0.25 mL, 1.28 mmol) drop-wise. When the reaction was shown to be complete by LC/MS, the mixture was concentrated to dryness. The crude material was purified by silica gel column chromatography (gradient 0-70% methyl *tert*-butylether (MTBE):hexanes) to afford (R)-2-chloro-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine as a colourless oil (0.13 g, 43 %). ¹H NMR (CDCl₃, 400 MHz): δ 7.71 (s, 1H), 7.41 – 7.34 (m, 3H), 7.17 (dd, J = 7.7, 1.6 Hz, 2H), 4.57 (t, J = 3.6 Hz, 1H), 4.27 (dd, J = 11.2, 3.3 Hz, 1H), 4.18 (dd, J =

11.2, 4.0 Hz, 1H), 3.08 (s, 3H); LRMS (ESpos) calcd for C₁₃H₁₂ClN₃O [M+H]⁺: 262.07.
found: 262.42.

Example 26

Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

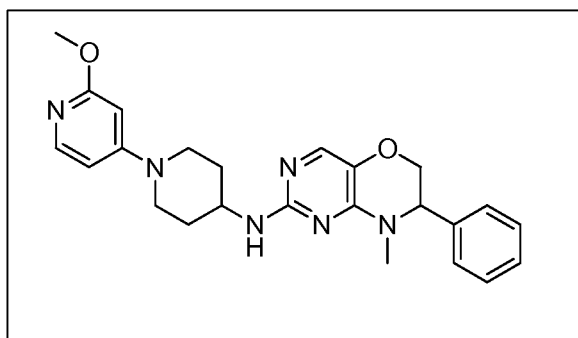
[0235] To a stirred solution of 2-chloro-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (80 mg, 0.30 mmol) in 1, 4-dioxane (2 mL) was added 1-(2-methoxypyridin-4-yl) piperidin-4-amine (82 mg, 0.33 mmol), Pd₂(dba)₃ (14 mg, 0.01 mmol), (±) BINAP (28 mg, 0.04 mmol), and sodium tertiary butoxide (88 mg, 0.91 mmol). The mixture was degassed under an argon atmosphere for 10 min. The reaction mixture was heated to 120 °C and stirred for 12 h in a sealed tube. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 4% MeOH:CH₂Cl₂ and further purified by preparative HPLC [Chiralpak IA (250 x 20 mm, 5 μm) (15 mg loading; 0.1 % DEA in n-hexane; CH₂Cl₂:MeOH (80: 20); (75: 25) as the mobile phase with a Flow rate=15 mL/min] to afford N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (50 mg, 38%) as a pale yellow solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.78 (d, 1H), 7.44 (s, 1H), 7.40-7.37 (m, 2H), 7.33-7.30 (m, 1H), 7.20 (d, 2H), 6.56-6.55 (m, 1H), 6.26 (br s, 1H), 6.11 (s, 1H), 4.71 (s, 1H), 4.15-4.09 (m, 2H), 3.86-3.83 (m, 3H), 3.76 (s, 3H), 2.95-2.90 (m, 5H), 1.92-1.90 (m, 2H), 1.48-1.42 (m, 2H); Mass (ESI): 433.4 [M+1]; LC-MS: 433.1 (M+1); (column; X-Bridge C-18 (50 × 3.0 mm, 3.5 μm); RT 2.48 min.

0.05% TFA in water: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18 2.1 X 50 mm, 1.7 μ m); RT 1.56 min. ACN: 0.025% Aq TFA; 0.50 mL/min. TLC: 10% MeOH:CH₂Cl₂ (R_f 0.5).

[0236] Racemic compound of Example 26 was separated using a Chiralpak IA (250 x 20 mm, 5 μ m (15 mg loading; 0.1 % DEA in *n*-hexane; CH₂Cl₂:MeOH (80:20); (75:25) as the mobile phase) to provide the compound of Example 26A Fraction I (-) and the compound of Example 26B Fraction II (+).

Example 26A

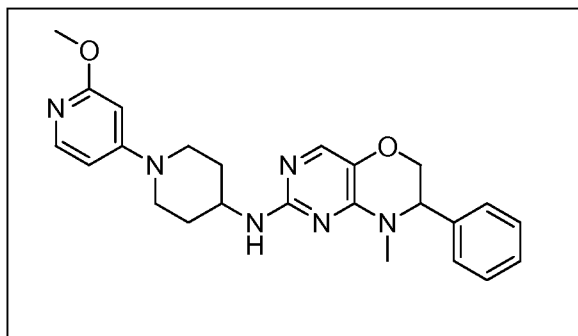
Synthesis of (-)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0237] The compound of Example 26A was produced as described in Example 26. Analytical data for product Fraction I (-): ¹H NMR (DMSO-d₆, 400 MHz): δ 7.68 (d, 1H), 7.44 (s, 1H), 7.38-7.35 (m, 2H), 7.32 (d, 1H), 7.20 (d, 2H), 6.57-6.56 (m, 1H), 6.30-6.28 (m, 1H), 6.10 (s, 1H), 4.74 (s, 1H), 4.23-4.20 (m, 2H), 3.86-3.82 (m, 3H), 2.98-2.95 (m, 5H), 2.78 (s, 3H), 1.93-1.90 (m, 2H), 1.42-1.39 (m, 2H); Mass (ESI): 433.5 [M+1]; LC-MS: 433.6 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μ m); RT 2.70 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 x 2.1mm, 1.7 μ m); RT 1.54 min. ACN: 0.025% TFA (Aq); 0.50 ml/min. Chiral HPLC: RT = 22.06 min (Chiralpak IA (250 x 4.6mm, 5 μ m; mobile phase (A) 0.1 % DEA in *n*-hexane; CH₂Cl₂: MeOH (80: 20); flow Rate: 1.0 mL/min); Optical rotation [α]_D^{24.99}: -93.00° (c = 0. 25%, DCM); TLC: 10% MeOH:CH₂Cl₂ (R_f 0.5).

Example 26B

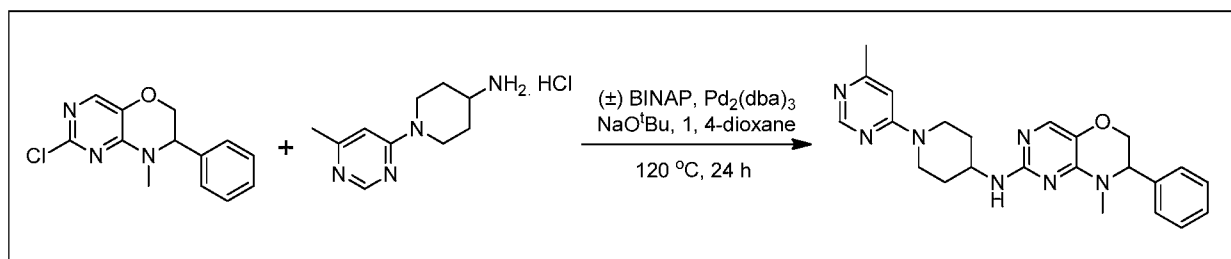
Synthesis of (+)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0238] The compound of Example 26B was produced as described in Example 26. Analytical data for product Fraction II (+): ^1H NMR (DMSO- d_6 , 400 MHz): δ 7.78 (d, 1H), 7.42 (s, 1H), 7.36-7.34 (m, 2H), 7.30-7.29 (m, 1H), 7.20 (d, 2H), 6.56-6.54 (m, 1H), 6.30-6.29 (m, 1H), 6.10 (s, 1H), 4.72-4.71 (m, 1H), 4.12-4.09 (m, 2H), 3.91-3.86 (m, 3H), 3.74 (s, 3H), 2.96 (s, 3H), 2.91-2.89 (m, 2H), 1.94-1.90 (m, 2H), 1.48-1.44 (m, 2H); Mass (ESI): 433.6 [M+1]; LC-MS: 433.7 (M+1); (column; X-select CSH C-18 (50 $\times$ 3.0 mm, 3.5 μm); RT 2.69 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 $\times$ 2.1mm, 1.7 μm); RT 1.54 min. ACN: 0.025% TFA (Aq); 0.50 ml/min. Chiral HPLC: RT = 24.93 min (Chiralpak IA (250 $\times$ 4.6mm, 5 μm ; mobile phase (A) 0.1 % DEA in *n*-hexane CH_2Cl_2 : MeOH (80: 20); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{25.00}$: +81.31 $^\circ$ (c = 0.25%, DCM); TLC: 10% MeOH: CH_2Cl_2 (R_f 0.5).

Example 27

Synthesis of 8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

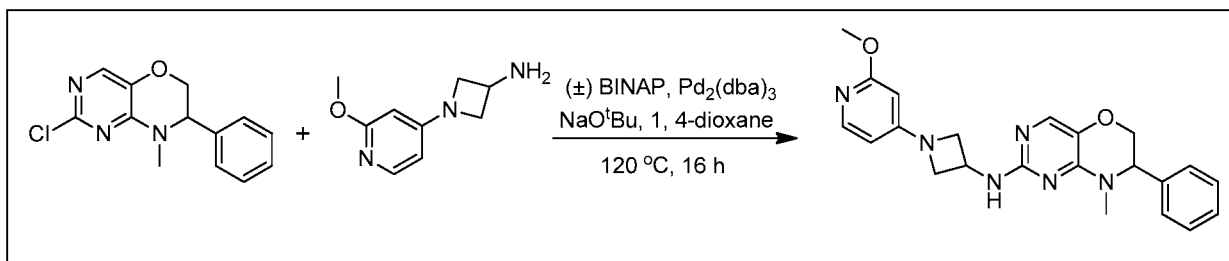


Synthesis of 8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0239] To a dry vial was added a suspension of Pd₂(dba)₃ (8.7 mg, 0.01 mmol) and (±) BINAP (18 mg, 0.03 mmol) in 1, 4-dioxane (0.25 mL) at RT. The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture 2-chloro-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (50 mg, 0.19 mmol), 1-(6-methylpyrimidin-4-yl) piperidin-4-amine hydrochloride (48 mg, 0.21 mmol) and sodium tertiary butoxide (55 mg, 0.57 mmol) in 1, 4-dioxane (0.25 mL) was degassed with argon and the catalyst premixure was added. The reaction mixture was heated to 120 °C and stirred for 24 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was diluted with water (20 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 4% MeOH:CH₂Cl₂ and further purified by preparative HPLC [Kromasil C18 (250 x 21.2mm 10 µm) (25 mg loading; n-hexane; CH₂Cl₂:MeOH (50:50); (85:10) as the mobile phase with a Flow rate=15 mL/min] to afford 8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (15 mg, 19%) as a white solid. ¹H-NMR (CD₃OD-*d*₄, 400 MHz): δ 8.33 (s, 1H), 7.39-7.32 (m, 4H), 7.22 (d, 2H), 6.68 (s, 1H), 4.64-4.62 (m, 1H), 4.42-4.39 (m, 2H), 4.20-4.10 (m, 2H), 4.02-3.97 (m, 1H), 3.18-3.11 (m, 2H), 3.03 (s, 3H), 2.32 (s, 3H), 2.11-2.08 (m, 2H), 1.51-1.47 (m, 2H); LC-MS: 418.7 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 µm); RT 2.68 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity BEH C-18 2.1 X 50 mm, 1.7 µm); RT 1.46 min. ACN: 0.025% TFA (Aq); 0.50 mL/min. TLC: 5% MeOH:CH₂Cl₂ (R_f 0.2).

Example 28

Synthesis of N-(1-(2-methoxypyridin-4-yl) azetidin-3-yl)-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

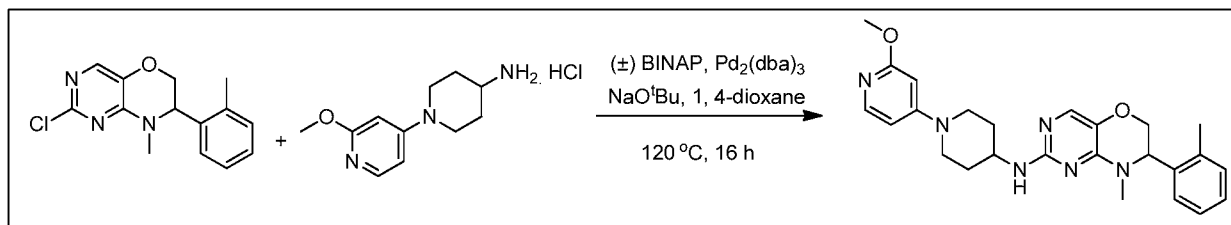


Synthesis of N-(1-(2-methoxypyridin-4-yl) azetidin-3-yl)-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0240] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (14 mg, 0.01 mmol) and ($\pm$) BINAP (28 mg, 0.04 mmol) in 1, 4-dioxane (1 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (80 mg, 0.03 mmol), 1-(2-methoxypyridin-4-yl) azetidin-3-amine (60 mg, 0.33 mmol) and sodium tertiary butoxide (88 mg, 0.91 mmol) in 1, 4-dioxane (1 mL) was degassed with argon and the catalyst premixure was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography using 2% $\text{MeOH}:\text{CH}_2\text{Cl}_2$ to afford N-(1-(2-methoxypyridin-4-yl) azetidin-3-yl)-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (10 mg, 8%) as an off-white solid. $^1\text{H-NMR}$ (DMSO-d_6 , 400 MHz): δ 7.75 (d, 1H), 7.45 (s, 1H), 7.39-7.31 (m, 3H), 7.19 (d, 2H), 7.00 (d, , 1H), 6.08-6.07 (m, 1H), 5.65 (s, 1H), 4.71-4.62 (m, 2H), 4.18-4.12 (m, 4H), 3.75-3.73(m, 2H), 3.72 (s, 3H), 2.94 (s, 3H); Mass (ESI): 405.4 [M+1]; LC-MS: 405.5 (M+1); (column; X-Bridge C-18 (50 x 3.0 mm, 3.5 μm); RT 3.01 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC-(column; Acquity UPLC BEH C-18 2.1 X 50 mm, 1.7 μm); RT 1.51 min. ACN: 0.025% TFA (Aq); 0.50 mL/min. TLC: 5% $\text{MeOH}:\text{CH}_2\text{Cl}_2$ (R_f 0.4).

Example 29

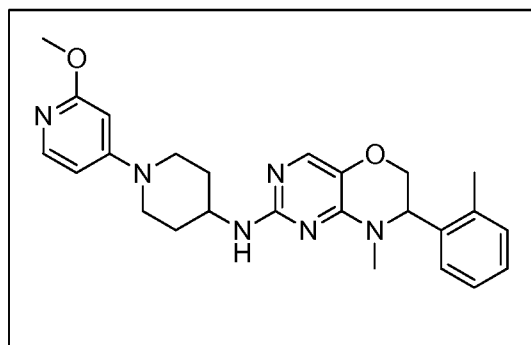
Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

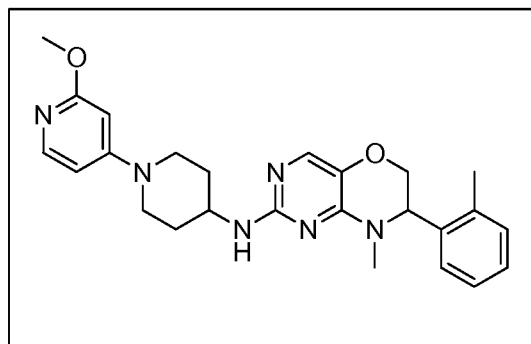
[0241] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (6 mg, 0.007 mmol) and ($\pm$) BINAP (13 mg, 0.02 mmol) in 1, 4-dioxane (0.2 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-8-methyl-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (40 mg, 0.14 mmol), 1-(2-methoxypyridin-4-yl)piperidin-4-amine (28 mg, 0.16 mmol) and sodium tertiary butoxide (41 mg, 0.43 mmol) in 1, 4-dioxane (0.2 mL) was degassed with argon and the catalyst premixure was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was concentrated *in vacuo*. The crude material was diluted with water (10 mL) and extracted with 5% MeOH: CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 5% MeOH: CH_2Cl_2 to afford N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (10 mg, 16%) as an off-white solid. ^1H -NMR ($\text{DMSO}-d_6$, 500 MHz): δ 7.80 (d, 1H), 7.41 (s, 1H), 7.21-7.16 (m, 3H), 6.84 (d, 1H), 6.59-6.57 (m, 1H), 6.23 (br s, 1H), 6.12 (s, 1H), 4.93-4.90 (m, 1H), 4.17-4.03 (m, 2H), 3.86-3.71 (m, 3H), 3.78 (s, 3H), 2.94-2.90 (m, 2H), 2.89 (s, 3H), 2.28 (s, 3H), 1.95-1.90 (m, 2H), 1.50-1.42 (m, 2H); Mass (ESI): 447.5 [M+1]; LC-MS: 447.7 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 2.90 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity BEH C-18 50 X 2.1 mm, 1.7 μm); RT 1.63 min. ACN: 0.025% Aq TFA; 0.5 mL/min. TLC: 10% MeOH: CH_2Cl_2 (R_f 0.3).

[0242] Racemic compound of Example 29 was separated using a Chiralpak IA (250 x 20 mm, 5 μm (50 mg loading; 0.1 % DEA in n-hexane; CH_2Cl_2 :MeOH (50: 50); (75: 25) as the mobile phase) to provide the compound of Example 29A Fraction I (-) and the compound of Example 29B Fraction II (+).

Example 29A**Synthesis of (-)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine**

[0243] The compound of Example 29A was produced as described in Example 29. Analytical data for product Fraction I (-): ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.78 (d, 1H), 7.42 (s, 1H), 7.24-7.14 (m, 3H), 6.84 (d, 1H), 6.56-6.52 (m, 1H), 6.22 (d, 1H), 6.11-6.09 (m, 1H), 5.90-5.88 (m, 1H), 4.11-4.02 (m, 2H), 3.91-3.88 (m, 3H), 3.77 (s, 3H), 2.93 (s, 5H), 2.38 (s, 3H), 1.94-1.90 (m, 2H), 1.45-1.38 (m, 2H); Mass (ESI): 447.6 [M+1]; LC-MS: 447.6 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.89 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1mm, 1.7 μm); RT 1.64 min. ACN: 0.025% TFA (Aq); 0.50 ml/min. Chiral HPLC: RT = 7.54 min (Chiralpak IA (250 x 4.6mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) DCM:MeOH (50:50); flow Rate: 1.0 mL/min); Optical rotation [α]_D^{19.98}: -94.91° (c = 0.25%, DCM).

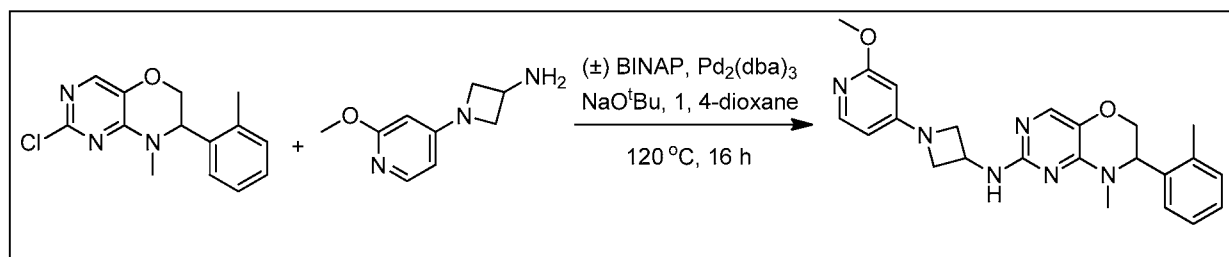
Example 29B**Synthesis of (+)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine**



[0244] The compound of Example 29B was produced as described in Example 29. Analytical data for product Fraction II (+): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ 7.76 (d, 1H), 7.41 (s, 1H), 7.25-7.14 (m, 3H), 6.85 (d, 1H), 6.56-6.52 (m, 1H), 6.23 (d, 1H), 6.11-6.09 (m, 1H), 5.90-5.87 (m, 1H), 4.11-4.03 (m, 2H), 3.90-3.88 (m, 3H), 3.78 (s, 3H), 2.91 (s, 5H), 2.37 (s, 3H), 1.92-1.87 (m, 2H), 1.47-1.40 (m, 2H); Mass (ESI): 447.6 $[\text{M}+1]$; LC-MS: 447.6 $(\text{M}+1)$; (column; X-select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.89 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50×2.1 mm, $1.7 \mu\text{m}$); RT 1.64 min. ACN: 0.025% TFA (Aq); 0.50 ml/min. Chiral HPLC: RT = 13.04 min (Chiralpak IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) DCM:MeOH (50:50); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.99}$: $+110.25^\circ$ ($c = 0.25\%$, DCM).

Example 30

Synthesis of N-(1-(2-methoxypyridin-4-yl) azetidin-3-yl)-8-methyl-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

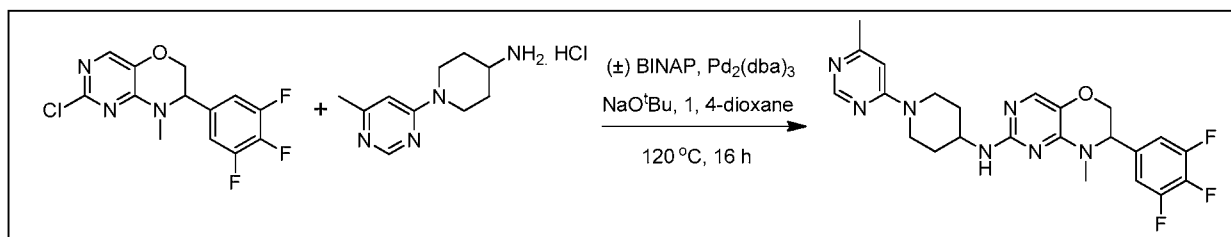


Synthesis of N-(1-(2-methoxypyridin-4-yl) azetidin-3-yl)-8-methyl-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0245] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (6 mg, 0.007 mmol) and ($\pm$) BINAP (13 mg, 0.02 mmol) in 1, 4-dioxane (0.2 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-8-methyl-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (40 mg, 0.14 mmol), 1-(2-methoxypyridin-4-yl) azetidin-3-amine (28 mg, 0.16 mmol) and sodium tertiary butoxide (41 mg, 0.43 mmol) in 1, 4-dioxane (0.2 mL) was degassed with argon and the catalyst premixure was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was concentrated *in vacuo*. The crude mixture was diluted with water (10 mL) and extracted with 5% MeOH: CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 5% MeOH: CH_2Cl_2 to afford N-(1-(2-methoxypyridin-4-yl) azetidin-3-yl)-8-methyl-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (7 mg, 12%) as an off-white solid. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ 7.73 (d, 1H), 7.41 (s, 1H), 7.22-7.10 (m, 3H), 6.99 (d, 1H), 6.81 (d, 1H), 6.08 (d, 1H), 5.61 (s, 1H), 4.91-4.89 (m, 1H), 4.64-4.60 (m, 1H), 4.19-4.01 (m, 4H), 3.73-3.71 (m, 2H), 3.69 (s, 3H), 2.90 (s, 3H), 2.32 (s, 3H); Mass (ESI): 419.5 [M+1]; LC-MS: 419.6 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 2.78 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity BEH C-18 50 X 2.1 mm, 1.7 μm); RT 1.52 min. ACN: 0.025% Aq TFA; 0.5 mL/min. TLC: 10% MeOH: CH_2Cl_2 (R_f 0.3).

Example 31

Synthesis of 8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



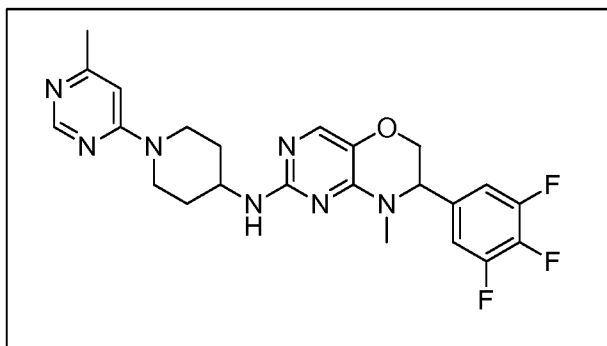
Synthesis of 8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0246] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (7 mg, 0.008 mmol) and ($\pm$) BINAP (15 mg, 0.02 mmol) in 1, 4-dioxane (0.25 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-8-methyl-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (50 mg, 0.15 mmol), 1-(6-methylpyrimidin-4-yl) piperidin-4-amine hydrochloride (40 mg, 0.17 mmol) and sodium tertiary butoxide (46 mg, 0.47 mmol) in 1, 4-dioxane (0.25 mL) was degassed with argon and the catalyst premixture was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by preparative HPLC [Kromasil C18, 250 x 21.2 mm, 5 μm) (45 mg loading; CH_3CN ; 5 mM Aq NH_4OAc (0.01/75, 15/40, 25/10, 35/10) as the mobile phase with a Flow rate=15 mL/min] to afford 8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (8 mg, 10%) as an off-white solid. ^1H -NMR (CD_3OD , 400 MHz): δ 8.30 (s, 1H), 7.41 (s, 1H), 7.01-6.95 (m, 2H), 6.69 (s, 1H), 4.69-4.65 (m, 1H), 4.41-4.39 (m, 2H), 4.12 (s, 2H), 4.02-3.98 (m, 1H), 3.16-3.10 (m, 2H), 3.02 (s, 3H), 2.31 (s, 3H), 2.11-2.08 (m, 2H), 1.53-1.47 (m, 2H); LC-MS: 472.5 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 3.44 min 5 mM NH_4OAc : ACN; 0.80 mL/min); HPLC (column; Eclipse XDB C-18 150 X 4.6 mm, 5 μm); RT 10.58 min. ACN: 5 mM NH_4OAc ; 0.5 mL/min. TLC: 5% MeOH: CH_2Cl_2 (R_f 0.4).

[0247] Racemic compound of Example 31 was separated using a Chiralpak ADH (250 x 20 mm, 5 μ 30 mg loading; (A) 0.1 % DEA in *n*-hexane (B) IPA (A:B : 70:30) as the mobile phase to provide the compound of Example 31A Fraction I (-) and the compound of Example 31B Fraction II (+).

Example 31A

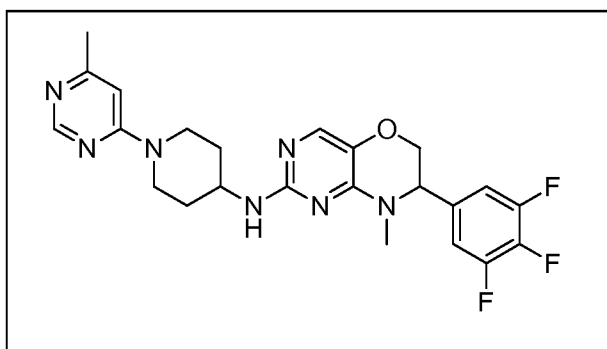
Synthesis of (-)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0248] The compound of Example 31A was produced as described in Example 31. Analytical data for product Fraction I (-): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.31 (s, 1H), 7.41 (s, 1H), 7.02-6.99 (m, 2H), 6.69 (s, 1H), 4.69-4.66 (m, 1H), 4.43-4.38 (m, 2H), 4.15 (d, 2H), 4.02-3.98 (m, 1H), 3.19-3.10 (m, 2H), 3.08 (s, 3H), 2.31 (s, 3H), 2.11-2.05 (m, 2H), 1.51-1.47 (m, 2H); Mass (ESI): 472.4 $[\text{M}+1]$; LC-MS: 472.6 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 3.55 min. 5 mM Aq NH_4OAc : ACN; 0.80 ml/min); UPLC (column; Eclipse-XDB-C-18, 150×4.6 mm, $5 \mu\text{m}$); RT 10.52 min. ACN: 5 mM Aq NH_4OAc ; 1.0 ml/min; Chiral HPLC: RT = 10.27 min (CHIRALPAK-AD-H (250×4.6 mm, $5 \mu\text{m}$); mobile phase (A) 0.1 % DEA in *n*-hexane (B) IPA (A:B : 70:30; flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{19.98}$: -59.92 (c 0.25, DCM); TLC: 5% MeOH: CH_2Cl_2 (R_f 0.4).

Example 31B

Synthesis of (+)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

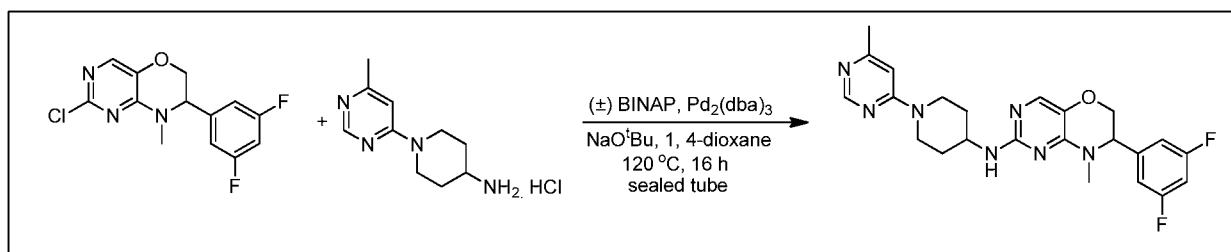


[0249] The compound of Example 31B was produced as described in Example 31. Analytical data for product Fraction II (+): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.31 (s, 1H), 7.41 (s, 1H), 7.02-6.99 (m, 2H), 6.69 (s, 1H), 4.69-4.66 (m, 1H), 4.43-4.38 (m, 2H), 4.15 (d,

2H), 4.02-3.98 (m, 1H), 3.19-3.10 (m, 2H), 3.08 (s, 3H), 2.31 (s, 3H), 2.11-2.05 (m, 2H), 1.51-1.47 (m, 2H); Mass (ESI): 472.5 [M+1]; LC-MS: 472.5 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.56 min. 5 mM Aq NH₄OAc: ACN; 0.80 ml/min); UPLC (column; Eclipse-XDB-C-18, 150 × 4.6 mm, 5 μm); RT 10.53 min. ACN: 5 mM Aq NH₄OAc; 1.0 ml/min; Chiral HPLC: RT = 12.05 min (CHIRALPAK-AD-H (250 × 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) IPA (A:B : 70:30; flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: +64.94 (c 0.25, DCM); TLC: 5% MeOH:CH₂Cl₂ (*R_f* 0.4).

Example 32

Synthesis of 7-(3, 5-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 7-(3, 5-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

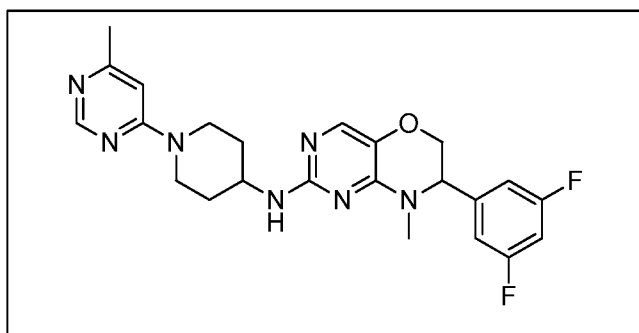
[0250] To a dry vial was added a suspension of Pd₂(dba)₃ (6 mg, 0.006 mmol) and (±) BINAP (12 mg, 0.02 mmol) in 1, 4-dioxane (0.4 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-7-(3, 5-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (40 mg, 0.13 mmol), 1-(6-methylpyrimidin-4-yl) piperidin-4-amine hydrochloride (33 mg, 0.14 mmol) and sodium tertiary butoxide (38 mg, 0.40 mmol) in 1, 4-dioxane (0.4 mL) was degassed with argon and the catalyst premixture was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was concentrated *in vacuo*. The crude material was diluted with water (5 mL) and extracted with 5% MeOH:CH₂Cl₂ (2 × 5 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified

by preparative HPLC [Kromasil C18, 250 x 21.2 mm, 5 μ m) (50 mg loading; CH₃CN; 0.05% TFA (0.01/90, 15/70, 25/10, 35/10) as the mobile phase with a Flow rate=15 mL/min] to afford 7-(3, 5-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (10 mg, 16%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.32 (s, 1H), 7.46 (s, 1H), 7.16 (t, 1H), 6.88 (d, 2H), 6.70 (s, 1H), 6.28 (d, 1H), 4.78 (s, 1H), 4.30 (d, 2H), 4.18 (d, 1H), 4.10 (d, 1H), 3.92-3.88 (m, 1H), 3.06-2.96 (m, 5H), 2.20 (s, 3H), 1.88 (d, 2H), 1.38 (d, 2H); Mass (ESI): 454.5 [M+1]; LC-MS: 454.5 (M+1); (column; X-Select CSH C-18 (50 $\times$ 3.0 mm, 3.5 μ m); RT 2.80 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity BEH C-18 50 X 2.1 mm, 1.7 μ m); RT 1.60 min. ACN: 0.025% Aq TFA; 0.5 mL/min. TLC: 5% MeOH:CH₂Cl₂ (R_f 0.2).

[0251] Racemic compound of Example 32 was separated using a Chiralpak ADH (250 x 20 mm, 5 μ 70 mg loading; (A) 0.1 % DEA in *n*-hexane (B) EtOH:MeOH (50:50) (A:B : 70:30) as the mobile phase) to provide the compound of Example 32A Fraction I (+) and the compound of Example 32B Fraction II (-).

Example 32A

Synthesis of (+)-7-(3, 5-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



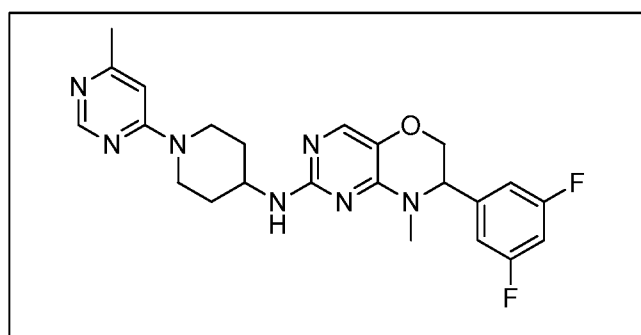
[0252] The compound of Example 32A was produced as described in Example 32.

Analytical data for product Fraction I (+): ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.32 (s, 1H), 7.45 (s, 1H), 7.22 (t, 1H), 6.88 (d, 2H), 6.70 (s, 1H), 6.26 (d, 1H), 4.79 (s, 1H), 4.36-4.29 (m, 2H), 4.18 (d, 1H), 4.10 (d, 1H), 3.94-3.86 (m, 1H), 3.07-3.00 (m, 2H), 2.99 (s, 3H), 2.22 (s, 3H), 1.92-1.85 (m, 2H), 1.40-1.32 (m, 2H); Mass (ESI): 454.4 [M+1]; LC-MS: 454.4 (M+1); (column; X-Select CSH C-18 (50 $\times$ 3.0 mm, 3.5 μ m); RT 2.77 min. 0.05% Aq TFA: ACN;

0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1 mm, 1.7 μm); RT 1.51 min.
 ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 15.91 min (CHIRALPAK-AD-H
 (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) EtOH:MeOH (50:50)
 (A:B : 70:30; flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.99}$: +63.32 (c 0.25, DCM).

Example 32B

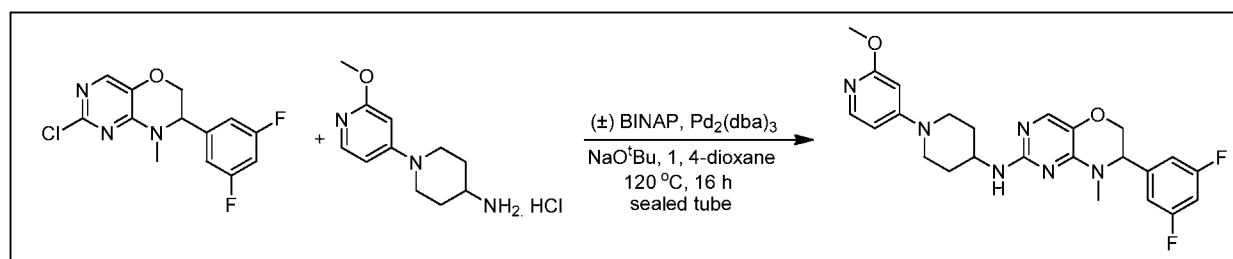
Synthesis of (-)-7-(3, 5-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0253] The compound of Example 32B was produced as described in Example 32.
 Analytical data for product Fraction II (-): $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 8.32 (s, 1H), 7.45 (s, 1H), 7.22 (t, 1H), 6.88 (d, 2H), 6.70 (s, 1H), 6.26 (d, 1H), 4.79 (s, 1H), 4.37-4.29 (m, 2H), 4.18 (d, 1H), 4.10 (d, 1H), 3.94-3.86 (m, 1H), 3.07-3.00 (m, 2H), 2.99 (s, 3H), 2.22 (s, 3H), 1.94-1.88 (m, 2H), 1.42-1.32 (m, 2H); Mass (ESI): 454.6 [M+1]; LC-MS: 454.3 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.77 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1 mm, 1.7 μm); RT 1.50 min.
 ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 24.37 min (CHIRALPAK-AD-H (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) EtOH:MeOH (50:50) (A:B : 70:30; flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: -69.96 (c 0.25, DCM).

Example 33

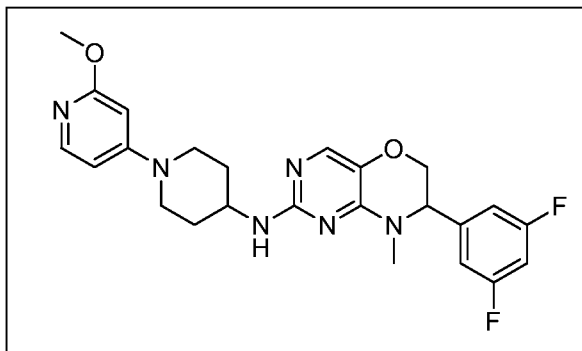
Synthesis of 7-(3, 5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 7-(3, 5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

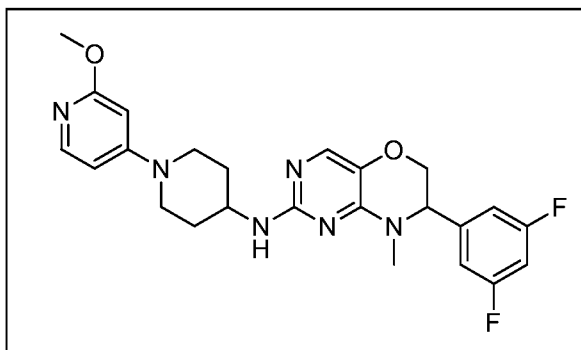
[0254] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (8 mg, 0.009 mmol) and ($\pm$) BINAP (17 mg, 0.02 mmol) in 1, 4-dioxane (0.25 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-7-(3, 5-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (50 mg, 0.18 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (48 mg, 0.19 mmol) and sodium tertiary butoxide (52 mg, 0.54 mmol) in 1, 4-dioxane (0.25 mL) was degassed with argon and the catalyst premixture was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 40% EtOAc:hexanes to afford 7-(3, 5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (35 mg, 41%) as an off-white solid. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ 7.80 (d, 1H), 7.48 (s, 1H), 7.20 (t, 1H), 6.90 (d, 2H), 6.55 (d, 1H), 6.32 (d, 1H), 6.10 (s, 1H), 4.80 (s, 1H), 4.18-4.12 (m, 2H), 3.90-3.80 (m, 3H), 3.74 (s, 3H), 2.97-2.90 (m, 5H), 1.92-1.89 (m, 2H), 1.46-1.43 (m, 2H); Mass (ESI): 469.6 $[\text{M}+1]$; LC-MS: 469.6 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 2.86 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity BEH C-18 50 X 2.1 mm, 1.7 μm); RT 1.64 min. ACN: 0.025% Aq TFA; 0.5 mL/min. TLC: 50% EtOAc:hexanes (R_f 0.4).

[0255] Racemic compound of Example 33 was separated using a Chiralpak IB (250 x 20 mm, 5 μ (20 mg loading; (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 :MeOH (80:20) (A:B : 90:10) as the mobile phase) to provide the compound of Example 33A Fraction I (+) and the compound of Example 33B Fraction II (-).

Example 33A**Synthesis of (+)-7-(3, 5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine**

[0256] The compound of Example 33A was produced as described in Example 33. Analytical data for product Fraction I (+): ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.77 (d, 1H), 7.45 (s, 1H), 7.21 (t, 1H), 6.90 (d, 2H), 6.53 (d, 1H), 6.28 (d, 1H), 6.10 (s, 1H), 4.79 (s, 1H), 4.20-4.10 (m, 2H), 3.88-3.80 (m, 3H), 3.75 (s, 3H), 2.98 (s, 3H), 2.97-2.90 (m, 2H), 1.90-1.85 (m, 2H), 1.48-1.40 (m, 2H); Mass (ESI): 454.6 [M+1]; LC-MS: 469.3 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.82 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1 mm, 1.7 μm); RT 1.57 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC RT = 24.35 min (CHIRALPAK-IB (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (80:20) (A:B : 90:10; flow Rate: 1.0 mL/min); Optical rotation [α]_D^{19.96}: +75.02 (c 0.25, DCM); TLC: 50% EtOAc:hexanes (R_f 0.4).

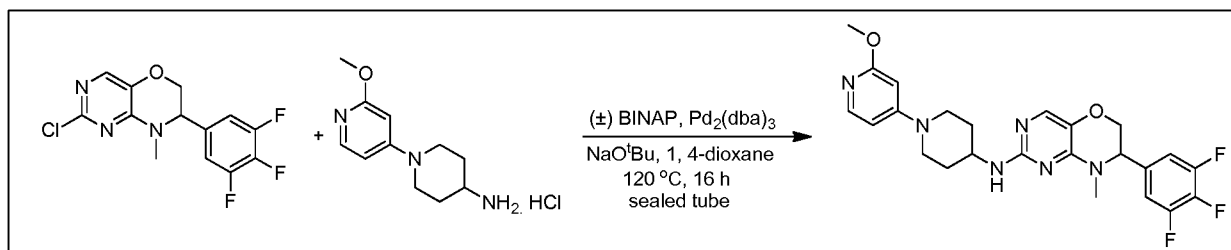
Example 33B**Synthesis of (-)-7-(3, 5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine**



[0257] The compound of Example 33B was produced as described in Example 33. Analytical data for product Fraction II (-): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 7.77 (d, 1H), 7.45 (s, 1H), 7.21 (t, 1H), 6.90 (d, 2H), 6.53 (d, 1H), 6.28 (d, 1H), 6.10 (s, 1H), 4.79 (s, 1H), 4.20-4.10 (m, 2H), 3.88-3.80 (m, 3H), 3.75 (s, 3H), 3.98 (s, 3H), 3.97-3.90 (m, 2H), 1.90-1.85 (m, 2H), 1.48-1.40 (m, 2H); Mass (ESI): 469.4 $[\text{M}+1]$; LC-MS: 469.3 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.81 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50×2.1 mm, $1.7 \mu\text{m}$); RT 1.57 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 29.92 min (CHIRALPAK-IB (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 :MeOH (80:20) (A:B : 90:10; flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.99}$: -67.56 (c 0.25, DCM); TLC: 50% EtOAc:hexanes (R_f : 0.4).

Example 34

Synthesis of *N*-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



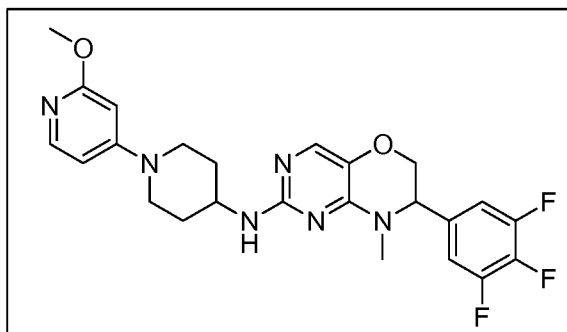
Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0258] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (22 mg, 0.02 mmol) and ($\pm$) BINAP (20 mg, 0.03 mmol) in 1, 4-dioxane (0.5 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-8-methyl-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (50 mg, 0.15 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (42 mg, 0.17 mmol) and sodium tertiary butoxide (61 mg, 0.60 mmol) in 1, 4-dioxane (0.5 mL) was degassed with argon and the catalyst premixture was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was diluted with water (5 mL) and extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 60% EtOAc:hexanes to afford 50 mgs further purified by preparative HPLC [Kromasil C18 (250 x 21.2mm 10 μm) (40mg loading; *n*-hexane; CH_2Cl_2 :MeOH (50:50); (85:15) as the mobile phase with a Flow rate=15 mL/min] to afford N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (12 mg, 15%) as an off-white solid. ^1H -NMR ($\text{CD}_3\text{OD}+\text{DMSO}-d_6$, 400 MHz): δ 7.76 (d, 1H), 7.42 (s, 1H), 7.02 (t, 2H), 6.56 (d, 1H), 6.16 (s, 1H), 4.68 (s, 1H), 4.16 (s, 2H), 3.98-3.92 (m, 3H), 3.84 (s, 3H), 3.10-3.02 (m, 5H), 2.12-2.09 (m, 2H), 1.57-1.54 (m, 2H); Mass (ESI): 487.5 [M+1]; LC-MS: 487.4 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 2.88 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity BEH C-18 50 X 2.1 mm, 1.7 μm); RT 1.64 min. ACN: 0.025% Aq TFA; 0.5 mL/min. TLC: 70% EtOAc:hexanes (R_f 0.2).

[0259] Racemic compound of Example 34 was separated using a Chiralpak IB (250 x 20 mm, 5 μ (20 mg loading; (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 :MeOH (50:50) (A:B : 90:10) as the mobile phase) to provide the compound of Example 34A Fraction I (+) and the compound of Example 34B Fraction II (-).

