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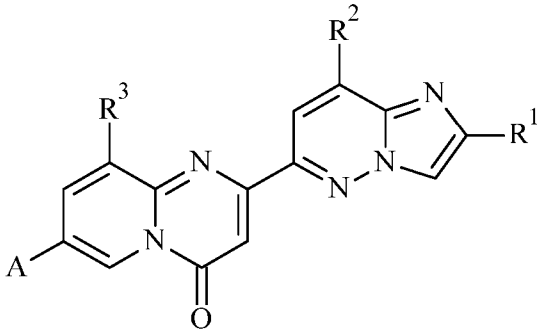
(54) Title: COMPOUNDS FOR TREATING AMYOTROPHIC LATERAL SCLEROSIS



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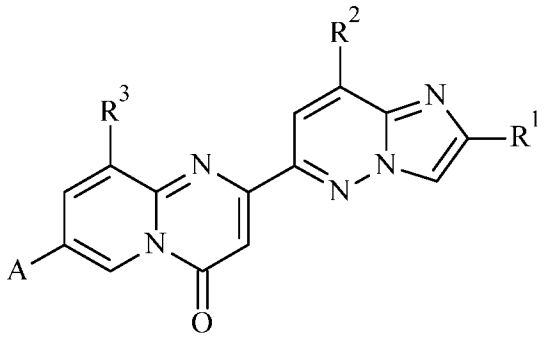
(57) Abstract: The present invention provides compounds of formula (I) (I) wherein A, R^1, R^2 and R^3 are as described herein, as well as pharmaceutically acceptable salts thereof for use in the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS). Further the present invention is concerned with the manufacture of the compounds of formula (I), pharmaceutical compositions comprising them and their use as medicaments.

Compounds for treating amyotrophic lateral sclerosis

Introduction

The present invention provides compounds which are SMN2 gene splicing modulators for use in the treatment, prevention and/or delay of progression of neuromuscular disorders, in particular of amyotrophic lateral sclerosis (ALS), their manufacture and pharmaceutical compositions comprising them.

In particular, the present invention relates to compounds of formula (I)



(I)

wherein A, R^1, R^2 and R^3 are as described herein, and pharmaceutically acceptable salts thereof, for use in the treatment, prevention and/or delay of amyotrophic lateral sclerosis (ALS).

Background

Neuromuscular disorders cover a range of conditions including neuropathies (either acquired or inherited), muscular dystrophies, ALS, spinal muscular atrophy (SMA), as well as a range of very rare muscle disorders. Neuromuscular disorders affect the nerves that control voluntary muscles or muscle homeostasis. When the neurons become unhealthy or die, communication between the nervous system and muscles breaks down. As a result, muscles weaken and waste away. The weakness can lead to twitching, cramps, aches and pains, and joint and movement problems. Sometimes it also affects heart function and your ability to breathe. There are many causes of progressive muscle weakness, which can strike any time from infancy through adulthood.

Muscular dystrophy (MD) is a subgroup of neuromuscular disorders. MD represents a family of inherited diseases of the muscles. Some forms affect children (e.g., Duchenne dystrophy) and are lethal within two to three decades. Other forms present in adult life and are more slowly progressive, such as facioscapulohumeral dystrophy (FSHD). The genes for several

dystrophies have been identified, including Duchenne dystrophy (caused by mutations in the dystrophin gene) and the teenage and adult onset Miyoshi dystrophy or its variant, limb girdle dystrophy 2B or LGMD-2B (caused by mutations in the dysferlin gene). These are "loss of function" mutations that prevent expression of the relevant protein in muscle and thereby cause muscle dysfunction. Mouse models for these mutations exist, either arising spontaneously in nature or generated by inactivation or deletion of the relevant genes. These models are useful for testing therapies that might replace the missing protein in muscle and restore normal muscle function.