Example 34A

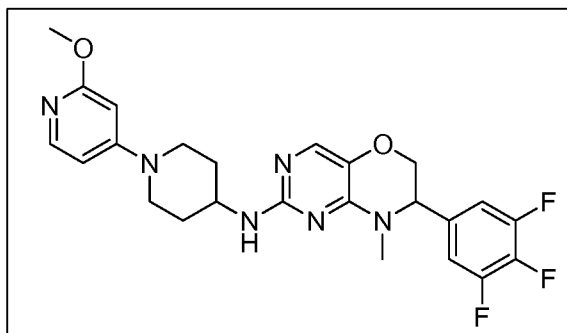
Synthesis of (+)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0260] The compound of Example 34A was produced as described in Example 34. Analytical data for product Fraction I (+): $^1\text{H-NMR}$ (CD_3OD + DMSO (2 drops), 400 MHz): δ 7.75 (d, 1H), 7.41 (s, 1H), 7.02 (t, 2H), 6.54 (d, 1H), 6.17 (s, 1H), 4.69-4.67 (m, 1H), 4.15 (d, 2H), 3.96-3.89 (m, 3H), 3.82 (s, 3H), 3.25 (s, 3H), 3.03-3.00 (m, 2H), 2.10-2.08 (m, 2H), 1.60-1.51 (m, 2H); Mass (ESI): 487.5 $[\text{M}+1]$; LC-MS: 487.4 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.82 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.65 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 29.09 min (CHIRALPAK-IB (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 :MeOH (50:50) (A:B : 90:10; flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{19.98}$: +71.24 (c 0.25, DCM); TLC: 70% EtOAc:hexanes (R_f : 0.2).

Example 34B

Synthesis of (-)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

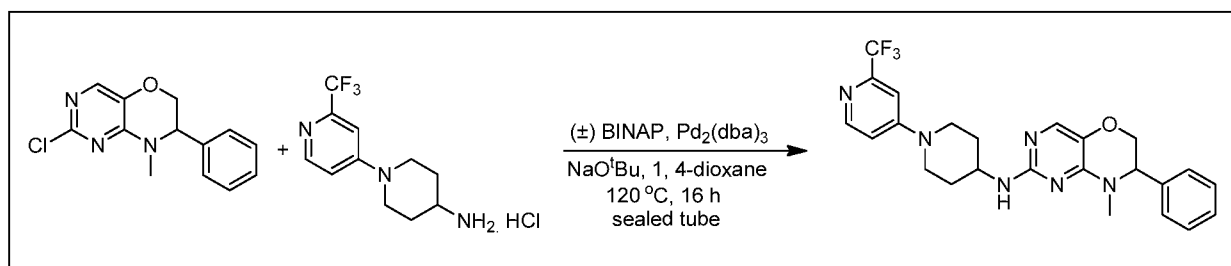


[0261] The compound of Example 34B was produced as described in Example 34. Analytical data for product Fraction II (-): $^1\text{H-NMR}$ (CD_3OD + DMSO (2 drops), 400 MHz):

δ 7.75 (d, 1H), 7.41 (s, 1H), 7.03-6.99 (m, 2H), 6.54 (d, 1H), 6.17 (s, 1H), 4.69-4.67 (m, 1H), 4.26 (d, 2H), 3.96-3.89 (m, 3H), 3.82 (s, 3H), 3.25 (s, 3H), 3.03-3.00 (m, 2H), 2.10-2.08 (m, 2H), 1.60-1.51 (m, 2H); Mass (ESI): 487.5 [M+1]; LC-MS: 487.4 (M+1); (column; X-Select CSH C-18 (50 $\times$ 3.0 mm, 3.5 μ m); RT 2.82 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 $\times$ 50 mm, 1.7 μ m); RT 1.65 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 34.06 min (CHIRALPAK-IB (250 $\times$ 4.6 mm, 5 μ m; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (50:50) (A:B : 90:10; flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: -54.96 (c 0.25, DCM); TLC: 70% EtOAc:hexanes (*R_f* 0.2).

Example 35

Synthesis of 8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

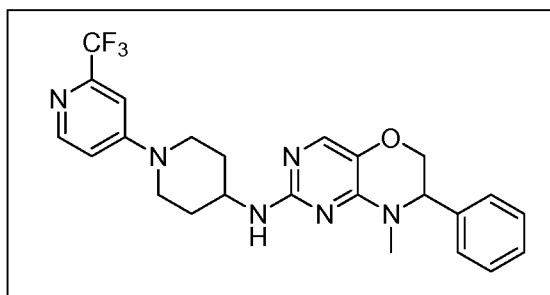
[0262] To a dry vial was added a suspension of Pd₂(dba)₃ (17 mg, 0.01 mmol) and (±) BINAP (36 mg, 0.05 mmol) in 1, 4-dioxane (0.5 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (100 mg, 0.38 mmol), 1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-amine hydrochloride (118 mg, 0.42 mmol) and sodium tertiary butoxide (110 mg, 1.14 mmol) in 1, 4-dioxane (0.5 mL) was degassed with argon and the catalyst premixure was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was diluted with water (50 mL) and extracted with CH₂Cl₂ (2 $\times$ 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*.

The crude material was purified by silica gel column chromatography using 4% MeOH:CH₂Cl₂ to afford 120 mgs further purified by preparative HPLC [Kromasil C18 (250 x 21.2mm 10 μm) (50 mg loading; CH₃CN;0.05% TFA Aq; (0.1/90, 15/70, 25/10, 35/10) as the mobile phase with a Flow rate=15 mL/min] to afford 8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (52 mg, 29%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.24 (d, 1H), 7.43 (s, 1H), 7.39-7.29 (m, 3H), 7.20-7.18 (m, 3H), 7.04-7.02 (m, 1H), 6.24 (d, 1H), 4.70-4.69 (m, 1H), 4.15-4.10 (m, 2H), 4.08-4.07 (m, 2H), 4.03-4.02 (m, 1H), 3.06 (t, 2H), 2.94 (s, 3H), 1.56-1.93 (m, 2H), 1.53-1.51 (m, 2H); LC-MS: 471.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.07 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity BEH C-18 50 X 2.1 mm, 1.7 μm); RT 1.83 min. ACN: 0.025% Aq TFA; 0.5 mL/min. TLC: 5% MeOH:DCM (R_f 0.2).

[0263] Racemic compound of Example 35 was separated using a Chiralpak IB (250 x 20 mm, 5μ (30 mg loading; (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (80:20) (A:B : 90:10) as the mobile phase) to provide the compound of Example 35A Fraction I (+) and the compound of Example 35B Fraction II (-).

Example 35A

Synthesis of (+)-8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

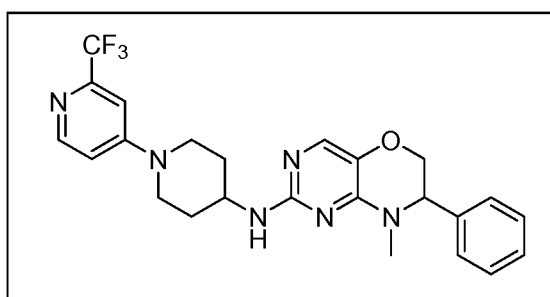


[0264] The compound of Example 35A was produced as described in Example 35. Analytical data for Fraction I (+): ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.25-8.20 (m, 1H), 7.41 (s, 1H), 7.40-7.33 (m, 3H), 7.20-7.18 (m, 3H), 7.04-7.02 (m, 1H), 6.22 (d, 1H), 4.70-4.68 (m, 1H), 4.12-4.09 (m, 2H), 4.01-3.98 (m, 2H), 3.91-3.86 (m, 1H), 3.06 (t, 2H), 2.92 (s, 3H), 1.97-1.89 (m, 2H), 1.51-1.40 (m, 2H); LC-MS: 471.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.10 min. 0.05% TFA in water: ACN; 0.80 ml/min); UPLC

(column; Acquity BEH C-18, 50 × 2.1 mm, 1.7 μm); RT 1.80 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 20.84 min (CHIRALPAK-IB (250 × 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (80:20) (A:B : 90:10; flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: +89.72 (c 0.25, DCM).

Example 35B

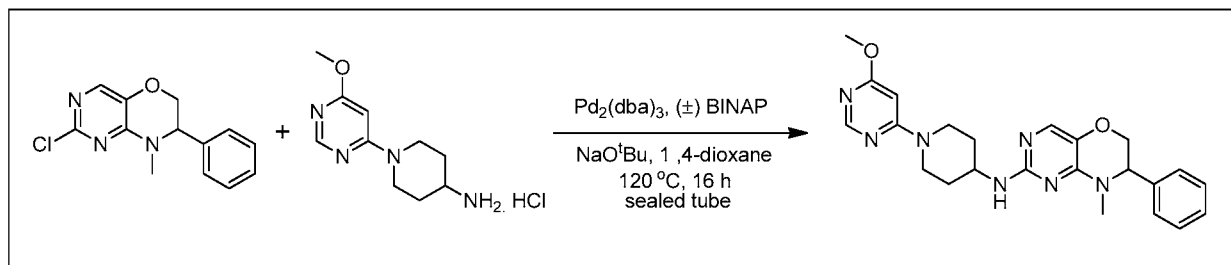
Synthesis of (-)-8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0265] The compound of Example 35B was produced as described in Example 35. Analytical data for Fraction II (-): ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.25-8.20 (m, 1H), 7.41 (s, 1H), 7.40-7.33 (m, 3H), 7.20-7.18 (m, 3H), 7.04-7.02 (m, 1H), 6.22 (d, 1H), 4.70-4.68 (m, 1H), 4.12-4.09 (m, 2H), 4.01-3.98 (m, 2H), 3.91-3.86 (m, 1H), 3.06 (t, 2H), 2.92 (s, 3H), 1.97-1.89 (m, 2H), 1.51-1.40 (m, 2H; LC-MS: 471.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.28 min. 0.05% TFA in water: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1 mm, 1.7 μm); RT 1.80 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 23.42 min (CHIRALPAK-IB (250 × 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (80:20) (A:B : 90:10; flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.98}$: -85.02 (c 0.25, DCM).

Example 36

Synthesis of N-(1-(6-methoxypyrimidin-4-yl) piperidin-4-yl)-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

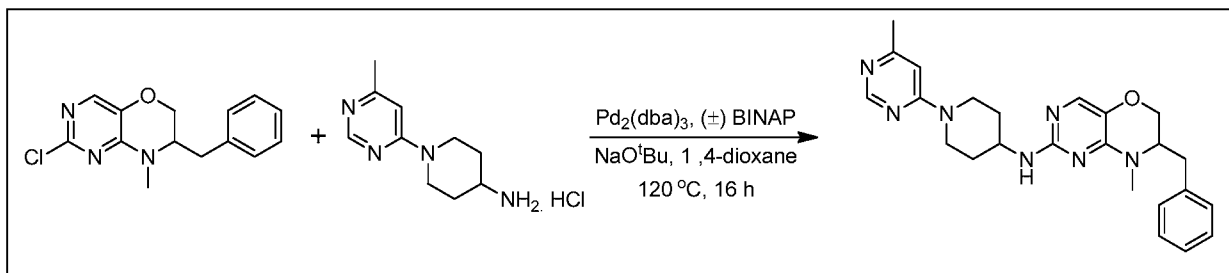


Synthesis of N-(1-(6-methoxypyrimidin-4-yl) piperidin-4-yl)-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0266] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (17 mg, 0.01 mmol) and ($\pm$) BINAP (36 mg, 0.05 mmol) in 1, 4-dioxane (0.5 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (100 mg, 0.38 mmol), 1-(6-methoxypyrimidin-4-yl) piperidin-4-amine hydrochloride (103 mg, 0.42 mmol) and sodium tertiary butoxide (110 mg, 1.14 mmol) in 1, 4-dioxane (0.5 mL) was degassed and the catalyst premixture was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 4% $\text{MeOH}:\text{CH}_2\text{Cl}_2$ and further purified by preparative HPLC [Kromasil C18 (250 x 21.2mm 10 μm) (50mg loading; CH_3CN : 0.05% TFA 0.01/90, 15/70, 25/10, 35/10 as mobile phase with a Flow rate =15 mL/min] to afford *N*-(1-(6-methoxypyrimidin-4-yl) piperidin-4-yl)-8-methyl-7-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (40 mg, 24%) as a white solid. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ 8.22 (s, 1H), 7.43 (s, 1H), 7.39-7.36 (m, 2H), 7.31 (d, 1H), 7.19 (d, 2H), 6.20 (d, 1H), 6.07 (s, 1H), 4.70 (d, 1H), 4.29-4.26 (m, 2H), 4.14-4.10 (m, 2H), 3.91-3.89 (m, 1H), 3.81 (s, 3H), 3.03-2.76 (m, 2H), 2.94 (s, 3H), 1.92-1.89 (m, 2H), 1.42-1.33 (m, 2H); LC-MS: 434.3 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 2.89 min. 0.05% Aq TFA:ACN; 0.80 mL/min); UPLC (column; Acquity BEH C-18 50 X 2.1 mm, 1.7 μm); RT 1.66 min. ACN: 0.025% TFA (Aq); 0.50 mL/min; TLC: 5% $\text{MeOH}:\text{CH}_2\text{Cl}_2$ (R_f 0.1).

Example 37

Synthesis of 7-benzyl-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



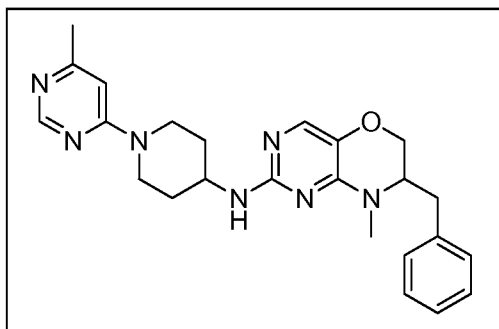
Synthesis of 7-benzyl-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0267] To a dry vial was added a suspension of Pd₂(dba)₃ (34 mg, 0.01 mmol) and (±) BINAP (68 mg, 0.54 mmol) in 1, 4-dioxane (0.5 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 7-benzyl-2-chloro-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (200 mg, 0.72 mmol), 1-(6-methylpyrimidin-4-yl) piperidin-4-amine hydrochloride (167 mg, 0.87 mmol) and sodium tertiary butoxide (279 mg, 2.90 mmol) in 1, 4-dioxane (0.5 mL) was degassed and the catalyst premixure was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC), the mixture was diluted with water (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 4% MeOH:CH₂Cl₂ and further purified by preparative HPLC to afford 7-benzyl-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (42 mg, 27%) as a pale yellow solid. LC-MS: 432.5 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.36 min. 5 mM NH₄OAc: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1mm, 1.7 μm); RT 1.62 min. ACN: 0.025% TFA (Aq); 0.50 ml/min.

[0268] Racemic compound of Example 37 was separated using a Chiralpak IA (250 x 20 mm, 5μm (35 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂:MeOH (50:50); (A:B: 75:25) as the mobile phase) to provide the compound of Example 37A Fraction I (+) and the compound of Example 37B Fraction II (-).

Example 37A

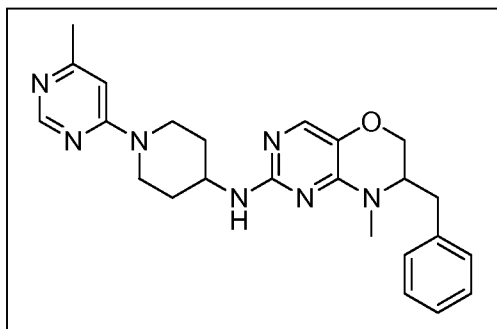
Synthesis of (+)-7-benzyl-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0269] The compound of Example 37A was produced as described in Example 37. Analytical data for product Fraction I (+): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.33 (s, 1H), 7.41 (s, 1H), 7.31-7.21 (m, 5H), 6.70 (s, 1H), 6.09 (d, 1H), 4.33-4.28 (m, 2H), 3.89 (d, 2H), 3.73-3.67 (m, 2H), 3.04-3.00 (m, 3H), 2.93 (s, 3H), 2.71-2.67 (m, 1H), 2.21 (s, 3H), 1.91-1.89 (m, 2H), 1.40-1.30 (m, 2H); Mass (ESI): 432.5 $[\text{M}+1]$; LC-MS: 432.5 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 3.64 min. 5 mM NH_4OAc : ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50×2.1 mm, $1.7 \mu\text{m}$); RT 1.63 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 11.58 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$); mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 :MeOH (50:50) (A:B : 75:25); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.99}$: +33.13 (c 0.25, DCM).

Example 37B

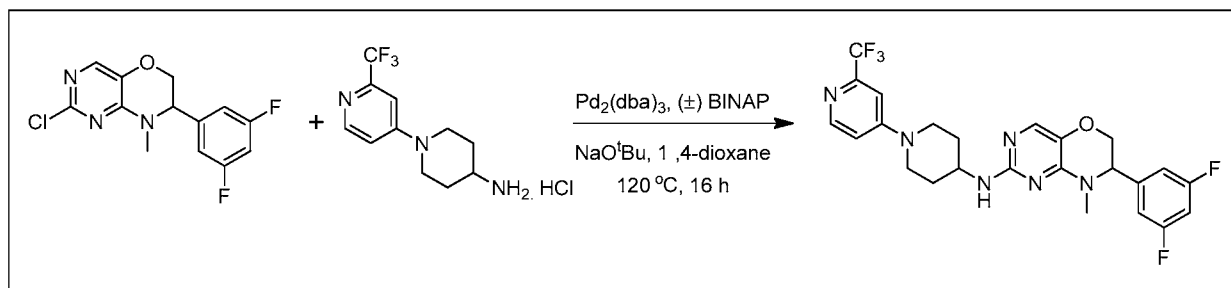
Synthesis of (-)-7-benzyl-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0270] The compound of Example 37B was produced as described in Example 37. Analytical data for product Fraction II (-): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.33 (s, 1H), 7.41 (s, 1H), 7.31-7.21 (m, 5H), 6.70 (s, 1H), 6.09 (d, 1H), 4.33-4.28 (m, 2H), 3.89 (d, 2H), 3.73-3.67 (m, 2H), 3.04-3.00 (m, 3H), 2.93 (s, 3H), 2.71-2.67 (m, 1H), 2.21 (s, 3H), 1.91-1.89 (m, 2H), 1.40-1.30 (m, 2H); Mass (ESI): 432.5 $[\text{M}+1]$; LC-MS: 432.5 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 3.61 min. 5 mM NH_4OAc : ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50×2.1 mm, $1.7 \mu\text{m}$); RT 1.63 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 22.98 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$); mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 :MeOH (50:50) (A:B : 75:25); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{20.00}$: -50.03 (c 0.25, DCM).

Example 38

Synthesis of 7-(3, 5-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 7-(3, 5-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

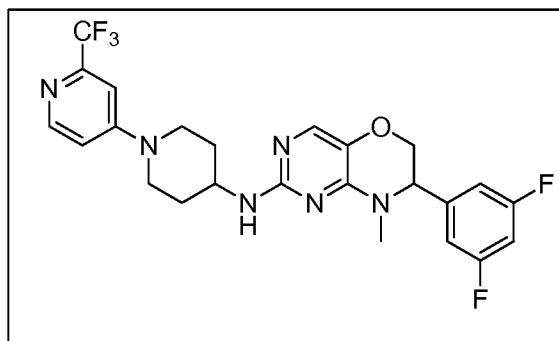
[0271] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (31 mg, 0.03 mmol) and (±) BINAP (63 mg, 0.10 mmol) in 1, 4-dioxane (1 mL). The suspension was degassed with argon, heated to 120°C and stirred for 3 min. A mixture of 2-chloro-7-(3, 5-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (200 mg, 0.67 mmol), 1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-amine hydrochloride (208 mg, 0.74 mmol) and sodium tertiary butoxide (194 mg, 2.01 mmol) in 1, 4-dioxane (1 mL) was degassed and the catalyst premixure was added. The reaction mixture was heated to 120°C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS),

the mixture was diluted with water (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 4% MeOH:CH₂Cl₂ to afford 7-(3, 5-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (200 mg, 59%) as a pale yellow solid. LC-MS: 507.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.14 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1 mm, 1.7 μm); RT 1.89 min. ACN: 0.025% TFA (Aq); 0.50 ml/min.

[0272] Racemic compound of Example 38 was separated using a Chiralpak IB (250 x 20 mm, 5μ (30 mg loading; (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (80:20) (A:B : 90:10) as the mobile phase) to provide the compound of Example 38A Fraction I (+) and the compound of Example 38B Fraction II (-).

Example 38A

Synthesis of (+)-7-(3, 5-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

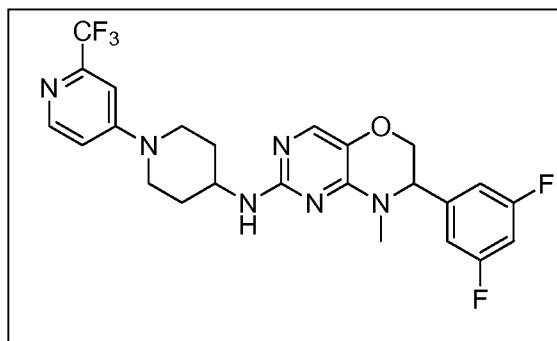


[0273] The compound of Example 38A was produced as described in Example 38. Analytical data for product Fraction I (+): ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.21 (d, 1H), 7.44 (s, 1H), 7.20-7.14 (m, 2H), 7.00-6.98 (m, 1H), 6.90-6.88 (m, 2H), 6.28 (d, 1H), 4.78-4.75 (m, 1H), 4.19-4.08 (m, 4H), 4.00-3.88 (m, 1H), 3.03 (t, 2H), 2.93 (s, 3H), 1.94-1.89 (m, 2H), 1.50-1.40 (m, 2H); LC-MS: 507.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.18 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1mm, 1.7 μm); RT 1.88 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 15.39 min (CHIRALPAK-IB (250 x 4.6mm, 5 μm; mobile phase (A) 0.1 %

DEA in *n*-hexane (B) CH₂Cl₂:MeOH (80:20) (A:B : 85:15); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.99}$: +62.08 (c 0.25, DCM).

Example 38B

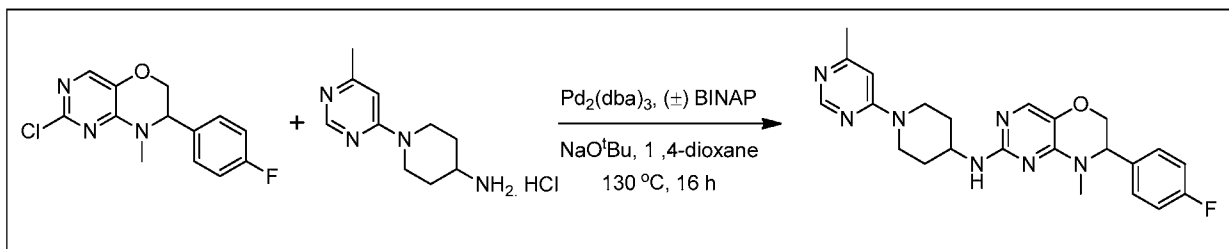
Synthesis of (-)-7-(3, 5-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0274] The compound of Example 38B was produced as described in Example 38. Analytical data for product Fraction II (-): ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.21 (d, 1H), 7.44 (s, 1H), 7.20-7.14 (m, 2H), 7.00-6.98 (m, 1H), 6.90-6.88 (m, 2H), 6.28 (d, 1H), 4.78-4.75 (m, 1H), 4.19-4.08 (m, 4H), 4.00-3.88 (m, 1H), 3.03 (t, 2H), 2.93 (s, 3H), 1.94-1.89 (m, 2H), 1.50-1.40 (m, 2H); LC-MS: 507.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.18 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1 mm, 1.7 μm); RT 1.89 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 17.65 min (CHIRALPAK-IB (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (80:20) (A:B : 85:15); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.99}$: -71.68 (c 0.25, DCM).

Example 39

Synthesis of 7-(4-fluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



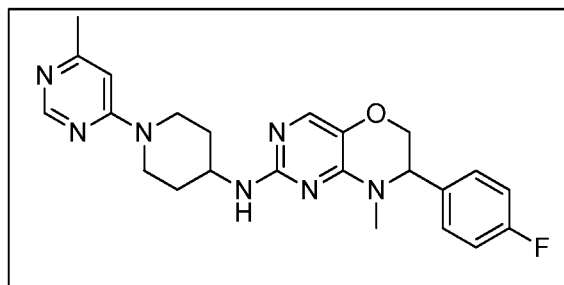
Synthesis of 7-(4-fluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0275] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (33 mg, 0.03 mmol) and ($\pm$) BINAP (67 mg, 0.10 mmol) in 1, 4-dioxane (2 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-7-(4-fluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (200 mg, 0.71 mmol), 1-(6-methylpyrimidin-4-yl) piperidin-4-amine hydrochloride (150 mg, 0.78 mmol) and sodium tertiary butoxide (205 mg, 2.14 mmol) in 1, 4-dioxane (1 mL) was degassed and the catalyst premixure was added. The reaction mixture was heated to 130 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 4% MeOH: CH_2Cl_2 to afford 7-(4-fluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (200 mg, 59%) as an off-white solid. UPLC (column; Acquity BEH C-18, 50 x 2.1mm, 1.7 μm); RT 1.56 min. ACN: 0.025% TFA (Aq); 0.50 ml/min.

[0276] Racemic compound of Example 39 was separated using a Chiralpak IA (250 x 20 mm, 5 μm (50 mg loading; 0.1 % DEA in *n*-hexane: CH_2Cl_2 :MeOH (50:50); (A:B : 85:15) as the mobile phase) to provide the compound of Example 39A Fraction I (+) and the compound of Example 39B Fraction II (-).

Example 39A

Synthesis of (+)-7-(4-fluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

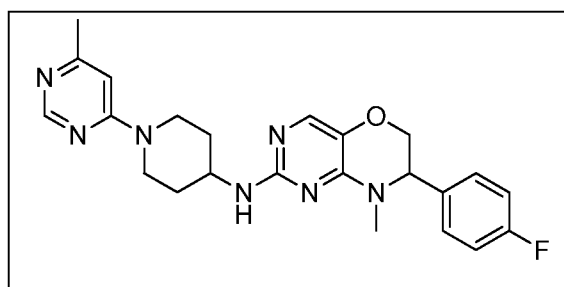


[0277] The compound of Example 39A was produced as described in Example 39.

Analytical data for product Fraction I (+): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.35 (s, 1H), 7.42 (s, 1H), 7.26-7.17 (m, 4H), 6.69 (s, 1H), 6.21 (d, 1H), 4.71-4.69 (m, 1H), 4.34-4.27 (m, 2H), 4.11-4.08 (m, 2H), 3.92-3.88 (m, 1H), 3.00 (t, 2H), 2.90 (s, 3H), 2.22 (s, 3H), 1.93-1.88 (m, 2H), 1.41-1.38 (m, 2H); Mass (ESI): 436.4 $[\text{M}+1]$; LC-MS: 436.5 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 3.52 min. 5 mM NH_4OAc :ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50×2.1 mm, $1.7 \mu\text{m}$); RT 1.53 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 23.11 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 :MeOH (50:50) (A:B : 85:15); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.01}$: +76.00 (c 0.25, DCM).

Example 39B

Synthesis of (-)-7-(4-fluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



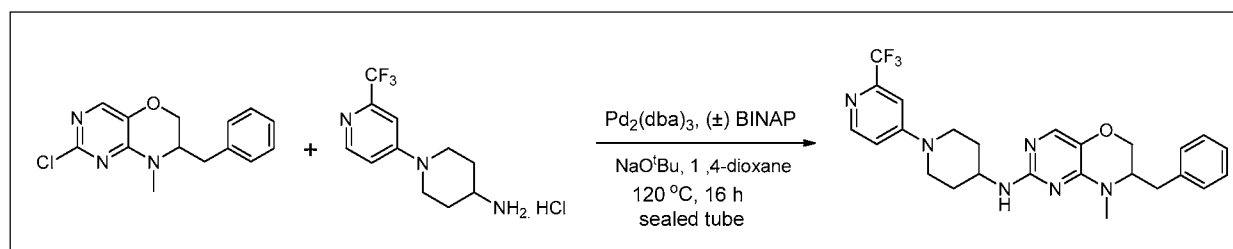
[0278] The compound of Example 39B was produced as described in Example 39.

Analytical data for product Fraction II (-): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.35 (s, 1H), 7.42 (s, 1H), 7.26-7.17 (m, 4H), 6.69 (s, 1H), 6.21 (d, 1H), 4.71-4.69 (m, 1H), 4.34-4.27 (m, 2H), 4.11-4.08 (m, 2H), 3.92-3.88 (m, 1H), 3.00 (t, 2H), 2.90 (s, 3H), 2.22 (s, 3H), 1.93-1.88 (m, 2H), 1.41-1.38 (m, 2H); Mass (ESI): 436.4 $[\text{M}+1]$; LC-MS: 436.5 (M+1); (column; X-

Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.34 min. 5 mM NH₄OAc:ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1mm, 1.7 μm); RT 1.52 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 32.68 min (CHIRALPAK-IA (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (50:50) (A:B : 85:15); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.95}$: -72.44 (c 0.25, DCM).

Example 40

Synthesis of 7-benzyl-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 7-benzyl-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

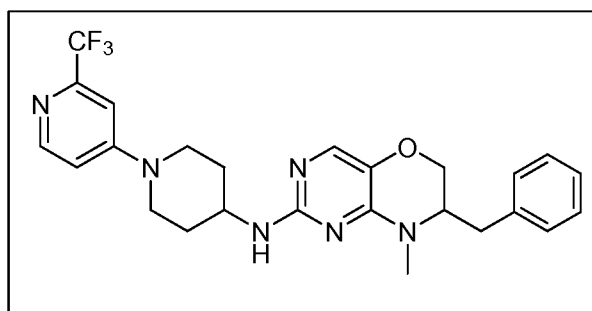
[0279] To a dry vial was added a suspension of Pd₂(dba)₃ (42 mg, 0.04 mmol) and (±) BINAP (85 mg, 0.13 mmol) in 1, 4-dioxane (1.25 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 7-benzyl-2-chloro-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 0.90 mmol), 1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-amine hydrochloride (281 mg, 1.00 mmol) and sodium tertiary butoxide (262 mg, 2.72 mmol) in 1, 4-dioxane (1.25 mL) was degassed and the catalyst premixure was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was diluted with water (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 2-4% MeOH:CH₂Cl₂ to afford 7-benzyl-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (200 mg, 45%) as an off-white solid. LC-MS: 485.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.20

min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1 mm, 1.7 μm); RT 1.88 min. ACN: 0.025% TFA (Aq); 0.50 ml/min.

[0280] Racemic compound of Example 40 was separated using a Chiralpak-IA (250 x 20 mm, 5μm (50 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂:MeOH (50:50); (A:B : 85:15) as the mobile phase to provide the compound of Example 40A Fraction I (+) and the compound of Example 40B Fraction II (-).

Example 40A

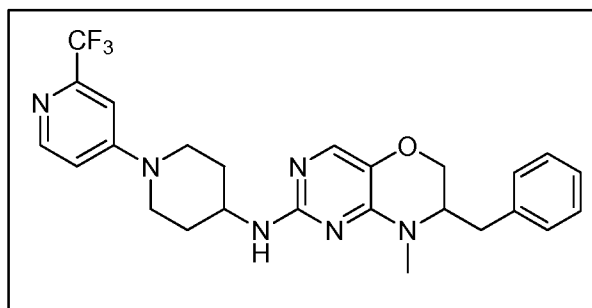
Synthesis of (+)-7-benzyl-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0281] The compound of Example 40A was produced as described in Example 40. Analytical data for product Fraction I (+): ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.21 (d, 1H), 7.41 (s, 1H), 7.35-7.27 (m, 2H), 7.25-7.20 (m, 3H), 7.19 (s, 1H), 7.02-7.00 (m, 1H), 6.11 (d, 1H), 4.00-3.96 (m, 2H), 3.91-3.82 (m, 2H), 3.71-3.65 (m, 2H), 3.09-3.00 (m, 3H), 2.91 (s, 3H), 2.70-2.67 (m, 1H), 1.93-1.89 (m, 2H), 1.47-1.39 (m, 2H); LC-MS: 485.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.15 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1 mm, 1.7 μm); RT 1.85 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 11.77 min (CHIRALPAK-IA (250 x 4.6mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (50:50) (A:B : 80:20); flow Rate: 1.0 mL/min); Optical rotation [α]_D^{21.41}: +44.78 (c 0.25, DCM).

Example 40B

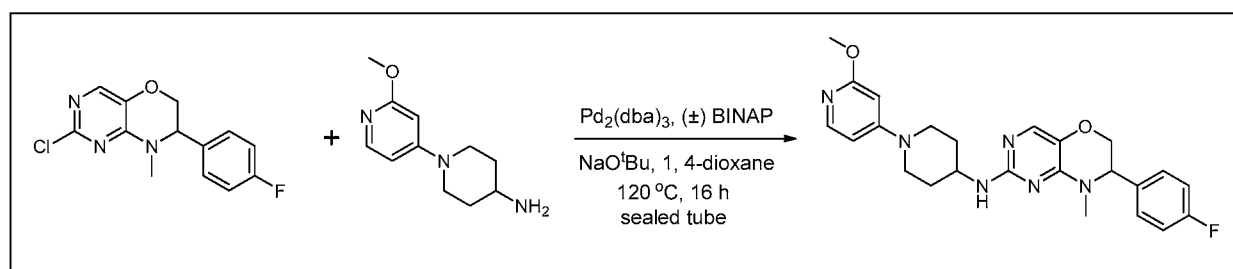
Synthesis of (-)-7-benzyl-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0282] The compound of Example 40B was produced as described in Example 40. Analytical data for product Fraction II (-): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.21 (d, 1H), 7.40 (s, 1H), 7.30-7.27 (m, 2H), 7.25-7.20 (m, 3H), 7.19 (s, 1H), 7.02-7.00 (m, 1H), 6.11 (d, 1H), 4.00-3.96 (m, 2H), 3.80-3.82 (m, 2H), 3.70-3.62 (m, 2H), 3.09-3.00 (m, 3H), 2.91 (s, 3H), 2.70-2.67 (m, 1H), 1.93-1.89 (m, 2H), 1.47-1.39 (m, 2H); LC-MS: 485.3 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 3.15 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50×2.1 mm, $1.7 \mu\text{m}$); RT 1.85 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 15.06 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 :MeOH (50:50) (A:B : 80:20); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{21.22}$: -41.69 (c 0.25, DCM).

Example 41

Synthesis of 7-(4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



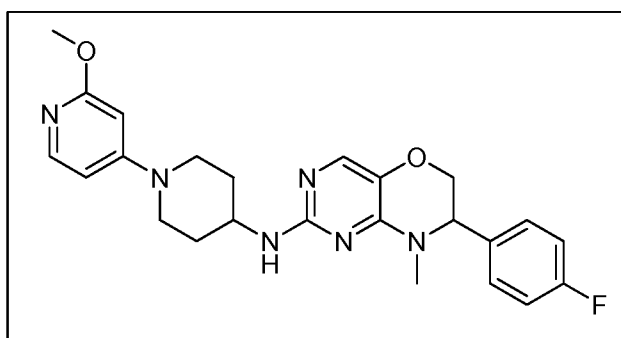
Synthesis of 7-(4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0283] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (66.8 mg, 0.03 mmol) and ($\pm$) BINAP (32 mg, 0.10 mmol) in 1, 4-dioxane (1 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-7-(4-fluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (200 mg, 0.71 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine (191 mg, 0.78 mmol) and sodium tertiary butoxide (232 mg, 2.14 mmol) in 1, 4-dioxane (1.5 mL) was degassed and the catalyst premixure was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 2% MeOH: CH_2Cl_2 to afford 7-(4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (180 mg, 37%) as an off-white solid. LC-MS: 451.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.66 min. 0.05% Aq TFA:ACN; 0.8 mL/min); UPLC (column; Acquity BEH C-18, 50 × 2.1 mm, 1.7 μm); RT 1.60 min. ACN: 0.025% TFA (Aq); 0.50 ml/min.

[0284] Racemic compound of Example 41 was separated using a Chiralpak-IB (250 x 20 mm, 5 μm) (20 mg loading; 0.1 % DEA in *n*-hexane: CH_2Cl_2 :MeOH (50:50); (A:B : 90:10) as the mobile phase to provide the compound of Example 41A Fraction I (+) and the compound of Example 41B Fraction II (-).

Example 41A

Synthesis of (+)-7-(4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

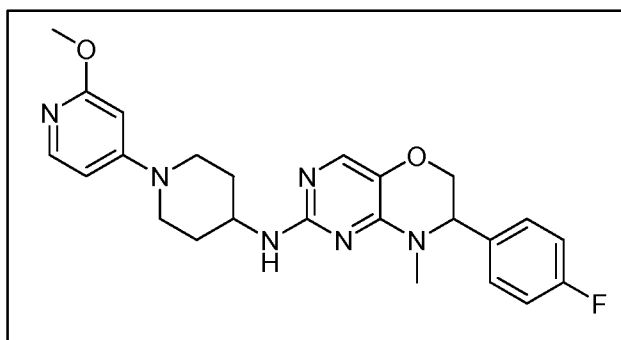


[0285] The compound of Example 41A was produced as described in Example 41. Analytical data for Fraction I (+): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.75 (d, 1H), 7.37 (s, 1H),

7.27-7.19 (m, 2H), 7.10 (t, 2H), 6.52-6.50 (m, 1H), 6.12 (s, 1H), 4.63-4.61 (m, 1H), 4.20-4.08 (m, 2H), 3.95-3.87 (m, 3H), 3.80 (s, 3H), 3.08-3.00 (m, 5H), 2.10-2.01 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 451.4 [M+1]; LC-MS: 451.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.78 min. 0.05% Aq TFA:ACN; 0.8 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.56 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 18.19 min (CHIRALPAK-IB (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (50:50) (90:10); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.01}$: +75.47 (c 0.25, DCM).

Example 41B

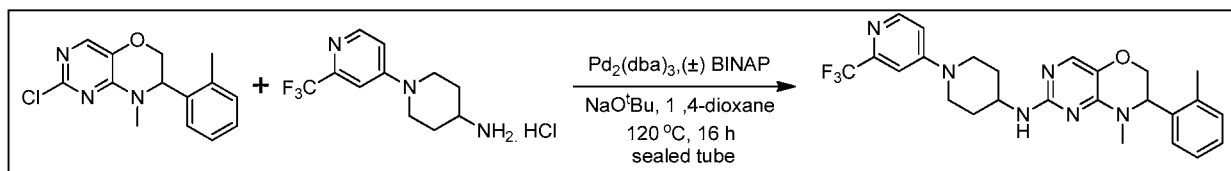
Synthesis of (-)-7-(4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0286] The compound of Example 41B was produced as described in Example 41. Analytical data for Fraction II (-): ¹H-NMR (CD₃OD, 400 MHz): δ 7.75 (d, 1H), 7.37 (s, 1H), 7.27-7.19 (m, 2H), 7.10 (t, 2H), 6.52-6.50 (m, 1H), 6.12 (s, 1H), 4.63-4.61 (m, 1H), 4.20-4.08 (m, 2H), 3.95-3.87 (m, 3H), 3.80 (s, 3H), 3.08-3.00 (m, 5H), 2.10-2.01 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 451.4 [M+1]; LC-MS: 451.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.78 min. 0.05% Aq TFA:ACN; 0.8 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.57 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 20.73 min (CHIRALPAK-IB (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (50:50) (A:B : 90:10); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.99}$: -60.96 (c 0.25, DCM).

Example 42

Synthesis of 8-methyl-7-(*o*-tolyl)-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine



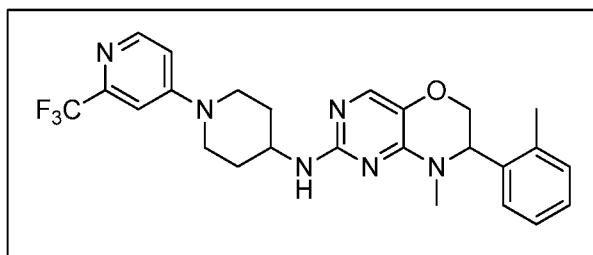
*Synthesis of 8-methyl-7-(*o*-tolyl)-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine*

[0287] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (33 mg, 0.03 mmol) and ($\pm$) BINAP (68 mg, 0.10 mmol) in 1, 4-dioxane (2 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-8-methyl-7-(*o*-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazine (200 mg, 0.72 mmol), 1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-amine hydrochloride (220 mg, 0.79 mmol) and sodium tertiary butoxide (210 mg, 2.18 mmol) in 1, 4-dioxane (2 mL) was degassed and the catalyst premixture was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 2-5% MeOH: CH_2Cl_2 to afford 8-methyl-7-(*o*-tolyl)-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine (100 mg, 28%) as an off-white solid. LC-MS: 485.4 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 3.16 min. 0.05% Aq TFA:ACN; 0.80 ml/min).

[0288] Racemic compound of Example 42 was separated using a Chiralpak IB (250 x 20 mm, 5 μm (30 mg loading; 0.1 % DEA in *n*-hexane: CH_2Cl_2 :MeOH (50:50); (90:10) as the mobile phase) to provide the compound of Example 42A Fraction I (+) and the compound of Example 42B Fraction II (-).

Example 42A

Synthesis of (+)-8-methyl-7-(o-tolyl)-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

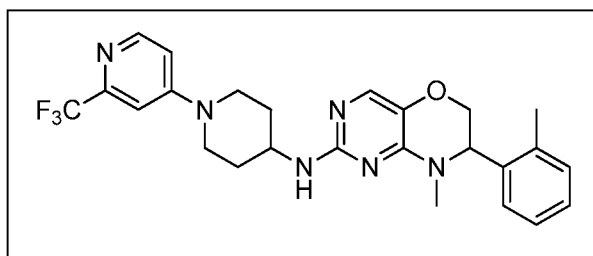


[0289] The compound of Example 42A was produced as described in Example 42.

Analytical data for product Fraction I (+): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.20 (d, 1H), 7.40 (s, 1H), 7.23-7.12 (m, 4H), 7.00-6.92 (m, 2H), 4.94-4.92 (m, 1H), 4.20-4.17 (m, 1H), 4.09-3.99 (m, 4H), 3.18 (t, 2H), 2.99 (s, 3H), 2.40 (s, 3H), 2.15-2.10 (m, 2H), 1.61-1.51 (m, 2H); Mass (ESI): 485.5 $[\text{M}+1]$; LC-MS: 485.4 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 3.21 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50×2.1 mm, $1.7 \mu\text{m}$); RT 1.86 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 12.71 min (CHIRALPAK-IB (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 :MeOH (50:50) (A:B : 90:10); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{20.00}$: +115.21 (c 0.25, DCM).

Example 42B

Synthesis of (-)-8-methyl-7-(o-tolyl)-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



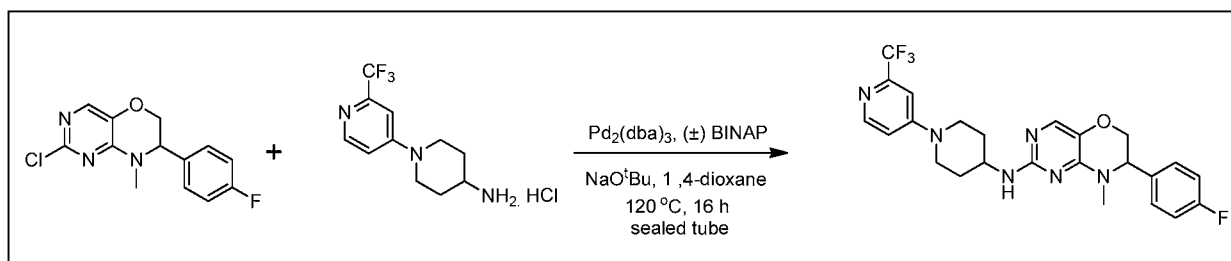
[0290] The compound of Example 42B was produced as described in Example 42.

Analytical data for product Fraction II (-): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.21 (d, 1H), 7.40 (s, 1H), 7.23-7.13 (m, 4H), 7.00-6.92 (m, 2H), 4.94-4.92 (m, 1H), 4.20-4.17 (m, 1H), 4.09-

3.99 (m, 4H), 3.17 (t, 2H), 2.99 (s, 3H), 2.40 (s, 3H), 2.15-2.10 (m, 2H), 1.61-1.51 (m, 2H); Mass (ESI): 485.5 [M+1]; LC-MS: 485.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.20 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1 mm, 1.7 μm); RT 1.85 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 14.76 min (CHIRALPAK-IB (250 x 4.6mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (50:50) (A:B : 90:10); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.98}$: -101.68 (c 0.25, DCM).

Example 43

Synthesis of 7-(4-fluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 7-(4-fluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

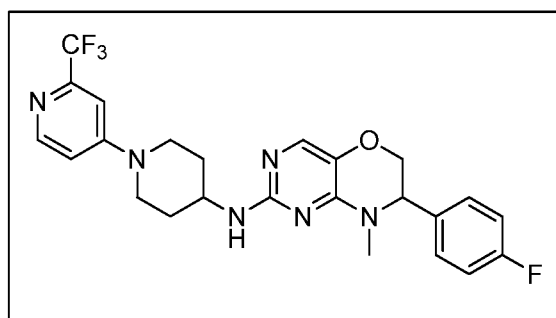
[0291] To a dry vial was added a suspension of Pd₂(dba)₃ (41 mg, 0.04 mmol) and (±) BINAP (83 mg, 0.13 mmol) in 1, 4-dioxane (1.25 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-7-(4-fluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 0.89 mmol), 1-(2-(trifluoromethyl)pyridin-4-yl) piperidin-4-amine hydrochloride (276 mg, 0.98 mmol) and sodium tertiary butoxide (257 mg, 2.68 mmol) in 1, 4-dioxane (1.25 mL) was degassed and the catalyst premixture was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was concentrated *in vacuo*. The crude material was diluted with water (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 3% MeOH:CH₂Cl₂ to afford 7-(4-fluorophenyl)-8-

methyl-*N*-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6*H*-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine (120 mg, 27%) as an off-white solid. LC-MS: 489.5 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.12 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1mm, 1.7 μm); RT 1.72 min. ACN: 0.025% TFA (Aq); 0.50 ml/min.