Neuromuscular disorders also include motor neuron diseases (MND) which belong to a group of neurological disorders attributed to the destruction of motor neurons of the central nervous system and degenerative changes in the motor neuron pathway down to muscular atrophy and degeneration, and are different from other neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, olivopontocerebellar atrophy, etc., which are caused by the destruction of neurons other than motor neurons. The National Institute of Neurological Diseases and Stroke (NINDS) calls motor neuron diseases (MNDs) progressive, degenerative disorders that affect nerves in the upper or lower parts of the body. Some are inherited, according to NINDS. Generally, MNDs strike in middle age. Symptoms may include difficulty swallowing, limb weakness, slurred speech, impaired gait, facial weakness and muscle cramps. Respiration may be affected in the later stages of these diseases. The cause(s) of most MNDs are not known, but environmental, toxic, viral or genetic factors are all suspects. Forms of MND include adult onset Spinal Muscular Atrophy (SMA), Amyotrophic Lateral Sclerosis (ALS) which is also known as Lou Gehrig's Disease, Infantile Progressive Spinal Muscular Atrophy (SMA1) which is also known as SMA Type 1 or Werdnig-Hoffman, Intermediate Spinal Muscular Atrophy (SMA2) which is also known as SMA Type 2, Juvenile Spinal Muscular Atrophy (SMA3) which is also known as SMA Type 3 or Kugelberg-Welander, Spinal Bulbar Muscular Atrophy (SBMA) which is also known as Kennedy's Disease or X-linked SBMA. Motor neuron diseases are disorders in which motor neurons degenerate and die. Motor neurons, including upper motor neurons and lower motor neurons, affect voluntary muscles, stimulating them to contract. Upper motor neurons originate in the cerebral cortex and send fibers through the brainstem and the spinal cord, and are involved in controlling lower motor neurons. Lower motor neurons are located in the brainstem and the spinal cord and send fibers out to muscles. Lower motor neuron diseases are diseases involving lower motor neuron degeneration. When a lower motor neuron degenerates, the muscle fibers it normally activates become disconnected and do not contract, causing muscle weakness and diminished reflexes. Loss of either type of neurons results in weakness, muscle atrophy (wasting) and painless weakness are the clinical hallmarks of MND.

ALS is a fatal motor neuron disease characterized by the selective and progressive loss of motor neurons in the spinal cord, brainstem and cerebral cortex. It typically leads to progressive

muscle weakness and neuromuscular respiratory failure. Approximately 2% of ALS are associated with point mutations in the gene coding for the Cu/Zn superoxide dismutase-1 enzyme (SOD1). The discovery of this primary genetic cause of ALS has provided a basis for testing various therapeutic possibilities. The potent neuroprotective activities of neurotrophic factors (NTFs), ranging from prevention of neuronal atrophy, axonal degeneration and cell death, generated a great deal of hope for the treatment of ALS in the early 90s. Ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1) have already been evaluated in ALS patients. The rationale for testing these factors in ALS patients was based on their trophic and antiapoptotic effects on naturally occurring cell death paradigms during development of in cultures of embryonic motoneurons, traumatic nerve injury or in animal models resembling ALS such as pmn or wobbler mice. Undesirable side effects and limited bioavailability have complicated the evaluation of their potential clinical benefits. A practical difficulty in applying neurotrophins is that these proteins all have a relatively short half life while the neurodegenerative diseases are chronic and require long term treatment.

Several publications have examined the relationship of SMN copy number and protein as a risk factor in Amyotrophic Lateral Sclerosis (ALS). Homozygous deletions or mutations in the SMN1 gene lead to Spinal Muscular Atrophy (SMA); and the severity of SMA is modulated by SMN2 copy number. There are several conceptual links between ALS and SMA. First, the two conditions share similar clinical features. They both result in muscle weakness and mobility impairment as a result of motor neuron loss. The conditions are both heterogeneous with a spectrum of severity and generally become progressively worse over time. Importantly, SMA patients with late adult onset are commonly misdiagnosed with ALS (*Sanderson, Kissel, Kolb et al., Muscle Nerve. 2015 Jul;52(1):83-7.*). Along with the shared clinical features, ALS and adult SMA have similar pathogenetic and morphological features that suggest a common pathogenesis of disease. The diseases are similar enough that many potential treatments have been tested in both ALS and SMA for efficacy. Thus there are several factors that connect SMA and ALS. Much attention has focused on determining SMN protein deficiency and SMN1 and SMN2 gene copy number in ALS patients.

A homozygous deletion or mutation of SMN1 is generally lethal (as has been examined in animal models). Humans have a gene called SMN2 which differs from SMN1 by one exonic nucleotide transition resulting in the mis-splicing of the gene; and, only low levels of full length, functional SMN protein can be produced from this gene. SMA results from a homozygous deletion/mutation for SMN1 and have at least one copy of the SMN2 gene. The number of copies of the SMN2 gene is generally seen as a modulator of the disease course in SMA. Mutations in the SMN1 gene and mis-splicing of the SMN2 gene result in low levels of functional SMN protein in people with SMA. As a result, SMA manifests in the loss of motor

neurons which ultimately results in muscle weakness and in severe cases, respiratory weakness, muscle paralysis and death. It is the most common genetic cause of death in infants and toddlers.

Amyotrophic Lateral Sclerosis is a degenerative disorder that also causes motor neuron loss resulting in the progressive weakening of muscle. There are multiple genes implicated in the pathogenesis of ALS, including genes that are highly associated with ALS such as SOD1, C9orf72, and TDP-43, for example. And there are several other risk factors known for ALS. It can present with lower motor neuron (LMN) signs and symptoms (muscle weakness, atrophy, fasciculation) as well as upper motor neuron (UMN) signs and symptoms (spasticity, hyperreflexia, abnormal gag reflex). Although the pathology of ALS occurs in the brain and spinal cord, the muscles are the end organ affected by nerve damage in the disease and, therefore, a clinically relevant measure of disease progression is muscle weakness and atrophy. Patients ultimately die from ALS due to the progressive wasting and paralysis of their muscles.

Along with shared clinical features, SMA and ALS share similar cellular morphologies. For example, one shared cellular feature of ALS and SMA is snRNP dysfunction. snRNPs are protein and snRNA that come together to form the SMN complex which in turn helps to form the splicesome. The splicesome is important for splicing various mRNAs in the cell. Various labs have looked at the levels of snRNAs and snRNPs involved in the SMN complex and found that they are reduced in ALS and SMA tissues (*Ishihara et al., Hum Mol Genet. 2013 Oct 15;22(20):4136-47.; Gerbino et al., Neurobiol Dis. 2013 Jul;55:120-8. ; Tsuiji et al., EMBO Mol Med. 2013 Feb;5(2):221-3; Sun et al., Nat Commun. 2015 Jan 27;6:6171.).* This suggests that perhaps snRNP assembly dependent upon SMN protein is dysfunctional in ALS.

In addition, there are other cellular features that point towards SMN dysfunction in ALS, similarly to what occurs in SMA. Gem depletion, a common feature in SMA, is also a feature in ALS. Gems are molecularly defined by the presence of SMN protein; gems also are indicated in creating splicesomes. Gem counts are lower in ALS fibroblast cells and also in the spinal motor neurons of sporadic ALS patients. This was also seen in some familial ALS mouse models (*Shan et al., Proc Natl Acad Sci U S A. 2010 Sep 14;107(37):16325-30, Yamazaki et al., Cell Rep. 2012 Oct 25;2(4):799-806., Tsuiji et al., EMBO Mol Med. 2013 Feb;5(2):221-3Ishihara et al., Hum Mol Genet. 2013 Oct 15;22(20):4136-47., Turner et al., Neurobiol Aging. 2014 Apr;35(4):906-15, Kariya et al., Hum Mol Genet. 2012 Aug 1;21(15):3421-34*).