[0292] Racemic compound of Example 43 was separated using a Chiralpak IA (250 x 20 mm, 5μm (30 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂:MeOH (50:50); (85:15) as the mobile phase) to provide the compound of Example 43A Fraction I (+) and the compound of Example 43B Fraction II (-).

Example 43A

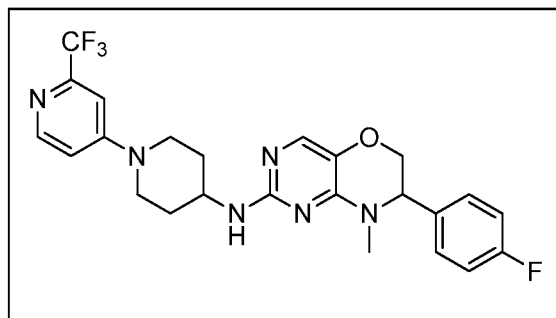
Synthesis of (+)-7-(4-fluorophenyl)-8-methyl-*N*-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6*H*-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine



[0293] The compound of Example 43A was produced as described in Example 43. Analytical data for product Fraction I (+): ¹H-NMR (CD₃OD, 400 MHz): δ 8.19 (d, 1H), 7.40 (s, 1H), 7.27-7.21 (m, 2H), 7.20-7.18 (m, 1H), 7.10 (t, 2H), 7.00-6.98 (m, 1H), 4.65-4.63 (m, 1H), 4.18-3.98 (m, 5H), 3.20-3.12 (m, 2H), 3.00 (s, 3H), 2.13-2.10 (m, 2H), 1.61-1.51 (m, 2H); Mass (ESI): 489.5 [M+1]; LC-MS: 489.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.07 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1mm, 1.7 μm); RT 1.67 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 18.09 min (CHIRALPAK-IA (250 x 4.6mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (50:50) (A:B : 85:15); flow Rate: 1.0 mL/min); Optical rotation [α]_D^{20.00}: +76.44 (c 0.25, DCM).

Example 43B

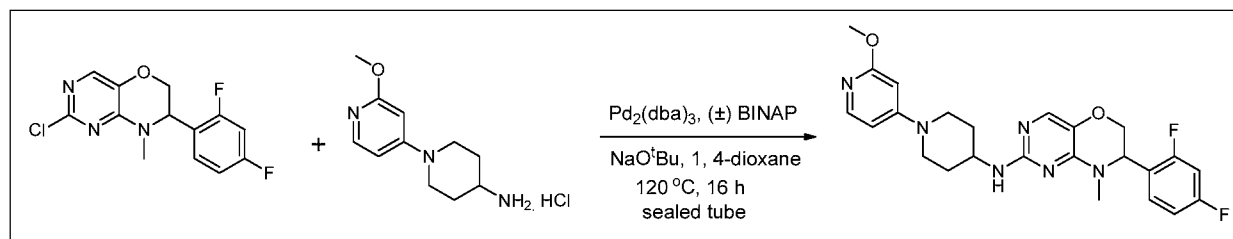
Synthesis of (-)-7-(4-fluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0294] The compound of Example 43B was produced as described in Example 43. Analytical data for product Fraction II (-): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 8.19 (d, 1H), 7.40 (s, 1H), 7.26-7.21 (m, 2H), 7.21-7.18 (m, 1H), 7.10 (t, 2H), 7.00-6.98 (m, 1H), 4.65-4.63 (m, 1H), 4.18-3.98 (m, 5H), 3.20-3.12 (m, 2H), 3.00 (s, 3H), 2.13-2.10 (m, 2H), 1.61-1.51 (m, 2H); Mass (ESI): 489.5 $[\text{M}+1]$; LC-MS: 489.4 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 3.07 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50×2.1 mm, $1.7 \mu\text{m}$); RT 1.68 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 21.11 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 :MeOH (50:50) (A:B : 85:15); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{20.01}$: -69.04 (c 0.25, DCM).

Example 44

Synthesis of 7-(2, 4-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



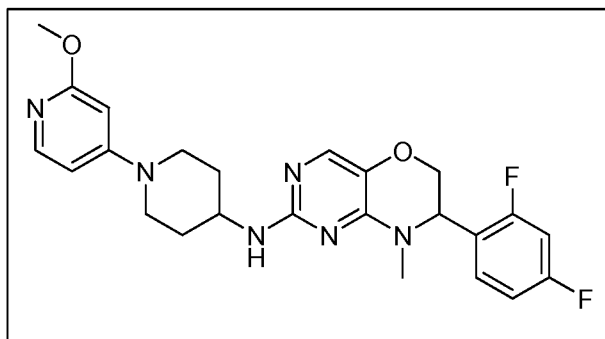
Synthesis of 7-(2, 4-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0295] To a dry vial was added a suspension of Pd₂(dba)₃ (41 mg, 0.04 mmol) and (±) BINAP (85 mg, 0.13 mmol) in 1, 4-dioxane (1.25 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-7-(2, 4-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 0.90 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (242 mg, 0.99 mmol) and sodium tertiary butoxide (262 mg, 2.72 mmol) in 1, 4-dioxane (1.25 mL) was degassed and the catalyst premixure was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was concentrated *in vacuo*. The crude material was diluted with water (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 3% MeOH:CH₂Cl₂ to afford 7-(2, 4-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (140 mg, 33%) as an off-white solid. LC-MS: 469.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.80 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.58 min. ACN: 0.025% TFA (Aq); 0.50 ml/min.

[0296] Racemic compound of Example 44 was separated using a Chiralpak-IA (250 x 20 mm, 5μm (50 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂:MeOH (50:50); (A:B : 70:30) as the mobile phase) to provide the compound of Example 44A Fraction I (-) and the compound of Example 44B Fraction II (+).

Example 44A

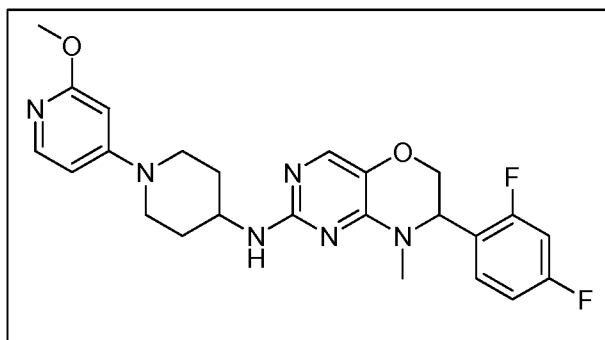
Synthesis of (-)-7-(2, 4-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0297] The compound of Example 44A was produced as described in Example 44. Analytical data for Fraction I (-): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.73 (d, 1H), 7.40 (s, 1H), 7.10-7.00 (m, 2H), 6.98-6.92 (m, 1H), 6.53 (d, 1H), 6.16 (s, 1H), 4.98-4.97 (m, 1H), 4.29-4.27 (m, 2H), 3.98-3.90 (m, 3H), 3.82 (s, 3H), 3.07 (s, 3H), 3.06-3.01 (m, 2H), 2.10-2.03 (m, 2H), 1.60-1.51 (m, 2H); Mass (ESI): 469.5 $[\text{M}+1]$; LC-MS: 469.4 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.89 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.60 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 9.41 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 :MeOH (50:50) (A:B : 70:30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{19.98}$: -90.38 (c 0.25, DCM).

Example 44B

Synthesis of (+)-7-(2, 4-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

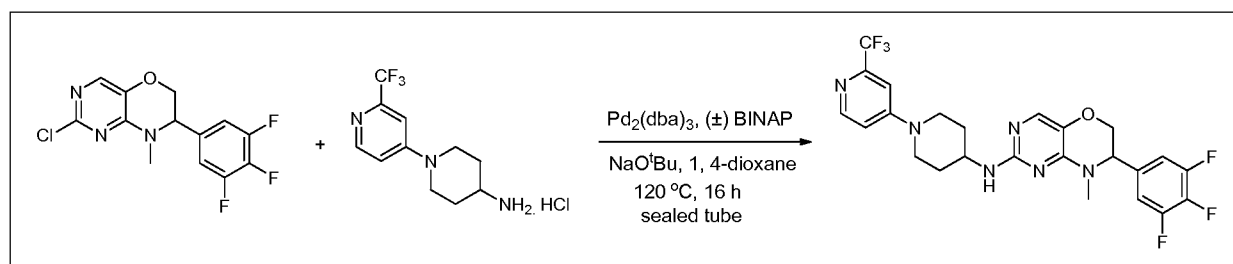


[0298] The compound of Example 44B was produced as described in Example 44. Analytical data for Fraction II (+): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.73 (d, 1H), 7.40 (s, 1H), 7.10-7.00 (m, 2H), 6.98-6.92 (m, 1H), 6.53 (d, 1H), 6.16 (s, 1H), 4.98-4.97 (m, 1H),

4.29-4.27 (m, 2H), 3.98-3.90 (m, 3H), 3.82 (s, 3H), 3.07 (s, 3H), 3.06-3.01 (m, 2H), 2.10-2.03 (m, 2H), 1.60-1.51 (m, 2H); Mass (ESI): 469.5 [M+1]; LC-MS: 469.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.90 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.60 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 13.33 min (CHIRALPAK-IA (250 × 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (50:50) (A:B : 70:30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.01}$: +93.02 (c 0.25, DCM).

Example 45

Synthesis of 8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

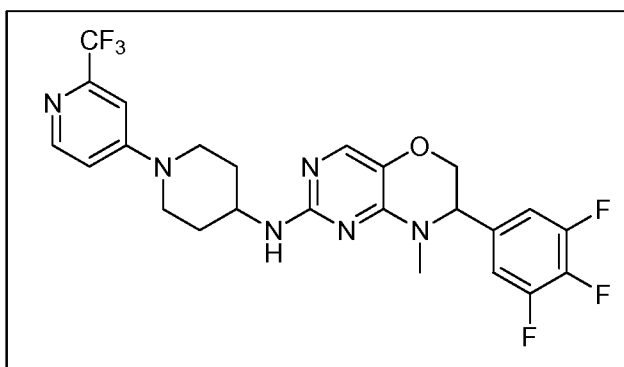
[0299] To a dry vial was added a suspension of Pd₂(dba)₃ (36 mg, 0.04 mmol) and (±) BINAP (74 mg, 0.11 mmol) in 1, 4-dioxane (1.25 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-8-methyl-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 0.79 mmol), 1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-amine hydrochloride (245 mg, 0.87 mmol) and sodium tertiary butoxide (229 mg, 2.38 mmol) in 1, 4-dioxane (1.25 mL) was degassed and the catalyst premixture was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was diluted with water (50 mL) and extracted with CH₂Cl₂ (2 × 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 2% MeOH:CH₂Cl₂ to afford 8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine.

(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6*H*-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine (150 mg, 36%) as an off-white solid. LC-MS: 525.3 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.26 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.90 min. ACN: 0.025% TFA (Aq); 0.50 ml/min.

[0300] Racemic compound of Example 45 was separated using a Chiralpak-ADH (250 x 20 mm, 5μm (20 mg loading; 0.1 % DEA in *n*-hexane: EtOH:MeOH (50:50); (A:B : 85:15) as the mobile phase) to provide the compound of Example 45A Fraction I (+) and the compound of Example 45B Fraction II (-).

Example 45A

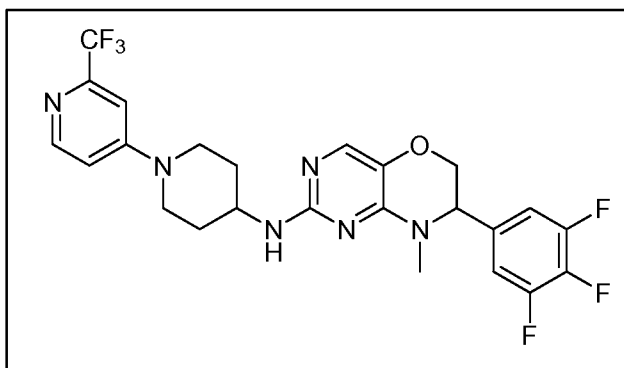
Synthesis of (+)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6*H*-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine



[0301] The compound of Example 45A was produced as described in Example 45. Analytical data for product Fraction I (+): ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.21 (d, 1H), 7.45 (s, 1H), 7.20-7.18 (m, 1H), 7.17-7.10 (m, 2H), 7.01 (d, 1H), 6.33-6.30 (m, 1H), 4.74-4.71 (m, 1H), 4.17-4.07 (m, 2H), 4.02-3.97 (m, 2H), 3.91-3.88 (m, 1H), 3.03 (t, 2H), 2.91 (s, 3H), 1.93-1.89 (m, 2H), 1.49-1.38 (m, 2H); LC-MS: 525.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.25 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.87 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC RT = 11.42 min (CHIRALPAK-IA (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) THF (70:30); flow Rate: 1.0 mL/min); Optical rotation [α]_D^{20.02}: +61.53 (c 0.25, DCM).

Example 45B

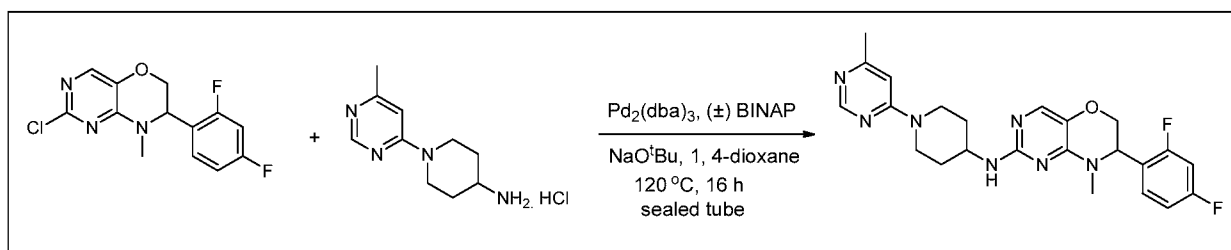
Synthesis of (-)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0302] The compound of Example 45B was produced as described in Example 45. Analytical data for product Fraction II (-): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.21 (d, 1H), 7.47 (s, 1H), 7.20-7.18 (m, 1H), 7.17-7.10 (m, 2H), 7.01 (d, 1H), 6.33-6.30 (m, 1H), 4.74-4.71 (m, 1H), 4.17-4.07 (m, 2H), 4.02-3.97 (m, 2H), 3.91-3.88 (m, 1H), 3.03 (t, 2H), 2.91 (s, 3H), 1.93-1.89 (m, 2H), 1.49-1.38 (m, 2H); LC-MS: 525.4 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 3.25 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.88 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 13.68 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) THF (70:30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.01}$: -52.08 (c 0.25, DCM).

Example 46

Synthesis of 7-(2, 4-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



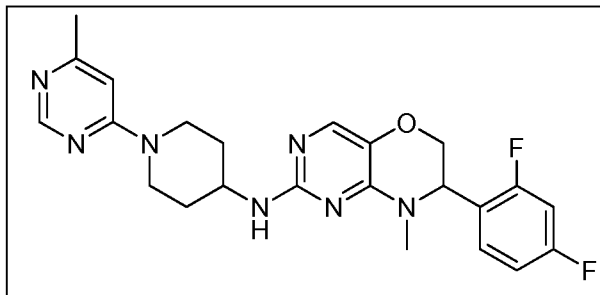
Synthesis of 7-(2, 4-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0303] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (31 mg, 0.03 mmol) and ($\pm$) BINAP (63 mg, 0.15 mmol) in 1, 4-dioxane (1 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-7-(2, 4-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (200 mg, 0.67 mmol), 1-(6-methylpyrimidin-4-yl) piperidin-4-amine hydrochloride (142 mg, 0.73 mmol) and sodium tertiary butoxide (193 mg, 2.01 mmol) in 1, 4-dioxane (1 mL) was degassed and the catalyst premixture was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 3% $\text{MeOH}:\text{CH}_2\text{Cl}_2$ to afford 7-(2, 4-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (38 mg, 12%) as an off-white solid. LC-MS: 454.5 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 3.43 min. 5 mM $\text{NH}_4\text{OAc}:\text{ACN}$; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 x 2.1mm, 1.7 μm); RT 1.88 min. ACN: 0.025% TFA (Aq); 0.50 ml/min.

[0304] Racemic compound of Example 46 was separated using a Chiralpak-ADH (250 x 20 mm, 5 μm (30 mg loading; 0.1 % DEA in *n*-hexane:EtOH (A:B : 75:25) as the mobile phase) to provide the compound of Example 46A Fraction I (-) and the compound of Example 46B Fraction II (+).

Example 46A

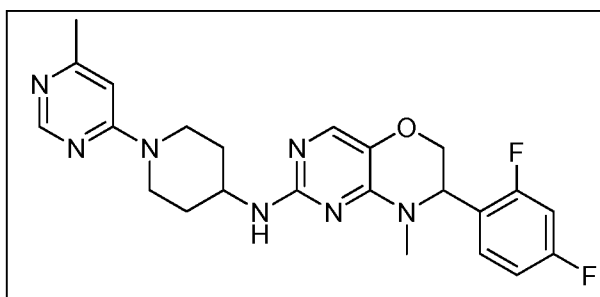
Synthesis of (-)-7-(2, 4-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0305] The compound of Example 46A was produced as described in Example 46. Analytical data for product Fraction I (-): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ 8.35 (s, 1H), 7.43 (s, 1H), 7.33 (t, 1H), 7.10-7.00 (m, 2H), 6.71 (s, 1H), 6.18 (d, 1H), 4.98 (s, 1H), 4.33-4.29 (m, 2H), 4.15-4.10 (m, 2H), 3.98-3.88 (m, 1H), 3.07-2.99 (m, 2H), 2.97 (s, 3H), 2.24 (s, 3H), 1.94-1.89 (m, 2H), 1.43-1.38 (m, 2H); Mass (ESI): 454.5 $[\text{M}+1]$; LC-MS: 454.5 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 3.50 min. 5 mM NH_4OAc :ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.56 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 13.28 min (CHIRALPAK-AD-H (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) EtOH (70:30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.98}$: -92.88 (c 0.25, DCM).

Example 46B

Synthesis of (+)-7-(2, 4-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

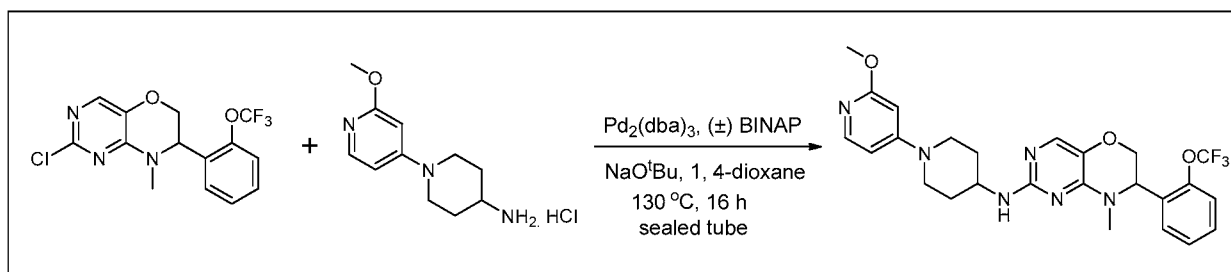


[0306] The compound of Example 46B was produced as described in Example 46. Analytical data for product Fraction II (+): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ 8.35 (s, 1H), 7.43 (s, 1H), 7.33 (t, 1H), 7.10-7.00 (m, 2H), 6.71 (s, 1H), 6.18 (d, 1H), 4.98 (s, 1H), 4.33-4.29 (m, 2H), 4.15-4.10 (m, 2H), 3.98-3.88 (m, 1H), 3.07-2.99 (m, 2H), 2.97 (s, 3H), 2.24 (s,

3H), 1.94-1.89 (m, 2H), 1.43-1.38 (m, 2H); Mass (ESI): 454.5 [M+1]; LC-MS: 454.5 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.55 min. 5 mM NH₄OAc:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.56 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 18.61 min (CHIRALPAK-AD-H (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) EtOH (70:30); flow Rate: 1.0 mL/min); Optical rotation [α]_D^{20.01}: +92.62 (c 0.25, DCM).

Example 47

Synthesis of *N*-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethoxy) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethoxy) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

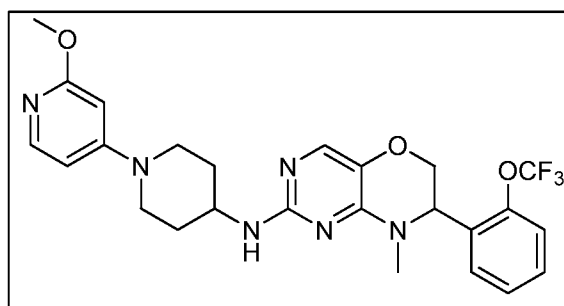
[0307] To a dry vial was added a suspension of Pd₂(dba)₃ (33 mg, 0.03 mmol) and (±) BINAP (67 mg, 0.10 mmol) in 1, 4-dioxane (1 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-8-methyl-7-(2-(trifluoromethoxy) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 0.72 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (190 mg, 0.79 mmol) and sodium tertiary butoxide (200 mg, 2.17 mmol) in 1, 4-dioxane (1.5 mL) was degassed and the catalyst premixture was added. The reaction mixture was heated to 130 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extract was dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 3% MeOH:CH₂Cl₂ to afford *N*-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-

(trifluoromethoxy) phenyl)-7, 8-dihydro-6*H*-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine (130 mg, 35%) as an off-white solid. LC-MS: 517.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.11 min. 0.05% Aq TFA:ACN; 0.8 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.76 min. ACN: 0.025% TFA (Aq); 0.50 ml/min.

[0308] Racemic compound of Example 47 was separated using a Chiralpak-IA (250 x 20 mm, 5μm (40 mg loading; 0.1 % DEA in *n*-hexane: EtOH:MeOH (50:50); (A:B : 90:10) as the mobile phase) to provide the compound of Example 47A Fraction I (-) and the compound of Example 47B Fraction II (+).

Example 47A

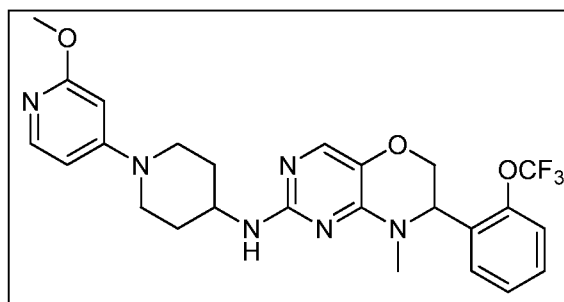
Synthesis of (-)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethoxy) phenyl)-7, 8-dihydro-6*H*-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine



[0309] The compound of Example 47A was produced as described in Example 47. Analytical data for product Fraction I (-): ¹H-NMR (CD₃OD, 400 MHz): δ 7.73 (d, 1H), 7.48-7.40 (m, 3H), 7.32 (t, 1H), 7.13 (d, 1H), 6.53 (d, 1H), 6.14 (s, 1H), 5.02-5.00 (m, 1H), 4.23-4.18 (m, 1H), 4.15-4.10 (m, 1H), 3.95-3.89 (m, 3H), 3.81 (s, 3H), 3.07-3.03 (nm, 2H), 3.02 (s, 3H), 2.10-2.03 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 517.5 [M+1]; LC-MS: 517.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.08 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.77 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 10.44 min (CHIRALPAK-IA (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (50:50) (A:B : 80:20; flow Rate: 1.0 mL/min); Optical rotation [α]_D^{20.01}: -83.10 (c 0.25, DCM).

Example 47B

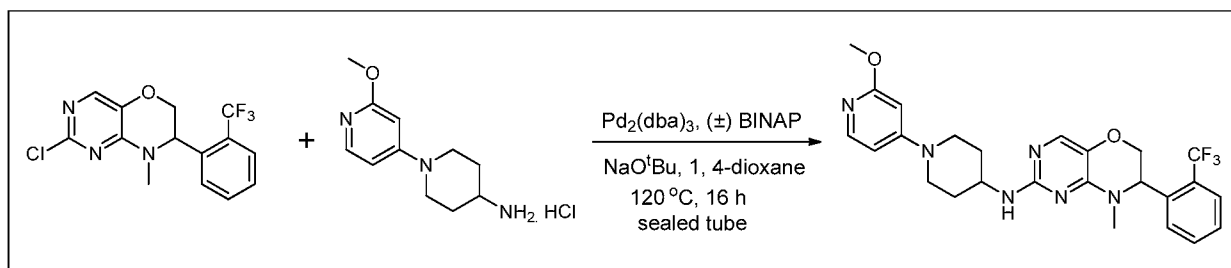
Synthesis of (+)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethoxy) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0310] The compound of Example 47B was produced as described in Example 47. Analytical data for product Fraction II (+): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.73 (d, 1H), 7.48-7.40 (m, 3H), 7.32 (t, 1H), 7.13 (d, 1H), 6.53 (d, 1H), 6.14 (s, 1H), 5.02-5.00 (m, 1H), 4.23-4.18 (m, 1H), 4.15-4.10 (m, 1H), 3.95-3.89 (m, 3H), 3.81 (s, 3H), 3.07-3.03 (m, 2H), 3.02 (s, 3H), 2.10-2.03 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 517.5 $[\text{M}+1]$; LC-MS: 517.5 ($\text{M}+1$); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 3.06 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.77 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 13.94 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 :MeOH (50:50) (A:B : 80:20; flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{19.99}$: +84.41 (c 0.25, DCM).

Example 48

Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethyl) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



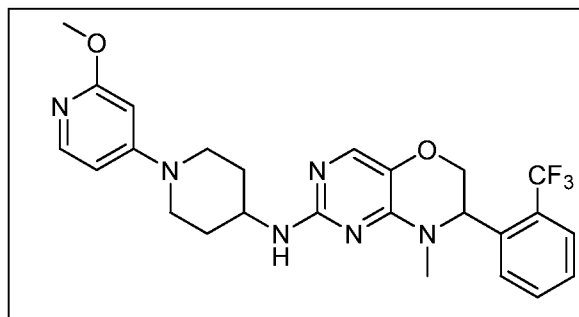
Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethoxy) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0311] To a dry vial was added a suspension of Pd₂(dba)₃ (35 mg, 0.03 mmol) and (±) BINAP (71 mg, 0.11 mmol) in 1, 4-dioxane (1.25 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-8-methyl-7-(2-(trifluoromethyl) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 0.75 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (203 mg, 0.83 mmol) and sodium tertiary butoxide (219 mg, 2.27 mmol) in 1, 4-dioxane (1.25 mL) was degassed and the catalyst premixure was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was concentrated *in vacuo*. The crude material was diluted with water (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using 3% MeOH:CH₂Cl₂ to afford *N*-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethyl) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (124 mg, 32%) as an off-white solid. LC-MS: 501.5 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.04 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.76 min. ACN: 0.025% TFA (Aq); 0.50 ml/min.

[0312] Racemic compound of Example 48 was separated using a Chiralpak-IA (250 x 20 mm, 5μm (40 mg loading; 0.1 % DEA in *n*-hexane: EtOH:MeOH (80:20); (A:B : 80:20) as the mobile phase) to provide the compound of Example 48A Fraction I (-) and the compound of Example 48B Fraction II (+).

Example 48A

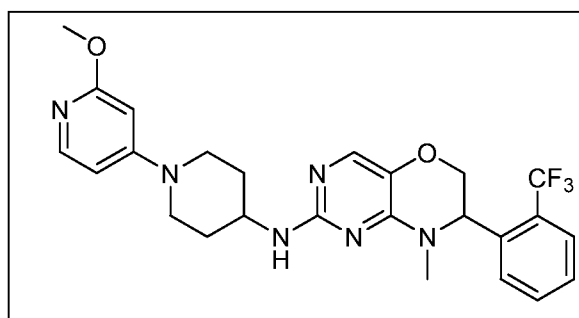
Synthesis of (-)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethyl) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0313] The compound of Example 48A was produced as described in Example 48. Analytical data for Fraction I (-): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.80 (d, 1H), 7.75 (d, 1H), 7.64-7.61 (m, 1H), 7.54-7.50 (m, 1H), 7.47 (s, 1H), 7.30 (d, 1H), 6.55 (d, 1H), 6.15 (s, 1H), 5.02-5.00 (m, 1H), 4.25-4.20 (m, 1H), 4.08-4.01 (m, 1H), 3.97-3.90 (m, 3H), 3.82 (s, 3H), 3.05 (t, 2H), 2.97 (s, 3H), 2.10-2.04 (m, 2H), 2.60-2.53 (m, 2H); Mass (ESI): 501.5 $[\text{M}+1]$; LC-MS: 501.4 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 3.00 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.71 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 11.75 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 :MeOH (80:20) (A:B : 80:20; flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{20.01}$: -28.52 (c 0.25, DCM).

Example 48B

Synthesis of (+)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethyl) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

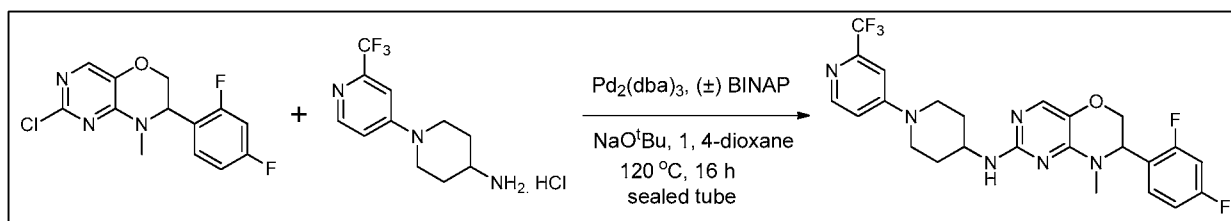


[0314] The compound of Example 48B was produced as described in Example 48. Analytical data for Fraction II (+): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.80 (d, 1H), 7.75 (d,

1H), 7.64-7.61 (m, 1H), 7.52 (t, 1H), 7.47 (s, 1H), 7.30 (d, 1H), 6.55 (d, 1H), 6.15 (s, 1H), 5.02-5.00 (m, 1H), 4.25-4.20 (m, 1H), 4.08-4.01 (m, 1H), 3.97-3.90 (m, 3H), 3.82 (s, 3H), 3.05 (t, 2H), 2.97 (s, 3H), 2.10-2.04 (m, 2H), 2.60-2.53 (m, 2H); Mass (ESI): 501.5 [M+1]; LC-MS: 501.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.00 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.71 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 14.60 min (CHIRALPAK-IA (250 × 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂:MeOH (80:20) (A:B : 80:20; flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: +35.28 (c 0.25, DCM).

Example 49

Synthesis of 7-(2, 4-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 7-(2, 4-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

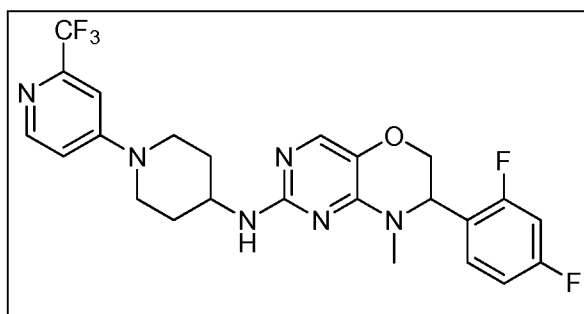
[0315] To a dry vial was added a suspension of Pd₂(dba)₃ (31 mg, 0.03 mmol) and (±) BINAP (63 mg, 0.10 mmol) in 1, 4-dioxane (1 mL). The suspension was degassed with argon, heated to 120 °C and stirred for 3 min. A mixture of 2-chloro-7-(2, 4-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (200 mg, 0.67 mmol), 1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-amine hydrochloride (208 mg, 0.74 mmol) and sodium tertiary butoxide (194 mg, 2.01 mmol) in 1, 4-dioxane (1 mL) was degassed and the catalyst premixure was added. The reaction mixture was heated to 120 °C and stirred for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the mixture was concentrated *in vacuo*. The crude material was diluted with water (50 mL) and extracted with CH₂Cl₂ (2 × 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica

gel column chromatography using 4% MeOH:CH₂Cl₂ to afford 7-(2, 4-difluorophenyl)-8-methyl-*N*-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6*H*-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine (200 mg, 59%) as an off-white solid. LC-MS: 507.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.14 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.70 min. ACN: 0.025% TFA (Aq); 0.50 ml/min.

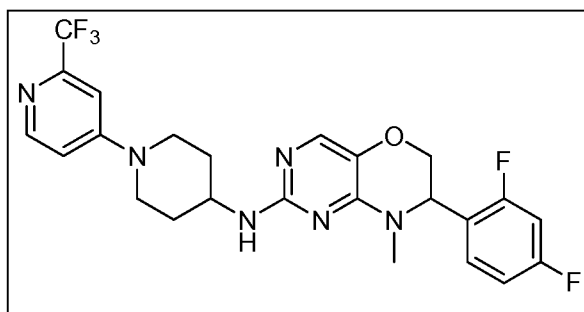
[0316] Racemic compound of Example 49 was separated using a Chiralpak-ADH (250 x 20 mm, 5μm (20 mg loading; *n*-hexane:EtOH (A:B : 80:20) as the mobile phase) to provide the compound of Example 49A Fraction I (-) and the compound of Example 49B Fraction II (+).

Example 49A

Synthesis of (-)-7-(2, 4-difluorophenyl)-8-methyl-*N*-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6*H*-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine

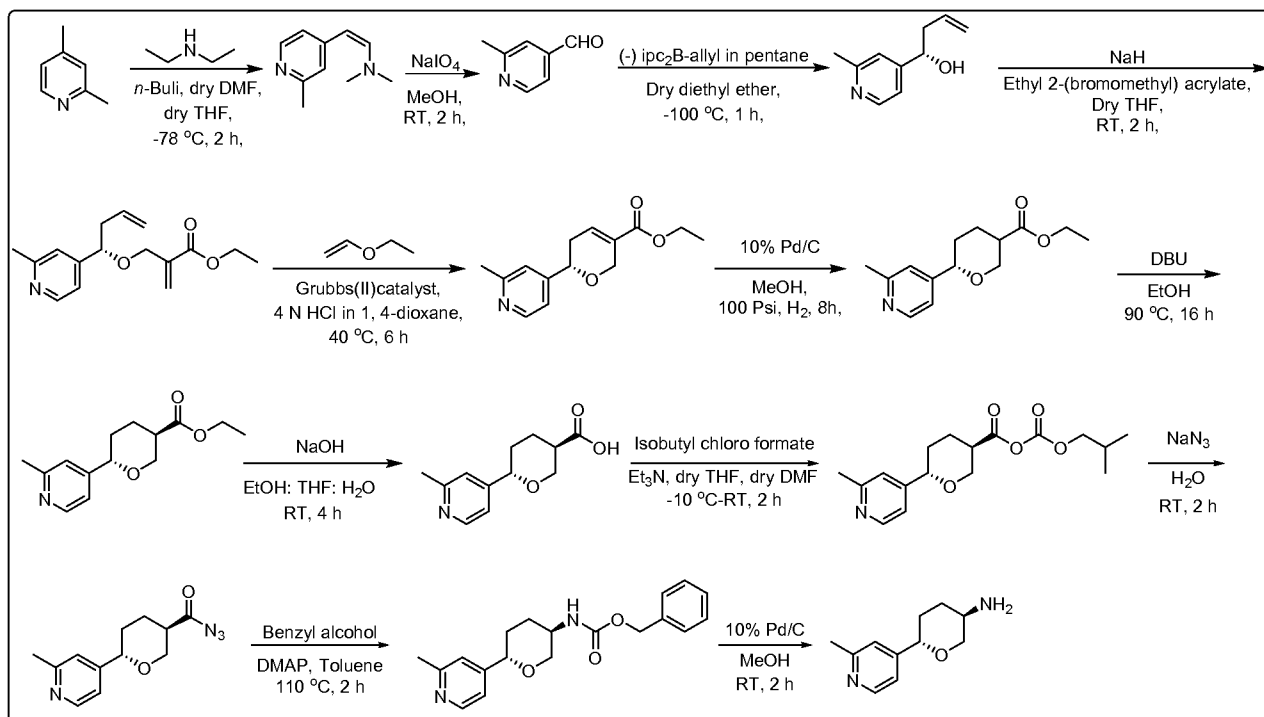


[0317] The compound of Example 49A was produced as described in Example 49. Analytical data for product Fraction I (-): ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.25 (d, 1H), 7.45 (s, 1H), 7.31 (t, 1H), 7.20-7.18 (m, 1H), 7.10-7.00 (m, 3H), 6.30 (d, 1H), 4.99-4.97 (m, 1H), 4.13-4.11 (m, 2H), 4.00-3.97 (m, 2H), 3.95-3.89 (m, 1H), 3.05 (t, 2H), 2.93 (s, 3H), 1.97-1.90 (m, 2H), 1.51-1.41 (m, 2H); LC-MS: 507.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.20 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.86 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 16.93 min (CHIRALPAK-AD-H (250 x 4.6 mm, 5 μm; mobile phase (A) *n*-hexane (B) EtOH (A:B : 80:20; flow Rate: 1.0 mL/min); Optical rotation [α]_D^{19.97}: -84.76 (c 0.25, DCM).

Example 49B**Synthesis of (+)-7-(2, 4-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine**

[0318] The compound of Example 49B was produced as described in Example 49. Analytical data for product Fraction II (+): ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.25 (d, 1H), 7.45 (s, 1H), 7.31 (t, 1H), 7.20-7.18 (m, 1H), 7.10-7.00 (m, 3H), 6.30 (d, 1H), 4.99-4.97 (m, 1H), 4.13-4.11 (m, 2H), 4.00-3.97 (m, 2H), 3.95-3.89 (m, 1H), 3.05 (t, 2H), 2.93 (s, 3H), 1.97-1.90 (m, 2H), 1.51-1.41 (m, 2H); LC-MS: 507.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.20 min. 0.05% Aq TFA:ACN; 0.80 ml/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.86 min. ACN: 0.025% TFA (Aq); 0.50 ml/min; Chiral HPLC: RT = 24.13 min (CHIRALPAK-AD-H (250 × 4.6 mm, 5 μm; mobile phase (A) *n*-hexane (B) EtOH (A:B : 80:20; flow Rate: 1.0 mL/min); Optical rotation [α]_D^{20.00}: +82.09 (c 0.25, DCM).

Example 50**Synthesis of (3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-amine**



Synthesis of (Z)-N, N-dimethyl-2-(2-methylpyridin-4-yl) ethen-1-amine

[0319] To a stirred solution of 2, 4-dimethylpyridine (14 g, 130.65 mmol) in dry THF (150 mL) under an argon atmosphere was added 2.5 M *n*-butyl lithium in hexane (67.5 mL, 169.85 mmol) drop-wise for 20 min at -78 °C. The reaction mixture was stirred for 1 h at -78 °C, then diethyl amine (19.5 mL, 1.89 mmol) was added drop-wise. The reaction mixture was stirred for 1 h at -78 °C then DMF (20 mL, 261.13 mmol) was added drop-wise at -78 °C and stirred for 30 min. After consumption of the starting materials (monitored by TLC), the reaction was quenched with an ammonium chloride solution (200 mL) and extracted with diethyl ether (3 x 300 mL). The combined organic extracts were washed with brine (300 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (Z)-N, N-dimethyl-2-(2-methylpyridin-4-yl) ethen-1-amine (23 g) as orange oil. This compound was used without further purification. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 8.02-7.99 (m, 1H), 7.31-7.23 (m, 1H), 6.90-6.83 (m, 2H), 4.94-4.88 (m, 1H), 2.82 (s, 6H), 2.30 (s, 3H); LCMS: 163.1 (M+1); (column; X-select C-18 (50 × 3.0 mm, 3.5 μm); RT 2.32 min 5mM NH₄OAc: ACN; 0.80 mL/min); HPLC (column; Acquity-UPLC-BEH-C-18 2.1 X 50 mm, 1.7 μm); RT 1.25 min. ACN: 0.025% Aq TFA; 0.5 mL/min; TLC: 10% MeOH/ CH₂Cl₂ + 2 drops NH₄OH solution (R_f 0.2).

Synthesis of 2-methylisonicotinaldehyde

[0320] To a stirred solution of sodium metaperiodate (91 g, 425.91 mmol) in methanol (90 mL) under an argon atmosphere was added a solution of (Z)-N, N-dimethyl-2-(2-methylpyridin-4-yl) ethen-1-amine (23 g, 141.97 mmol) in methanol (90 mL). After 5 mins an exothermic reaction was observed, then the reaction mixture was cooled to RT and stirred for 2 h. After consumption of the starting materials (monitored by TLC), the reaction was filtered, washed with an excess of methanol and the filtrate was concentrated *in vacuo*. The crude material was diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (300 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 12% EtOAc:hexanes to afford 2-methylisonicotinaldehyde (6 g, 35%) as light brown liquid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 10.04 (s, 1H), 8.74-8.72 (m, 1H), 7.68 (s, 1H), 7.60-7.59 (m, 1H), 2.60 (s, 3H); LCMS: 122.7 (M+1); (column; Eclipse XDB C-18 (150 × 4.6 mm, 5 μm); RT 1.93 min 0.05% Aq TFA: ACN; 1.0 mL/min); UPLC (column; Acquity-UPLC-HSS-T3 2.1 X 100 mm, 1.8 μm); RT 1.10 min. ACN: 0.025% Aq TFA; 0.3 mL/min; TLC: 10% MeOH/ CH₂Cl₂/NH₄OH solution (R_f 0.7).

Synthesis of (S)-1-(2-methylpyridin-4-yl) but-3-en-1-ol

[0321] To a stirred solution of 1M (-) ipc₂B-allyl in pentane (16.66 g (51 mL), 50.90 mmol) under an argon atmosphere was cooled to -100 °C was drop-wise added a solution of 2-methyl isonicotinaldehyde (2.8 g, 23.14 mmol) in dry ether (24 mL) at -78 °C over a period of 30 min. The reaction mixture was then stirred at -100 °C for 1 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with methanol (4 mL) and 1 N HCl (60 mL) and warmed to RT. The reaction was extracted with EtOAc (60 mL), the aqueous layer was basified with 10% sodium hydroxide solution (adjust to pH ~ 10) at 0 °C and extracted with EtOAc (2 x 60 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 70% EtOAc:hexanes to afford (S)-1-(2-methylpyridin-4-yl) but-3-en-1-ol (3 g, 80%) as a brown liquid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 8.34-8.33 (m, 1H), 7.17 (s, 1H), 7.11-7.10 (m, 1H), 5.78-5.73 (m, 1H), 5.42-5.41 (m, 1H), 5.01-4.97 (m, 2H), 4.59-4.55 (m, 1H), 2.43 (s, 3H), 2.37-2.35 (m, 2H); LCMS: 164.3 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 0.48 min 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Eclipse-XDB-C-18 150 X 4.6 mm, 5.0 μm); RT 7.27 min. ACN: 5 mM Aq NH₄OAc; 1.0 mL/min; Chiral HPLC: 96.9% RT = 17.80 min (Chiralpak IC (250 x 4.6mm,

5 μ m; mobile phase (A) 0.1 % DEA in *n*-hexane (B) DCM: MeOH (90: 10); flow Rate: 1.0 mL/min; TLC: EtOAc (R_f 0.3).

Synthesis of ethyl (S)-2-(((1-(2-methylpyridin-4-yl) but-3-en-1-yl) oxy) methyl) acrylate

[0322] To a stirred solution of (S)-1-(2-methylpyridin-4-yl) but-3-en-1-ol (3.2 g, 19.63 mmol) in dry THF (38 mL) under an argon atmosphere was added 60% sodium hydride (1.4 g, 58.89 mmol) portion-wise for 15 min at 20 °C. The reaction mixture stirred for 20 mins, then warmed to RT and stirred for an additional 2 h. A solution of ethyl 2-(bromo methyl) acrylate (7.5 g, 39.26 mmol) in dry THF (38 mL) was added over a period of 20 min at 20 °C and stirred at RT for 1 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with a saturated ammonium chloride solution (120 mL) and EtOAc (150 mL). The organic layer separated and the aqueous layer was extracted with EtOAc (2 x 60 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 20% EtOAc:hexanes to afford ethyl (S)-2-(((1-(2-methylpyridin-4-yl) but-3-en-1-yl) oxy) methyl) acrylate (2.6 g, 48%) as yellow liquid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 8.40-8.39 (m, 1H), 7.17 (s, 1H), 7.11-7.10 (m, 1H), 6.17 (s, 1H), 5.90 (s, 1H), 5.75-5.69 (m, 1H), 5.03-4.98 (m, 2H), 4.45-4.43 (m, 1H), 4.14-4.10 (m, 2H), 4.04-4.01 (m, 2H), 2.45 (s, 4H), 2.44-2.35 (m, 1H), 1.21 (s, 3H); LCMS: 276.4 (M+1); (column; X-select CSH C-18 (50 $\times$ 3.0 mm, 3.5 μ m); RT 2.90 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity BEH C-18 50 X 2.1 mm, 1.7 μ m); RT 1.70 min. ACN: 0.025% TFA (Aq); 0.50 mL/min; TLC: 75% EtOAc/hexanes (R_f 0.7).

Synthesis of ethyl (S)-6-(2-methylpyridin-4-yl)-5, 6-dihydro-2H-pyran-3-carboxylate

[0323] To a stirred solution of ethyl (S)-2-(((1-(2-methylpyridin-4-yl) but-3-en-1-yl) oxy) methyl) acrylate (2.6 g, 9.45 mmol) in CH₂Cl₂ (52 mL) under an argon atmosphere was added 4 N HCl in 1, 4-dioxane (4.73 mL, 18.90 mmol) drop-wise at 0 °C. The reaction mixture was warmed to RT and stirred for 5 min. The volatile components were evaporated *in vacuo*. To the above residue in CH₂Cl₂ (316 mL) under an argon atmosphere was added Grubbs (II) catalyst (401 mg, 0.47 mmol) at RT. The reaction mixture was heated to 40 °C for 6 h. After consumption of the starting materials (monitored by TLC), the reaction mixture was cooled RT and ethyl vinyl ether (1.3 mL) was added. After consumption of the starting materials, the volatile components were concentrated *in vacuo*. The residue was diluted with

a saturated sodium bicarbonate solution (50 mL) and extracted with EtOAc (100 mL). The combined organic extracts were washed with brine (100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 20- 50% EtOAc:hexanes to afford ethyl (*S*)-6-(2-methylpyridin-4-yl)-5, 6-dihydro-2*H*-pyran-3-carboxylate (1.75 g, 75%) as a brown liquid. ¹H-NMR (CDCl₃, 400 MHz): δ 8.49-8.48 (m, 1H), 7.23 (s, 1H), 7.15-7.08 (m, 2H), 4.69-4.64 (m, 1H), 4.50-4.41 (m, 2H), 4.26-4.21 (m, 2H), 2.61 (s, 3H), 2.57-2.48 (m, 1H), 2.42-2.32 (m, 1H), 1.29 (s, 3H); LCMS: 248.3 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.81 min 5 mM Aq NH₄OAc: ACN; 0.80 mL/min); HPLC (column; Eclipse-XDB-C-18 150 X 4.6 mm, 5 μm); RT 9.69 min. ACN: 5 mM NH₄OAc (Aq); 1.0 mL/min; TLC: 50% EtOAc/hexanes (R_f 0.3).

*Synthesis of ethyl (6*S*)-6-(2-methylpyridin-4-yl) tetrahydro-2*H*-pyran-3-carboxylate*

[0324] To a stirred solution of ethyl (*S*)-6-(2-methylpyridin-4-yl)-5, 6-dihydro-2*H*-pyran-3-carboxylate (1.75 g, 7.08 mmol) in MeOH (50 mL) under an argon atmosphere was added wet 10% Pd/C (185 mg) in methanol (20 mL) at RT. The suspension was stirred under H₂ atmosphere (100 Psi) for 8 h in a steel bomb. After consumption of the starting materials (monitored by LCMS), the reaction was filtered through celite and the filtrate was concentrated *in vacuo* to afford ethyl (6*S*)-6-(2-methylpyridin-4-yl) tetrahydro-2*H*-pyran-3-carboxylate (1.7 g, 96%) as a brown liquid [*cis/trans* (3: 1) isomers]. ¹H-NMR (CDCl₃, 400 MHz): δ 8.44-8.41 (m, 1H), 7.13-7.11 (m, 1H), 7.04-7.01 (m, 1H), 4.56-4.52 (m, 1H), 4.35-4.11 (m, 3H), 3.79-3.76 (m, 1H), 2.54 (s, 3H), 2.38-2.36 (m, 1H), 1.82-1.78 (m, 4H), 1.30 (s, 3H); LCMS: 29.6%; 250.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.87 min, 2.99 min 5 mM NH₄OAc: ACN; 0.80 mL/min); TLC: 50% EtOAc/hexanes (R_f 0.5).

*Synthesis of ethyl (3*R*, 6*S*)-6-(2-methylpyridin-4-yl) tetrahydro-2*H*-pyran-3-carboxylate*

[0325] To a stirred solution of ethyl (6*S*)-6-(2-methylpyridin-4-yl) tetrahydro-2*H*-pyran-3-carboxylate (580 mg, 2.32 mmol) in EtOH (24 mL) under an argon atmosphere was added DBU (355 mg, 2.32 mmol) at RT. The reaction mixture was stirred at 90 °C for 16 h. After consumption of the starting materials (monitored by LCMS), the volatile components were evaporated *in vacuo*. The residue was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over

sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 50% EtOAc:hexanes to afford ethyl (3*R*, 6*S*)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-carboxylate (470 mg, 81%) as a brown liquid [*cis/trans* (1: 3) isomers]. ¹H-NMR (CDCl₃, 400 MHz): δ 8.43 (d, 1H), 7.23 (s, 1H), 7.03 (d, 1H), 4.39-4.30 (m, 2H), 4.19-4.12 (m, 2H), 3.62 (t, 1H), 2.70-2.63 (m, 1H), 2.53 (s, 3H), 1.99-1.90 (m, 1H), 1.87-1.80 (m, 2H), 1.57-1.50 (m, 1H), 1.29 (s, 3H); LCMS: 250.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.99, 3.16 min 5 mM NH₄OAc: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH-C-18 2.1 X 50 mm, 1.7 μm); RT 1.24 min. ACN: 0.025% TFA (Aq); 0.5 mL/min; Chiral HPLC: 24.4%, 68.2% RT = 9.14, 13.96 min (Chiralpak IA (250 x 4.6mm, 5 μm; mobile phase (A) 0.1 % TFA in *n*-hexane (B) DCM: MeOH (50: 50) (80: 20); flow Rate: 1.0 mL/min); TLC: 50% EtOAc/hexanes (R_f 0.5).
[0326] Diastereomeric mixture (*cis* and *trans*-mixture) was purified by Chiralpak IA (250 x 4.6 mm: 5 μm; (20 mg loading; 0.1 % TFA in *n*-hexane: CH₂Cl₂: MeOH (50: 50); (A: B: 80: 20) as mobile phase) to afford *cis* and *trans* characterization details of both fractions are as follows:

Ethyl (3*S*,6*S*)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-carboxylate (*cis*-isomer)

¹H-NMR (CDCl₃, 400 MHz) (Cis): δ 8.41 (d, 1H), 7.11 (s, 1H), 7.01 (d, 1H), 4.57-4.51 (m, 1H), 4.39-4.32 (m, 1H), 4.28-4.21 (m, 2H), 3.75 (d, 1H), 2.56 (s, 3H), 2.55-2.54 (m, 1H), 2.39-2.31 (m, 1H), 1.89-1.75 (m, 3H), 1.31 (t, 3H); LCMS: 250.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.98 min 5 mM NH₄OAc: ACN; 0.80 mL/min); HPLC (column; Acquity UPLC BEH-C-18 2.1 X 50 mm, 1.7 μm); RT 1.34 min. ACN: 0.025% TFA (Aq); 0.5 mL/min; Chiral HPLC: 96.1% RT = 8.00 min (Chiralpak IA (250 x 4.6mm, 5 μm; mobile phase (A) 0.1 % TFA in *n*-hexane (B) DCM: MeOH (50: 50) (80: 20); flow Rate: 1.0 mL/min).

Ethyl (3*R*,6*S*)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-carboxylate (*trans*-isomer)

¹H-NMR (CDCl₃, 400 MHz) (Trans): δ 8.42 (d, 1H), 7.13 (s, 1H), 7.05 (d, 1H), 4.39-4.23 (m, 2H), 4.19-4.01 (m, 2H), 3.60 (t, 1H), 2.75-2.65 (m, 1H), 2.55 (s, 3H), 2.29-2.21 (m, 1H), 2.00-1.91 (m, 1H), 1.89-1.79 (m, 1H), 1.58-1.48 (m, 1H), 1.30 (t, 3H); LCMS: 250.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.15 min 5 mM NH₄OAc: ACN; 0.80 mL/min); HPLC (column; Acquity UPLC BEH-C-18 2.1 X 50 mm, 1.7 μm); RT 1.41 min. ACN: 0.025% TFA (Aq); 0.5 mL/min; Chiral HPLC: 96.4% RT = 11.71 min (Chiralpak

IA (250 x 4.6mm, 5 μ m; mobile phase (A) 0.1 % TFA in *n*-hexane (B) DCM: MeOH (50: 50) (80: 20); flow Rate: 1.0 mL/min).

Synthesis of (3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-carboxylic acid

[0327] To a stirred solution of ethyl (3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-carboxylate (1.7 g, 6.82 mmol) in THF: EtOH (2: 1, 44 mL) under an argon atmosphere was added sodium hydroxide (2.73 g, 68.27 mmol) in water (30 mL) at RT. The reaction mixture was stirred at RT for 4 h. After consumption of the starting materials (monitored by LCMS), the volatile components were evaporated *in vacuo* and diluted with water (10 mL). The reaction was neutralized with a 6 N HCl solution (10 mL) to pH ~7 and concentrated *in vacuo*. The residue was dissolved in MeOH (20 mL), filtered and the filtrate was concentrated *in vacuo*. The crude material was washed with ether (2 x 20 mL), pentane (20 mL) and dried *in vacuo* to afford (3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-carboxylic acid (1.3 g, 90%) as a pale brown solid. ¹H-NMR (CD₃OD, 500 MHz): δ 8.35-8.30 (m, 1H), 7.31 (s, 1H), 7.21-7.19 (m, 1H), 4.38-4.35 (m, 1H), 4.31-4.25 (m, 1H), 3.61 (t, 1H), 2.50-2.41 (m, 4H), 2.33 (s, 1H), 2.22-2.19 (m, 1H), 2.00-1.80 (m, 1H), 1.50-1.40 (m, 1H); LCMS: 222.2 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μ m); RT 0.61, 0.85 min 5 mM NH₄OAc: ACN; 0.80 mL/min); Chiral HPLC: 76.5%, 19.30% RT = 7.36, 12.69 min (Chiralpak IA (250 x 4.6mm, 5 μ m; mobile phase (A) 0.1 % TFA in *n*-hexane (B) DCM: MeOH (50: 50); flow Rate: 1.0 mL/min); TLC: 75% EtOAc/hexanes (R_f 0.1).

Synthesis of (3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-carbonyl azide

[0328] To a stirred solution of (3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-carboxylic acid (1.35 g, 6.10 mmol) in dry THF (63 mL) and dry DMF (10 mL) under an argon atmosphere were added triethylamine (1.36 g, 0.01 mmol) followed by isobutyl chloroformate (1.25 mL, 9.16 mmol) drop-wise at -10 °C for 10 min. The reaction mixture was stirred at -10 °C for 2 h. After consumption of the starting materials (monitored by TLC), a solution of NaN₃ (600 mg, 9.16 mmol) in water (10 mL) was added and stirred at RT for 2 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (50 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-carbonyl azide (1.5 g,) and used without further purification. TLC: 50% EtOAc:hexanes (R_f 0.7).

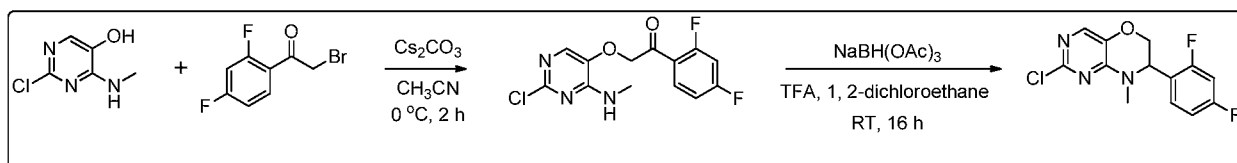
Synthesis of benzyl ((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl) carbamate

[0329] To a stirred solution of (3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-carbonyl azide (1.5 g) in dry toluene (36 mL) under an argon atmosphere were added dimethylaminopyridine (150 mg, 1.21 mmol) and benzyl alcohol (987 mg, 9.28 mmol) at RT. The reaction mixture was stirred at 110 °C for 2 h. After consumption of the starting materials (monitored by TLC), the volatile components were evaporated *in vacuo*. The crude material was purified by silica gel column chromatography using 70% EtOAc:hexanes to afford benzyl ((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl) carbamate (500 mg, 25%) as a brown solid. ¹H-NMR (CDCl₃, 400 MHz): δ 8.45 (d, 1H), 7.39-7.30 (m, 5H), 7.20 (s, 1H), 7.18-7.10 (m, 1H), 5.15-5.10 (m, 2H), 4.60-4.56 (m, 1H), 4.30 (d, 1H), 3.90-3.73 (m, 2H), 3.20 (t, 1H), 2.60 (s, 3H), 2.25-2.20 (m, 1H), 2.00-1.80 (m, 1H), 1.70-1.60 (m, 1H), 1.59-1.50 (m, 1H); LCMS: 327.3 (M+1); (column; X-Select CSH-C18 (50 × 3.0 mm, 3.5 μm); RT 4.84 min, 4.91 min. 5 mM NH₄OAc: ACN; 0.80 ml/min); TLC: 50% EtOAc:hexanes (R_f 0.7).

Synthesis of (3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-amine

[0330] To a stirred solution of benzyl ((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl) carbamate (500 mg, 1.53 mmol) in methanol (30 mL) under an argon atmosphere was added 10% Pd/C (200 mg) at RT. The suspension was stirred under hydrogen atmosphere for 2 h. After consumption of the starting materials (monitored by TLC), the reaction was filtered through celite and the filtrate was concentrated *in vacuo* to afford (3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-amine (280 mg) as a brown liquid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.35 (d, 1H), 7.20 (s, 1H), 7.09 (d, 1H), 4.23 (d, 1H), 3.93-3.89 (m, 1H), 3.76-3.63 (m, 1H), 3.01 (t, 1H), 2.70-2.62 (m, 1H), 2.42 (s, 3H), 1.96-1.90 (m, 2H), 1.70-1.60 (m, 1H), 1.40-1.30 (m, 2H); LCMS: 193.3 (M+1); (column; zorbax SB-C18 (150 × 3.0 mm, 5 μm); RT 6.48 min. 5 mM NH₄OAc: ACN; 1.0 ml/min); TLC: 50% EtOAc:hexanes (R_f 0.1).

Example 51**Synthesis of 2-chloro-7-(2, 4-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine**



Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4-difluorophenyl) ethan-1-one

[0331] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (500 mg, 3.14 mmol) in CH₃CN (10 mL) under an argon atmosphere was added cesium carbonate (2 g, 6.28 mmol) at 0 °C. After stirring for 5 mins, 2-bromo-1-(2, 4-difluorophenyl) ethan-1-one (812 mg, 3.46 mmol) was added at 0 °C and stirred for 2 h. After consumption of the starting materials (monitored by TLC), water (20 mL) was added to the reaction and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 15-20% EtOAc:hexanes to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4-difluorophenyl) ethan-1-one (620 mg, 63%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.85 (s, 1H), 7.70-7.67 (m, 1H), 7.39 (s, 1H), 7.30 (t, 1H), 7.19 (t, 1H), 4.15 (d AB q, 1H), 4.08 (d AB q, 1H), 2.80 (s, 3H); LC-MS: 313.8 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.43 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 50% EtOAc/hexanes (R_f 0.3).

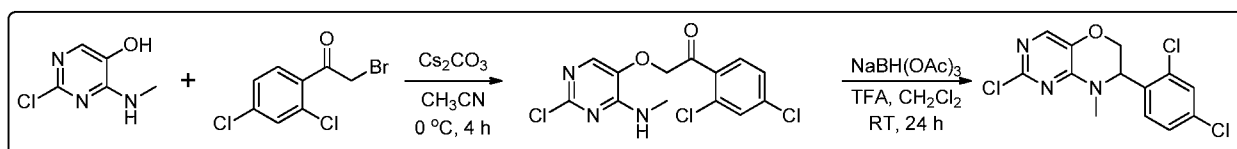
Synthesis of 2-chloro-7-(2, 4-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0332] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4-difluorophenyl) ethan-1-one (600 mg, 1.91 mmol) in 1, 2-dichloroethane (12 mL) under an argon atmosphere was added sodiumtriacetoxo borohydride (812 mg, 3.83 mmol) and trifluoroacetic acid (147 mL, 1.91 mmol) at RT. The reaction mixture was stirred at RT for 16 h. After consumption of the starting materials (monitored by TLC), the reaction was basified with a 1N sodium hydroxide solution (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude compound was purified by column chromatography using 10-15% EtOAc:hexanes to afford 2-chloro-7-(2,4-difluorophenyl)-8-methyl-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (500 mg, 87%) as a pale yellow solid. ¹H-NMR (CDCl₃, 400

MHz): δ 7.70 (s, 1H), 6.99-6.81 (m, 3H), 4.92-4.90 (m, 1H), 4.24-4.20 (m, 2H), 3.10 (s, 3H); LC-MS: 298.1 (M+1); (column; X-Select CSH C-18 (50 $\times$ 3.0 mm, 3.5 μ m); RT 4.20 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 50% EtOAc/hexanes (R_f 0.6).

Example 52

Synthesis of 2-chloro-7-(2, 4-dichlorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4-dichlorophenyl) ethan-1-one

[0333] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (500 mg, 3.14 mmol) in CH₃CN (10 mL) under an argon atmosphere were added 2-bromo-1-(2, 4-dichlorophenyl) ethan-1-one (927 mg, 3.45 mmol) and cesium carbonate (2 g, 6.28 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 4 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (20 mL) and extracted with EtOAc (2 $\times$ 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 15-20% EtOAc:hexanes to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4-dichlorophenyl) ethan-1-one (650 mg, 60%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.92-7.88 (m, 2H), 7.69 (s, 1H), 7.60 (d, 1H), 7.49 (s, 1H), 4.31-4.29 (m, 1H), 4.06-4.01 (m, 1H), 2.77 (s, 3H); LCMS: 347 (M+1); (column; X-Select CSH C-18 (50 $\times$ 3.0 mm, 3.5 μ m); RT 4.50 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 60% EtOAc/hexanes (R_f 0.5).

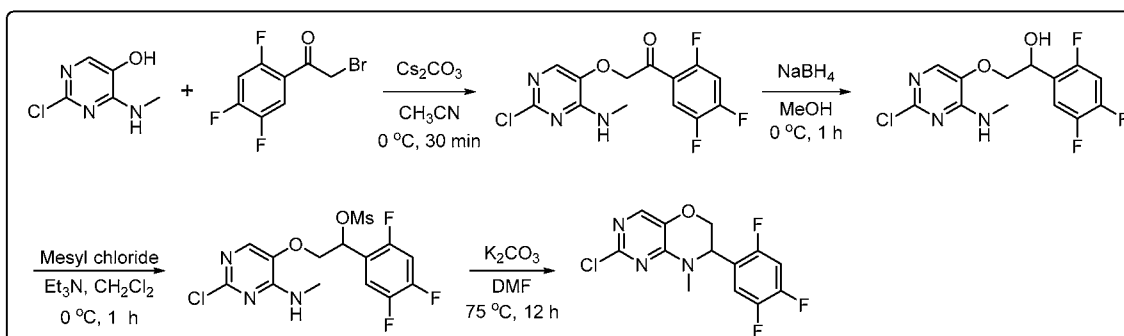
Synthesis of 2-chloro-7-(2, 4-dichlorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0334] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4-dichlorophenyl) ethan-1-one (650 mg, 1.87 mmol) in 1, 2-dichloroethane (15 mL) under an argon atmosphere were added sodium triacetoxo borohydride (796 mg, 3.75 mmol) followed

by trifluoroacetic acid (0.14 mL, 1.87 mmol) at RT. The reaction mixture was stirred at RT for 24 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with a 1 N sodium hydroxide solution (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 10-20% EtOAc:hexanes to afford 2-chloro-7-(2, 4-dichlorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (350 mg, 56%) as an off-white solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.70 (s, 1H), 7.49 (s, 1H), 7.25 (s, 1H), 6.91 (d, 1H), 5.03-5.01 (m, 1H), 4.30 (d, 1H), 4.21 (d, 1H), 3.13 (s, 3H); LCMS: 332.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.78 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 50% EtOAc/hexanes (R_f 0.4).

Example 53

Synthesis of 2-chloro-7-(2-chloro-4, 5-difluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4, 5-trifluorophenyl) ethan-1-one

[0335] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (500 mg, 3.14 mmol) in acetonitrile (5 mL) under an argon atmosphere was added cesium carbonate (2.2 g, 6.91 mmol) at 0 °C. After stirring for 10 mins 2-bromo-1-(2, 4, 5-trifluorophenyl) ethan-1-one (800 mg, 3.45 mmol) was added to the reaction mixture and stirred for 30 min. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was washed with EtOAc:hexane (1:1, 2 x 20 mL) to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl)

oxy)-1-(2, 4, 5-trifluorophenyl) ethan-1-one (550 mg, 55%) as a pale yellow solid which was used without further purification. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.88 (s, 1H), 7.70-7.63 (m, 2H), 7.53 (s, 1H), 4.17-4.10 (m, 2H), 2.81 (s, 3H); LCMS: 332.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.07 min 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 30% EtOAc/hexanes (R_f 0.7).

Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4, 5-trifluorophenyl) ethan-1-ol

[0336] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4, 5-trifluorophenyl) ethan-1-one (200 mg, 0.60 mmol) in MeOH (1 mL) under an argon atmosphere was added sodium borohydride (35 mg, 0.90 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with an ammonium chloride solution (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4, 5-trifluorophenyl) ethan-1-ol (140 mg) as a pale yellow solid and used without further purification. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.69 (s, 1H), 7.68-7.53 (m, 2H), 7.41-7.39 (m, 1H), 6.00 (s, 1H), 5.20-5.18 (m, 1H), 4.20-4.17 (m, 1H), 3.99 (t, 1H), 2.83 (d, 3H); LCMS: 334.3 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.86 min 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 50% EtOAc/hexanes (R_f 0.2).

Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4, 5-trifluorophenyl) ethyl methanesulfonate

[0337] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4, 5-trifluorophenyl) ethan-1-ol (140 mg, 0.42 mmol) in CH₂Cl₂ (2 mL) under an argon atmosphere were added triethylamine (0.12 mL, 0.84 mmol) followed by mesyl chloride (0.05 mL, 0.63 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. After consumption of the starting materials (monitored by TLC), the reaction was basified with water (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4, 5-trifluorophenyl) ethyl methanesulfonate (200 mg) as a pale yellow solid and used without further purification. ¹H-NMR (CDCl₃, 500

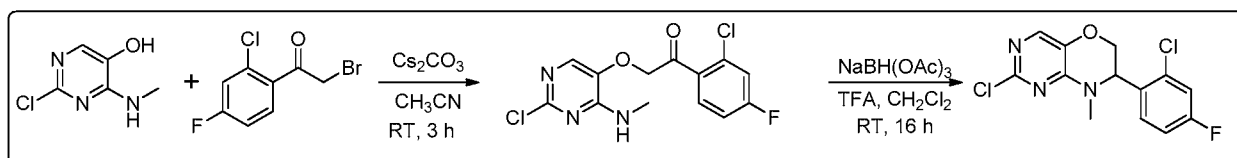
MHz): δ 7.43 (s, 1H), 7.35-7.30 (m, 1H), 7.09-7.04 (m, 1H), 6.20-6.18 (m, 1H), 6.13 (br s, 1H), 4.25-4.20 (m, 2H), 3.13 (s, 3H), 3.06-3.03 (m, 3H); TLC: 50% EtOAc/hexanes (R_f 0.5).

Synthesis of 2-chloro-8-methyl-7-(2, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0338] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2, 4, 5-trifluorophenyl) ethyl methanesulfonate (200 mg, 0.48 mmol) in DMF (1 mL) under an argon atmosphere was added potassium carbonate (100 mg, 0.72 mmol) at RT. The reaction mixture was heated to 75 °C for 12 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 10% EtOAc:hexane to afford 2-chloro-8-methyl-7-(2, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (80 mg, 52%) as an off-white solid. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.73 (s, 1H), 7.06-7.00 (m, 1H), 6.88-6.81 (m, 1H), 4.90 (s, 1H), 4.30-4.20 (m, 2H), 3.17 (s, 3H); LCMS: 316.3 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 4.34 min 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 50% EtOAc/hexanes (R_f 0.7).

Example 54

Synthesis of 2-chloro-7-(2-chloro-4-fluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-chloro-4-fluorophenyl) ethan-1-one

[0339] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (547 mg, 3.44 mmol) in acetonitrile (5 mL) under an argon atmosphere were added cesium carbonate (2.3 g, 6.88 mmol) and 2-bromo-1-(2-chloro-4-fluorophenyl) ethan-1-one (1 g, 3.78 mmol) at 0 °C. The reaction mixture was stirred at RT for 3 h. After consumption of the starting materials

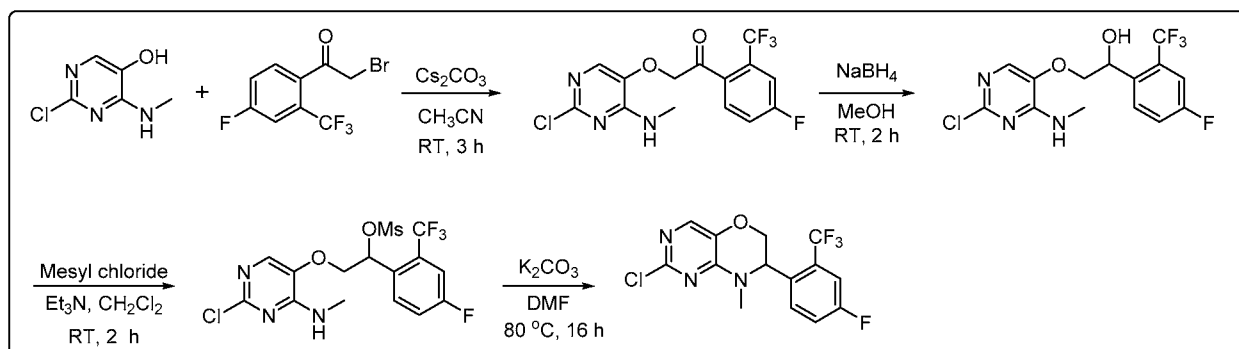
(monitored by TLC), the reaction was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-chloro-4-fluorophenyl) ethan-1-one (1 g) as a brown solid. LCMS: 331.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.18 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 30% EtOAc/hexanes (*R_f* 0.6).

Synthesis of 2-chloro-7-(2-chloro-4-fluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0340] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(2-chloro-4-fluorophenyl) ethan-1-one (1 g, 3.03 mmol) in 1, 2-dichloroethane (10 mL) under an argon atmosphere were added sodium triacetoxy borohydride (1.2 g, 6.06 mmol) followed by Trifluoroacetic acid (345 mg, 3.03 mmol) at RT and stirred for 16 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with a 1 N sodium hydroxide solution (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 15% EtOAc:hexanes to afford 2-chloro-7-(2-chloro-4-fluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (300 mg, 32%) as a pale brown solid. ¹H-NMR (CDCl₃, 500 MHz): δ 7.74 (s, 1H), 7.21 (d, 1H), 7.00-6.93 (m, 2H), 5.03 (s, 1H), 4.33-4.29 (m, 1H), 4.25-4.20 (m, 1H), 3.15 (s, 3H); LCMS: 314.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.38 min. 0.05% TFA in water: ACN; 0.8 mL/min); TLC: 30% EtOAc/hexanes (*R_f* 0.6).

Example 55

Synthesis of 2-chloro-7-(4-fluoro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluoro-2-(trifluoromethyl) phenyl) ethan-1-one

[0341] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (600 mg, 3.77 mmol) in acetonitrile (6 mL) under an argon atmosphere were added cesium carbonate (2.4 g, 7.54 mmol) and 2-bromo-1-(4-fluoro-2-(trifluoromethyl) phenyl) ethan-1-one (1.1 g, 4.15 mmol) at RT. The reaction mixture was stirred at RT for 3 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 20% EtOAc:hexane to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluoro-2-(trifluoromethyl) phenyl) ethan-1-one (500 mg, 36%) as an off-white solid. ¹H-NMR (CDCl₃, 500 MHz): δ 7.56-7.50 (m, 3H), 7.40 (t, 1H), 5.75 (br s, 1H), 5.05 (s, 2H), 3.09 (d, 3H); TLC: 30% EtOAc/hexanes (R_f 0.4).

Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluoro-2-(trifluoromethyl) phenyl) ethan-1-ol

[0342] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluoro-2-(trifluoromethyl) phenyl) ethan-1-one (500 mg, 1.37 mmol) in MeOH (2 mL) under an argon atmosphere was added sodium borohydride (76 mg, 2.06 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. After consumption of the starting materials (monitored by TLC), volatile components were evaporated, water (50 mL) was added and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluoro-2-(trifluoromethyl) phenyl) ethan-1-ol (450 mg, 89%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.94-7.90 (m, 1H), 7.66-7.60 (m, 3H),

7.45-7.40 (m, 1H), 6.00 (s, 1H), 5.23-5.20 (m, 1H), 4.09-4.00 (m, 1H), 3.99-3.91 (m, 1H), 2.88 (d, 3H); LCMS: 366.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.97 min 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 40% EtOAc/hexanes (R_f 0.5).

Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluoro-2-(trifluoromethyl) phenyl) ethyl methanesulfonate

[0343] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluoro-2-(trifluoromethyl) phenyl) ethan-1-ol (450 mg, 1.23 mmol) in dichloroethane (2 mL) under an argon atmosphere were added triethylamine (0.2 mL, 1.47 mmol) and mesyl chloride (140 mg, 1.23 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h. After consumption of the starting materials (monitored by TLC), the reaction was basified with water (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluoro-2-(trifluoromethyl) phenyl) ethyl methanesulfonate (500 mg) as an off-white solid. ¹H-NMR (CDCl₃, 500 MHz): δ 7.79-7.74 (m, 1H), 7.50-7.45 (m, 1H), 7.45-7.40 (m, 2H), 6.10 (br s, 1H), 4.20-4.10 (m, 2H), 3.13 (s, 1H), 3.08 (d, 3H), 2.99 (s, 3H); LCMS: 444.3 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.69 min 5 mM Aq NH₄OAc: ACN; 0.80 mL/min); TLC: 30% EtOAc/hexanes (R_f 0.4).

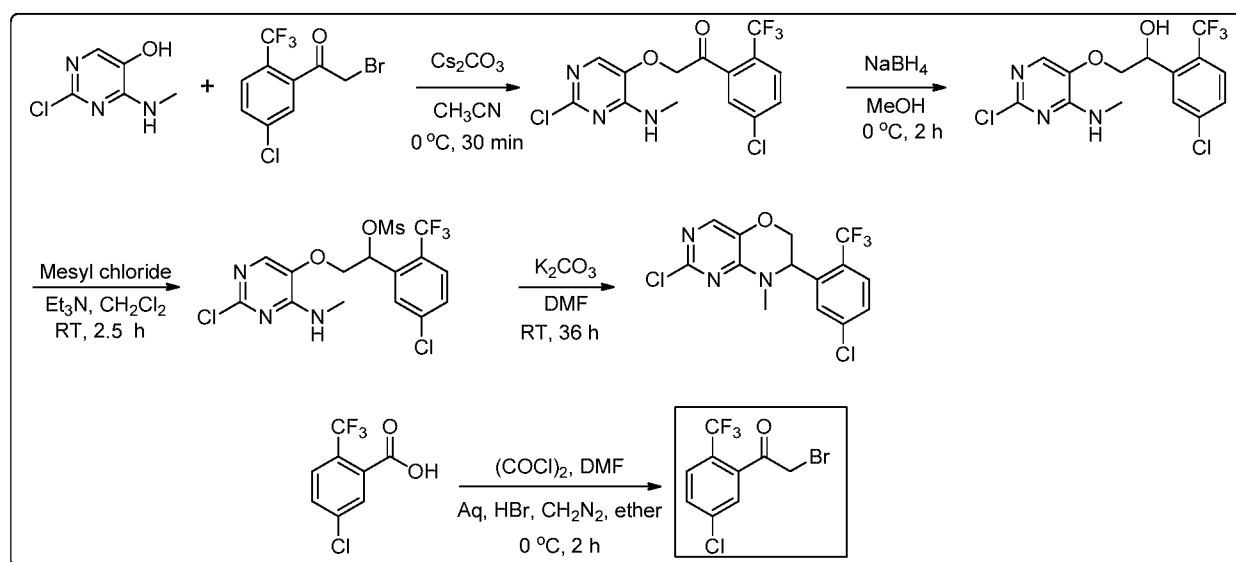
Synthesis of 2-chloro-7-(4-fluoro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0344] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(4-fluoro-2-(trifluoromethyl) phenyl) ethyl methanesulfonate (500 mg, 1.12 mmol) in DMF (5 mL) under an argon atmosphere was added potassium carbonate (233 mg, 1.69 mmol) at RT. The reaction mixture was heated at 80 °C for 16 h. After consumption of the starting materials (monitored by TLC), the volatile components were evaporated *in vacuo*. The reaction was diluted with ice cold water (50 mL) and extracted with ether (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 15% EtOAc:hexane to afford 2-chloro-7-(4-fluoro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (120 mg, 30%) as an off-white solid. ¹H-NMR (CD₃OD, 500 MHz): δ 7.75 (s, 1H), 7.70 (d, 1H), 7.46-7.40 (m, 1H), 7.37-7.30 (m, 1H), 5.16-5.13 (m, 1H), 4.35-

4.30 (m, 1H), 4.20-4.18 (m, 1H), 3.03 (s, 3H); LCMS: 348.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.66 min 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 30% EtOAc/hexanes (R_f 0.7).

Example 56

Synthesis of 2-chloro-7-(5-chloro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-bromo-1-(5-chloro-2-(trifluoromethyl) phenyl) ethan-1-one

[0345] To a stirred solution of 5-chloro-2-(trifluoromethyl) benzoic acid (4 g, 17.85 mmol) in CH_2Cl_2 (100 mL) under an argon atmosphere was added oxalyl chloride (2 mL, 19.64 mmol) and DMF (0.2 mL) at 0°C . The reaction mixture was stirred at 0°C for 2 h. After consumption of acid (monitored by TLC), the volatile components were evaporated *in vacuo*. The obtained residue was dissolved in ether and a CH_2N_2 in ether solution was added at 0°C . The reaction mixture was stirred at 0°C for 2 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with 48% Aq HBr solution (40 mL) at 0°C and stirred for 2 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with water (800 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were washed with a sodium bicarbonate solution (50 mL), water (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-bromo-1-(5-chloro-2-(trifluoromethyl) phenyl) ethan-1-one (5 g, 93%) as a pale yellow

liquid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.79 (d, 1H), 7.59 (d, 1H), 7.49 (s, 1H), 4.33 (s, 2H); LCMS: 301 (M-2); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.86 min. 5 mM Aq NH₄OAc: ACN; 0.8 mL/min); TLC: 20% EtOAc/hexanes (R_f 0.7).

Synthesis of 1-(5-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-one

[0346] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (2.7 g, 16.98 mmol) in CH₃CN (110 mL) under an argon atmosphere was added cesium carbonate (16 g, 33.96 mmol) at 0 °C. After stirring for 5 mins 2-bromo-1-(5-chloro-2-(trifluoromethyl) phenyl) ethan-1-one (6.4 g, 21.22 mmol) was added and stirred for 30 min. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was washed with hexane (2 x, 10 mL) to afford 1-(5-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-one (5.5 g, 86%) as a pale yellow solid. LCMS: 380.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.29 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 30% EtOAc/hexanes (R_f 0.5).

Synthesis of 1-(5-chloro-2-(trifluoromethyl)phenyl)-2-((2-chloro-4-(methylamino)pyrimidin-5-yl)oxy)ethan-1-ol

[0347] To a stirred solution of 1-(5-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-one (5.5 g, 14.43 mmol) in MeOH (110 mL) under an argon atmosphere was added sodium borohydride (1.1 g, 28.86 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with cold water. The volatile components were evaporated *in vacuo*, saturated ammonium chloride solution (100 mL) was added and the resulting solution was extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 1-(5-chloro-2-(trifluoromethyl)phenyl)-2-((2-chloro-4-(methylamino)pyrimidin-5-yl) oxy) ethan-1-ol (5.5 g) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.93 (s, 1H), 7.77 (d, 1H), 7.70-7.60 (m, 2H), 7.50-7.43 (m, 1H), 6.13 (d, 1H), 5.27-5.20 (m, 1H), 4.11-4.10 (m, 2H), 2.88 (d, 3H); LCMS: 383.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.23 min. 0.05% Aq TFA: ACN; 0.8 mL/min); TLC: 30% EtOAc/hexanes (R_f 0.4).

Synthesis of 1-(5-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethyl methanesulfonate

[0348] To a stirred solution of 1-(5-chloro-2-(trifluoromethyl)phenyl)-2-((2-chloro-4-(methylamino)pyrimidin-5-yl) oxy) ethan-1-ol (5.3 g, 14.00 mmol) in CH₂Cl₂ (100 mL) under an argon atmosphere was added triethylamine (6.82 mL, 49.00 mmol) followed by mesyl chloride (2.2 mL, 28.00 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 2.5 h. After consumption of the starting materials (monitored by TLC), the reaction was neutralized with a 5% sodium bicarbonate solution (100 mL) and extracted with CH₂Cl₂ (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 1-(5-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethyl methanesulfonate (5 g, 78%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.99 (s, 1H), 7.83 (d, 1H), 7.75-7.71 (m, 2H), 7.43-7.40 (m, 1H), 6.10 (d, 1H), 4.62-4.58 (m, 1H), 4.23-4.20 (m, 1H), 3.30 (s, 3H), 2.87 (d, 3H); LCMS: 461.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.44 min. 0.05% Aq TFA: ACN; 0.8 mL/min); UPLC (column; Acquity UPLC-BEH-C18 2.1 X 50 mm, 1.7 μm); RT 2.49 min. ACN: 0.025% Aq TFA; 0.5 mL/min; TLC: 30% EtOAc/hexanes (R_f 0.5).

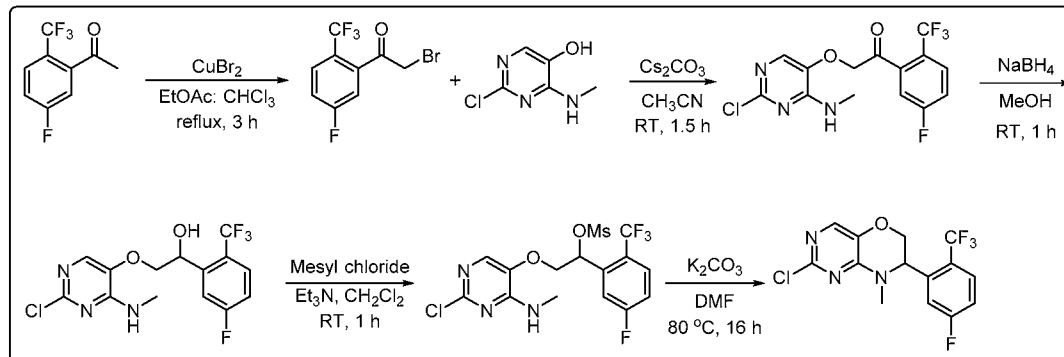
Synthesis of 2-chloro-7-(5-chloro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0349] To a stirred solution of 1-(5-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethyl methanesulfonate (900 mg, 1.95 mmol) in DMF (30 mL) under an argon atmosphere was added potassium carbonate (808 mg, 5.85 mmol) at RT. The reaction mixture was stirred at 120 °C for 36 h. After consumption of the starting materials (monitored by TLC), the reaction was quenched with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 15% EtOAc:hexanes to afford 2-chloro-7-(5-chloro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (300 mg, 42%) as a pale yellow solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.90-7.84 (m, 2H), 7.80 (d, 1H), 7.30 (s, 1H), 5.01-4.99 (m, 1H), 4.33-4.30 (m, 1H), 4.21-4.18 (m, 1H), 2.95 (s, 3H); LCMS: 365.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.75 min. 0.05% Aq TFA: ACN; 0.8 mL/min); UPLC (column; Acquity UPLC-BEH-C18 2.1 X 50

mm, 1.7 μ m); RT 2.73 min. ACN: 0.025% Aq TFA; 0.5 mL/min; TLC: 30% EtOAc/hexanes (R_f 0.7).

Example 57

Synthesis of 2-chloro-7-(5-fluoro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-bromo-1-(5-fluoro-2-(trifluoromethyl) phenyl) ethan-1-one

[0350] To a stirred solution of copper bromide (4.1 g, 18.40 mmol) in EtOAc (25 mL) under an argon atmosphere was added 1-(5-fluoro-2-(trifluoromethyl) phenyl) ethan-1-one (2 g, 9.70 mmol) in chloroform (10 mL) at 80 °C and stirred for 3 h. After consumption of the starting materials (monitored by TLC), the reaction was filtered, washed with CHCl_3 and concentrated *in vacuo* to afford 2-bromo-1-(5-fluoro-2-(trifluoromethyl) phenyl) ethan-1-one (2 g) as a yellow liquid, used without further purification. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.79-7.72 (m, 1H), 7.31 (t, 1H), 7.20 (d, 1H), 4.32 (s, 2H); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, 1.7 μ m); RT 2.45 min. ACN: 0.025% Aq TFA; 0.5 ml/min; TLC: 10% EtOAc/hexane (R_f 0.4).

Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(5-fluoro-2-(trifluoromethyl) phenyl) ethan-1-one

[0351] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (1.2 g, 7.50 mmol) in CH_3CN (40 mL) under an argon atmosphere were added cesium carbonate (4.9 g, 15.10 mmol) and 2-bromo-1-(5-fluoro-2-(trifluoromethyl) phenyl) ethan-1-one (2.1 g, 7.50 mmol) at RT. The reaction mixture was stirred at RT for 1.5 h. After consumption of the

starting materials (monitored by TLC), the reaction was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 20-30% EtOAc:hexanes to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(5-fluoro-2-(trifluoromethyl) phenyl) ethan-1-one (1.2 g, 47%) as an off-white solid. LCMS: 364.3 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 µm); RT 4.31 min 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 30% EtOAc/hexane (*R_f* 0.6).

Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(5-fluoro-2-(trifluoromethyl) phenyl) ethan-1-ol

[0352] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(5-fluoro-2-(trifluoromethyl) phenyl) ethan-1-one (300 mg, 0.82 mmol) in MeOH (3 mL) under an argon atmosphere was added sodium borohydride (62 mg, 1.65 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 1 h. After consumption of the starting materials (monitored by TLC), the volatile components were evaporated *in vacuo*. The residue was diluted with water (10 mL) and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(5-fluoro-2-(trifluoromethyl) phenyl) ethan-1-ol (300 mg) as an off-white solid and used without further purification. LCMS: 366.3 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 µm); RT 4.03 min 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 30% EtOAc/hexane (*R_f* 0.6).

Synthesis of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(5-fluoro-2-(trifluoromethyl) phenyl) ethyl methanesulfonate

[0353] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(5-fluoro-2-(trifluoromethyl) phenyl) ethan-1-ol (300 mg, 0.82 mmol) in CH₂Cl₂ (10 mL) under an argon atmosphere were added mesylchloride (140 mg, 1.23 mmol) and triethylamine (166 mg, 1.64 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 1 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (10 mL) and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(5-fluoro-2-(trifluoromethyl) phenyl) ethyl methanesulfonate (405 mg) as an off-white solid and used without further purification.

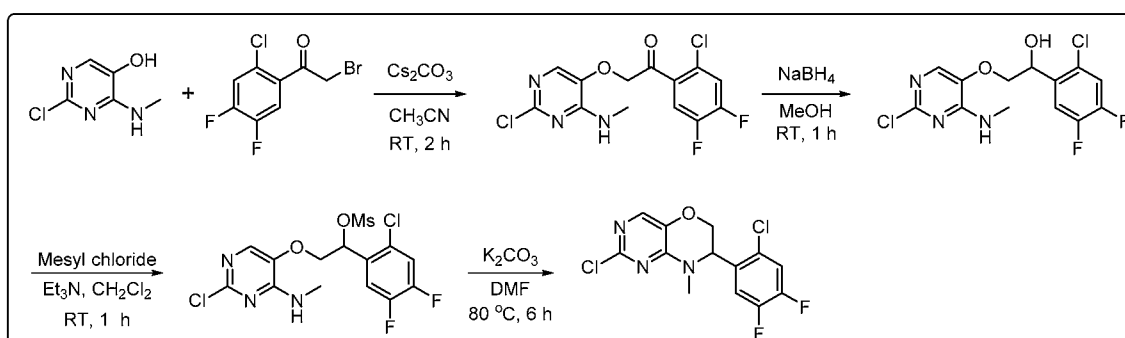
LCMS: 444.3 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.28 min 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 30% EtOAc/hexane (R_f 0.6).

Synthesis of 2-chloro-7-(5-fluoro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0354] To a stirred solution of 2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy)-1-(5-fluoro-2-(trifluoromethyl) phenyl) ethyl methanesulfonate (400 mg, 0.90 mmol) in DMF (4 mL) under an argon atmosphere was added potassium carbonate (248 mg, 1.80 mmol) at RT. The reaction mixture was stirred at 80 °C for 16 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 10-20% EtOAc:hexanes to afford 2-chloro-7-(5-fluoro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (200 mg, 64%) as a pale yellow solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.80 (s, 1H), 7.79-7.74 (m, 1H), 7.25 (t, 1H), 6.90-6.86 (m, 1H), 5.01-5.00 (m, 1H), 4.27-4.22 (m, 1H), 4.15-4.10 (m, 1H), 3.06 (s, 3H); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 2.61 min. ACN: 0.025% Aq TFA; 0.5 ml/min; TLC: 30% EtOAc/hexane (R_f 0.6).

Example 58

Synthesis of 2-chloro-7-(2-chloro-4, 5-difluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 1-(2-chloro-4, 5-difluorophenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-one

[0355] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (1.47 g, 9.24 mmol) in CH₃CN (25 mL) under an argon atmosphere were added cesium carbonate (6 g, 18.49 mmol) and 2-bromo-1-(2-chloro-4, 5-difluorophenyl) ethan-1-one (2.5 g, 9.29 mmol) at RT. The reaction mixture was stirred at RT for 2 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 1-(2-chloro-4, 5-difluorophenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-one (2.5 g, 78%) as an off-white solid and used without further purification. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.92-7.80 (m, 3H), 7.60 (s, 1H), 4.28 (d, 1H), 4.08 (d, 1H), 2.76 (s, 3H); TLC: 30% EtOAc/hexanes (R_f 0.5).

Synthesis of 1-(2-chloro-4, 5-difluorophenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-ol

[0356] To a stirred solution of 1-(2-chloro-4, 5-difluorophenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-one (2.5 g, 7.18 mmol) in MeOH (25 mL) under an argon atmosphere was added sodium borohydride (531 mg, 14.36 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 1 h. After consumption of the starting materials (monitored by TLC), the volatile components were evaporated *in vacuo*. The residue was diluted with water (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 1-(2-chloro-4, 5-difluorophenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-ol (2.2 g) as an off-white solid and used without further purification. LCMS: 350 (M⁺); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.39 min 5mM Aq NH₄OAc: ACN; 0.80 mL/min); TLC: 50% EtOAc/hexanes (R_f 0.4).