Beyond shared morphological features of the disease, researchers have examined SMN levels in cellular and animal models of ALS with the most common genetic associations to determine if they were lower than in healthy wildtype controls. For example, SMN levels in two cell types with TDP-43-siRNA had SMN protein levels at less than half of control levels (*Ishihara et al., Hum Mol Genet. 2013 Oct 15;22(20):4136-47*In another study, where SMN

protein levels were examined at P30 and P120 of a SOD1-ALS model, results suggest that mutant SOD1 disrupts endogenous and transgenic SMN expression in the spinal cord of SOD1 mice (*Turner et al., Neurobiol Aging. 2014 Apr;35(4):906-15*In a second experiment in this study, SMN protein levels were examined at different ages of the SOD1 mice. At 120 days, where SOD1 animals become symptomatic, the SMN protein levels are below wildtype. When overexpressing SMN in the SOD1 mice by introducing the PrP-SMN transgenic model which has 8-9 copies of the SMN1 gene (2-3 fold of the normal endogenous levels), SMN was restored without any deleterious effects even though it is expressed more than wildtype. These data suggest that restoring SMN protein in ALS models has some beneficial effects and perhaps even over expression of SMN protein may have some more beneficial effects.

A recent study examined the overexpression of SMN protein in motor neurons, using a (DOX)-inducible lentivirus to express SMN, and then initiate cell death by withdrawing trophic factors. The overexpression of SMN protein in motor neurons lead to a dose-dependent increase in survival. These data suggest that overexpressing SMN above endogenous (normal physiological) levels could also promote survival in control motor neurons (*Muela et al.,NatMed in press*). This study also examined the SMN levels in SOD1-ALS iPSC-derived MNs together with a WT control line, with either a RFP control or with SMN dox-inducible lentivirus and treated the cells with 0.5ug/mL dox for 5 days (*Muela et al., NatMed in press*).

This study also demonstrated that overexpression of SMN protein in the ALS-SOD1 iPSC motor neuron model promotes survival (the SMN copy number of this model is unknown). In addition, a small molecule SMN2 splicing modifier (SMN-C3, *Naryshkin et al., Science (2014):345(6197):688-693*) was also tested in two iPSC-derived ALS models, using the SOD1-ALS iPS cell and a TDP43-47A iPS cell line. The SMN genotype is also unknown for these lines. SMN-C3 was able to increase SMN levels in a dose dependent manner up to 1.4 fold. Whether this translates into an improvement in survival in these cell lines was not tested. This is the first evidence where SMN2 splicing modifiers were tested in an ALS model. The proof-of-principle that SMN protein levels can increase with splicing modifiers has been shown with this study.

These previous data suggest that splicing modifiers can increase SMN protein in ALS-derived motor neurons. Moreover, increasing SMN protein in ALS models ameliorates the disease phenotype. For example, overexpression of SMN (8-9 copies of human SMN1) delayed the onset of disease from 78 to 84 days (pk body weight before wasting) and a 15% delay in the onset of motor deficits; however, it did not prolong lifespan (*Turner et al., Neurobiol Aging. 2014 Apr;35(4):906-15*. In addition, upregulated SMN protein levels in motor neurons conferred greater resistance to the degenerative effects of mutant SOD1-expressing astrocytes (*Kariya et al., Hum Mol Genet. 2012 Aug 1;21(15):3421-34*. Lastly, overexpressing the SMN protein in SOD1G86R mice (8 copies of SMN2 transgene expressing 2.5x as much as SOD1 mice) delayed

the loss of gems, and protected against the characteristic, aggressive loss of spinal motor neurons and delayed disease onset (*Kariya et al., Hum Mol Genet. 2012 Aug 1;21(15):3421-34*. These data suggest that an increase in SMN protein confers benefit on the ALS models.