Synthesis of 1-(2-chloro-4, 5-difluorophenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethyl methanesulfonate

[0357] To a stirred solution of 1-(2-chloro-4, 5-difluorophenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-ol (2.2 g, 6.28 mmol) in CH₂Cl₂ (25 mL) under an argon atmosphere were added triethylamine (1.26 g, 12.57 mmol) and mesyl chloride (859 mg, 7.54 mmol) at RT. The reaction mixture was stirred at RT for 1 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (50 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried over sodium

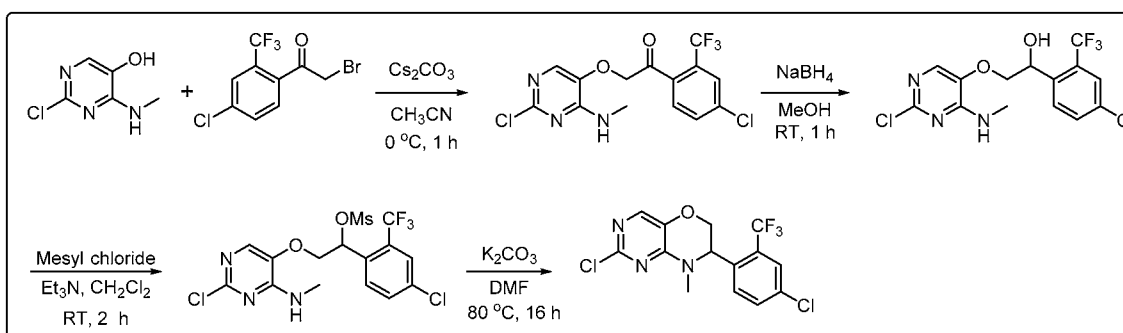
sulfate, filtered and concentrated *in vacuo* to afford 1-(2-chloro-4, 5-difluorophenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethyl methanesulfonate (2.5 g) as an off-white solid and used without further purification. LCMS: 428 (M⁺); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.39 min 5mM Aq NH₄OAc: ACN; 0.80 mL/min); TLC: 50% EtOAc/hexanes (R_f 0.6).

Synthesis of 2-chloro-7-(2-chloro-4, 5-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0358] To a stirred solution of 1-(2-chloro-4, 5-difluorophenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethyl methanesulfonate (2.5 g, 5.84 mmol) in DMF (25 mL) under an argon atmosphere was added potassium carbonate (1.61 g, 11.68 mmol) at RT. The reaction mixture was heated at 80 °C for 6 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (200 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with water (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 5% EtOAc:hexane to afford 2-chloro-7-(2-chloro-4, 5-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (1.3 g, 68%) as an off-white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 7.90-7.87 (m, 1H), 7.79 (s, 1H), 7.18-7.10 (m, 1H), 5.19-5.17 (m, 1H), 4.30 (s, 2H), 3.01 (s, 3H); LCMS: 332.1 (M+2); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.79 min 5mM Aq NH₄OAc: ACN; 0.80 mL/min); TLC: 30% EtOAc/hexanes (R_f 0.7).

Example 59

Synthesis of 2-chloro-7-(4-chloro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 1-(4-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-one

[0359] To a stirred solution of 2-chloro-4-(methylamino) pyrimidin-5-ol (250 mg, 1.57 mmol) in CH₃CN (10 mL) under an argon atmosphere was added cesium carbonate (1 g, 3.14 mmol) at 0 °C. After stirring for 10 mins, 2-bromo-1-(4-chloro-2-(trifluoromethyl) phenyl) ethan-1-one (560 mg, 1.88 mmol) was added to the reaction mixture and stirred for 1 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 5% EtOAc:hexane to afford 1-(4-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-one (200 mg, 30%) as an off-white solid. ¹H-NMR (CDCl₃, 500 MHz): δ 7.78 (s, 1H), 7.66 (d, 1H), 7.50 (s, 1H), 7.43 (d, 1H), 5.70 (s, 1H), 5.00 (s, 2H), 3.02 (d, 3H); TLC: 40% EtOAc/hexanes (R_f 0.6).

Synthesis of 1-(4-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-ol

[0360] To a stirred solution of 1-(4-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-one (200 mg, 0.52 mmol) in MeOH (5 mL) under an argon atmosphere was added sodium borohydride (29 mg, 0.78 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 1 h. After consumption of the starting materials (monitored by TLC), the volatile components were evaporated *in vacuo*, water (20 mL) was added and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 1-(4-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-ol (150 mg, 75%) as a pale yellow solid and used without further purification. ¹H-NMR (CDCl₃, 500 MHz): δ 7.80 (d, 1H), 7.67 (s, 1H), 7.61 (d, 1H), 7.50 (br s, 1H), 5.60 (br s, 1H), 5.55-5.49 (m, 1H), 4.10-4.07 (m, 1H), 4.01-3.97 (m, 1H), 3.05 (d, 3H), 2.67 (s, 1H); LCMS: 382.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.62 min 5mM Aq NH₄OAc: ACN; 0.80 mL/min); TLC: 40% EtOAc/hexanes (R_f 0.5).

Synthesis of 1-(4-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethyl methanesulfonate

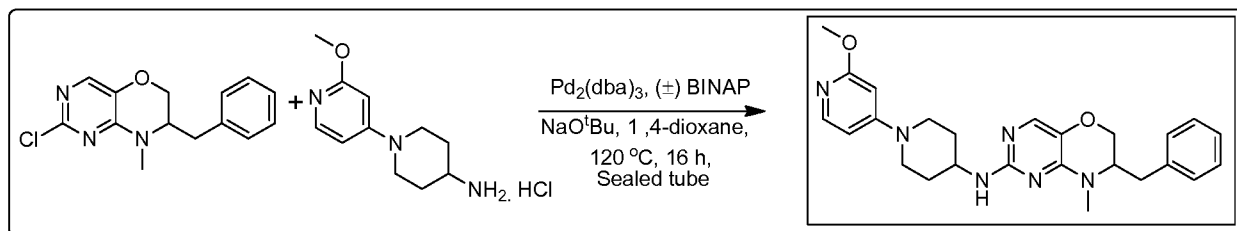
[0361] To a stirred solution of 1-(4-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethan-1-ol (150 mg, 0.39 mmol) in CH₂Cl₂ (4 mL) under an argon atmosphere were added triethylamine (0.1 mL, 0.78 mmol) followed by mesyl chloride (0.05 mL, 0.58 mmol) at 0 °C. The reaction mixture was warmed to RT for 2 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 1-(4-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethyl methanesulfonate (180 mg) as a pale yellow solid and used without further purification. TLC: 40% EtOAc/hexanes (R_f 0.6).

Synthesis of 2-chloro-7-(4-chloro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0362] To a stirred solution of 1-(4-chloro-2-(trifluoromethyl) phenyl)-2-((2-chloro-4-(methylamino) pyrimidin-5-yl) oxy) ethyl methanesulfonate (180 mg, 0.39 mmol) in DMF (4 mL) under an argon atmosphere was added potassium carbonate (100 mg, 0.78 mmol) at RT. The reaction mixture was heated at 80 °C for 16 h. After consumption of the starting materials (monitored by TLC), the reaction was diluted with water (2 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 5% EtOAc:hexane to afford 2-chloro-7-(4-chloro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (140 mg, 36%) as a pale yellow solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.75 (s, 1H), 7.74 (s, 1H), 7.51 (d, 1H), 7.11 (d, 1H), 5.09-5.07 (m, 1H), 4.28-4.26 (m, 1H), 4.13-4.11 (m, 1H), 3.01 (s, 3H); TLC: 40% EtOAc/hexanes (R_f 0.7).

Example 60

Synthesis of 7-benzyl-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



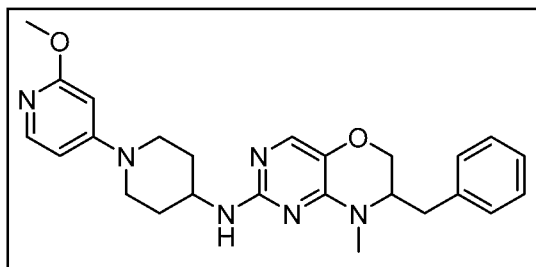
Synthesis of 7-benzyl-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0363] A dry vial charged with $\text{Pd}_2(\text{dba})_3$ (33 mg, 0.03 mmol) and ($\pm$) BINAP (67 mg, 0.10 mmol) in 1, 4-dioxane (1 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 2-benzyl-7-chloro-1-methyl-2, 3-dihydro-1H-pyrido [3, 4-b] [1, 4] oxazine (200 mg, 0.72 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (194 mg, 0.79 mmol) and sodium tert-butoxide (209 mg, 2.18 mmol) in 1, 4-dioxane (1 mL) was degassed and the catalyst pre-mixture was added. The resultant mixture was stirred at 120 °C for a 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the volatile components were concentrated *in vacuo*. The residue was diluted with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 40% EtOAc:hexanes to afford 7-benzyl-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (47 mg, 14%) as an off-white solid. LCMS: 474.5 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 3.07 min. 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Acquity UPLC-BEH-C18 2.1 X 50 mm, 1.7 μm); RT 1.70 min. ACN: 0.025% Aq TFA; 0.5 mL/min; TLC: 50% EtOAc/hexanes (R_f 0.3).

[0364] Racemic compound of Example 60 was separated using a Chiralpak IA (250 x 20 mm, 5 μm (20 mg loading; 0.1 % DEA in *n*-hexane: DCM: MeOH (50: 50); (85: 15) as mobile phase) to provide the compound of Example 60A Fraction I (+) and the compound of Example 60B Fraction II (-).

Example 60A

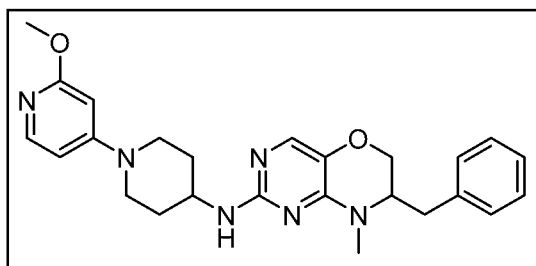
Synthesis of (+)-7-benzyl-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0365] The compound of Example 60A was produced as described above. Analytical data for product Fraction (I) (+): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.73 (d, 1H), 7.37-7.30 (m, 3H), 7.29-7.22 (m, 3H), 6.54 (d, 1H), 6.15 (s, 1H), 4.01-3.97 (m, 1H), 3.94-3.85 (m, 3H), 3.84 (s, 3H), 3.76-3.72 (m, 1H), 3.67-3.61 (m, 1H), 3.10-3.01 (m, 3H), 3.00 (s, 3H), 2.85-2.80 (m, 1H), 2.04 (d, 2H), 1.59-1.47 (m, 2H); Mass (ESI): 447.4 $[\text{M}+1]$; LCMS: 447.5 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.91 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC-BEH-C18 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.62 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 100% RT = 16.11 min (CHIRALPAK-IB (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) EtOH (A: B: 90: 10); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{20.01}$: +57.24 ($c = 0.25$, DCM).

Example 60B

Synthesis of (-)-7-benzyl-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

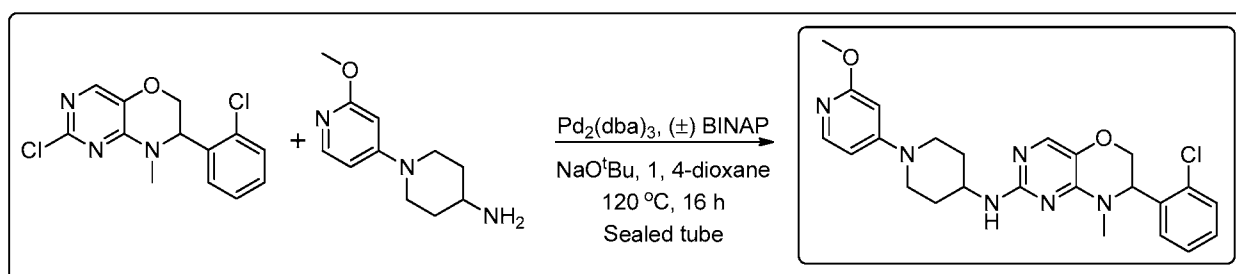


[0366] The compound of Example 60B was produced as described above. Analytical data for product Fraction (II) (-): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.73 (d, 1H), 7.37-7.30 (m, 3H), 7.29-7.22 (m, 3H), 6.54 (d, 1H), 6.15 (s, 1H), 4.01-3.97 (m, 1H), 3.94-3.85 (m, 3H), 3.84 (s, 3H), 3.76-3.72 (m, 1H), 3.67-3.61 (m, 1H), 3.10-3.01 (m, 3H), 3.00 (s, 3H), 2.85-2.80 (m, 1H), 2.04 (d, 2H), 1.59-1.47 (m, 2H); Mass (ESI): 447.5 $[\text{M}+1]$; LCMS: 447.5 (M+1);

(column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.91 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC-BEH-C18 2.1 X 50 mm, 1.7 μm); RT 1.62 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 95.3% RT = 18.13 min (CHIRALPAK-IB (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) EtOH (A: B: 90: 10); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: -47.79 (c = 0.25, DCM).

Example 61

Synthesis of 7-(2-chlorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 7-(2-chlorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

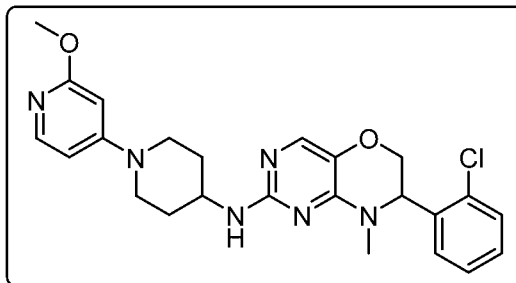
[0367] A dry vial charged with $\text{Pd}_2(\text{dba})_3$ (88 mg, 0.09 mmol) and (±) BINAP (18 mg, 0.03 mmol) in 1, 4-dioxane (2.5 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 2-chloro-7-(2-chlorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (200 mg, 0.64 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine (170 mg, 0.70 mmol) and sodium tert-butoxide (185 mg, 1.93 mmol) in 1, 4-dioxane (2.5 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the volatile components were evaporated *in vacuo*. The crude material was purified by column chromatography using 2% MeOH: CH_2Cl_2 to afford 7-(2-chlorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (150 mg, 49%) as an off-white solid. LCMS: 467.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.97 min 0.05% Aq TFA: ACN; 0.80 mL/min); TLC: 5% MeOH/ CH_2Cl_2 (R_f 0.4).

[0368] Racemic compound of Example 61 was separated using a Chiralpak-ADH (250 x 20 mm; 5μm; (15 mg loading; 0.1% DEA in *n*-hexane: EtOH (A: B: 60: 40) as mobile phase)

to provide the compound of Example 61A Fraction I (-) and the compound of Example 61B Fraction II (+).

Example 61A

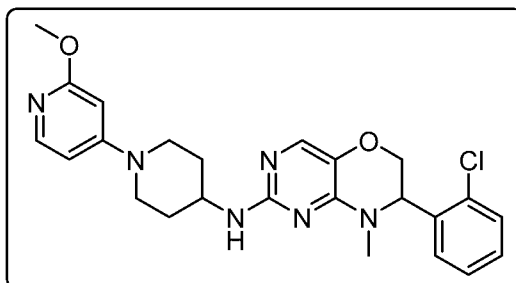
Synthesis of (-)-7-(2-chlorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0369] The compound of Example 61A was produced as described above. Analytical data for product Fraction I (-): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.73 (d, 1H), 7.49 (d, 1H), 7.40 (s, 1H), 7.37-7.30 (m, 2H), 7.05 (d, 1H), 6.55 (d, 1H), 6.08 (s, 1H), 5.12-5.10 (m, 1H), 4.24-4.19 (m, 2H), 3.99-3.90 (m, 3H), 3.84 (s, 3H), 3.08-3.01 (m, 5H), 2.11-2.09 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 467.6 $[\text{M}+1]$; LCMS: 467.6 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.87 min. 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Eclipse XDB C-18, 150×4.6 mm, $5 \mu\text{m}$); RT 11.58 min. ACN: 5 mM Aq NH_4OAc ; 1.0 mL/min; Chiral HPLC: 100% RT = 19.32 min (CHIRALPAK-ADH (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) EtOH (A: B: 60: 40); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: -120.38 ($c = 0.25$, DCM).

Example 61B

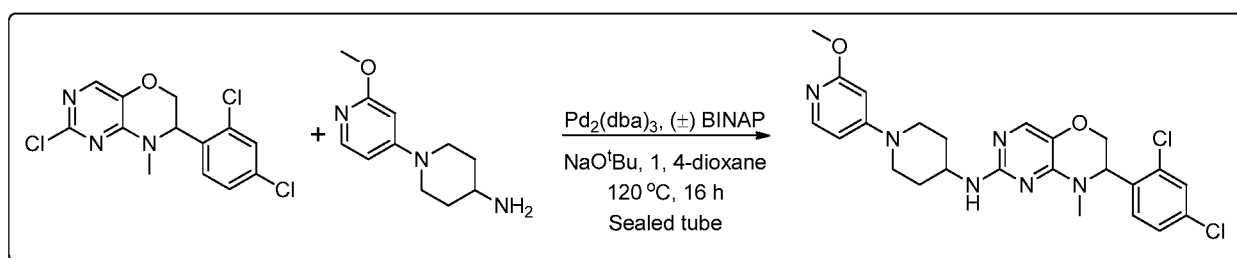
Synthesis of (+)-7-(2-chlorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0370] The compound of Example 61B was produced as described above. Analytical data for product Fraction II (+): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.73 (d, 1H), 7.49 (d, 1H), 7.40 (s, 1H), 7.37-7.30 (m, 2H), 7.05 (d, 1H), 6.55 (d, 1H), 6.08 (s, 1H), 5.12-5.10 (m, 1H), 4.24-4.19 (m, 2H), 3.99-3.90 (m, 3H), 3.84 (s, 3H), 3.08-3.01 (m, 5H), 2.11-2.09 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 467.5 $[\text{M}+1]$; LCMS: 467.5 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.87 min. 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Eclipse XDB C-18, 150×4.6 mm, $5 \mu\text{m}$); RT 11.58 min. ACN: 5 mM Aq NH_4OAc ; 1.0 mL/min; Chiral HPLC: 99.5% RT = 32.89 min (CHIRALPAK-ADH (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) EtOH (A: B: 60: 40); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{20.01}$: +116.32 ($c = 0.25$, DCM).

Example 62

Synthesis of 7-(2, 4-dichlorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 7-(2, 4-dichlorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

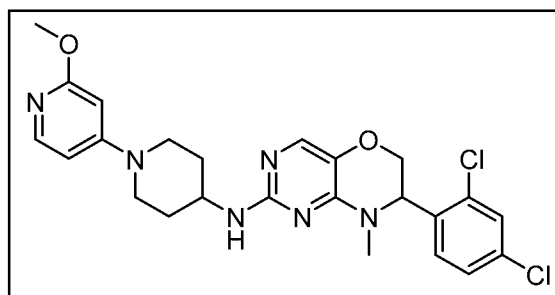
[0371] A dry vial charged with $\text{Pd}_2(\text{dba})_3$ (28 mg, 0.03 mmol) and $(\pm)$ BINAP (56 mg, 0.09 mmol) in 1, 4-dioxane (2 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 2-chloro-7-(2, 4-dichlorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (200 mg, 0.60 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine (138 mg, 0.66 mmol) and sodium tert-butoxide (175 mg, 1.81 mmol) in 1, 4-dioxane (2 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction was diluted with water (50 mL) and extracted with 20% MeOH/ CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 2%

MeOH: CH₂Cl₂ to afford 7-(2, 4-dichlorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine (110 mg, 33%) as an off-white solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.88 (d, 1H), 7.52 (s, 1H), 7.43 (s, 1H), 7.22-7.20 (m, 1H), 7.00-6.98 (m, 1H), 6.55 (d, 1H), 6.08 (s, 1H), 4.94-4.92 (m, 1H), 4.79-4.71 (m, 1H), 4.20-4.10 (m, 2H), 4.00-3.90 (m, 1H), 3.89 (s, 3H), 3.80-3.75 (m, 2H), 3.06-3.00 (m, 5H), 2.16-2.10 (m, 2H), 1.60-1.58 (m, 2H); LCMS: 501.7 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.09 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.84 min. ACN: 0.025% Aq TFA; 0.5 ml/min; TLC: 10% MeOH/ CH₂Cl₂ (R_f 0.5).

[0372] Racemic compound of Example 62 was separated using a Chiralpak IA (250 x 20 mm: 5μm; (50 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂: MeOH (50: 50); (A: B: 55: 45) as mobile phase) to provide the compound of Example 62A Fraction I (-) and the compound of Example 62B Fraction II (+).

Example 62A

Synthesis of (-)-7-(2, 4-dichlorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine

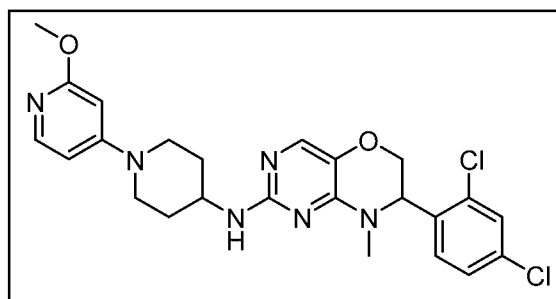


[0373] The compound of Example 62A was produced as described above. Analytical data for product Fraction I (-): ¹H-NMR (CD₃OD, 400 MHz): δ 7.73-7.71 (m, 1H), 7.56 (s, 1H), 7.40 (s, 1H), 7.37-7.31 (m, 1H), 7.04-7.00 (m, 1H), 6.55 (d, 1H), 6.17 (s, 1H), 5.10-5.08 (m, 1H), 4.25-4.16 (m, 2H), 3.97-3.80 (m, 3H), 3.83 (s, 3H), 3.10-3.06 (m, 1H), 3.05 (s, 3H), 3.04-3.01 (m, 1H), 2.10-2.07 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 501.9 [M+1]; LCMS: 501 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.61 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.85 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 99.2% RT = 11.84 min (CHIRALPAK-IA (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B)

CH₂Cl₂: MeOH (50: 50) (A: B: 55: 45); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.99}$: -135.24 (c = 0.25, DCM).

Example 62B

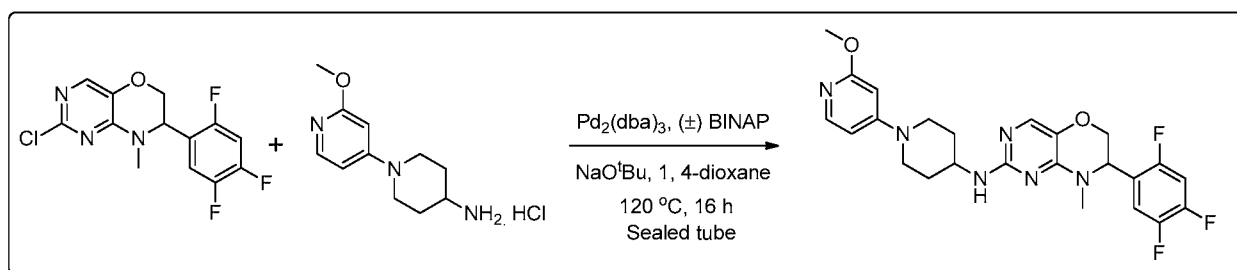
Synthesis of (+)-7-(2, 4-dichlorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0374] The compound of Example 62B was produced as described above. Analytical data for product Fraction II (+): ¹H-NMR (CD₃OD, 400 MHz): δ 7.73-7.71 (m, 1H), 7.56 (s, 1H), 7.40 (s, 1H), 7.37-7.31 (m, 1H), 7.04-7.00 (m, 1H), 6.55 (d, 1H), 6.17 (s, 1H), 5.10-5.08 (m, 1H), 4.25-4.16 (m, 2H), 3.97-3.80 (m, 3H), 3.83 (s, 3H), 3.10-3.06 (m, 1H), 3.05 (s, 3H), 3.04-3.01 (m, 1H), 2.10-2.07 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 501.8 [M+1]; LCMS: 501 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μ m); RT 2.61 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μ m); RT 1.85 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 99.1% RT = 19.64 min (CHIRALPAK-IA (250 × 4.6 mm, 5 μ m; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B: 55: 45); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.99}$: +95.85 (c = 0.25, DCM).

Example 63

Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



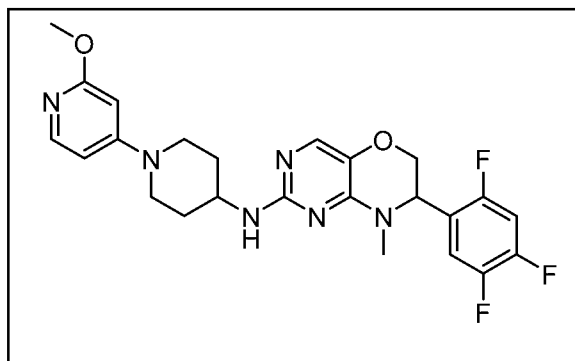
Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0375] A dry vial charged with $\text{Pd}_2(\text{dba})_3$ (36 mg, 0.04 mmol) and ($\pm$) BINAP (74 mg, 0.11 mmol) in 1, 4-dioxane (1.25 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 2-chloro-8-methyl-7-(2, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 0.79 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (385 mg, 1.58 mmol) and sodium tert-butoxide (152 mg, 1.58 mmol) in 1, 4-dioxane (1.25 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the volatile components were evaporated *in vacuo*. The residue was diluted with water (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 3% MeOH: CH_2Cl_2 to afford *N*-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (100 mg, 26%) as an off-white solid. LCMS: 487.1 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 2.40 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity BEH C-18 2.1 X 50 mm, 1.7 μm); RT 1.65 min. ACN: 0.025% Aq TFA; 0.5 mL/min; TLC: 5% MeOH/ CH_2Cl_2 (R_f 0.4).

[0376] Racemic compound of Example 63 was separated using a Chiralpak IA (250 x 20 mm; 5 μm ; (30 mg loading; 0.1 % DEA in *n*-hexane: CH_2Cl_2 : MeOH (50: 50); (A: B: 70: 30) as mobile phase) to provide the compound of Example 63A Fraction I (-) and the compound of Example 63B Fraction II (+).

Example 63A

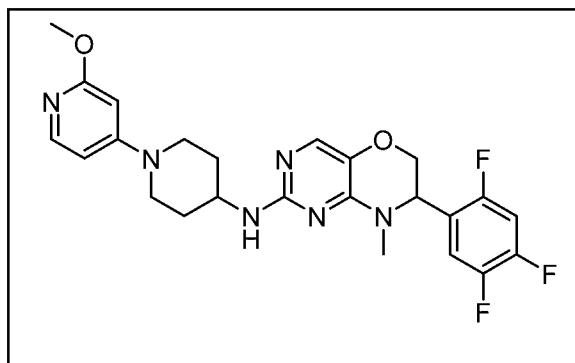
Synthesis of (-)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0377] The compound of Example 63A was produced as described above. Analytical data for product Fraction I (-): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.76-7.72 (m, 1H), 7.44 (s, 1H), 7.30-7.23 (m, 1H), 7.00-6.92 (m, 1H), 6.57 (d, 1H), 6.16 (s, 1H), 5.00-4.97 (m, 1H), 4.20-4.16 (m, 2H), 3.98-3.90 (m, 3H), 3.82 (s, 3H), 3.10 (s, 3H), 3.09-3.05 (m, 2H), 2.10-2.04 (m, 2H), 1.61-1.50 (m, 2H); Mass (ESI): 487.5 $[\text{M}+1]$; LCMS: 487 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.36 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.61 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 99.5% RT = 9.20 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 : MeOH (50: 50) (A: B: 70: 30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{20.02}$: -78.51 ($c = 0.25$, CH_2Cl_2).

Example 63B

Synthesis of (+)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

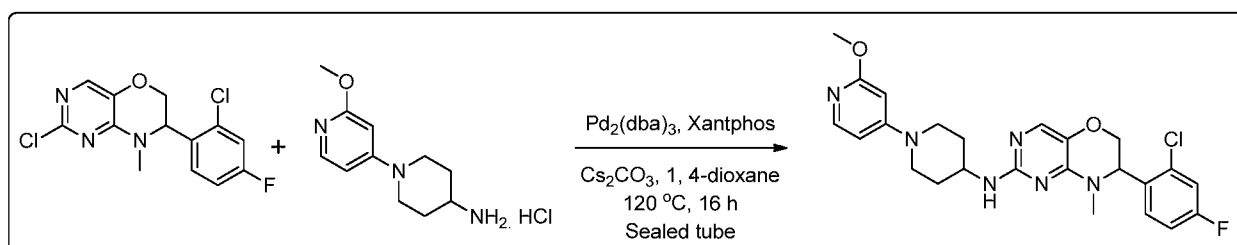


[0378] The compound of Example 63B was produced as described above. Analytical data for product Fraction II (+): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.78-7.72 (m, 1H), 7.48 (s, 1H), 7.32-7.25 (m, 1H), 7.00-6.92 (m, 1H), 6.57 (d, 1H), 6.16 (s, 1H), 5.00-4.97 (m, 1H), 4.20-

4.16 (m, 2H), 3.98-3.90 (m, 3H), 3.82 (s, 3H), 3.10 (s, 3H), 3.09-3.05 (m, 2H), 2.10-2.03 (m, 2H), 1.61-1.50 (m, 2H); Mass (ESI): 487.6 [M+1]; LCMS: 487 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.36 min. 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.62 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 99.7% RT = 19.10 min (CHIRALPAK-IA (250 × 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B: 70: 30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.97}$: +83.61 (c = 0.25, CH₂Cl₂).

Example 64

Synthesis of 7-(2-chloro-4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 7-(2-chloro-4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

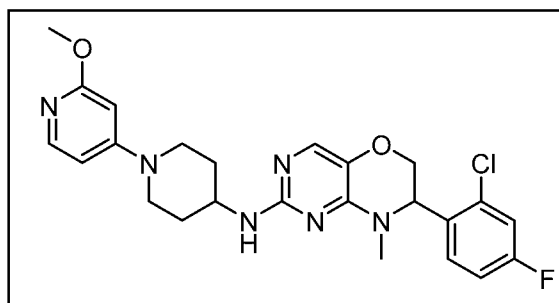
[0379] A dry vial charged with Pd₂(dba)₃ (37 mg, 0.04 mmol) and Xantphos (70 mg, 0.12 mmol) in 1, 4-dioxane (1.25 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 2-chloro-7-(2-chloro-4-fluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 0.80 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (389 mg, 1.60 mmol) and cesium carbonate (366 mg, 1.12 mmol) in 1, 4-dioxane (1.25 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the volatile components were evaporated *in vacuo*. The residue was diluted with water (50 mL) and extracted with CH₂Cl₂ (2 × 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 3% MeOH: CH₂Cl₂ to afford 7-(2-chloro-4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (100 mg, 25.8%) as an off-white solid.

LCMS: 485 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.45 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18 2.1 X 50 mm, 1.7 μm); RT 1.70 min. ACN: 0.025% Aq TFA; 0.5 mL/min; TLC: 5% MeOH/ CH₂Cl₂ (R_f 0.3).

[0380] Racemic compound of Example 64 was separated using a Chiralpak IA (250 x 4.6 mm: 5μm; (50 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂: MeOH (50: 50) (A: B: 70: 30) as mobile phase) to provide the compound of Example 64A Fraction I (-) and the compound of Example 64B Fraction II (+).

Example 64A

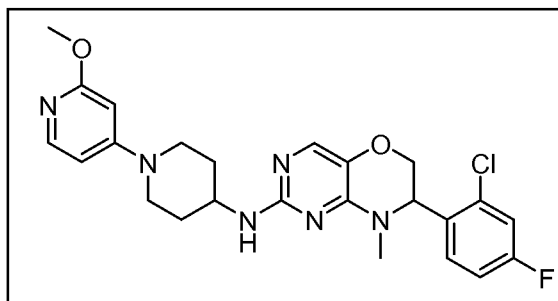
Synthesis of (-)-7-(2-chloro-4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0381] The compound of Example 64A was produced as described above. Analytical data for product Fraction I (-): ¹H-NMR (CD₃OD, 400 MHz): δ 7.72-7.70 (m, 1H), 7.39 (s, 1H), 7.31 (d, 1H), 7.06 (d, 2H), 6.53 (d, 1H), 6.14 (s, 1H), 5.08-5.06 (m, 1H), 4.20-4.12 (m, 2H), 3.94-3.87 (m, 3H), 3.80 (s, 3H), 3.08-3.06 (m, 2H), 3.05 (s, 3H), 2.10-2.02 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 485 [M+1]; LCMS: 485.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.67 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.74 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 99.8% RT= 8.42 min (CHIRALPAK-IA (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B: 70: 30); flow Rate: 1.0 mL/min); Optical rotation [α]_D^{20.01}: -122.20 (c = 0.25, CH₂Cl₂).

Example 64B

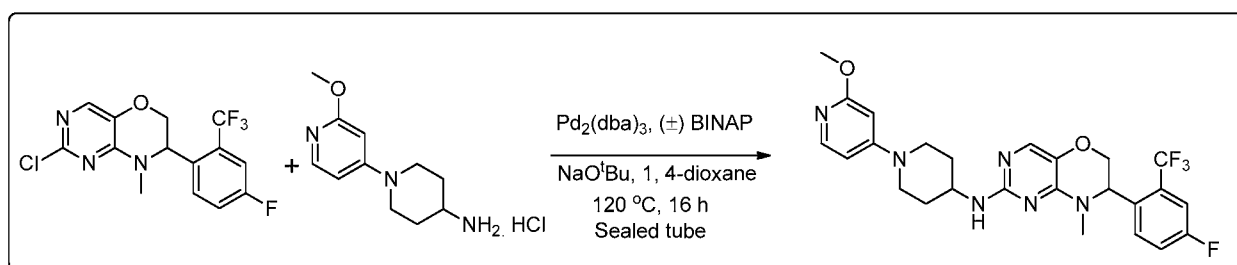
Synthesis of (+)-7-(2-chloro-4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0382] The compound of Example 64B was produced as described above. Analytical data for product Fraction II (+): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.72-7.70 (m, 1H), 7.39 (s, 1H), 7.31 (d, 1H), 7.05 (d, 2H), 6.53 (d, 1H), 6.14 (s, 1H), 5.08-5.06 (m, 1H), 4.20-4.12 (m, 2H), 3.94-3.87 (m, 3H), 3.80 (s, 3H), 3.08-3.06 (m, 2H), 3.05 (s, 3H), 2.10-2.02 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 485.1 $[\text{M}+1]$; LCMS: 485.1 (M+1); (column; X-Select CSH C-18 (50 $\times$ 3.0 mm, 3.5 μm); RT 2.66 min. 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Acquity UPLC BEH C-18, 2.1 $\times$ 50 mm, 1.7 μm); RT 1.74 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 99.4% RT = 14.00 min (CHIRALPAK-IA (250 $\times$ 4.6 mm, 5 μm ; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 : MeOH (50: 50) (A: B: 70: 30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{19.99}$: +120.27 (c = 0.25, CH_2Cl_2).

Example 65

Synthesis of 7-(4-fluoro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 7-(4-fluoro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

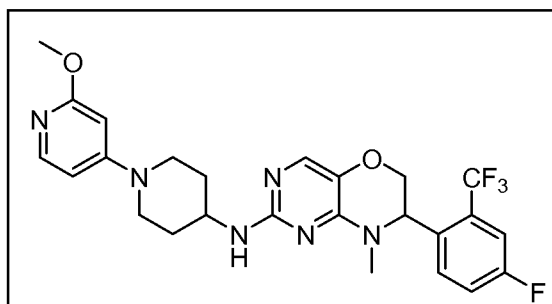
[0383] A dry vial charged with $\text{Pd}_2(\text{dba})_3$ (33 mg, 0.03 mmol) and ($\pm$) BINAP (67 mg, 0.10 mmol) in 1, 4-dioxane (1.25 mL) at RT was degassed with argon and stirred at 120 $^\circ\text{C}$ for 3 min. A mixture of 2-chloro-7-(4-fluoro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-

dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 0.72 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (192 mg, 0.79 mmol) and sodium tert-butoxide (207 mg, 2.16 mmol) in 1, 4-dioxane (1.25 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction was diluted with water (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by preparative HPLC (Column YMC polymer C-18 (300 x 20 mm, 10µm (70 mg loading; CH₃CN: 0.05% TFA (0.1/90, 2/80, 15/70, 25/20, 35/10)) to afford 7-(4-fluoro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (115 mg, 31%) as an off-white solid. LCMS: 519.6 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 µm); RT 3.12 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18 2.1 X 50 mm, 1.7 µm); RT 1.77 min. ACN: 0.025% Aq TFA; 0.5 mL/min; TLC: 10% MeOH/ CH₂Cl₂ (R_f 0.3).

[0384] Racemic compound of Example 65 was separated using a Chiralpak IA (250 x 20 mm: 5µm; (20 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂: MeOH (50: 50); (A: B: 80: 20) as mobile phase) to provide the compound of Example 65A Fraction I (-) and the compound of Example 65B Fraction II (+).

Example 65A

Synthesis of (-)-7-(4-fluoro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

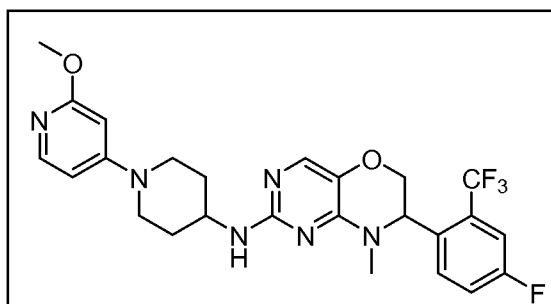


[0385] The compound of Example 65A was produced as described above. Analytical data for product Fraction I (-): ¹H-NMR (CD₃OD, 400 MHz): δ 7.74-7.71 (m, 1H), 7.57 (d, 1H), 7.47 (s, 1H), 7.42-7.31 (m, 2H), 6.54 (d, 1H), 6.15 (s, 1H), 5.01-4.99 (m, 1H), 4.22-4.20 (m,

1H), 4.09-4.01 (m, 1H), 3.99-3.90 (m, 3H), 3.82 (s, 3H), 3.02 (t, 2H), 2.98 (s, 3H), 2.10-2.02 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 519.1 [M+1]; LCMS: 519.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.77 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18 2.1 X 50 mm, 1.7 μm); RT 1.83 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 100% RT = 17.68 min (CHIRALPAK-IA (250 x 4.6mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B: 80: 20); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.03}$: -44.67 (c = 0.25, DCM); TLC: 10% MeOH/ CH₂Cl₂ (R_f: 0.3).

Example 65B

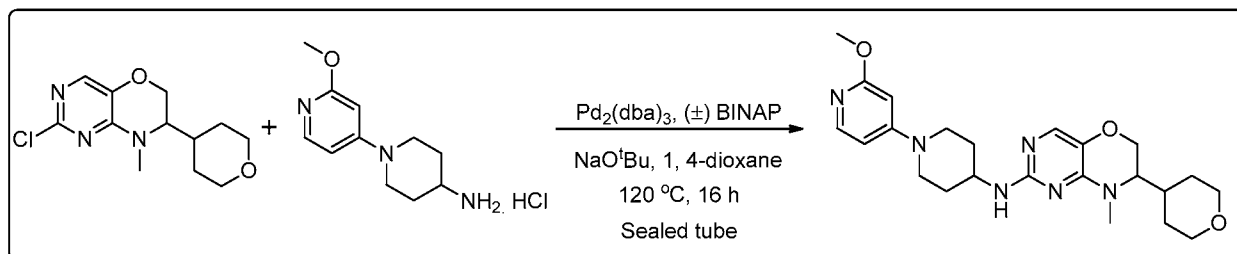
Synthesis of (+)-7-(4-fluoro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0386] The compound of Example 65B was produced as described above. Analytical data for product Fraction II (+): ¹H-NMR (CD₃OD, 400 MHz): δ 7.74-7.71 (m, 1H), 7.57 (d, 1H), 7.47 (s, 1H), 7.42-7.31 (m, 2H), 6.54 (d, 1H), 6.15 (s, 1H), 5.01-4.99 (m, 1H), 4.22-4.20 (m, 1H), 4.09-4.01 (m, 1H), 3.99-3.90 (m, 3H), 3.82 (s, 3H), 3.02 (t, 2H), 2.98 (s, 3H), 2.10-2.02 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 519.1 [M+1]; LCMS: 519.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.77 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18 2.1 X 50 mm, 1.7 μm); RT 1.83 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 98.5% RT = 21.87 min (CHIRALPAK-IA (250 x 4.6mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B: 80: 20); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: +45.28 (c = 0.25, DCM).

Example 66

Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(tetrahydro-2H-pyran-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



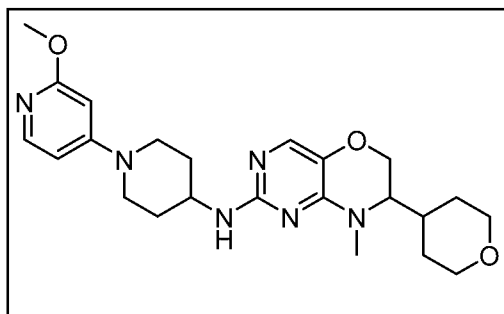
Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(tetrahydro-2H-pyran-4-yl)-7,8-dihydro-6H-pyrimido [5,4-b] [1,4] oxazin-2-amine

[0387] A dry vial charged with $\text{Pd}_2(\text{dba})_3$ (42 mg, 0.04 mmol) and ($\pm$) BINAP (86 mg, 0.13 mmol) in 1,4-dioxane (1.25 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 2-chloro-8-methyl-7-(tetrahydro-2H-pyran-4-yl)-7,8-dihydro-6H-pyrimido [5,4-b] [1,4] oxazine (250 mg, 0.92 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (247 mg, 1.01 mmol) and sodium tert-butoxide (267 mg, 2.78 mmol) in 1,4-dioxane (1.25 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 3% MeOH: CH_2Cl_2 to afford *N*-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(tetrahydro-2H-pyran-4-yl)-7,8-dihydro-6H-pyrimido [5,4-b] [1,4] oxazin-2-amine (150 mg, 37%) as an off-white solid. LCMS: 441.1 ($\text{M}+1$); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 1.91 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 x 50 mm, 1.7 μm); RT 1.27 min. ACN: 0.025% Aq TFA; 0.5 mL/min.

[0388] Racemic compound of Example 66 was separated using a Chiralpak IA (250 x 20 mm; 5 μm ; (50 mg loading; 0.1 % DEA in *n*-hexane: CH_2Cl_2 : MeOH (50: 50) (A: B: 70: 30) as mobile phase) to provide the compound of Example 66A Fraction I (-) and the compound of Example 66B Fraction II (+).

Example 66A

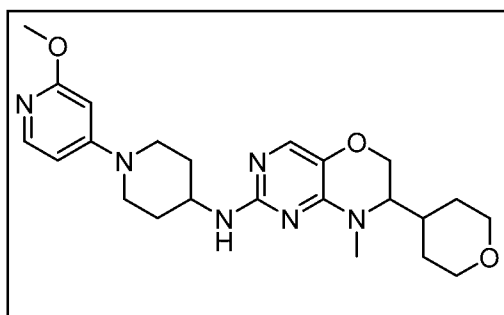
Synthesis of (-)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(tetrahydro-2H-pyran-4-yl)-7,8-dihydro-6H-pyrimido [5,4-b] [1,4] oxazin-2-amine



[0389] The compound of Example 66A was produced as described above. Analytical data for product Fraction I (-): $^1\text{H-NMR}$ (CD_3OD , 500 MHz): δ 7.73 (d, 1H), 7.33 (s, 1H), 6.56 (d, 1H), 6.18 (s, 1H), 4.40-4.36 (m, 1H), 4.02-3.88 (m, 5H), 3.86 (s, 3H), 3.80-3.76 (m, 1H), 3.44-3.36 (m, 2H), 3.32-3.30 (m, 1H), 3.20 (s, 3H), 3.06 (t, 2H), 2.13-2.00 (m, 3H), 1.62-1.45 (m, 6H); Mass (ESI): 441.2 $[\text{M}+1]$; LCMS: 441.1 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 1.97 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.30 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 99.3% RT = 10.94 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$); mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 : MeOH (50: 50) (A: B: 70: 30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{20.00}$: -25.16 ($c = 0.25$, CH_2Cl_2).

Example 66B

Synthesis of (+)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(tetrahydro-2H-pyran-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

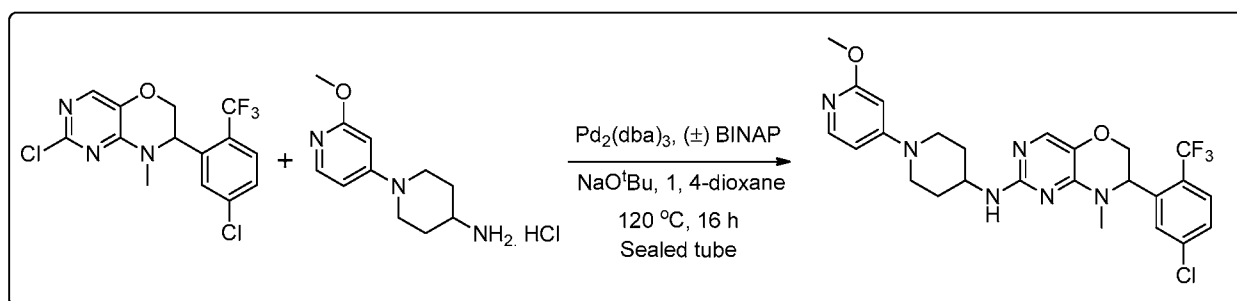


[0390] The compound of Example 66B was produced as described above. Analytical data for product Fraction II (+): $^1\text{H-NMR}$ (CD_3OD , 500 MHz): δ 7.73 (d, 1H), 7.33 (s, 1H), 6.56 (d, 1H), 6.18 (s, 1H), 4.40-4.36 (m, 1H), 4.02-3.88 (m, 5H), 3.86 (s, 3H), 3.80-3.76 (m, 1H), 3.44-3.36 (m, 2H), 3.32-3.30 (m, 1H), 3.20 (s, 3H), 3.06 (t, 2H), 2.13-2.00 (m, 3H), 1.62-1.45 (m, 6H); Mass (ESI): 441.1 $[\text{M}+1]$; LCMS: 441 (M+1); (column; X-Select CSH C-18 ($50 \times$

3.0 mm, 3.5 μ m); RT 1.88 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 $\times$ 50 mm, 1.7 μ m); RT 1.30 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 100% RT = 22.65 min (CHIRALPAK-IA (250 $\times$ 4.6 mm, 5 μ m; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B: 70: 30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.98}$: +28.01 (*c* = 0.25, CH₂Cl₂).