Given the evidence that upregulation of SMN protein improves outcomes in both animal and cellular models of ALS, it is also of interest to examine whether ALS patients have lower baseline levels of SMN protein. Few studies have been published on SMN protein in ALS patients. Turner et al., evaluated 9 post-mortem spinal cords of patients with sporadic ALS and found the SMN protein levels by Western Blot analysis to be roughly half that of control samples (*Turner et al., Neurobiol Aging. 2014 Apr;35(4):906-15*. Another study found that SMN protein levels are reduced in two ALS patient spinal anterior horn cells with 2 copies of SMN1 and 1 copy of SMN2 (*Coovert et al., Hum. Mol. Genet. (1997) 6(6):1205-1214*) compared to control.

A final set of investigations are around whether ALS patients have an abnormal SMN1 or SMN2 copy numbers, such that it may result in lower levels of SMN protein. There have been several investigations into the possibility of SMN copy number as a risk factor for ALS. Recently, a meta-analysis was conducted in 2014 on eight separate studies which evaluated the frequency of SMN1 and SMN2 copy numbers on the consolidated ALS population of over 2000 ALS patients. From analyzing these combined results, they found that there was a higher frequency of abnormal number of SMN1 copy numbers either 1 or 3 in ALS patients than in controls. They did not find any difference in the frequency of SMN2 copy numbers (*Wang et al., J Neurol Sci. 2014 May 15;340(1-2):63-8.*. Given the heterogeneity of the disease, and multiple genes influencing ALS, it was of note that ALS patients had a higher frequency of abnormal SMN1 copy numbers.

Lastly, one study had the initiative to look at the combined genotype of SMN1 and SMN2 copy number; to examine whether ALS patients had a lower combined genotype than perhaps the general population and thus may produce lower levels of SMN protein. The calculations were based on a theoretical prediction formula equal to 1.0 times the SMN1 copy number plus 0.20 times the SMN2 copy number. Thus a value of 2.2 could equal 2 SMN1 copies and 1 copy of SMN2 (*Veldink et al., Neurology. 2005 Sep 27;65(6):820-5*. Interestingly, in this study of 242 ALS patients, 61% of ALS patients were predicted to have a lower combine copy number ≤ 2.2 based upon their genotype than in controls, 36% (n=175). This value was statistically different compared to controls suggesting that combined SMN1 and SMN2 gene copy number may be a risk factor in the disease.

The body of evidence from ALS models as well as tissue samples from ALS patients and genotype information suggest that SMN protein modulates the phenotype of ALS patients. The

proof-of-principle for SMN2 splicing modifiers has been shown and suggests that SMN protein levels can be increased (even though the SMN genotype is unknown for these studies).

Despite the progress made in understanding the genetic basis and pathophysiology of ALS, there remains a need to identify compounds that alter the course of amyotrophic lateral sclerosis.

Detailed description of the invention

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 to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The nomenclature used in this Application is based on IUPAC systematic nomenclature, unless indicated otherwise.

Any open valency appearing on a carbon, oxygen, sulfur or nitrogen atom in the structures herein indicates the presence of a hydrogen, unless indicated otherwise.

The definitions described herein apply irrespective of whether the terms in question appear alone or in combination. It is contemplated that the definitions described herein can be appended to form chemically-relevant combinations, such as e.g. “heterocycloalkylaryl”, “haloalkylheteroaryl”, “arylalkylheterocycloalkyl”, or “alkoxyalkyl”. The last member of the combination is the radical which is binding to the rest of the molecule. The other members of the combination are attached to the binding radical in reversed order in respect of the literal sequence, e.g. the combination amino-C_{1-7}-alkyl refers to a C_{1-7}-alkyl which is substituted by amino, or e.g. the combination arylalkylheterocycloalkyl refers to a heterocycloalkyl-radical which is substituted by an alkyl which is substituted by an aryl.

The term “moiety” refers to an atom or group of chemically bonded atoms that is attached to another atom or molecule by one or more chemical bonds thereby forming part of a molecule. For example, the variables A, R^1, R^2 and R^3 of formula (I) refer to moieties that are attached to the core structure of formula (I) by a covalent bond.

When indicating the number of substituents, the term "one or more" refers to the range from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

The term "optional" or "optionally" denotes that a subsequently described event or circumstance can but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

The term "substituent" denotes an atom or a group of atoms replacing a hydrogen atom on the parent molecule.

The term "substituted" denotes that a specified group bears one or more substituents. Where any group can carry multiple substituents and a variety of possible substituents is provided, the substituents are independently selected and need not to be the same. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents, independently chosen from the group of possible substituents. When indicating the number of substituents, the term "one or more" means from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

The terms "compound(s) of this invention" and "compound(s) of the present invention" refer to compounds as disclosed herein and stereoisomers, tautomers, solvates, and salts (e.g., pharmaceutically acceptable salts) thereof.
When the compounds of the invention are solids, it is understood by those skilled in the art that these compounds, and their solvates and salts, may exist in different solid forms, particularly different crystal forms, all of which are intended to be within the scope of the present invention and specified formulae.

The term "pharmaceutically acceptable salts" denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts.
The term "pharmaceutically acceptable acid addition salt" denotes those pharmaceutically acceptable salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, maloneic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid,

ethanesulfonic acid, p-toluenesulfonic acid, and salicyclic acid.

The term "pharmaceutically acceptable base addition salt" denotes those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, and polyamine resins.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The substituents attached to the chiral center under consideration are ranked in accordance with the Sequence Rule of Cahn, Ingold and Prelog. (Cahn et al. Angew. Chem. Inter. Edit. 1966, 5, 385; errata 511). The prefixes D and L or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or L designating that the compound is levorotatory. A compound prefixed with (+) or D is dextrorotatory.

The term "chiral center" denotes a carbon atom bonded to four nonidentical substituents. The term "chiral" denotes the ability of non-superimposability with the mirror image, while the term "achiral" refers to embodiments which are superimposable with their mirror image. Chiral molecules are optically active, i.e., they have the ability to rotate the plane of plane-polarized light.

Compounds of the present invention can have one or more chiral centers and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. Whenever a chiral center is present in a chemical structure, it is intended that all stereoisomers associated with that chiral center are encompassed by the present invention.

The terms "halo", "halogen", and "halide" are used interchangeably herein and denote fluoro, chloro, bromo, or iodo. One particular example of halogen is fluoro.

The term "alkyl" denotes a monovalent linear or branched saturated hydrocarbon group of 1 to 12 carbon atoms. In particular embodiments, alkyl has 1 to 7 carbon atoms, and in more particular embodiments 1 to 4 carbon atoms. Examples of alkyl include methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, or tert-butyl. Particular examples for alkyl are methyl and ethyl.

The term "haloalkyl" denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkyl include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, or trifluoromethyl and the like. The term "perhaloalkyl" denotes an alkyl group where all hydrogen atoms of the alkyl group have been replaced by the same or different halogen atoms.

The term "bicyclic ring system" denotes two rings which are fused to each other via a common single or double bond (annelated bicyclic ring system), via a sequence of three or more common atoms (bridged bicyclic ring system) or via a common single atom (spiro bicyclic ring system). Bicyclic ring systems can be saturated, partially unsaturated, unsaturated or aromatic. Bicyclic ring systems can comprise heteroatoms selected from N, O and S.

The term "cycloalkyl" denotes a saturated monocyclic or bicyclic hydrocarbon group of 3 to 10 ring carbon atoms. In particular embodiments cycloalkyl denotes a monovalent saturated monocyclic hydrocarbon group of 3 to 8 ring carbon atoms. Bicyclic means consisting of two saturated carbocycles having one or more carbon atoms in common. Particular cycloalkyl groups are monocyclic. Examples for monocyclic cycloalkyl are cyclopropyl, cyclobutanyl, cyclopentyl, cyclohexyl or cycloheptyl. Examples for bicyclic cycloalkyl are bicyclo[2.2.1]heptanyl, or bicyclo[2.2.2]octanyl. One particular example of cycloalkyl is cyclopropyl.