Example 67

Synthesis of 7-(5-chloro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



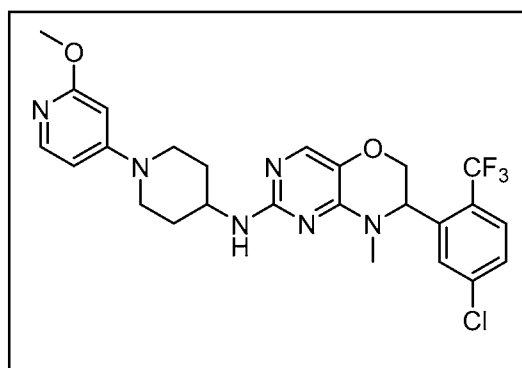
Synthesis of 7-(5-chloro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0391] A dry vial charged with Pd₂(dba)₃ (31 mg, 0.03 mmol) and (±) BINAP (64 mg, 0.10 mmol) in 1, 4-dioxane (0.5 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 2-chloro-7-(5-chloro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 0.68 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (200 mg, 0.82 mmol) and sodium tert-butoxide (197 mg, 2.06 mmol) in 1, 4-dioxane (0.5 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the volatile components were concentrated *in vacuo*. The crude material was purified by column chromatography using 4% MeOH: CH₂Cl₂ to afford 7-(5-chloro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (140 mg, 38%) as an off-white solid. LCMS: 535.8 (M+1); (column; Eclipse XDB C-18 (150 $\times$ 4.6 mm, 5 μ m); RT 11.96 min. 5mMAq NH₄OAc: ACN; 1.0 mL/min); TLC: 5% MeOH/ CH₂Cl₂ (R_f 0.3).

[0392] Racemic compound of Example 67 was separated using a Chiralpak IA (250 x 4.6 mm: 5 μ m; (30 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂: MeOH (50: 50); (A: B: 80: 20) as mobile phase) to provide the compound of Example 67A Fraction I (-) and the compound of Example 67B Fraction II (+).

Example 67A

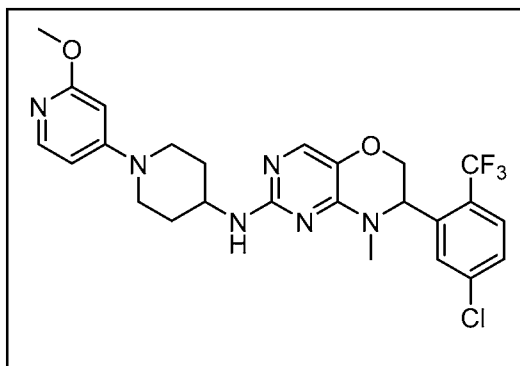
Synthesis of (-)-7-(5-chloro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0393] The compound of Example 67A was produced as described above. Analytical data for product Fraction I (-): ¹H-NMR (CD₃OD, 400 MHz): δ 7.80 (d, 1H), 7.75 (d, 1H), 7.58 (d, 1H), 7.50 (s, 1H), 7.28-7.25 (m, 1H), 6.56 (d, 1H), 6.18-6.16 (m, 1H), 5.02-5.00 (m, 1H), 4.24-4.20 (m, 1H), 4.09-4.04 (m, 1H), 3.98-3.90 (m, 3H), 3.83 (s, 3H), 3.10-3.02 (m, 2H), 3.00 (s, 3H), 2.10 (d, 2H), 1.60-1.51 (m, 2H); Mass (ESI): 535.1 [M+1]; LCMS: 535 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μ m); RT 2.80 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 x 50 mm, 1.7 μ m); RT 1.85 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 99.6% RT= 9.55 min (CHIRALPAK-IA (250 x 4.6 mm, 5 μ m; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B: 80: 20); flow Rate: 1.0 mL/min); Optical rotation [α]_D^{19.99}: -68.51 (c = 0.25, CH₂Cl₂).

Example 67B

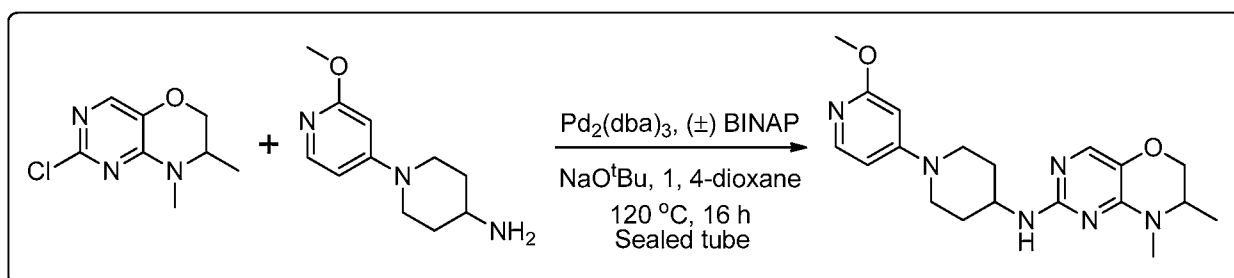
Synthesis of (+)-7-(5-chloro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0394] The compound of Example 67B was produced as described above. Analytical data for product Fraction II (+): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.80 (d, 1H), 7.75 (d, 1H), 7.58 (d, 1H), 7.50 (s, 1H), 7.28-7.25 (m, 1H), 6.56 (d, 1H), 6.18-6.16 (m, 1H), 5.02-5.00 (m, 1H), 4.24-4.20 (m, 1H), 4.09-4.04 (m, 1H), 3.98-3.90 (m, 3H), 3.83 (s, 3H), 3.10-3.02 (m, 2H), 3.00 (s, 3H), 2.10 (d, 2H), 1.60-1.51 (m, 2H); Mass (ESI): 535.1 $[\text{M}+1]$; LCMS: 535.1 ($\text{M}+1$); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.80 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.85 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 100% RT= 18.01 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 : MeOH (50: 50) (A: B: 80: 20); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{20.01}$: +66.65 ($c = 0.25$, CH_2Cl_2).

Example 68

Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-7, 8-dimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



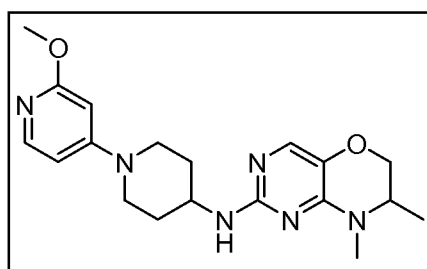
Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-7, 8-dimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0395] A dry vial charged with Pd₂(dba)₃ (57 mg, 0.06 mmol) and (±) BINAP (117 mg, 0.18 mmol) in 1, 4-dioxane (1 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 2-chloro-7, 8-dimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 1.25 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine (286 mg, 1.38 mmol) and sodium tert-butoxide (362 mg, 3.76 mmol) in 1, 4-dioxane (1 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction was diluted with water (20 mL) and extracted EtOAc (2 x 50 mL), 20% MeOH/CH₂Cl₂ (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 2-5% MeOH: CH₂Cl₂ to afford *N*-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-7, 8-dimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (300 mg, 64%) as a yellow solid. ¹H-NMR (CDCl₃, 500 MHz): δ 7.88 (d, 1H), 7.41 (s, 1H), 6.40-6.38 (m, 1H), 6.08-6.05 (m, 2H), 4.00-3.90 (m, 3H), 3.87 (s, 3H), 3.79-3.72 (m, 2H), 3.57-3.50 (m, 2H), 3.10 (s, 3H), 3.02 (t, 2H), 2.11-2.02 (m, 3H), 1.60-1.50 (m, 4H), 1.30 (d, 6H); LCMS: 371 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 1.93 min. 0.05% Aq TFA: ACN; 0.80 ml/min); HPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.28 min. ACN: 0.025% Aq TFA; 0.5 ml/min; TLC: 5% MeOH/ CH₂Cl₂ (R_f 0.2).

[0396] Racemic compound of Example 68 was separated using a Chiralpak IA (250 x 20 mm; 5μm; (50 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂: MeOH (50: 50); (A: B: 70: 30) as mobile phase) to provide the compound of Example 68A Fraction I (-) and the compound of Example 68B Fraction II (+).

Example 68A

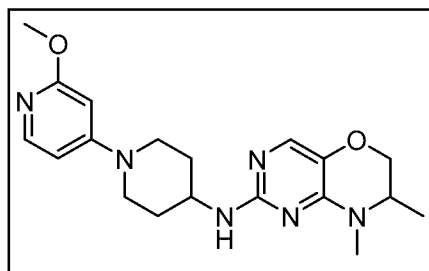
Synthesis of (-)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-7, 8-dimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0397] The compound of Example 68A was produced as described above. Analytical data for product Fraction I (-): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ 7.78 (d, 1H), 7.39 (s, 1H), 6.53-6.50 (m, 1H), 6.10-6.07 (m, 2H), 3.95-3.78 (m, 5H), 3.75 (s, 3H), 3.59-3.53 (m, 1H), 2.99 (s, 3H), 2.90 (t, 2H), 1.89-1.81 (m, 2H), 1.45-1.35 (m, 2H), 1.17 (d, 3H); Mass (ESI): 371 [M+1]; LCMS: 371 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 1.94 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.26 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 100% RT = 10.46 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 : MeOH (50: 50) (A: B: 70: 30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: -19.08 ($c = 0.25$, DCM).

Example 68B

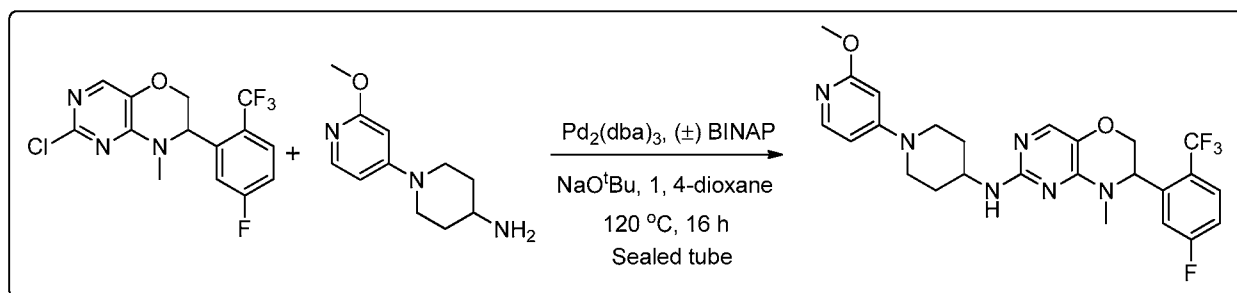
Synthesis of (+)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-7, 8-dimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0398] The compound of Example 68B was produced as described above. Analytical data for product Fraction II (+): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ 7.78 (d, 1H), 7.39 (s, 1H), 6.53-6.50 (m, 1H), 6.10-6.07 (m, 2H), 3.95-3.78 (m, 5H), 3.75 (s, 3H), 3.59-3.53 (m, 1H), 2.99 (s, 3H), 2.90 (t, 2H), 1.89-1.81 (m, 2H), 1.45-1.35 (m, 2H), 1.17 (d, 3H); Mass (ESI): 371 [M+1]; LCMS: 371 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 1.94 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.27 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 100% RT = 19.24 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 : MeOH (50: 50) (A: B: 70: 30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.99}$: +12.94 ($c = 0.25$, DCM).

Example 69

Synthesis of 7-(5-fluoro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



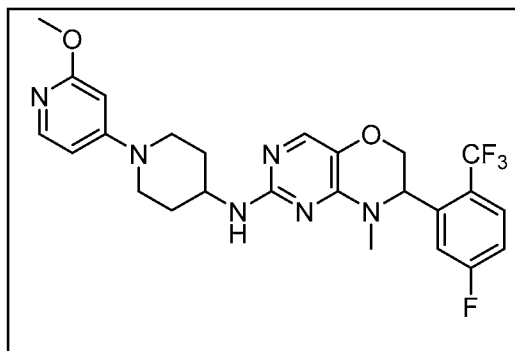
Synthesis of 7-(5-fluoro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0399] A dry vial charged with $\text{Pd}_2(\text{dba})_3$ (33 mg, 0.03 mmol) and ($\pm$) BINAP (67 mg, 0.10 mmol) in 1, 4-dioxane (1.5 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 2-chloro-7-(5-fluoro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 0.72 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine (164 mg, 0.79 mmol) and sodium tert-butoxide (207 mg, 2.16 mmol) in 1, 4-dioxane (1.5 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 4% MeOH: CH_2Cl_2 to afford 7-(5-fluoro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (100 mg, 27%) as an off-white solid. LCMS: 519.1 (M+1); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 2.54 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18 2.1 X 50 mm, 1.7 μm); RT 1.75 min. ACN: 0.025% Aq TFA; 0.5 mL/min; TLC: 5% MeOH/ CH_2Cl_2 (R_f 0.4).

[0400] Racemic compound of Example 69 was separated using a Chiralpak IA (250 x 4.6 mm: 5 μm ; (25 mg loading; 0.1 % DEA in *n*-hexane: THF: MeOH (50: 50); (A: B: 70: 30) as mobile phase) to provide the compound of Example 69A Fraction I (-) and the compound of Example 69B Fraction II (+).

Example 69A

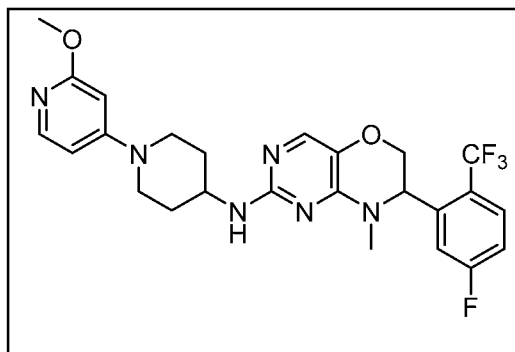
Synthesis of (-)-7-(5-fluoro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0401] The compound of Example 69A was produced as described above. Analytical data for product Fraction I (-): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.88-7.83 (m, 1H), 7.74 (d, 1H), 7.49 (s, 1H), 7.29 (t, 1H), 6.99 (d, 1H), 6.55-6.51 (m, 1H), 6.16 (s, 1H), 5.02-5.00 (m, 1H), 4.22 (d, 1H), 4.08 (d, 1H), 3.97-3.89 (m, 3H), 3.81 (s, 3H), 3.08-3.01 (m, 2H), 3.00 (s, 3H), 2.10-2.06 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 519 [M+1]; LCMS: 519.1 (M+1); (column; X-Select CSH C-18 (50 $\times$ 3.0 mm, 3.5 μm); RT 2.45 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 $\times$ 50 mm, 1.7 μm); RT 1.75 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 100% RT = 6.62 min (CHIRALPAK-IA (250 $\times$ 4.6 mm, 5 μm ; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 : MeOH (50: 50) (A: B; 70: 30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{20.00}$: -26.80 ($c = 0.25$, CH_2Cl_2).

Example 69B

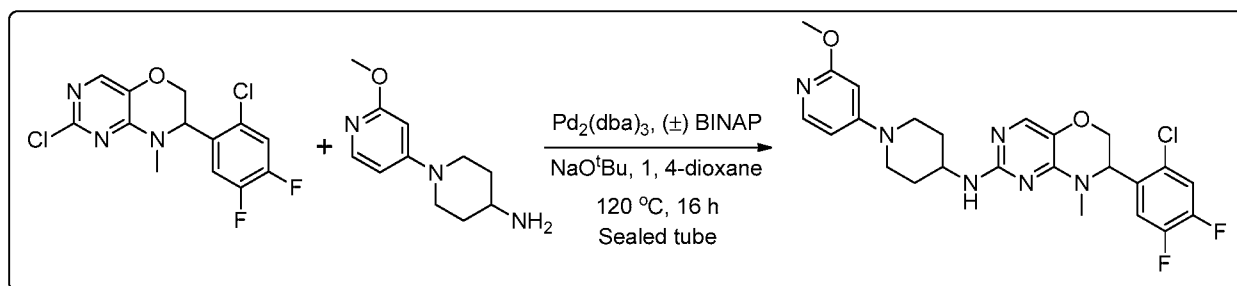
Synthesis of (+)-7-(5-fluoro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0402] The compound of Example 69B was produced as described above. Analytical data for product Fraction II (+): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.88-7.83 (m, 1H), 7.74 (d, 1H), 7.49 (s, 1H), 7.29 (t, 1H), 6.99 (d, 1H), 6.55-6.51 (m, 1H), 6.16 (s, 1H), 5.02-5.00 (m, 1H), 4.22 (d, 1H), 4.08 (d, 1H), 3.97-3.89 (m, 3H), 3.81 (s, 3H), 3.08-3.01 (m, 2H), 3.00 (s, 3H), 2.10-2.06 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 519 [M+1]; LCMS: 519 (M+1); (column: X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.42 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.74 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 100% RT = 9.84 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 : MeOH (50: 50) (A:B; 70: 30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{20.00}$: +38.64 ($c = 0.25$, CH_2Cl_2).

Example 70

Synthesis of 7-(2-chloro-4, 5-difluorophenyl)-N-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 7-(2-chloro-4, 5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

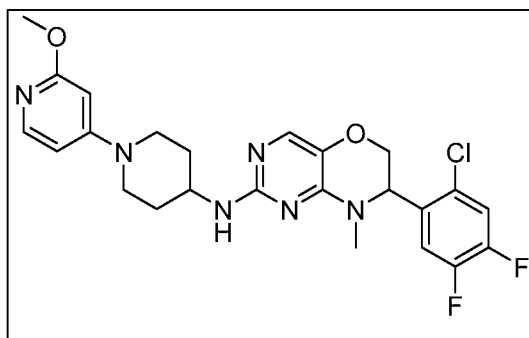
[0403] A dry vial charged with $\text{Pd}_2(\text{dba})_3$ (34 mg, 0.03 mmol) and (±) BINAP (70 mg, 0.11 mmol) in 1, 4-dioxane (1.25 mL) at RT was degassed with argon and stirred at 120°C for 3 min. A mixture of 2-chloro-7-(2-chloro-4, 5-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 0.75 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine (201 mg, 0.83 mmol) and sodium tert-butoxide (217 mg, 0.22 mmol) in 1, 4-dioxane (1.25 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120°C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and

concentrated *in vacuo*. The crude material was purified by column chromatography using 3% MeOH:CH₂Cl₂ to afford 7-(2-chloro-4, 5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine (100 mg, 26%) as an off-white solid. ¹H-NMR (CD₃OD, 400 MHz): δ 7.72 (d, 1H), 7.55-7.50 (m, 1H), 7.41 (s, 1H), 6.92-6.89 (m, 1H), 6.55 (d, 1H), 6.16 (s, 1H), 5.09-5.07 (m, 1H), 4.24-4.11 (m, 2H), 3.99-3.90 (m, 3H), 3.83 (s, 3H), 3.10-3.03 (m, 5H), 2.10-2.05 (m, 2H), 1.60-1.50 (m, 2H); UPLC (column; Acquity UPLC BEH C-18 2.1 X 50 mm, 1.7 μm); RT 1.74 min. ACN: 0.025% Aq TFA; 0.5 mL/min; TLC: 5% MeOH/ CH₂Cl₂ (R_f 0.4).

[0404] Racemic compound of Example 70 was separated using a Chiralpak IA (250 x 4.6 mm; 5μm; (25 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂: MeOH (50: 50); (A: B: 70: 30) as mobile phase) to provide the compound of Example 70A Fraction I (-) and the compound of Example 70B Fraction II (+).

Example 70A

Synthesis of (-)-7-(2-chloro-4, 5-difluorophenyl)-N-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine

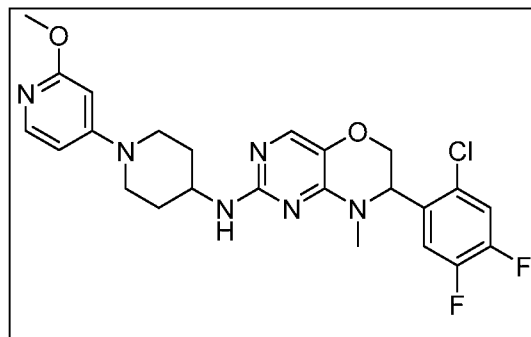


[0405] The compound of Example 70A was produced as described above. Analytical data for product Fraction I (-): ¹H-NMR (CD₃OD, 400 MHz): δ 7.73 (d, 1H), 7.54-7.55 (m, 1H), 7.44 (s, 1H), 6.91 (t, 1H), 6.55 (d, 1H), 6.15 (s, 1H), 5.10-5.06 (m, 1H), 4.21-4.11 (m, 2H), 3.99-3.90 (m, 3H), 3.81 (s, 3H), 3.10-3.01 (m, 5H), 2.10-2.05 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 502.9 [M+1]; LCMS: 502.9 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.47 min. 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Eclipse XDB C-18, 150 × 4.6 mm, 5.0 μm); RT 12.51 min. ACN: 5 mM Aq NH₄OAc; 1.0 mL/min; Chiral HPLC: 97.1% RT = 7.78 min (CHIRALPAK-IA (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1

% DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B; 70: 30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.02}$: -88.64 (c = 0. 25, CH₂Cl₂).

Example 70B

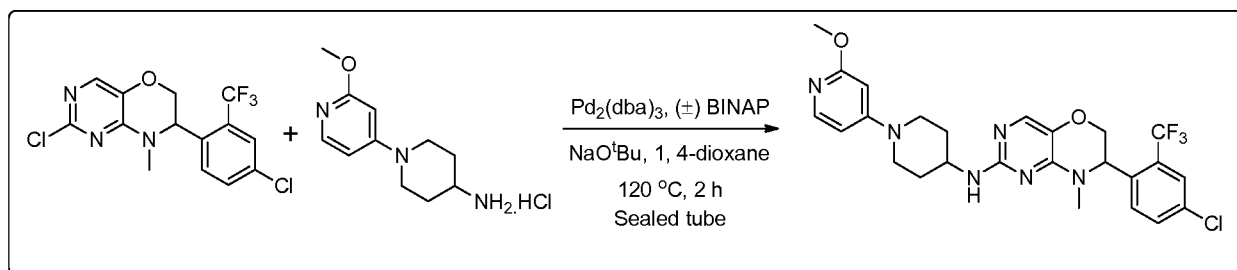
Synthesis of (+)-7-(2-chloro-4, 5-difluorophenyl)-N-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0406] The compound of Example 70B was produced as described above. Analytical data for product Fraction II (+): ¹H-NMR (CD₃OD, 400 MHz): δ 7.73 (d, 1H), 7.53 (t, 1H), 7.44 (s, 1H), 6.91 (t, 1H), 6.55 (d, 1H), 6.15 (s, 1H), 5.10-5.06 (m, 1H), 4.21-4.11 (m, 2H), 3.99-3.90 (m, 3H), 3.81 (s, 3H), 3.10-3.01 (m, 5H), 2.10-2.05 (m, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 502.9 [M+1]; LCMS: 502.9 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.46 min. 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Eclipse XDB C-18, 150 × 4.6 mm, 5.0 μm); RT 12.49 min. ACN: 5 mM Aq NH₄OAc; 1.0 mL/min; Chiral HPLC: 96.9% RT = 18.34 min (CHIRALPAK-IA (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B; 70: 30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: +95.05 (c = 0. 25, CH₂Cl₂).

Example 71

Synthesis of 7-(4-chloro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



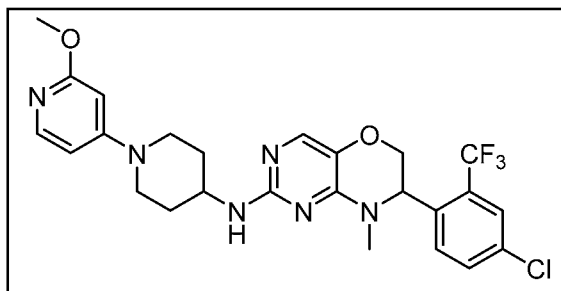
Synthesis of 7-(4-chloro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0407] A dry vial charged with $\text{Pd}_2(\text{dba})_3$ (25 mg, 0.02 mmol) and ($\pm$) BINAP (47 mg, 0.08 mmol) in 1, 4-dioxane (1 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 2-chloro-7-(4-chloro-2-(trifluoromethyl) phenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (200 mg, 0.55 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (148 mg, 0.60 mmol) and sodium tert-butoxide (158 mg, 1.60 mmol) in 1, 4-dioxane (1 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 2 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction was diluted with water (50 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 10-50% EtOAc:hexanes to afford 7-(4-chloro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (150 mg, 51%) as a pale yellow solid. LCMS: 535.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.69 min 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Eclipse XDB-C18 (150 X 4.6 mm, 5.0 μm); RT 12.59 min. ACN: 5 mM Aq NH_4OAc ; 1.0 mL/min; TLC: 5% MeOH/ CH_2Cl_2 (R_f 0.3).

[0408] Racemic compound of Example 71 was separated using a Chiralpak IA (250 x 4.6 mm; 5 μm ; (25 mg loading; 0.1 % DEA in *n*-hexane: CH_2Cl_2 : MeOH (50: 50); (A: B: 85: 15) as mobile phase) to provide the compound of Example 71A Fraction I (-) and the compound of Example 71B Fraction II (+).

Example 71A

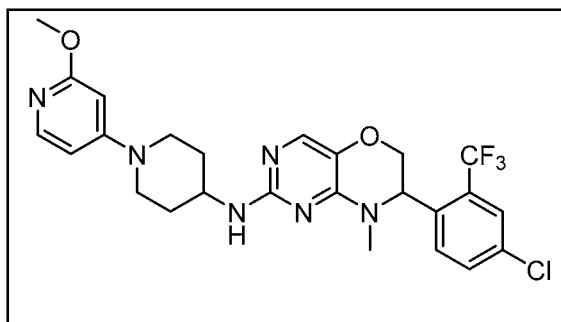
Synthesis of (-)-7-(4-chloro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0409] The compound of Example 71A was produced as described above. Analytical data for product Fraction I (-): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.80 (s, 1H), 7.73 (d, 1H), 7.65 (d, 1H), 7.46 (s, 1H), 7.30 (d, 1H), 6.53 (d, 1H), 6.13 (s, 1H), 5.00-4.98 (m, 1H), 4.21 (d, 1H), 4.04 (d, 1H), 3.92-3.87 (m, 3H), 3.81 (s, 3H), 3.02 (t, 2H), 2.99 (s, 3H), 2.08 (d, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 535.7 $[\text{M}+1]$; LCMS: 535.6 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 3.20 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.90 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 99.5% RT= 11.49 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 : MeOH (50: 50) (A: B; 75: 25); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{20.00}$: -61.95 ($c = 0.25$, CH_2Cl_2).

Example 71B

Synthesis of (+)-7-(4-chloro-2-(trifluoromethyl) phenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

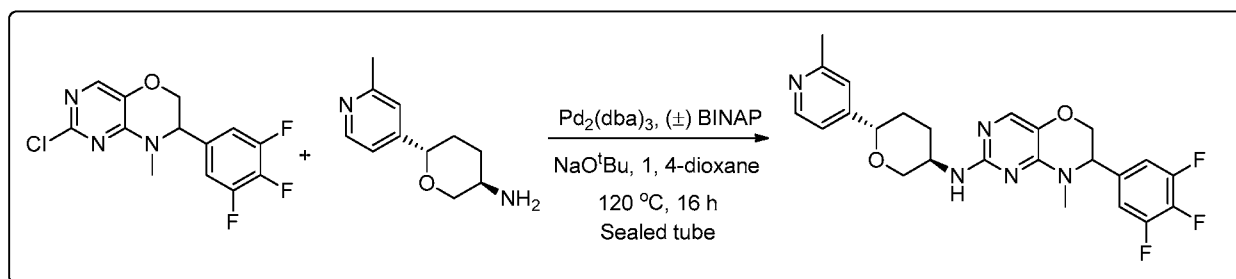


[0410] The compound of Example 71B was produced as described above. Analytical data for product Fraction II (+): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.80 (s, 1H), 7.73 (d, 1H), 7.65 (d, 1H), 7.46 (s, 1H), 7.30 (d, 1H), 6.53 (d, 1H), 6.13 (s, 1H), 5.00-4.98 (m, 1H), 4.21 (d, 1H),

4.04 (d, 1H), 3.92-3.87 (m, 3H), 3.81 (s, 3H), 3.02 (t, 2H), 2.99 (s, 3H), 2.08 (d, 2H), 1.60-1.50 (m, 2H); Mass (ESI): 535.7 [M+1]; LCMS: 535.6 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.20 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18, 2.1 × 50 mm, 1.7 μm); RT 1.89 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 98.9% RT = 14.08 min (CHIRALPAK-IA (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B; 75: 25); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.01}$: +56.36 (c = 0.25, CH₂Cl₂).

Example 72

Synthesis of 8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

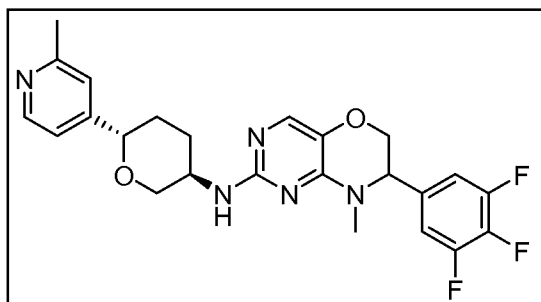
[0411] A dry vial charged with Pd₂(dba)₃ (33 mg, 0.72 mmol) and (±) BINAP (66 mg, 0.10 mmol) in 1, 4-dioxane (1 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 2-chloro-8-methyl-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (230 mg, 0.73 mmol), (3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-amine (154 mg, 0.80 mmol) and sodium tert-butoxide (210 mg, 2.19 mmol) in 1, 4-dioxane (1 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), The reaction was diluted with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 3% MeOH: CH₂Cl₂ to afford 8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-

pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine (225 mg, 60%) as a brown solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 8.36-8.34 (m, 1H), 7.48 (s, 1H), 7.22-7.20 (m, 1H), 7.20-7.13 (m, 3H), 6.30-3.627 (m, 1H), 4.78-4.76 (m, 1H), 4.30 (d, 1H), 4.20-4.14 (m, 3H), 3.90-3.83 (m, 1H), 3.20 (t, 1H), 2.99 (s, 3H), 2.42 (s, 3H), 2.07-1.98 (m, 2H), 1.70-1.63 (m, 1H), 1.50-1.43 (m, 1H); LCMS: 472.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.36 min 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Eclipse XDB C-18 150 X 4.6 mm, 5.0 μm); RT 10.88 min. ACN: 5 mM Aq NH₄OAc; 1.0 mL/min; TLC: 5% MeOH/ CH₂Cl₂ (R_f 0.4).

[0412] Racemic compound of Example 72 was separated using a (Chiralpak-IA (250 x 4.6 mm, 5μm (25 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂: MeOH (50: 50); (A: B: 85: 15) as mobile phase) to provide the compound of Example 72A Fraction I (+) and the compound of Example 72B Fraction II (-).

Example 72A

Synthesis of (+)-8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine

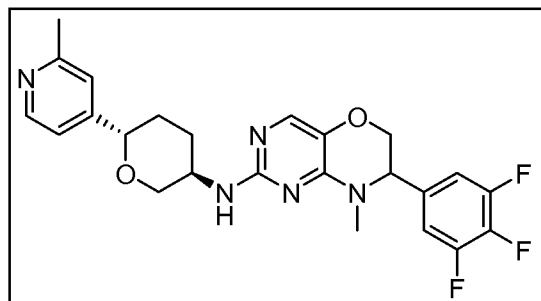


[0413] The compound of Example 72A was produced as described above. Analytical data for product Fraction I (+): ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.37-8.35 (m, 1H), 7.48 (s, 1H), 7.21-7.19 (m, 1H), 7.17-7.10 (m, 3H), 6.29 (d, 1H), 4.78-4.76 (m, 1H), 4.30 (d, 1H), 4.18-4.16 (m, 3H), 3.90-3.80 (m, 1H), 3.20 (t, 1H), 2.99 (s, 3H), 2.41 (s, 3H), 2.08-1.99 (m, 2H), 1.71-1.61 (m, 1H), 1.50-1.41 (m, 1H); Mass (ESI): 472.1 [M+1]; LCMS: 472.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.34 min. 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Eclipse XDB-C-18, 150 × 4.6 mm, 5.0 μm); RT 10.94 min. ACN: 5mM Aq NH₄OAc; 0.5 mL/min; Chiral HPLC: 99.2% RT = 16.10 min (CHIRALPAK-IA (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B)

CH₂Cl₂: MeOH (50: 50) (A: B: 85: 15); flow Rate: 1.0 mL/min); Optical rotation [α]_D^{20.00}: +32.17 (c = 0.25, CH₂Cl₂).

Example 72B

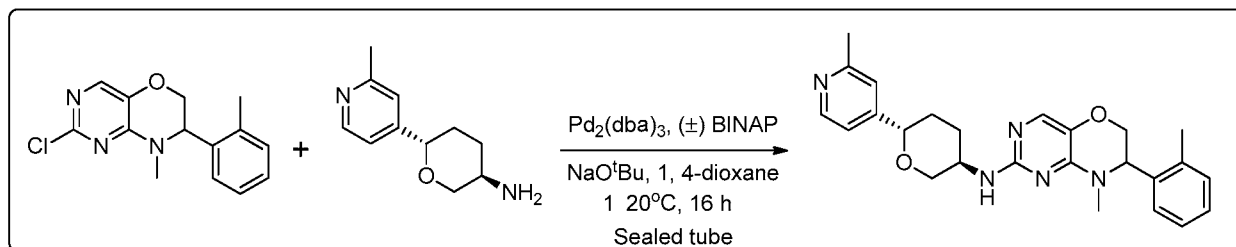
Synthesis of (-)-8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0414] The compound of Example 72B was produced as described above. Analytical data for product Fraction II (-): ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.37-8.35 (m, 1H), 7.48 (s, 1H), 7.21-7.19 (m, 1H), 7.17-7.10 (m, 3H), 6.29 (d, 1H), 4.78-4.76 (m, 1H), 4.30 (d, 1H), 4.18-4.16 (m, 3H), 3.90-3.80 (m, 1H), 3.20 (t, 1H), 2.99 (s, 3H), 2.41 (s, 3H), 2.08-1.99 (m, 2H), 1.71-1.61 (m, 1H), 1.50-1.41 (m, 1H); Mass (ESI): 472.1 [M+1]; LCMS: 472.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μ m); RT 2.38 min. 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Eclipse XDB-C-18, 150 × 4.6 mm, 5.0 μ m); RT 11.00 min. ACN: 5mM Aq NH₄OAc; 1.0 mL/min; Chiral HPLC: 99.6% RT = 15.15 min (CHIRALPAK-IA (250 x 4.6 mm, 5 μ m; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B: 85: 15); flow Rate: 1.0 mL/min); Optical rotation [α]_D^{20.02}: -42.24 (c = 0.25, CH₂Cl₂).

Example 73

Synthesis of 8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



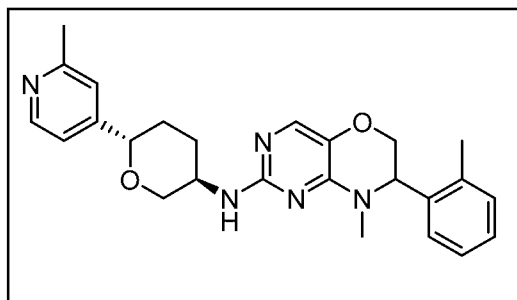
Synthesis of 8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0415] A dry vial charged with $\text{Pd}_2(\text{dba})_3$ (38 mg, 0.04 mmol) and (±) BINAP (78 mg, 0.12 mmol) in 1, 4-dioxane (1 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 2-chloro-8-methyl-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (230 mg, 0.83 mmol), (3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-amine (176 mg, 0.91 mmol) and sodium tert-butoxide (240 mg, 2.51 mmol) in 1, 4-dioxane (1 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction was diluted with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 2% MeOH: CH_2Cl_2 to afford 8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (190 mg, 49%) as a brown solid. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ 8.39-8.37 (m, 1H), 7.42 (s, 1H), 7.22-7.10 (m, 5H), 6.83 (d, 1H), 6.39 (br s, 1H), 4.97-4.95 (m, 1H), 4.30 (d, 1H), 4.18-4.03 (m, 2H), 3.90-3.81 (m, 1H), 3.20 (t, 1H), 2.96 (s, 3H), 2.42 (s, 3H), 2.35 (s, 3H), 2.07-1.97 (m, 2H), 1.70-1.64 (m, 1H), 1.50-1.42 (m, 1H), 1.22-1.20 (m, 1H); LCMS: 432.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.30 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity BEH C-18 50 X 2.1 mm, 1.7 μm); RT 1.68 min. ACN: 0.025% Aq TFA; 0.5 mL/min; TLC: 5% MeOH/ CH_2Cl_2 (R_f 0.4).

[0416] Racemic compound of Example 73 was purified by (Chiral pack-ADH (250 x 4.6 mm, 5 μm (30 mg loading; 0.1 % DEA in *n*-hexane: EtOH: MeOH (50: 50); (A: B: 75: 25) as mobile phase) to provide the compound of Example 73A Fraction I (+) and the compound of Example 73B Fraction II (-)

Example 73A

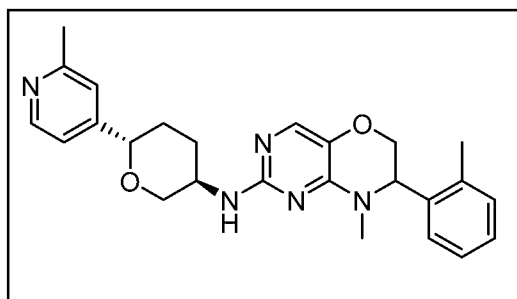
Synthesis of (+)-8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0417] The compound of Example 73A was produced as described above. Analytical data for product Fraction I (+) $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ 8.37-8.35 (m, 1H), 7.42 (s, 1H), 7.24-7.10 (m, 5H), 6.86 (d, 1H), 6.20 (d, 1H), 4.92-4.89 (m, 1H), 4.30 (d, 1H), 4.18-4.10 (m, 2H), 4.08-4.03 (m, 1H), 3.90-3.81 (m, 1H), 3.20 (t, 1H), 2.94 (s, 3H), 2.41 (s, 3H), 2.36 (s, 3H), 2.08-1.98 (m, 2H), 1.70-1.62 (m, 1H), 1.52-1.42 (m, 1H); Mass (ESI): 432.1 $[\text{M}+1]$; LCMS: 432.1 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.35 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity BEH-C-18, 50×2.1 mm, $1.7 \mu\text{m}$); RT 1.63 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 99.6% RT = 10.86 min (CHIRALPAK-IA (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 : MeOH (50: 50) (A: B: 85: 15); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: +75.15 ($c = 0.25$, CH_2Cl_2).

Example 73B

Synthesis of (-)-8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7-(o-tolyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

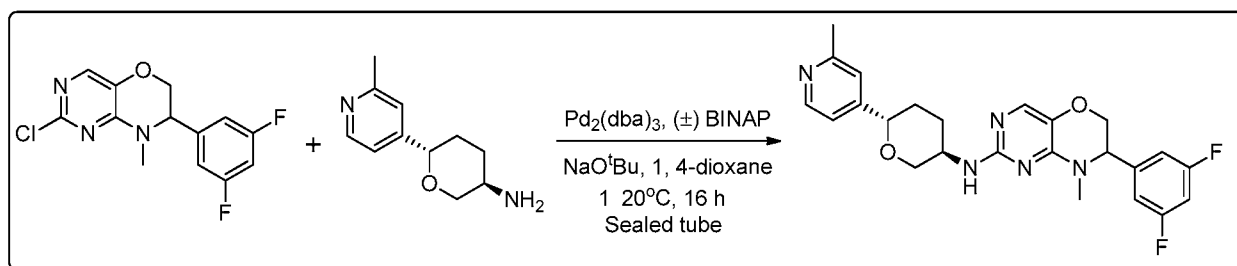


[0418] The compound of Example 73B was produced as described above. Analytical data for product Fraction II (-): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ 8.37-8.35 (m, 1H), 7.42 (s,

1H), 7.24-7.10 (m, 5H), 6.86 (d, 1H), 6.20 (d, 1H), 4.92-4.89 (m, 1H), 4.29 (d, 1H), 4.18-4.10 (m, 2H), 4.08-4.03 (m, 1H), 3.90-3.81 (m, 1H), 3.20 (t, 1H), 2.92 (s, 3H), 2.41 (s, 3H), 2.36 (s, 3H), 2.08-1.98 (m, 2H), 1.70-1.62 (m, 1H), 1.52-1.42 (m, 1H); Mass (ESI): 432.2 [M+1]; LCMS: 432.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.33 min. 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity BEH-C-18, 50 × 2.1 mm, 1.7 μm); RT 1.60 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 99.3% RT = 10.30 min (CHIRALPAK-IA (250 × 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B: 85: 15); flow Rate: 1.0 mL/min); Optical rotation [α]_D^{19.99}: -87.04 (c = 0.25, CH₂Cl₂).

Example 74

Synthesis of 7-(3, 5-difluorophenyl)-8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 7-(3, 5-difluorophenyl)-8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

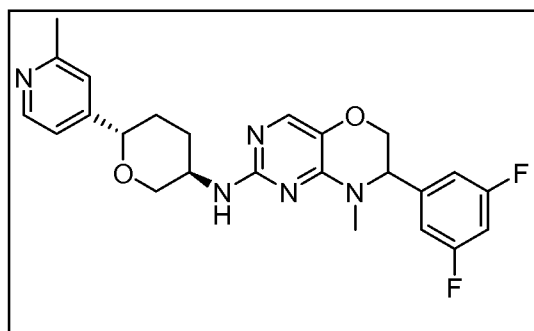
[0419] A dry vial charged with Pd₂(dba)₃ (38 mg, 0.04 mmol) and (±) BINAP (78 mg, 0.12 mmol) in 1, 4-dioxane (1 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 2-chloro-7-(3, 5-difluorophenyl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (250 mg, 0.83 mmol), (3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-amine (177 mg, 0.88 mmol) and sodium tert-butoxide (242 mg, 2.51 mmol) in 1, 4-dioxane (1 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction was diluted with water (30 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 2% MeOH: CH₂Cl₂ to afford 7-(3, 5-difluorophenyl)-8-methyl-N-

((3*R*, 6*S*)-6-(2-methylpyridin-4-yl) tetrahydro-2*H*-pyran-3-yl)-7, 8-dihydro-6*H*-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine (230 mg, 60%) as a pale yellow solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 8.37-8.35 (m, 1H), 7.47 (s, 1H), 7.21-7.17 (m, 2H), 7.16-7.10 (m, 1H), 6.92-6.89 (m, 2H), 6.30-6.28 (m, 1H), 4.81-4.79 (m, 1H), 4.30 (d, 1H), 4.20-4.10 (m, 3H), 3.90-3.80 (m, 1H), 3.20 (t, 1H), 3.00 (s, 3H), 2.41 (s, 3H), 2.01-1.90 (m, 2H), 1.71-1.61 (m, 1H), 1.50-1.40 (m, 1H); LCMS: 454.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.32 min 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Eclipse XDB C-18 150 X 4.6 mm, 5.0 μm); RT 10.70 min. ACN: 5 mM Aq NH₄OAc; 1.0 mL/min; TLC: 5% MeOH/CH₂Cl₂ (R_f 0.4).

[0420] Racemic compound of Example 74 was separated using a (Chiralpak-ADH (250 x 4.6 mm, 5μm (40 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂: MeOH (50: 50); (A: B: 70: 30) as mobile phase to provide the compound of Example 74A Fraction I (+) and the compound of Example 74B Fraction II (-).

Example 74A

Synthesis of (+)-7-(3, 5-difluorophenyl)-8-methyl-N-((3*R*, 6*S*)-6-(2-methylpyridin-4-yl) tetrahydro-2*H*-pyran-3-yl)-7, 8-dihydro-6*H*-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine

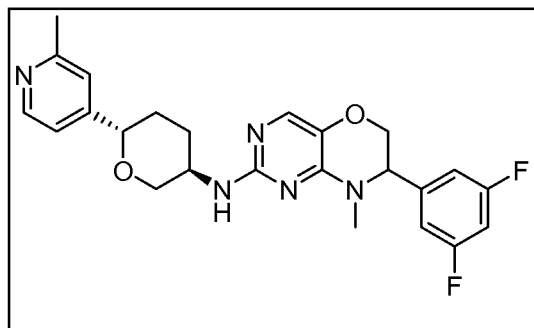


[0421] The compound of Example 74 was produced as described above. Analytical data for product Fraction I (+): ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.37-8.35 (m, 1H), 7.47 (s, 1H), 7.22-7.17 (m, 2H), 7.16-7.10 (m, 1H), 6.92-6.88 (m, 2H), 6.28 (d, 1H), 4.80-4.78 (m, 1H), 4.30 (d, 1H), 4.20-4.10 (m, 3H), 3.90-3.80 (m, 1H), 3.20 (t, 1H), 2.99 (s, 3H), 2.44 (s, 3H), 2.06-1.95 (m, 2H), 1.70-1.60 (m, 1H), 1.50-1.43 (m, 1H); Mass (ESI): 454.4 [M+1]; LCMS: 454.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.30 min. 0.05% Aq TFA: ACN; 0.80 ml/min); HPLC (column; Eclipse XDB C-18, 150 × 4.6 mm, 5.0 μm); RT 10.89 min. ACN: 5 mM aq NH₄OAc; 1.0 mL/min; Chiral HPLC: 98.3% RT = 8.94 min (CHIRALPAK-AD-H (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane

(B) EtOH: MeOH (50: 50) (A: B: 70: 30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: +41.63 ($c = 0.25$, CH_2Cl_2).

Example 74B

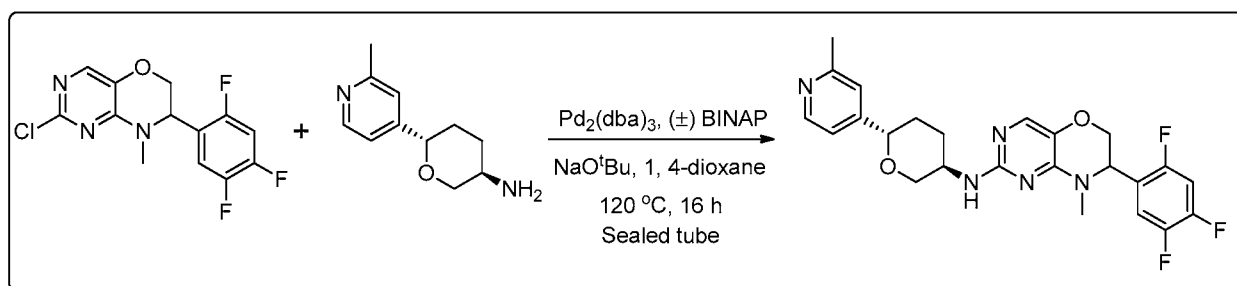
Synthesis of (-)-7-(3, 5-difluorophenyl)-8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0422] The compound of Example 74B was produced as described above. Analytical data for product Fraction II (-): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.37-8.35 (m, 1H), 7.47 (s, 1H), 7.22-7.17 (m, 2H), 7.16-7.10 (m, 1H), 6.92-6.88 (m, 2H), 6.28 (d, 1H), 4.80-4.78 (m, 1H), 4.30 (d, 1H), 4.20-4.10 (m, 3H), 3.90-3.80 (m, 1H), 3.20 (t, 1H), 2.99 (s, 3H), 2.44 (s, 3H), 2.06-1.95 (m, 2H), 1.70-1.60 (m, 1H), 1.50-1.43 (m, 1H); Mass (ESI): 454.4 $[\text{M}+1]$; LCMS: 454.1 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.28 min. 0.05% Aq TFA: ACN; 0.80 mL/min); HPLC (column; Eclipse XDB C-18, 150×4.6 mm, $5.0 \mu\text{m}$); RT 10.76 min. ACN: 5 mM aq NH_4OAc ; 1.0 mL/min; Chiral HPLC: 99.6% RT = 17.14 min (CHIRALPAK-AD-H (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) EtOH: MeOH (50: 50) (A: B: 70: 30); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.97}$: -36.17 ($c = 0.25$, CH_2Cl_2).

Example 75

Synthesis of 1-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-2-(2, 4, 5-trifluorophenyl)-2, 3-dihydro-1H-pyrido [3, 4-b] [1, 4] oxazin-7-amine



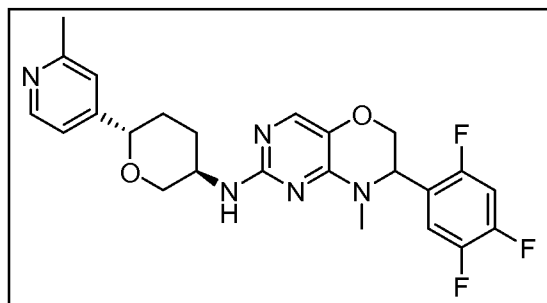
Synthesis of 1-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-2-(2,4,5-trifluorophenyl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-amine

[0423] A dry vial charged with $\text{Pd}_2(\text{dba})_3$ (36 mg, 0.04 mmol) and ($\pm$) BINAP (74 mg, 0.12 mmol) in 1, 4-dioxane (1.25 mL) at RT was degassed with argon and stirred at 120 °C for 3 min. A mixture of 7-chloro-1-methyl-2-(2, 4, 5-trifluorophenyl)-2, 3-dihydro-1H-pyrido [3, 4-*b*] [1, 4] oxazine (250 mg, 0.79 mmol), (3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-amine (167 mg, 0.87 mmol) and sodium tert-butoxide (228 mg, 2.38 mmol) in 1, 4-dioxane (1.25 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction was diluted with water (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 3% MeOH: CH_2Cl_2 to afford 1-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-2-(2, 4, 5-trifluorophenyl)-2, 3-dihydro-1H-pyrido [3, 4-*b*] [1, 4] oxazin-7-amine (105 mg, 28%) as an off-white solid. LCMS: 472.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.31 min 0.05% Aq TFA: ACN; 0.80 mL/min); UPLC (column; Acquity UPLC BEH C-18 50 X 2.1 mm, 1.7 μm); RT 1.64 min. ACN: 0.025% Aq TFA; 0.5 mL/min; TLC: 5% MeOH/ CH_2Cl_2 (R_f 0.3).

[0424] Racemic compound of Example 75 was separated using a Chiralpak IC (250 x 4.6 mm; 5 μm ; (15 mg loading; 0.1 % DEA in *n*-hexane: CH_2Cl_2 : MeOH (50: 50); (A: B: 80: 20) as mobile phase) to provide the compound of Example 75A Fraction I (+) and the compound of Example 75B Fraction II (-).

Example 75A

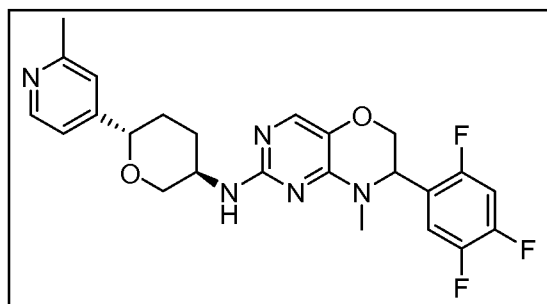
Synthesis of (+)-1-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-2-(2, 4, 5-trifluorophenyl)-2, 3-dihydro-1H-pyrido [3, 4-*b*] [1, 4] oxazin-7-amine



[0425] The compound of Example 75 was produced as described above. Analytical data for product Fraction I (+): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.36-8.34 (m, 1H), 7.69-7.61 (m, 1H), 7.50 (s, 1H), 7.21 (s, 1H), 7.16-7.14 (m, 1H), 7.09-7.00 (m, 1H), 6.28 (d, 1H), 5.00-4.98 (m, 1H), 4.29 (d, 1H), 4.18-4.10 (m, 3H), 3.90-3.80 (m, 1H), 3.20 (t, 1H), 3.00 (s, 3H), 2.41 (s, 3H), 2.05-1.92 (m, 2H), 1.70-1.61 (m, 1H), 1.50-1.40 (m, 1H); Mass (ESI): 472.1 $[\text{M}+1]$; LCMS: 472.1 ($\text{M}+1$); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.45 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50×2.1 mm, $1.7 \mu\text{m}$); RT 1.62 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 99.4% RT = 16.05 min (CHIRALPAK-IC (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 : MeOH (50: 50) (A: B; 80: 20); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.95}$: +42.00 ($c = 0.25$, CH_2Cl_2).

Example 75B

Synthesis of (-)-1-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-2-(2, 4, 5-trifluorophenyl)-2, 3-dihydro-1H-pyrido [3, 4-b] [1, 4] oxazin-7-amine

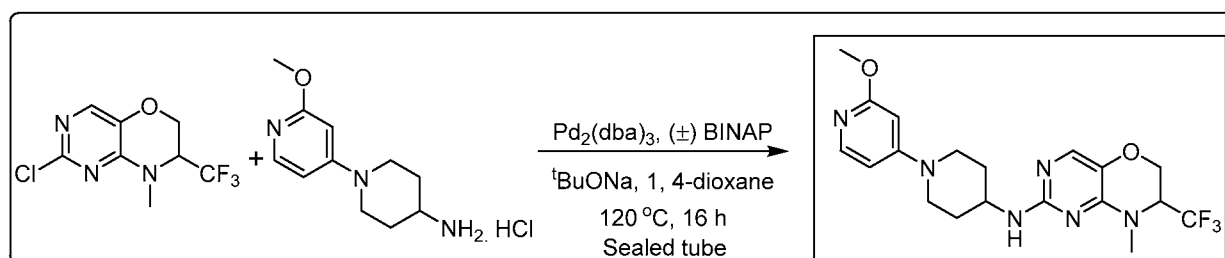


[0426] The compound of Example 75B was produced as described above. Analytical data for product Fraction II (-): $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ 8.36-8.34 (m, 1H), 7.69-7.61 (m, 1H), 7.50 (s, 1H), 7.21 (s, 1H), 7.16-7.14 (m, 1H), 7.09-7.00 (m, 1H), 6.28 (d, 1H), 5.00-4.98 (m, 1H), 4.29 (d, 1H), 4.18-4.10 (m, 3H), 3.90-3.80 (m, 1H), 3.20 (t, 1H), 3.00 (s, 3H),

2.41 (s, 3H), 2.05-1.92 (m, 2H), 1.70-1.61(m, 1H), 1.50-1.40 (m, 1H); Mass (ESI): 472.1 [M+1]; LCMS: 472.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.43 min. 0.05% Aq TFA: ACN; 0.80 ml/min); UPLC (column; Acquity BEH C-18, 50 × 2.1 mm, 1.7 μm); RT 1.59 min. ACN: 0.025% Aq TFA; 0.5 mL/min; Chiral HPLC: 99.3% RT = 17.81 min (CHIRALPAK-IC (250 x 4.6 mm, 5 μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B; 80: 20); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{19.96}$: -49.53 (c = 0.25, CH₂Cl₂).

Example 76

Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

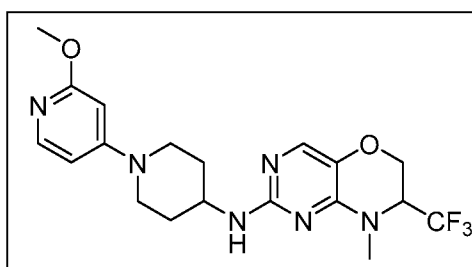
[0427] To a dry vial was added a suspension of Pd₂(dba)₃ (21 mg, 0.02 mmol) and (±) BINAP (44 mg, 0.07 mmol) in 1, 4-dioxane (0.25 mL) at room temperature. The suspension was degassed with argon, heated to 120 °C, and stirred at 120 °C for 3 min. A mixture of 2-chloro-8-methyl-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (120 mg, 0.47 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (126 mg, 0.52 mmol), sodium tert-butoxide (136 mg, 1.42 mmol) in 1, 4-dioxane (0.25 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by preparative HPLC (X-select CSH C-18 (250 x 19 mm, 5 μm (65 mg loading; CH₃CN: 0.05% TFA (0.1/90, 1/90, 18/70, 25/30, 30/10, 35/10)) to afford N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(trifluoromethyl)-7, 8-

dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine (30 mg, 15%) as an off-white solid. LCMS: 425 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.11 min; mobile phase: 0.05% Aq TFA: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 9/90; flow rate: 0.80 ml/min) (Gradient); TLC: 5% MeOH/ CH₂Cl₂ (R_f: 0.3).

[0428] Racemic compound of Example 76 was separated using a Chiralpak-IB column (250 x 20 mm, 5μm) (15 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂: MeOH (80: 20) (A: B: 85: 15) as mobile phase) to provide the compound of Example 76A (Fraction I) and the compound of Example 76B (Fraction II).

Example 76A

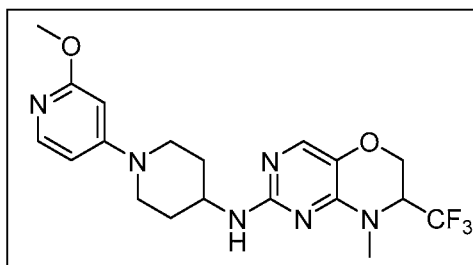
Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine



[0429] The compound of Example 76A was produced as described in Example 76. Analytical data for product Fraction I: ¹H NMR (CD₃OD, 400 MHz): δ 7.72 (d, 1H), 7.43 (d, 1H), 6.51 (d, 1H), 6.15 (s, 1H), 4.49 (d, 1H), 4.29-4.21 (m, 1H), 3.97-3.90 (m, 4H), 3.80 (s, 3H), 3.11 (s, 3H), 3.05 (t, 2H), 2.09-2.01 (m, 2H), 1.58-1.50 (m, 2H); Mass (ESI): 425.4 [M+1]; LCMS: 425 (M+1); (column; X-select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.01 min; mobile phase: 0.05% Aq TFA: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 8/90; flow rate 0.8 ml/min (Gradient); UPLC (column; Acquity BEH C-18, 50 × 2.1 mm, 1.7 μ); RT 1.43 min; mobile phase: ACN: 0.025% Aq TFA; flow rate: 0.5 mL/min; Gradient program: T/B% 0.01/90, 0.5/90, 3/10, 6/10; diluent: CH₃CN: Water; Chiral HPLC: 98.4% RT = 12.33 min (Chiralpak-IB (250 x 4.6 mm, 5μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (80: 20) (A: B; 85: 15); flow Rate: 1.0 mL/min).

Example 76B

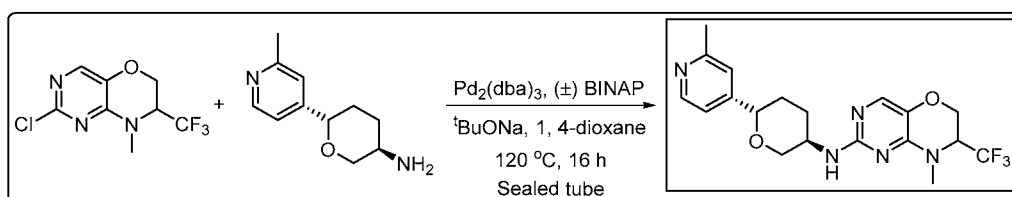
Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0430] The compound of Example 76B was produced as described in Example 76. Analytical data for product Fraction II: ^1H NMR (CD_3OD , 400MHz): δ 7.72 (d, 1H), 7.43 (d, 1H), 6.51 (d, 1H), 6.15 (s, 1H), 4.49 (d, 1H), 4.29-4.21 (m, 1H), 3.97-3.90 (m, 4H), 3.80 (s, 3H), 3.11 (s, 3H), 3.05 (t, 2H), 2.09-2.01 (m, 2H), 1.58-1.50 (m, 2H); Mass (ESI): 425.4 $[\text{M}+1]$; LCMS: 425 ($\text{M}+1$); (column; X-select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 2.00 min. mobile phase: 0.05% Aq TFA: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 8/90; flow rate 0.8 ml/min (Gradient); UPLC (column; Acquity BEH C-18, 50×2.1 mm, $1.7 \mu\text{m}$); RT 1.45 min; mobile phase: ACN: 0.025% Aq TFA; flow rate: 0.5 mL/min; Gradient program: T/B% 0.01/90, 0.5/90, 3/10, 6/10; diluent: CH_3CN : Water; Chiral HPLC: 96.6% RT = 15.17 min (Chiralpak-IB (250×4.6 mm, $5 \mu\text{m}$; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 : MeOH (80: 20) (A: B; 85: 15); flow Rate: 1.0 mL/min).

Example 77

Synthesis of 8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



Synthesis of 8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

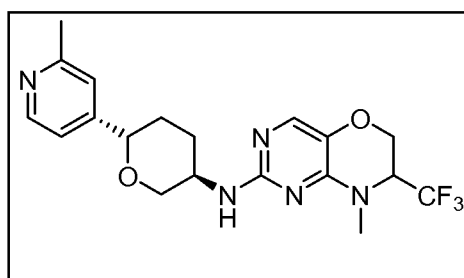
[0431] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (36 mg, 0.04 mmol) and ($\pm$) BINAP (73 mg, 0.12 mmol) in 1, 4-dioxane (1 mL) at room temperature. The suspension was

degassed with argon, heated to 120 °C, and stirred at 120 °C for 3 min. A mixture of 2-chloro-8-methyl-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazine (200 mg, 0.79 mmol), (3*R*, 6*S*)-6-(2-methylpyridin-4-yl) tetrahydro-2*H*-pyran-3-amine (166 mg, 0.87 mmol) and sodium tert-butoxide (227 mg, 2.37 mmol) in 1, 4-dioxane (1 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by column chromatography using 3% MeOH/ CH₂Cl₂ to afford (8-methyl-*N*-((3*R*, 6*S*)-6-(2-methylpyridin-4-yl) tetrahydro-2*H*-pyran-3-yl)-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine (85 mg, 26%) as colorless oil. ¹H NMR (CD₃OD, 400 MHz): δ 8.34 (d, 1H), 7.46 (s, 1H), 7.32 (s, 1H), 7.25 (d, 1H), 4.50 (d, 1H), 4.39 (d, 1H), 4.31-4.26 (m, 2H), 4.00-3.91 (m, 2H), 3.30-3.27 (m, 4H), 2.53 (s, 3H), 2.26- 2.20 (m, 1H), 2.10-2.04 (m, 1H), 1.76-1.60 (m, 2H); TLC: 5%MeOH/ CH₂Cl₂ (*R_f*: 0.3).

[0432] Racemic compound of Example 77 was separated using a Chiralpak-IC column (250 x 20 mm, 5μm) (15 mg loading; 0.1 % DEA in *n*-hexane: CH₂Cl₂: MeOH (80: 20) (A: B: 80: 20) as mobile phase) to provide the compound of Example 77A (Fraction I (-)) and the compound of Example 77B (Fraction II (+)).

Example 77A

Synthesis of (-)-8-methyl-*N*-((3*R*, 6*S*)-6-(2-methylpyridin-4-yl) tetrahydro-2*H*-pyran-3-yl)-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-*b*] [1, 4] oxazin-2-amine

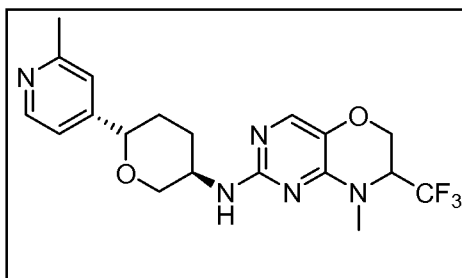


[0433] The compound of Example 77A was produced as described in Example 77. Analytical data for product Fraction I (-): ¹H NMR (CD₃OD, 400 MHz): δ 8.34 (d, 1H), 7.46 (s, 1H), 7.32 (s, 1H), 7.25 (d, 1H), 4.50 (d, 1H), 4.39 (d, 1H), 4.31-4.26 (m, 2H), 4.00-3.91 (m, 2H), 3.30-3.27 (m, 4H), 2.53 (s, 3H), 2.26- 2.20 (m, 1H), 2.10-2.04 (m, 1H), 1.76-1.60

(m, 2H); Mass (ESI): 410.4 [M+1]; LCMS: 410 (M+1); (column; Ascentis Express C-18 (50 × 3.0 mm, 2.7 μm); RT 1.52 min; mobile phase: 0.025% Aq TFA+5% ACN: 5%ACN+0.025% Aq TFA; T/B%: 0.01/5, 0.5/5, 3/100, 5/100; flow rate: 1.2 mL/min (Gradient); HPLC (column; Eclipse XDB-C-18, 150 × 4.6 mm, 5.0 μm); RT 9.43 min. mobile phase: ACN: 5mM Aq NH₄OAc; flow rate: 1.0 mL/min; Gradient program: T/B% 0.01/80, 3/80, 10/10, 20/10: diluent: CH₃CN: Water; Chiral HPLC: 99.7% RT = 21.03 min (Chiralpak-IC (250 x 4.6 mm, 5μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (80: 20) (A: B; 80: 20); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: -83.21 (c = 0.25, CH₂Cl₂).

Example 77B

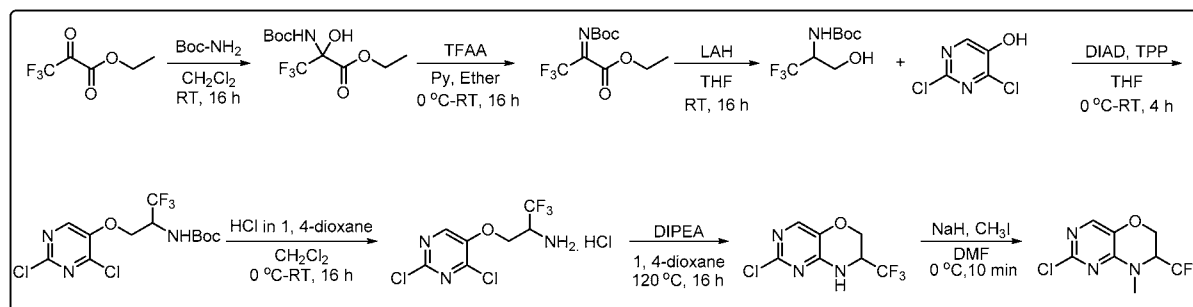
Synthesis of (+)-8-methyl-N-((3R, 6S)-6-(2-methylpyridin-4-yl) tetrahydro-2H-pyran-3-yl)-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine



[0434] The compound of Example 77B was produced as described in Example 77. Analytical data for product Fraction II (+): ¹H NMR (CD₃OD, 400 MHz): δ 8.34 (d, 1H), 7.46 (s, 1H), 7.32 (s, 1H), 7.25 (d, 1H), 4.50 (d, 1H), 4.39 (d, 1H), 4.31-4.26 (m, 2H), 4.00-3.91 (m, 2H), 3.30-3.27 (m, 4H), 2.53 (s, 3H), 2.26- 2.20 (m, 1H), 2.10-2.04 (m, 1H), 1.76-1.60 (m, 2H); Mass (ESI): 410.4 [M+1]; LCMS: 410 (M+1); (column; Ascentis Express C-18 (50 × 3.0 mm, 2.7 μm); RT 1.49 min; mobile phase: 0.025% Aq TFA+5% ACN: 5%ACN+0.025% Aq TFA; T/B%: 0.01/5, 0.5/5, 3/100, 5/100; flow rate: 1.2 mL/min (Gradient); HPLC (column; Eclipse XDB-C-18, 150 × 4.6 mm, 5.0 μm); RT 9.41 min. mobile phase: ACN: 5mM Aq NH₄OAc; flow rate: 1.0 mL/min; Gradient program: T/B% 0.01/80, 3/80, 10/10, 20/10: diluent: CH₃CN: Water; Chiral HPLC: 98.3% RT = 23.06 min (Chiralpak-IC (250 x 4.6 mm, 5μm; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (80: 20) (A: B; 80: 20); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.00}$: +44.00 (c = 0.25, CH₂Cl₂).

Example 78

Synthesis of 2-chloro-8-methyl-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of ethyl 2-((tert-butoxycarbonyl) amino)-3, 3, 3-trifluoro-2-hydroxypropanoate

[0435] To a stirred solution of ethyl 3, 3, 3-trifluoro-2-oxopropanoate (25 g, 147.05 mmol) in CH_2Cl_2 (250 mL) under an argon atmosphere was added Boc-amine (19 g, 161.76 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature. After consumption of the starting materials (monitored by TLC), the volatiles were evaporated *in vacuo* to obtain ethyl 2-((tert-butoxycarbonyl) amino)-3, 3, 3-trifluoro-2-hydroxypropanoate (40 g, 95%) as pale yellow syrup used in the next step without further purification. TLC: 20% EtOAc/ hexane (R_f : 0.5).

Synthesis of ethyl (Z)-2-((tert-butoxycarbonyl) imino)-3, 3, 3-trifluoropropanoate

[0436] To a stirred solution of ethyl 2-((tert-butoxycarbonyl) amino)-3, 3, 3-trifluoro-2-hydroxypropanoate (20 g, 69.56 mmol) in ether (300 mL) under an argon atmosphere were added trifluoroacetic anhydride (14.6 g, 69.56 mmol) and pyridine (11.2 mL, 139.12 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. After consumption of the starting materials (monitored by TLC), the reaction mixture was filtered. The filtrate was washed with water (100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain ethyl (Z)-2-((tert-butoxycarbonyl) imino)-3, 3, 3-trifluoropropanoate (11 g, 59%) as an off-white solid used in the next step without further purification. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 4.26-4.11 (m, 2H), 1.38 (s, 9H), 1.19 (t, 3H); TLC: 20% EtOAc/ hexane (R_f : 0.5).

Synthesis of tert-butyl (Z)-(1, 1, 1-trifluoro-3-hydroxypropan-2-ylidene) carbamate

[0437] To a stirred solution of ethyl (Z)-2-((*tert*-butoxycarbonyl) imino)-3, 3, 3-trifluoropropanoate (11 g, 40.81 mmol) in THF (2.75 mL) under an argon atmosphere was added lithium aluminum hydride (4.65 g, 122.44 mmol) portion wise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. After consumption of the starting materials (monitored by TLC), the reaction mixture was diluted with water (5 mL) and basified with a 15% sodium hydroxide solution (5 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was filtered and washed with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain *tert*-butyl (Z)-(1, 1, 1-trifluoro-3-hydroxypropan-2-ylidene) carbamate (6 g, 64%) as an off-white solid. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 6.11 (br s, 1H), 5.04 (br s, 1H), 4.21-4.07 (m, 1H), 3.69-3.45 (m, 2H), 1.37 (d, 9H); TLC: 30% EtOAc/ hexane (R_f: 0.3).

Synthesis of tert-butyl (Z)-(3-((2, 4-dichloropyrimidin-5-yl) oxy)-1, 1, 1-trifluoropropan-2-ylidene) carbamate

[0438] To a stirred solution of *tert*-butyl (Z)-(1, 1, 1-trifluoro-3-hydroxypropan-2-ylidene) carbamate (65 g, 26.20 mmol) in THF (180 mL) under an argon atmosphere were added diisopropyl azodicarboxylate (7.9 g, 39.30 mmol), triphenylphosphine (10 g, 39.30 mmol) and 2, 4-dichloropyrimidin-5-ol (4.3 g, 26.20 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. After consumption of the starting materials (monitored by TLC), the volatiles were concentrated *in vacuo*. The crude material was purified by column chromatography using 20-30% EtOAc: hexane to afford *tert*-butyl (Z)-(3-((2, 4-dichloropyrimidin-5-yl) oxy)-1, 1, 1-trifluoropropan-2-ylidene) carbamate (3.5 g, 36%) as an off-white solid. ¹H NMR (CDCl₃, 400 MHz): δ 8.21 (s, 1H), 5.21-5.18 (m, 1H), 4.74 (br s, 1H), 4.43-4.18 (m, 2H), 1.48 (s, 9H); TLC: 50% EtOAc/ hexane (R_f: 0.5).

Synthesis of 3-((2, 4-dichloropyrimidin-5-yl) oxy)-1, 1, 1-trifluoropropan-2-amine hydrochloride

[0439] To a stirred solution of *tert*-butyl (Z)-(3-((2, 4-dichloropyrimidin-5-yl) oxy)-1, 1, 1-trifluoropropan-2-ylidene) carbamate (3.5 g, 9.30 mmol) in CH₂Cl₂ (30 mL) under an argon atmosphere was added 4M HCl in 1, 4-dioxane (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. After consumption of the starting materials (monitored by TLC), the volatiles were concentrated *in vacuo*. The crude material was

washed with *n*-pentane (2 x 10 mL) to obtain 3-((2, 4-dichloropyrimidin-5-yl) oxy)-1, 1, 1-trifluoropropan-2-amine hydrochloride (2.2 g, as HCl salt) as an off-white solid. TLC: 30% EtOAc/ hexane (R_f : 0.3).

Synthesis of 2-chloro-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0440] To a stirred solution of 3-((2, 4-dichloropyrimidin-5-yl) oxy)-1, 1, 1-trifluoropropan-2-amine hydrochloride (2.2 g, 7.97 mmol) in 1, 4-dioxane (5.5 mL) under an argon atmosphere was added diisopropylethylamine (5.5 mL, 31.88 mmol) at room temperature. The reaction mixture was stirred at 120 °C for 16 h. After consumption of the starting materials (monitored by TLC), the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain 2-chloro-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (1.6 g, 84%) as a pale yellow solid. ^1H NMR (CDCl_3 , 400 MHz): δ 7.90 (s, 1H), 7.43 (br s, 1H), 5.01-4.97 (m, 1H), 4.61-4.58 (m, 1H), 4.17-4.09 (m, 1H); LCMS: 239.8 (M+1); (column; Ascentis Express C-18 (50 x 3.0 mm, 2.7 μm); RT 1.82 min; mobile phase: 0.025% Aq TFA+5% ACN: ACN+5% 0.025% Aq TFA; flow rate: T/B%: 0.01/5, 0.5/5, 3/100, 5/100; 1.2 mL/min) (Gradient); TLC: 30% EtOAc/ hexane (R_f : 0.4).

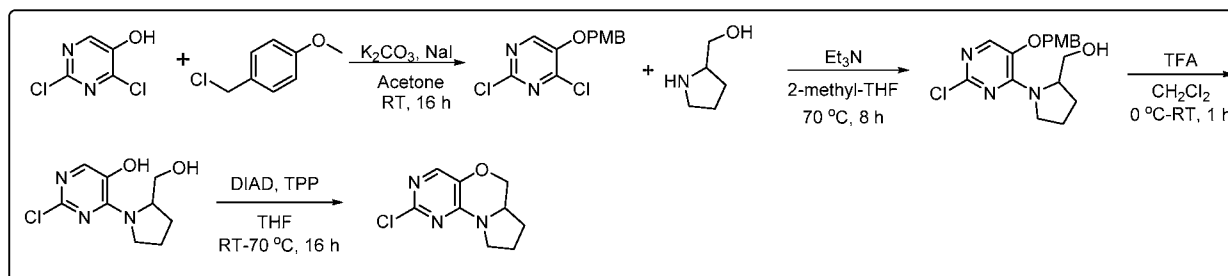
Synthesis of 2-chloro-8-methyl-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0441] To a stirred solution of 2-chloro-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (1.6 g, 6.69 mmol) in DMF (20 mL) under an argon atmosphere was added sodium hydride (193 mg, 8.03 mmol) at 0 °C. The reaction mixture was stirred for 5 min at 0 °C. Then methyl iodide (1.14 g, 8.03 mmol) was added to the reaction mixture at 0 °C and stirred for 5 min at 0 °C. After consumption of the starting materials (monitored by TLC), the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 20% EtOAc: hexane to afford 2-chloro-8-methyl-7-(trifluoromethyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (1.2 g, 71%) as a pale yellow syrup. ^1H NMR (400 MHz, CDCl_3): δ 7.82 (s, 1H), 4.62 (d, 1H), 4.03-4.00 (m, 1H), 3.99-3.95 (m, 1H), 3.31 (s, 3H); LCMS: 253.8 (M+1); (column; Ascentis Express C-18 (50 x 3.0 mm, 2.7 μm); RT 2.18 min;

mobile phase: 0.025% Aq TFA+5% ACN: ACN+5% 0.025% Aq TFA; T/B%: 0.01/5, 0.5/5, 3/100, 5/100; flow rate: 1.2 mL/min) (Gradient); TLC: 30% EtOAc/ hexane (R_f : 0.3).

Example 79

Synthesis of 2-chloro-6a, 7, 8, 9-tetrahydro-6H-pyrimido [5, 4-b] pyrrolo [1, 2-d] [1, 4] oxazine



Synthesis of 2, 4-dichloro-5-((4-methoxybenzyl) oxy) pyrimidine

[0442] To a stirred solution of 2, 4-dichloropyrimidin-5-ol (7 g, 42.68 mmol) in acetone (100 mL) under an argon atmosphere were added 1-(chloromethyl)-4-methoxybenzene (10 g, 64.02 mmol), potassium carbonate (14.7 g, 106.70 mmol) and sodium iodide (600 mg, 4.26 mmol) at room temperature. The reaction mixture was stirred for 16 h at room temperature. After consumption of the starting materials (monitored by TLC), the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 10% EtOAc: hexanes to afford 2, 4-dichloro-5-((4-methoxybenzyl) oxy) pyrimidine (6.2 g, 51%) as a pale yellow solid. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 8.19 (s, 1H), 7.34 (d, 2H), 6.93 (d, 2H), 5.19 (s, 2H), 3.80 (s, 3H); TLC: 30% EtOAc/ hexane (R_f : 0.6).

Synthesis of (1-(2-chloro-5-((4-methoxybenzyl) oxy) pyrimidin-4-yl) pyrrolidin-2-yl) methanol

[0443] To a stirred solution of 2, 4-dichloro-5-((4-methoxybenzyl) oxy) pyrimidine (100 mg, 0.35 mmol) in 2-methyl THF (1 mL) under an argon atmosphere were added pyrrolidin-2-ylmethanol (40 mg, 0.39 mmol) and triethylamine (0.12 mL, 0.87 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 8 h. After consumption of the

starting materials (monitored by TLC), the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 50% EtOAc: hexanes to afford (1-(2-chloro-5-((4-methoxybenzyl) oxy) pyrimidin-4-yl) pyrrolidin-2-yl) methanol (120 mg, 98%) as colorless syrup. ¹H-NMR (CDCl₃, 500 MHz): δ 7.67 (s, 1H), 7.41 (d, 2H), 6.91 (d, 2H), 4.90 (s, 2H), 4.48-4.41 (m, 1H), 3.88-3.78 (m, 5H), 3.69-3.60 (m, 2H), 3.21 (br s, 1H), 2.00-1.80 (m, 4H); LCMS: 350.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.91 min; mobile phase: 0.05% Aq TFA: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 9/90; flow rate: 0.80 mL/min) (Gradient); TLC: 50% EtOAc/ hexane (R_f: 0.3).

Synthesis of 2-chloro-4-(2-(hydroxymethyl) pyrrolidin-1-yl) pyrimidin-5-ol

[0444] To a stirred solution of (1-(2-chloro-5-((4-methoxybenzyl) oxy) pyrimidin-4-yl) pyrrolidin-2-yl) methanol (120 mg, 0.34 mmol) in CH₂Cl₂ (2 mL) under an argon atmosphere was added trifluoroacetic acid (1 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. After consumption of the starting materials (monitored by TLC), the reaction mixture was diluted with a saturated sodium bicarbonate solution (20 mL) and extracted with 5% MeOH/ CH₂Cl₂ (2 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain 2-chloro-4-(2-(hydroxymethyl) pyrrolidin-1-yl) pyrimidin-5-ol (50 mg 64%) as a white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 9.80 (s, 1H), 7.50 (s, 1H), 4.79 (br s, 1H), 4.50-4.40 (m, 1H), 3.75-3.69 (m, 1H), 3.67-3.60 (m, 1H), 3.59-3.50 (m, 1H), 2.00-1.71 (m, 4H); LCMS: 230.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.06 min; mobile phase: 0.05% Aq TFA: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 9/90; flow rate: 0.80 mL/min) (Gradient); TLC: 50% EtOAc/ hexane (R_f: 0.3).

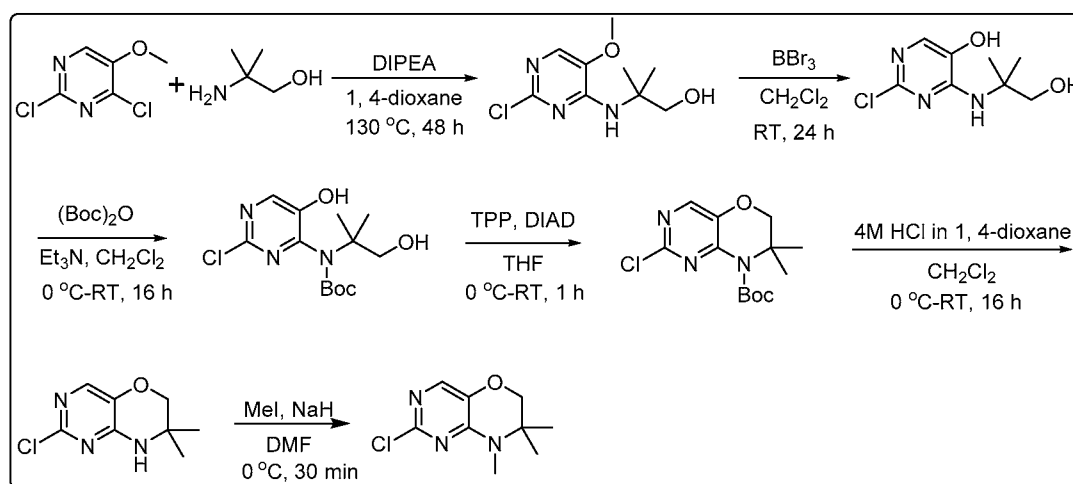
Synthesis of 2-chloro-6a, 7, 8, 9-tetrahydro-6H-pyrimido [5, 4-b] pyrrolo [1, 2-d] [1, 4] oxazine

[0445] To a stirred solution of 2-chloro-4-(2-(hydroxymethyl) pyrrolidin-1-yl) pyrimidin-5-ol (1.8 g, 0.56 mmol) in THF (20 mL) under an argon atmosphere were added triphenylphosphine (2.2 g, 0.85 mmol) and diisopropyl azodicarboxylate (1.7 mL, 0.85 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 16 h. After consumption of the starting materials (monitored by TLC), the reaction mixture was diluted

with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 30% EtOAc: hexanes to afford 2-chloro-6a, 7, 8, 9-tetrahydro-6H-pyrimido [5, 4-b] pyrrolo [1, 2-d] [1, 4] oxazine (800 mg, 66%) as an off-white solid. ¹H-NMR (CDCl₃, 500 MHz): δ 7.68 (d, 1H), 4.52 (d, 1H), 3.78-3.70 (m, 2H), 3.60-3.56 (m, 1H), 3.39 (t, 1H), 2.20-2.10 (m, 2H), 2.08-1.99 (m, 1H), 1.53-1.40 (m, 1H); LCMS: 212.2 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.73 min; mobile phase: 0.05% Aq TFA: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 9/90; flow rate: 0.80 mL/min) (Gradient); TLC: 50% EtOAc/ hexanes (R_f: 0.5).

Example 80

Synthesis of 2-chloro-7, 7-dimethyl-8-phenyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine



Synthesis of 2-((2-chloro-5-methoxypyrimidin-4-yl) amino)-2-methylpropan-1-ol:

[0446] To a stirred solution of 2, 4-dichloro-5-methoxypyrimidine (5 g, 27.93 mmol) in 1, 4-dioxane (50 mL) under an argon atmosphere were added diisopropylethylamine (7.2 g, 55.86 mmol) and 2-amino-2-methylpropan-1-ol (2.4 g, 27.93 mmol) at room temperature. The reaction mixture was stirred at 130 °C for 48 h. After consumption of the starting materials (monitored by TLC), the volatiles were evaporated *in vacuo*. The residue was diluted with a saturated sodium bicarbonate solution (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 10% EtOAc: hexanes to afford 2-((2-chloro-5-methoxypyrimidin-4-yl) amino)-2-

methylpropan-1-ol (5.5 g, 84%) as a white solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.69 (s, 1H), 6.19 (s, 1H), 6.11 (t, 1H), 3.82 (s, 3H), 3.45 (d, 2H), 1.33 (s, 6H); TLC: 50% EtOAc: hexanes (R_f: 0.3).

Synthesis of 2-chloro-4-((1-hydroxy-2-methylpropan-2-yl) amino) pyrimidin-5-ol:

[0447] To a stirred solution of 2-((2-chloro-5-methoxypyrimidin-4-yl) amino)-2-methylpropan-1-ol (5.5 g, 23.80 mmol) in CH₂Cl₂ (100 mL) was added boron tribromide (34 mL, 357.14 mmol) at 0 °C under an argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 24 h. After consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with methanol (50 mL) at 0 °C and concentrated *in vacuo*. The residue was dissolved in EtOAc (2 x 100 mL) and washed with a sodium bicarbonate solution (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain 2-chloro-4-((1-hydroxy-2-methylpropan-2-yl) amino) pyrimidin-5-ol (4 g, 81%) as a white solid used in the next step without further purification. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 10.38 (br s, 1H), 7.48 (s, 1H), 6.03 (s, 1H), 5.11 (br s, 1H), 3.45 (s, 2H), 1.37 (s, 6H); TLC: 80% EtOAc: hexanes (R_f: 0.3).

Synthesis of tert-butyl (2-chloro-5-hydroxypyrimidin-4-yl) (1-hydroxy-2-methylpropan-2-yl) carbamate:

[0448] To a stirred solution of 2-chloro-4-((1-hydroxy-2-methylpropan-2-yl) amino) pyrimidin-5-ol (4.3 g, 19.90 mmol) in CH₂Cl₂ (50 mL) under an argon atmosphere were added triethylamine (4.3 mL, 29.80 mmol) and Boc anhydride (4.3 g, 19.90 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. After consumption of the starting materials (monitored by TLC), the volatiles were evaporated *in vacuo*. The crude material was purified by column chromatography using 40% EtOAc: hexanes to afford *tert*-butyl (2-chloro-5-hydroxypyrimidin-4-yl) (1-hydroxy-2-methylpropan-2-yl) carbamate (3 g, 48%) as a white solid. ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 8.00 (s, 1H), 6.61 (s, 1H), 5.07 (t, 1H), 3.49 (d, 2H), 1.50 (s, 9H), 1.37 (s, 6H); TLC: 50% EtOAc: hexanes (R_f: 0.5).

Synthesis of tert-butyl 2-chloro-7, 7-dimethyl-6, 7-dihydro-8H-pyrimido [5, 4-b] [1, 4] oxazine-8-carboxylate:

[0449] To a stirred solution of *tert*-butyl (2-chloro-5-hydroxypyrimidin-4-yl) (1-hydroxy-2-methylpropan-2-yl) carbamate (3 g, 9.46 mmol) in THF (30 mL) under an argon atmosphere were added triphenylphosphine (2.9 g, 11.36 mmol) and diisopropyl azodicarboxylate (2.3 g, 11.35 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. After consumption of the starting materials (monitored by TLC), the volatiles were evaporated *in vacuo*. The crude material was purified by column chromatography using 20% EtOAc: hexanes to afford *tert*-butyl 2-chloro-7, 7-dimethyl-6, 7-dihydro-8*H*-pyrimido [5, 4-*b*] [1, 4] oxazine-8-carboxylate (1.5 g, 53%) as a white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.11 (s, 1H), 4.01 (s, 2H), 1.52 (s, 9H), 1.38 (s, 6H); LCMS: 300.3 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.69 min; mobile phase: 5 mM Aq NH₄OAc: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 9/90; flow rate: 0.80 mL/min) (Gradient); TLC: 30% EtOAc: hexanes (*R*_f: 0.3).

Synthesis of 2-chloro-7, 7-dimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine:

[0450] To a stirred solution of *tert*-butyl 2-chloro-7, 7-dimethyl-6, 7-dihydro-8*H*-pyrimido [5, 4-*b*] [1, 4] oxazine-8-carboxylate (500 mg, 1.67 mmol) in CH₂Cl₂ (5 mL) under an argon atmosphere was added 4M HCl in 1, 4-dioxane (5 mL) at 0 °C. The reaction mixture was stirred for 16 h at room temperature. After consumption of the starting materials (monitored by TLC), the volatiles were evaporated *in vacuo*. The residue was diluted with a saturated sodium bicarbonate solution (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the 2-chloro-7, 7-dimethyl-7, 8-dihydro-6*H*-pyrimido [5, 4-*b*] [1, 4] oxazine (260 mg, 78%) as a white solid. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 8.50 (s, 1H), 7.71 (s, 2H), 1.20 (s, 6H); TLC: 50% EtOAc: hexanes (*R*_f: 0.3).

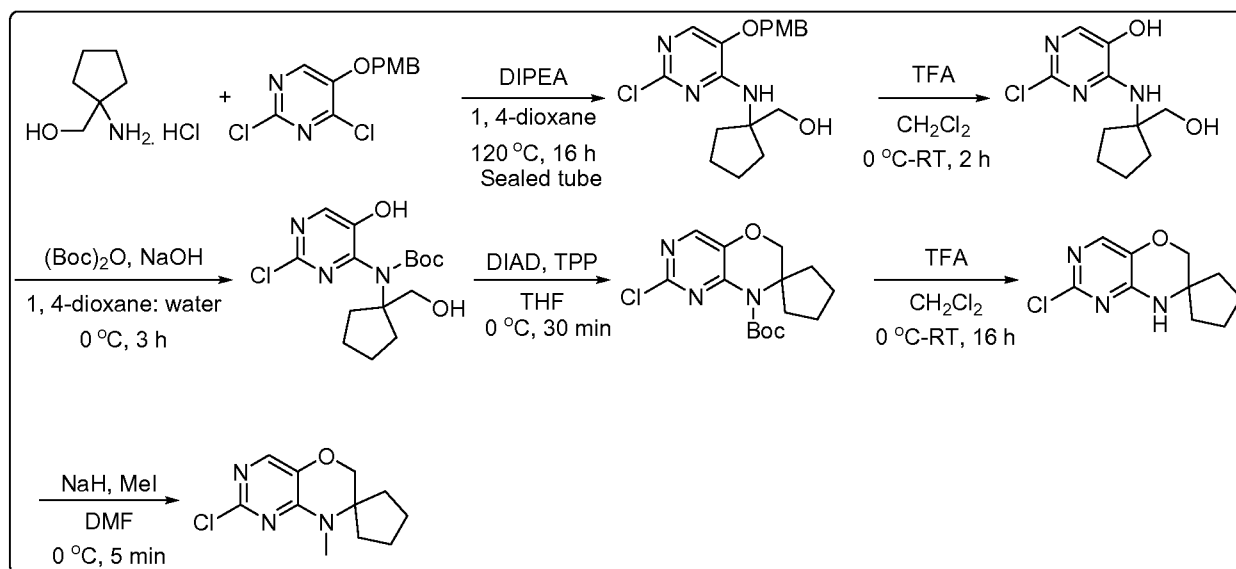
Synthesis of 2-chloro-7, 7, 8-trimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine

[0451] To a stirred solution of 2-chloro-7, 7-dimethyl-7, 8-dihydro-6*H*-pyrimido [5, 4-*b*] [1, 4] oxazine (50 mg, 0.25 mmol) in DMF (0.5 mL) under an argon atmosphere were added sodium hydride (8.8 mg, 0.37 mmol) and methyl iodide (35.5 mg, 0.25 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. After consumption of the starting materials (monitored by TLC), the volatiles were evaporated *in vacuo*. The residue was diluted with ice cold water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was

purified by column chromatography using 20% EtOAc: hexanes to afford 2-chloro-7, 7, 8-trimethyl-7, 8-dihydro-6*H*-pyrimido [5, 4-*b*] [1, 4] oxazine (30 mg, 56%) as a white solid. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 7.68 (s, 1H), 3.93 (s, 2H), 3.00 (s, 3H), 1.24 (s, 6H); TLC: 50% EtOAc: hexanes (*R*_f: 0.4).

Example 81

Synthesis of 2'-chloro-6'H, 8'H-spiro [cyclopentane-1, 7'-pyrimido [5, 4-*b*] [1, 4] oxazine]



Synthesis of (1-((2-chloro-5-((4-methoxybenzyl) oxy) pyrimidin-4-yl) amino) cyclopentyl) methanol

[0452] To a stirred solution of 2, 4-dichloro-5-((4-methoxybenzyl) oxy) pyrimidine (1.5 g, 5.26 mmol) in 1, 4-dioxane (4 mL) under an argon atmosphere were added diisopropylethylamine (1.3 g, 21.05 mmol) and (1-aminocyclopentyl) methanol hydrochloride (1 g, 6.84 mmol) at room temperature. The reaction mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC), the volatiles were evaporated *in vacuo* to obtain (1-((2-chloro-5-((4-methoxybenzyl) oxy) pyrimidin-4-yl) amino) cyclopentyl) methanol (700 mg, 37%) as a brown liquid. LCMS: 364.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 4.29 min; mobile phase: 0.05% Aq TFA: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 9/90; flow rate: 0.80 mL/min) (Gradient); TLC: 20% EtOAc/ hexane (*R*_f: 0.4).

Synthesis of 2-chloro-4-((1-(hydroxymethyl) cyclopentyl) amino) pyrimidin-5-ol

[0453] To a stirred solution of (1-((2-chloro-5-((4-methoxybenzyl) oxy) pyrimidin-4-yl) amino) cyclopentyl) methanol (120 mg, 0.33 mmol) in CH₂Cl₂ (1.2 mL) under an argon atmosphere was added trifluoroacetic acid (150 mg, 1.32 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. After consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with a saturated sodium bicarbonate solution (10 mL) and extracted with CH₂Cl₂ (2 x 10 mL). The aqueous layer was acidified with a citric acid solution up to pH 5 and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain 2-chloro-4-((1-(hydroxymethyl) cyclopentyl) amino) pyrimidin-5-ol (80 mg, 99%) as an off-white solid used in the next step without further purification. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ 10.30 (br s, 1H), 8.13-8.11 (m, 1H), 7.46 (s, 1H), 6.13 (s, 1H), 3.70 (s, 2H), 2.00-1.93 (m, 2H), 1.90-1.88 (m, 2H), 1.80-1.61 (m, 4H); TLC: 50% EtOAc/ hexane (R_f: 0.1).

Synthesis of tert-butyl (2-chloro-5-hydroxypyrimidin-4-yl) (1-(hydroxymethyl) cyclopentyl) carbamate

[0454] To a stirred solution of 2-chloro-4-((1-(hydroxymethyl) cyclopentyl) amino) pyrimidin-5-ol (500 mg, 2.05 mmol) in 1, 4-dioxane: water (1: 1, 10 mL) under an argon atmosphere were added sodium hydroxide (98 mg, 2.46 mmol) and Boc anhydride (538 mg, 2.46 mmol) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C. After consumption of the starting materials (monitored by TLC), the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 10 mL). The aqueous layer was acidified with a citric acid solution up to pH 5 and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain *tert*-butyl (2-chloro-5-hydroxypyrimidin-4-yl) (1-(hydroxymethyl) cyclopentyl) carbamate (700 mg, 99%) as a brown liquid. LCMS: 344.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.70 min; mobile phase: 0.05% Aq TFA: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 9/90; flow rate: 0.80 mL/min) (Gradient); TLC: 50% EtOAc/ hexane (R_f: 0.6).

Synthesis of tert-butyl 2'-chloro-6'H, 8'H-spiro [cyclopentane-1, 7'-pyrimido [5, 4-b] [1,4]oxazine]-8'-carboxylate

[0455] To a stirred solution of *tert*-butyl (2-chloro-5-hydroxypyrimidin-4-yl) (1-(hydroxymethyl) cyclopentyl) carbamate (150 mg, 0.43 mmol) in THF (2 mL) under an argon atmosphere were added diisopropyl azodicarboxylate (132 g, 0.65 mmol) and triphenylphosphine (171 mg, 0.65 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. After consumption of the starting materials (monitored by TLC), the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 10% EtOAc; hexanes to afford *tert*-butyl 2'-chloro-6'*H*, 8'*H*-spiro [cyclopentane-1, 7'-pyrimido [5, 4-*b*] [1, 4] oxazine]-8'-carboxylate (60 mg, 42%) as colorless liquid. ¹H-NMR (CD₃OD, 400 MHz): δ 7.93 (s, 1H), 3.99 (s, 2H), 2.08-1.94 (m, 4H), 1.80-1.65 (m, 4H), 1.95 (s, 9H); TLC: 20% EtOAc/ hexane (R_f: 0.7).

*Synthesis of 2'-chloro-6'*H*, 8'*H*-spiro [cyclopentane-1, 7'-pyrimido [5, 4-*b*] [1, 4] oxazine]*

[0456] To a stirred solution of *tert*-butyl 2'-chloro-6'*H*, 8'*H*-spiro [cyclopentane-1, 7'-pyrimido [5, 4-*b*] [1, 4] oxazine]-8'-carboxylate (400 mg, 1.23 mmol) in CH₂Cl₂ (4 mL) under an argon atmosphere was added trifluoroacetic acid (561 mg, 4.92 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. After consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with a saturated sodium bicarbonate solution (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain 2'-chloro-6'*H*, 8'*H*-spiro [cyclopentane-1, 7'-pyrimido [5, 4-*b*] [1, 4] oxazine] (270 mg, 97%) as a brown solid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.75 (s, 1H), 5.50-5.43 (m, 1H), 3.90 (s, 2H), 1.89-1.80 (m, 4H), 1.79-1.70 (m, 4H); TLC: 20% EtOAc/ hexane (R_f: 0.3).

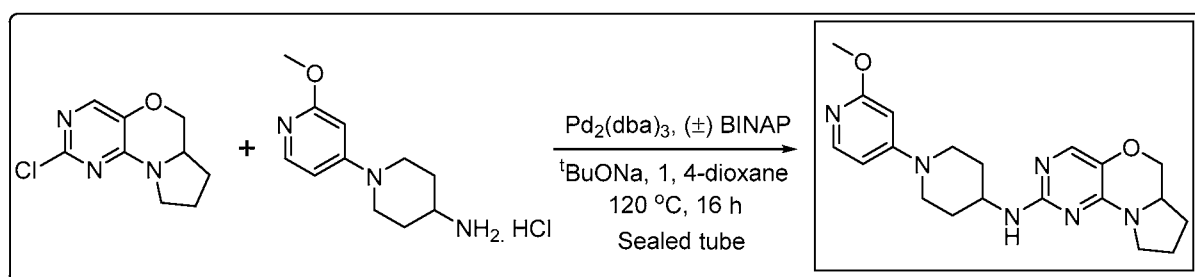
*Synthesis of 2'-chloro-6'*H*, 8'*H*-spiro [cyclopentane-1, 7'-pyrimido [5, 4-*b*] [1, 4] oxazine]*

[0457] To a stirred solution of 2'-chloro-6'*H*, 8'*H*-spiro [cyclopentane-1, 7'-pyrimido [5, 4-*b*] [1, 4] oxazine] (100 mg, 0.44 mmol) in DMF (1 mL) under an argon atmosphere was added sodium hydride (26 mg, 0.66 mmol) and methyl iodide (94 mg, 0.66 mmol) at 0 °C. The reaction mixture was stirred for 5 min at 0 °C. After consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with ice water (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain 2'-chloro-6'*H*,

8'*H*-spiro [cyclopentane-1, 7'-pyrimido [5, 4-*b*] [1, 4] oxazine] (100 mg, 95%) as a brown liquid. ¹H-NMR (CDCl₃, 400 MHz): δ 7.61 (s, 1H), 3.82 (s, 2H), 3.09 (s, 3H), 1.87-1.80 (m, 4H), 1.73-1.67 (m, 4H); LCMS: 240.1 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 3.32 min; mobile phase: 0.05% Aq TFA: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 9/90; flow rate: 0.80 mL/min) (Gradient); TLC: 20% EtOAc/ hexane (R_f: 0.3).

Example 82

Synthesis of *N*-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-6a, 7, 8, 9-tetrahydro-6*H*-pyrimido [5, 4-*b*] pyrrolo [1, 2-*d*] [1, 4] oxazin-2-amine



Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-6a, 7, 8, 9-tetrahydro-6*H*-pyrimido [5, 4-*b*] pyrrolo [1, 2-*d*] [1, 4] oxazin-2-amine

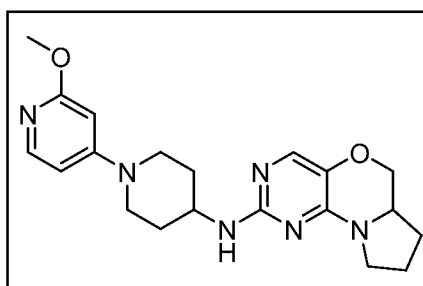
[0458] To a dry vial was added a suspension of Pd₂(dba)₃ (54 mg, 0.05 mmol) and (±) BINAP (110 mg, 0.19 mmol) in 1, 4-dioxane (2.5 mL) at room temperature. The suspension was degassed with an argon atmosphere, heated to 120 °C, and stirred at 120 °C for 3 min. A mixture of 2-chloro-6a, 7, 8, 9-tetrahydro-6*H*-pyrimido [5, 4-*b*] pyrrolo [1, 2-*d*] [1, 4] oxazine (250 mg, 0.12 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (316 mg, 0.13 mmol) and sodium tert-butoxide (350 mg, 3.55 mmol) in 1, 4-dioxane (2.5 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by column chromatography using 8% MeOH: CH₂Cl₂ to afford *N*-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-6a, 7, 8, 9-tetrahydro-6*H*-pyrimido [5, 4-*b*] pyrrolo [1, 2-*d*] [1, 4] oxazin-2-amine (130 mg, 28%) as an off-white solid. LCMS: 383.4 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 1.21 min; mobile phase: 0.05% Aq TFA: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 9/90; flow rate: 0.80 mL/min) (Gradient); UPLC (column; Acquity UPLC BEH C-18 2.1 X 50 mm, 1.7 μ); RT 1.27 min;

mobile phase: ACN: 0.025% Aq TFA; flow rate: 0.5 mL/min; Gradient program: T/B% 0.01/90, 0.5/90, 3/10, 6/10; diluent: CH₃CN: Water; TLC: 10% MeOH/ CH₂Cl₂ (R_f: 0.3).

[0459] Racemic compound of Example 82 was separated using a Chiralpak-AD-H column (250 x 20 mm, 5 μ m (20 mg loading; 0.1 % DEA in *n*-hexane: EtOH (A: B: 85: 15) as mobile phase) to provide the compound of Example 82A (Fraction I (+)) and the compound of Example 82B (Fraction II (-)).

Example 82A

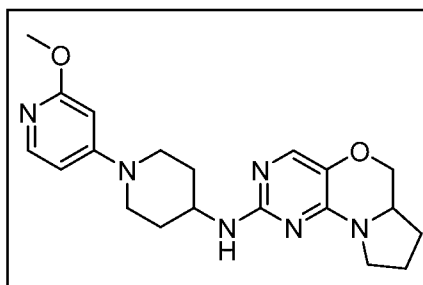
Synthesis of (+)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-6a, 7, 8, 9-tetrahydro-6H-pyrimido [5, 4-b] pyrrolo [1, 2-d] [1, 4] oxazin-2-amine



[0460] The compound of Example 82A was produced as described in Example 82. Analytical data for product Fraction I (+): ¹H-NMR (CD₃OD, 400 MHz): δ 7.74 (d, 1H), 7.33 (s, 1H), 6.54 (d, 1H), 6.14 (s, 1H), 4.47-4.40 (m, 1H), 3.91-3.84 (m, 3H), 3.81 (s, 3H), 3.77-3.70 (m, 1H), 3.62-3.49 (m, 2H), 3.32-3.30 (m, 1H), 3.02 (t, 2H), 2.20-1.90 (m, 5H), 1.59-1.45 (m, 3H); Mass (ESI): 383.4 [M+1]; LCMS: 383.4 (M+1); (column; X-Select CSH C-18 (50 $\times$ 3.0 mm, 3.5 μ m); RT 3.77 min; mobile phase: 5 mM Aq NH₄OAc: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 9/90; flow rate 0.8 ml/min (Gradient); UPLC (column; Acquity UPLC BEH C-18, 2.1 $\times$ 50 mm, 1.7 μ m); RT 1.31 min; mobile phase: ACN: 0.025% Aq TFA; flow rate: 0.5 mL/min; Gradient program: T/B% 0.01/90, 0.5/90, 3/10, 6/10; Diluent: CH₃CN: Water: Chiral HPLC: 99.5% RT = 6.37 min (Chiralpak-IA (250 x 4.6 mm, 5 μ m; mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH₂Cl₂: MeOH (50: 50) (A: B: 50: 50); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_D^{20.02}$: +29.12 (c = 0.25, CH₂Cl₂).

Example 82B

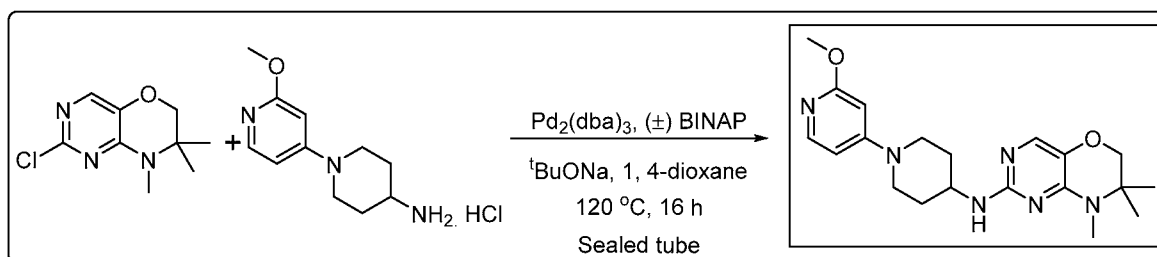
Synthesis of (-)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-6a, 7, 8, 9-tetrahydro-6H-pyrimido [5, 4-b] pyrrolo [1, 2-d] [1, 4] oxazin-2-amine



[0461] The compound of Example 82B was produced as described in Example 82. Analytical data for product Fraction II (-): $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.74 (d, 1H), 7.33 (s, 1H), 6.54 (d, 1H), 6.14 (s, 1H), 4.47-4.40 (m, 1H), 3.91-3.84 (m, 3H), 3.81 (s, 3H), 3.77-3.70 (m, 1H), 3.62-3.49 (m, 2H), 3.32-3.30 (m, 1H), 3.02 (t, 2H), 2.20-1.90 (m, 5H), 1.59-1.45 (m, 3H); Mass (ESI): 383.4 $[\text{M}+1]$; LCMS: 383.4 (M+1); (column; X-Select CSH C-18 (50×3.0 mm, $3.5 \mu\text{m}$); RT 3.78 min; mobile phase: 5 mM Aq NH_4OAc : ACN; T/B%: 0.01/10, 0.5/10, 4/90, 9/90 flow rate 0.8 ml/min (Gradient); UPLC (column; Acquity UPLC BEH C-18, 2.1×50 mm, $1.7 \mu\text{m}$); RT 1.31 min; mobile phase: ACN: 0.025% Aq TFA; flow rate: 0.5 ml/min; Gradient program: T/B% 0.01/90, 0.5/90, 3/10, 6/10; diluent: CH_3CN : Water; Chiral HPLC: 99.3% RT = 9.02 min (Chiralpak-IA (250×4.6 mm, $5 \mu\text{m}$); mobile phase (A) 0.1 % DEA in *n*-hexane (B) CH_2Cl_2 : MeOH (50: 50) (A: B: 50: 50); flow Rate: 1.0 mL/min); Optical rotation $[\alpha]_{\text{D}}^{19.99}$: -24.80 ($c = 0.25$, CH_2Cl_2).

Example 83

Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-7, 7, 8-trimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

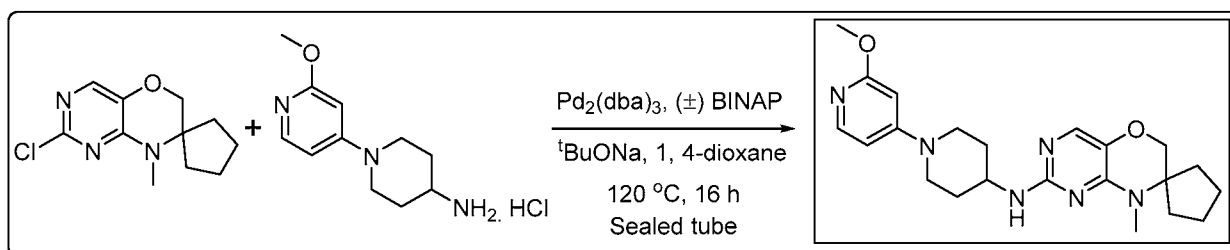


Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-7, 7, 8-trimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine

[0462] To a dry vial was added a suspension of Pd₂(dba)₃ (32 mg, 0.03 mmol) and (±) BINAP (65 mg, 0.10 mmol) in 1, 4-dioxane (1.5 mL) at room temperature. The suspension was degassed with argon, heated to 120 °C, and stirred at 120 °C for 3 min. A mixture of 2-chloro-7, 7, 8-trimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazine (150 mg, 0.70 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (187 mg, 0.77 mmol) and sodium tert-butoxide (202 mg, 2.10 mmol) in 1, 4-dioxane (1.5 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction mixture was diluted with water (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 4% MeOH: CH₂Cl₂ to afford N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-7, 7, 8-trimethyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine (60 mg, 22%) as an off-white solid. ¹H-NMR (CD₃OD, 500 MHz): δ 7.76 (d, 1H), 7.35 (s, 1H), 6.55 (d, 1H), 6.18 (s, 1H), 3.95-3.90 (m, 3H), 3.82 (s, 3H), 3.81 (s, 2H), 3.09 (s, 3H), 3.08-3.03 (m, 2H), 2.07 (d, 2H), 1.60-1.50 (m, 2H), 1.30 (s, 6H); Mass (ESI): 385 [M+1]; LCMS: 385 (M+1); (column; X-Select CSH C-18 (50 × 3.0 mm, 3.5 μm); RT 2.05 min; mobile phase: 0.05% Aq TFA: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 8/90; flow rate 0.8 ml/min (Gradient); UPLC (column; Acquity UPLC BEH C-18 2.1 X 50 mm, 1.7 μm); RT 1.37 min; mobile phase: ACN: 0.025% Aq TFA; flow rate: 0.5 mL/min; Gradient program: T/B% 0.01/90, 0.5/90, 3/10, 6/10; Diluent: CH₃CN: Water; TLC: 5% MeOH/ CH₂Cl₂ (R_f: 0.3).

Example 84

Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8'-methyl-6'H, 8'H-spiro [cyclopentane-1, 7'-pyrimido [5, 4-b] [1, 4] oxazin]-2'-amine



*Synthesis of N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8'-methyl-6'H, 8'H-spiro [cyclopentane-1, 7'-pyrimido [5, 4-*b*] [1, 4] oxazin]-2'-amine*

[0463] To a dry vial was added a suspension of $\text{Pd}_2(\text{dba})_3$ (25 mg, 0.02 mmol) and ($\pm$) BINAP (51 mg, 0.08 mmol) in 1, 4-dioxane (1 mL) at room temperature. The suspension was degassed with argon, heated to 120 °C, and stirred at 120 °C for 3 min. A mixture of 2'-chloro-8'-methyl-6'*H*, 8'*H*-spiro [cyclopentane-1, 7'-pyrimido [5, 4-*b*] [1, 4] oxazin] (130 mg, 0.54 mmol), 1-(2-methoxypyridin-4-yl) piperidin-4-amine hydrochloride (124 mg, 0.59 mmol) and sodium tert-butoxide (156 mg, 1.63 mmol) in 1, 4-dioxane (1 mL) was degassed and the catalyst premix was added. The resultant mixture was stirred at 120 °C for 16 h in a sealed tube. After consumption of the starting materials (monitored by TLC and LCMS), the reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography using 3% MeOH: CH_2Cl_2 to afford *N*-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8'-methyl-6'*H*, 8'*H*-spiro [cyclopentane-1, 7'-pyrimido [5, 4-*b*] [1, 4] oxazin]-2'-amine (50 mg, 22%) as an off-white solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.72-7.70 (m, 1H), 7.30 (s, 1H), 6.52 (d, 1H), 6.13 (s, 1H), 3.90-3.83 (m, 3H), 3.81 (s, 3H), 3.78 (s, 2H), 3.04-3.02 (m, 2H), 3.01 (s, 3H), 2.10-2.00 (m, 2H), 1.90-1.80 (m, 4H), 1.70-1.63 (m, 4H), 1.57-1.46 (m, 2H); Mass (ESI): 411.5 [$\text{M}+1$]; LCMS: 411.2 ($\text{M}+1$); (column; X-Select CSH C-18 (50 x 3.0 mm, 3.5 μm); RT 2.21 min; mobile phase: 0.05% Aq TFA: ACN; T/B%: 0.01/10, 0.5/10, 4/90, 8/90; flow rate: 0.8 mL/min (Gradient); UPLC (column; Acquity UPLC BEH C-18, 2.1 x 50 mm, 1.7 μm); RT 1.54 min; mobile phase: ACN: 0.025% Aq TFA; flow rate: 0.5 mL/min; Gradient program: T/B% 0.01/90, 0.5/90, 3/10, 6/10; Diluent: CH_3CN : Water; TLC: 5% MeOH/ CH_2Cl_2 (R_f : 0.3).

Example 85

***In Vitro* Cell screening Assay and Quantification of $\text{A}\beta_{(1-x)}$ and $\text{A}\beta_{(1-42)}$ Peptides**

[0464] Human neuroglioma H4 cells were transfected with a pcDNA3.1 plasmid expressing human wild type APP751 cDNA and a stable cell line was generated using G418 selection. Cells were plated at 15,000 cells/well in Costar 96-well plates and placed at 37°C and 5% CO₂. Six hours after plating, cells were washed three times with Pro293™ chemically defined medium, followed by addition of compounds (0.003–10 μM, final DMSO concentration of 0.33%). Plates were incubated overnight (16–18 h) and supernatant was removed for quantification of Aβ peptides by sandwich ELISA. Cytotoxicity was evaluated using Cell-Titer 96W AQueous One Solution Cell Proliferation Assay according to the manufacturer's protocol.

ELISA measurements of Aβ peptides

[0465] Aβ peptide levels were quantified by sandwich ELISA. 96-well plates were coated with C-terminal specific Aβ antibodies recognizing either Aβ37, Aβ38, Aβ40, Aβ42, Aβ43 or a N-terminal specific Aβ antibody to detect Aβ 1-x. Plates were then blocked overnight at 4°C with 1% bovine serum albumin (BSA) in PBS-T. Plates were washed and 100 μl of cultured cell supernatant or synthetic Aβ peptide standards and a detection antibody (4G8-HRP) were applied to the blocked plate and incubated overnight at 4°C. The next day, wells were washed before the addition of detection substrate (TMB peroxidase). Plates were then read for absorbance at 450 nm on a Molecular Devices SpectraMax M5e Microplate Reader.

[0466] Compound-treated samples were normalized to samples treated with DMSO alone (no inhibition) and to samples treated with DAPT. IC₅₀ values were calculated from values reported as percent of DMSO controls using nonlinear regression, based on a sigmoidal dose-response (variable slope) model. GraphPAD software from Prism used for calculation.

Table III. Biological Assay

Compound of Example	Structure	Name	Aβ42 H4 Prot Fre IC50 (μM)
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26		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)	0.1728
26A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.8469
26B		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.104
27		8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.7611
28		N-(1-(2-methoxypyridin-4-yl)azetidin-3-yl)-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	1.1062
29		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)	0.1409
29A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.753

29B		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.1336
30		N-(1-(2-methoxypyridin-4-yl)azetidin-3-yl)-8-methyl-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.7459
31		8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)	0.167
31A		(-)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	>10
31B		(+)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.1107
32		7-(3,5-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)	0.3133
32A		(+)-7-(3,5-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.2683

32B		(-)-7-(3,5-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	>10
33		7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)	0.0727
33A		(+)-7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.0521
33B		(-)-7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	1.2545
34		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)	0.0841
34A		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.0269

34B		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.3492
35		8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine (racemic)	0.1768
35A		(+)-8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.1808
35B		(-)-8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	1.2894
36		N-(1-(6-methoxypyrimidin-4-yl)piperidin-4-yl)-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	2.5659
37A		(+)-7-benzyl-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.2583
37B		(-)-7-benzyl-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	1.9748

38A		(+)-7-(3,5-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.1122
38B		(-)-7-(3,5-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	2.4225
39A		(+)-7-(4-fluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.2415
39B		(-)-7-(4-fluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	7.4673
40A		(+)-7-benzyl-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.1134
40B		(-)-7-benzyl-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	3.1979
41A		(+)-7-(4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.0661

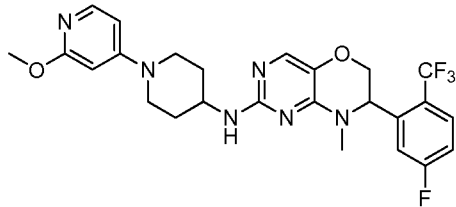
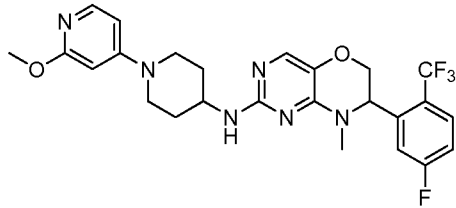
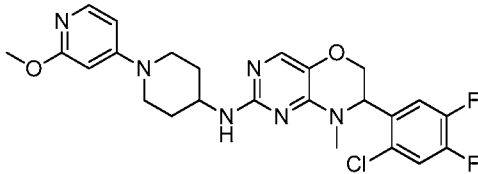
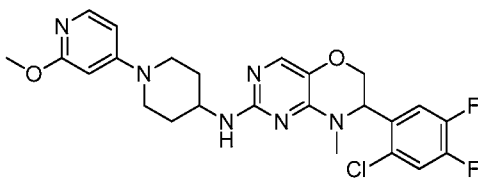
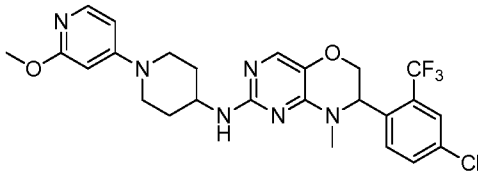
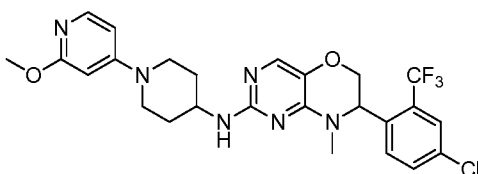
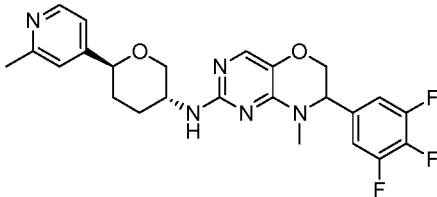
41B		(-)-7-(4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	1.2097
42A		(+)-8-methyl-7-(o-tolyl)-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.2051
42B		(-)-8-methyl-7-(o-tolyl)-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	1.7502
43A		(+)-7-(4-fluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.122
43B		(-)-7-(4-fluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	5.7283
44A		(-)-7-(2, 4-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.9716
44B		(+)-7-(2, 4-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.0775

45A		(+)-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.067
45B		(-)-8-methyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	1.2917
46A		(-)-7-(2,4-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	>10
46B		(+)-7-(2,4-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.1537
47A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2-(trifluoromethoxy)phenyl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.5375
47B		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2-(trifluoromethoxy)phenyl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.3564
48A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2-(trifluoromethyl)phenyl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.2224

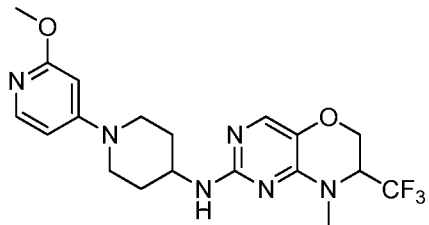
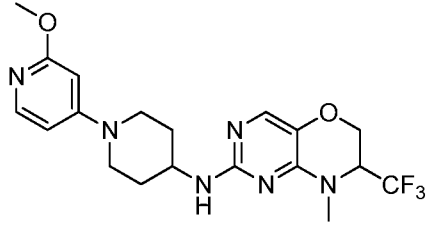
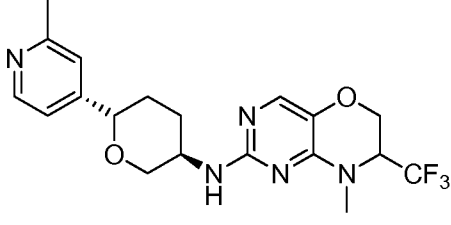
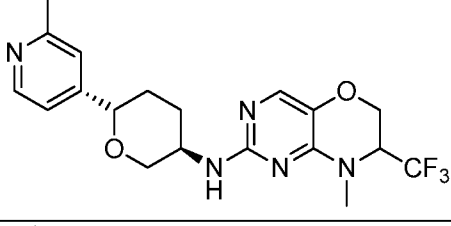
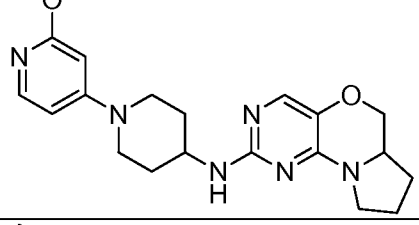
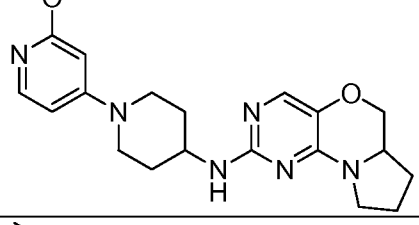
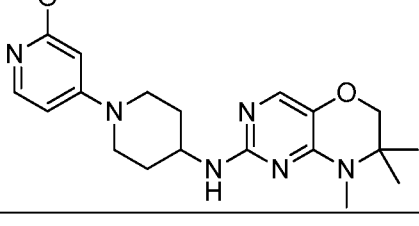
48B		(+)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethyl) phenyl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.1985
49A		(-)-7-(2, 4-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	>10
49B		(+)-7-(2, 4-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7,8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine	0.1153
60A		(+)-7-benzyl-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.0241
60B		(-)-7-benzyl-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.1488
61A		(-)-7-(2-chlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.7707
61B		(+)-7-(2-chlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.0912

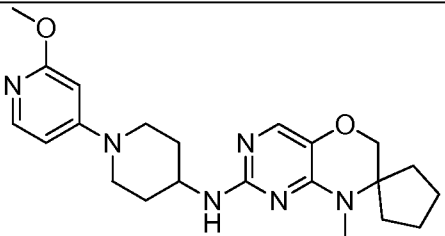
62A		(-)-7-(2,4-dichlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	>1
62B		(+)-7-(2,4-dichlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.030
63A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	>1
63B		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.0202
64A		(-)-7-(2-chloro-4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.3182
64B		(+)-7-(2-chloro-4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.0811
65A		(-)-7-(4-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.6997

65B		(+)-7-(4-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.1913
66A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(tetrahydro-2H-pyran-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	3.1057
66B		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(tetrahydro-2H-pyran-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.9774
67A		(-)-7-(5-chloro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.4001
67B		(+)-7-(5-chloro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.0916
68A		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-7,8-dimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.677
68B		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-7,8-dimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	1.144

69A		(-)-7-(5-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.4235
69B		(+)-7-(5-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.0884
70A		(-)-7-(2-chloro-4,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	>3
70B		(+)-7-(2-chloro-4,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.051
71A		(-)-7-(4-chloro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.8807
71B		(+)-7-(4-chloro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.3655
72A		(+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.0266

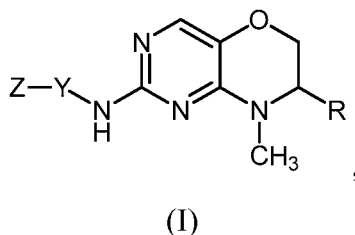
72B		(-)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.5799
73A		(+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.1266
73B		(-)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.7534
74A		(+)-7-(3,5-difluorophenyl)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.0477
74B		(-)-7-(3,5-difluorophenyl)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.8427
75A		(+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.0435
75B		(-)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.1892

76A		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.0708
76B		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	2.3428
77A		(-)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.1375
77B		(+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(trifluoromethyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	0.6552
82A		(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine	0.8656
82B		(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-6a,7,8,9-tetrahydro-6H-pyrimido[5,4-b]pyrrolo[1,2-d][1,4]oxazin-2-amine	0.615
83		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-7,7,8-trimethyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine	1.1539

84		N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8'-methyl-6',8'-dihydrospiro[cyclopentane-1,7'-pyrimido[5,4-b][1,4]oxazin]-2'-amine	1.0816
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We claim:

1. A compound of Formula (I)



or a pharmaceutically acceptable salt thereof,

wherein:

R is phenyl, C₁-C₄ alkylene-phenyl, -C₁-C₆ alkyl or 3- to 7-membered monocyclic heterocycle, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -NH₂, -C₁-C₄ alkyl, halo-substituted C₁-C₄ alkyl, amino-substituted C₁-C₄ alkyl, -NH-C₁-C₄ alkyl, -NHC(O)-C₁-C₄ alkyl, -N(C₁-C₄ alkyl)(C(O)(C₁-C₄ alkyl)), -C(O)NH-C₁-C₄ alkyl, -C(O)N(C₁-C₄ alkyl)₂, hydroxy-substituted C₁-C₄ alkyl, -S(O)₂-C₁-C₄ alkyl, -S(O)₂-halo-substituted C₁-C₄ alkyl, -S(O)₂-NH-C₁-C₄ alkyl, -S(O)₂-N(C₁-C₄ alkyl)₂, -NH-S(O)₂-C₁-C₄ alkyl, -N(C₁-C₄ alkyl)-S(O)₂-C₁-C₄ alkyl, -C₁-C₄ alkoxy, halo-substituted C₁-C₄ alkoxy, 3- to 7-membered monocyclic heterocycle, C₃-C₈ monocyclic cycloalkyl and -C(O)NH₂;

Y is 4- to 6- membered nonaromatic heterocycle, which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -C₁-C₄ alkoxy, halo-substituted C₁-C₄ alkoxy, -C₁-C₄ alkyl, halo-substituted C₁-C₄ alkyl, amino-substituted C₁-C₄ alkoxy, (C₁-C₄ alkyl)₂N-C₁-C₄ alkoxy, -NH-C₁-C₄ alkyl, -CN, -OH and -NH₂; and

Z is nitrogen-containing 5- to 6-membered aromatic monocyclic heterocycle which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -NH₂, -OH, -C₁-C₄ alkyl, -C₁-C₄ alkoxy, halo-substituted C₁-C₄ alkyl, C₁-C₄ alkoxy, halo-substituted C₁-C₄ alkoxy and 3- to 7-membered monocyclic heterocycle.

2. A compound of claim 1, wherein R is phenyl or C₁-C₄ alkylene-phenyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -NH₂, -C₁-C₄ alkyl, halo-substituted C₁-C₄ alkyl, amino-substituted C₁-C₄ alkyl, -NH-C₁-C₄ alkyl, -NHC(O)-C₁-C₄ alkyl, -N(C₁-C₄ alkyl)(C(O)(C₁-C₄ alkyl)), -C(O)NH-C₁-C₄ alkyl, -C(O)N(C₁-C₄ alkyl)₂, hydroxy-substituted C₁-C₄ alkyl, -S(O)₂-C₁-C₄ alkyl, -S(O)₂-halo-substituted C₁-C₄ alkyl, -S(O)₂-NH-C₁-C₄ alkyl, -S(O)₂-N(C₁-C₄ alkyl)₂, -NH-S(O)₂-C₁-C₄ alkyl, -N(C₁-C₄ alkyl)-S(O)₂-C₁-C₄ alkyl, -C₁-C₄ alkoxy, halo-substituted C₁-C₄ alkoxy, 3- to 7-membered monocyclic heterocycle, C₃-C₈ monocyclic cycloalkyl and -C(O)NH₂; or a pharmaceutically acceptable salt thereof.

3. The compound of any one of claims 1-2, wherein R is phenyl or C₁-C₄ alkylene-phenyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -C₁-C₄ alkyl, -C₁-C₄ alkoxy, halo-substituted C₁-C₄ alkyl and halo-substituted C₁-C₄ alkoxy; or a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1-3, wherein Y is piperidinyl or azetidiny, each of which is unsubstituted; or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1-4, wherein Z is pyridinyl or pyrimidinyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of -C₁-C₄ alkyl, halo-substituted C₁-C₄ alkyl and -C₁-C₄ alkoxy; or a pharmaceutically acceptable salt thereof.

6. The compound of any one of claims 1-5, wherein:
R is phenyl or C₁-C₄ alkylene-phenyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen or -C₁-C₄ alkyl;

Y is piperidinyl; and

Z is pyridinyl or pyrimidinyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of -C₁-C₄ alkyl, halo-substituted C₁-C₄ alkyl and -C₁-C₄ alkoxy;

or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1-6, wherein:

R is phenyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen and -C₁-C₄ alkyl; and

Z is pyridinyl which is unsubstituted or substituted with -C₁-C₄ alkoxy;

or a pharmaceutically acceptable salt thereof.

8. The compound of any one of claims 1-7, wherein R is phenyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen and -C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof.

9. The compound of any one of claims 1-8, wherein R is phenyl which is unsubstituted; or a pharmaceutically acceptable salt thereof.

10. The compound of any one of claims 1-8, wherein R is phenyl substituted with two or three -F; or a pharmaceutically acceptable salt thereof.

11. The compound of any one of claims 1-10, wherein each -C₁-C₄ alkyl is methyl and each C₁-C₄ alkylene is methylene; or a pharmaceutically acceptable salt thereof.

12. The compound of any one of claims 1-8 and 10-11, wherein R is phenyl substituted with one methyl; or a pharmaceutically acceptable salt thereof.

13. The compound of any one of claims 1-12, wherein Y is piperidinyl; or a pharmaceutically acceptable salt thereof.

14. The compound of any one of claims 1-12, wherein Y is azetidiny; or a pharmaceutically acceptable salt thereof.
15. The compound of any one of claims 1-14, wherein Z is pyridinyl or pyrimidinyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of -C₁-C₄ alkyl, -CF₃ and -C₁-C₄ alkoxy; or a pharmaceutically acceptable salt thereof.
16. The compound of any one of claims 1-15, wherein Z is pyridinyl substituted with one -CF₃; or a pharmaceutically acceptable salt thereof.
17. The compound of any one of claims 1-15, wherein Z is pyridinyl substituted with one methyl; or a pharmaceutically acceptable salt thereof.
18. The compound of any one of claims 1-15, wherein Z is pyridinyl substituted with one methoxy; or a pharmaceutically acceptable salt thereof.
19. The compound of any one of claims 1-15, wherein Z is pyrimidinyl which is unsubstituted or substituted with one to three -C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof.
20. The compound of any one of claims 1-15 and 19, wherein Z is pyrimidinyl substituted with one methyl; or a pharmaceutically acceptable salt thereof.
21. A compound selected from the group consisting of:

N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-8-methyl-N-(1-(6-methylpyrimidin-4-yl)piperidin-4-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(-)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-8-methyl-7-phenyl-N-(1-(2-(trifluoromethyl)pyridin-4-yl)piperidin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-benzyl-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(+)-7-(3, 5-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(+)-7-(4-fluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(+)-7-benzyl-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(+)-7-(4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(+)-8-methyl-7-(o-tolyl)-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(+)-7-(4-fluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(+)-7-(2, 4-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(+)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(+)-7-(2, 4-difluorophenyl)-8-methyl-N-(1-(6-methylpyrimidin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(-)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethoxy) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(+)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7-(2-(trifluoromethoxy) phenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine; and

(+)-7-(2, 4-difluorophenyl)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(+)-7-benzyl-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(-)-7-benzyl-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(2-chlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(2,4-dichlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(2-chloro-4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(4-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(5-chloro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(5-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(2-chloro-4,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(o-tolyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(3,5-difluorophenyl)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(-)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

or a pharmaceutically acceptable salt thereof.

22. The compound of claim 21 selected from the group consisting of:

7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(3,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(+)-7-(2, 4-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl) piperidin-4-yl)-8-methyl-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine; and

(+)-8-methyl-N-(1-(2-(trifluoromethyl) pyridin-4-yl) piperidin-4-yl)-7-(3, 4, 5-trifluorophenyl)-7, 8-dihydro-6H-pyrimido [5, 4-b] [1, 4] oxazin-2-amine;

(+)-7-benzyl-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(2-chlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(2,4-dichlorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(2-chloro-4-fluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(5-fluoro-2-(trifluoromethyl)phenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(2-chloro-4,5-difluorophenyl)-N-(1-(2-methoxypyridin-4-yl)piperidin-4-yl)-8-methyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(3,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-7-(3,5-difluorophenyl)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

(+)-8-methyl-N-((3R,6S)-6-(2-methylpyridin-4-yl)tetrahydro-2H-pyran-3-yl)-7-(2,4,5-trifluorophenyl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-2-amine;

or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or vehicle and an effective amount of a compound or a pharmaceutically acceptable salt of a compound of any one of claims 1-22.

24. A method for treating a neurodegenerative disease, comprising administering to a subject in need thereof an effective amount of a compound or a pharmaceutically acceptable salt of a compound of any one of claims 1-22.

25. The method of claim 24, wherein the neurodegenerative disease is panic disorder, obsessive compulsive disorder, delusional disorder, drug-induced psychosis, post-traumatic stress disorder, age-related cognitive decline, attention deficit/hyperactivity disorder, personality disorder of the paranoid type, personality disorder of the schizoid type, dyskinesia, choreiform condition, psychosis associated with Parkinson's disease, psychotic symptoms associated with Alzheimer's disease, mood disorder, or dementia.

26. A method for treating Alzheimer's disease, comprising administering to a subject in need thereof an effective amount of a compound or a pharmaceutically acceptable salt of a compound of any one of claims 1-22.

27. A method for improving an impaired cognitive function, comprising administering to a subject having impaired cognitive function an effective amount of a compound or a pharmaceutically acceptable salt of a compound of any one of claims 1-22.

28. A method for ameliorating a symptom of Alzheimer's disease, comprising administering to a subject in need thereof an effective amount of a compound or a pharmaceutically acceptable salt of a compound of any one of claims 1-22.
29. The method of any one of claims 26 and 28, wherein Alzheimer's disease is early onset Alzheimer's disease.
30. The method of any one of claims 24-29, wherein the subject is a human.
31. The method of claim 28, wherein the symptom is progressive loss of memory, progressive loss of cognition, progressive loss of reasoning and/or progressive loss of judgment.
32. The method of claim 27, wherein the cognitive function impaired is one or more of attention, learning, delayed memory, working memory, visual learning, speed of processing, vigilance, verbal learning, visual motor function, social cognition, long term memory or executive function.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/20114

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/5383; A61P 25/28; C07D 498/04 (2015.01)

CPC - A61K 31/5383; C07D 498/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A61K 31/5383; A61P 25/28; C07D 498/04 (2015.01)

CPC: A61K 31/5383; C07D 498/04 USPC: 514/275; 544/105, 116

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PATSEER (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); ProQuest; Google Scholar; IP.com; EBSCO; SureChem; KEYWORDS: pyrimido oxazin*, gamma secretase modulat*, pyrimido 5 4 b 1 4 oxazin*, 7 8 dihydro 6H, pyridin 4 yl, pyrimidin 4 yl, piperidin 4 yl, oxazin 2 amine, treat*, neurodegenerative disease*, Alzheimer*, amyloid beta modulat*, dementia

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0298359 A1 (HUANG, X et al.) 25 November 2010; paragraphs [0035], [0037]-[0038], [0419], [0515], [0524], [0661]	1-2, 3/1-2, 21-22
Y	US 2011/0201605 A1 (BAUMANN, K et al.) 18 August 2011; paragraphs [0005], [0036], [1183]	1-2, 3/1-2, 21-22
Y	RICHTER, L et al., Amyloid beta 42 peptide (Abeta42)-lowering compounds directly bind to Abeta and interfere with amyloid precursor protein (APP) transmembrane dimerization, PNAS 107(33), pages 14597-14602, 2010; [retrieved on 2015-05-09]. Retrieved from the Internet: <URL: http://www.pnas.org/content/107/33/14597.full.pdf > <DOI: 10.1073/pnas.1003026107>; abstract; page 14599, column 2, paragraph 2; page 14600, column 1, paragraph 1 - column 2, paragraph 1	1-2, 3/1-2, 21-22

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

11 May 2015 (11.05.2015)

Date of mailing of the international search report

17 JUN 2015

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

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PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US15/20114

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 4-20 and 23-32
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.