The term "heterocycloalkyl" denotes a saturated or partly unsaturated mono-, bi- or tricyclic ring system of 3 to 9 ring atoms, comprising 1, 2, or 3 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon. In particular embodiments, heterocycloalkyl is a monovalent saturated monocyclic ring system of 4 to 7 ring atoms, comprising 1, 2, or 3 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Examples for monocyclic saturated heterocycloalkyl are aziridinyl, oxiranyl, azetidinyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydro-thienyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholin-4-yl, azepanyl, diazepanyl, homopiperazinyl, or oxazepanyl. Examples for bicyclic saturated heterocycloalkyl are 8-aza-bicyclo[3.2.1]octyl, quinuclidinyl, 8-oxa-3-aza-bicyclo[3.2.1]octyl, 9-aza-bicyclo[3.3.1]nonyl, 3-oxa-9-aza-bicyclo[3.3.1]nonyl, or 3-thia-9-aza-bicyclo[3.3.1]nonyl. Examples of a partly unsaturated

heterocycloalkyl are dihydrofuryl, imidazolinyl, dihydro-oxazolyl, tetrahydro-pyridinyl, or dihydropyranyl. Particular examples of heterocycloalkyl are 1,4-diazepanyl, hexahydropyrrolo[1,2-a]pyrazinyl, piperidinyl, piperazinyl and pyrrolidinyl. More particular examples of heterocycloalkyl are hexahydropyrrolo[1,2-a]pyrazinyl and piperazinyl.

The term "N-heterocycloalkyl" denotes a heterocycloalkyl radical containing at least one nitrogen ring atom and where the point of attachment of the heterocycloalkyl radical to the rest of the molecule is through a nitrogen ring atom. Particular examples of N-heterocycloalkyl are 1,4-diazepanyl, hexahydropyrrolo[1,2-a]pyrazinyl, piperidinyl, piperazinyl and pyrrolidinyl. More particular examples of N-heterocycloalkyl are hexahydropyrrolo[1,2-a]pyrazinyl and piperazinyl.

The term "basicity" in reference to a compound is expressed herein by the negative decadic logarithm of the acidity constant of the conjugate acid (pKa = -log Ka). The larger the pKa of the conjugate acid, the stronger the base (pKa + pKb = 14). In this application, an atom or functional group is denoted "basic" if it is suitable to accept a proton and if the calculated pKa of its conjugate acid is at least 7, more particularly if the calculated pKa of its conjugate acid is at least 7.8, most particularly if the calculated pKa of its conjugate acid is at least 8. pKa values were calculated in-silico as described in F. Milletti et al., *J. Chem. Inf. Model (2007) 47:2172-2181.*

The term "alkylene" denotes a linear saturated divalent hydrocarbon group of 1 to 7 carbon atoms or a divalent branched saturated hydrocarbon group of 3 to 7 carbon atoms. Examples of alkylene groups include methylene, ethylene, propylene, 2-methylpropylene, butylene, 2-ethylbutylene, pentylene, hexylene. Particular examples for alkylene are ethylene, propylene, and butylene.

The term "amino" denotes a group of the formula -NR'R" wherein R' and R" are independently hydrogen, alkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl or as described herein. Alternatively, R' and R", together with the nitrogen to which they are attached, can form a heterocycloalkyl. The term "primary amino" denotes a group wherein both R' and R" are hydrogen. The term "secondary amino" denotes a group wherein R' is hydrogen and R" is a group other than hydrogen. The term "tertiary amino" denotes a group wherein both R' and R" are other than hydrogen. Particular secondary and tertiary amines are methylamine, ethylamine, propylamine, isopropylamine, phenylamine, benzylamine dimethylamine, diethylamine, dipropylamine and diisopropylamine.

The term "active pharmaceutical ingredient" (or "API") denotes the compound or molecule in a pharmaceutical composition that has a particular biological activity.

The terms "pharmaceutical composition" and "pharmaceutical formulation" (or "formulation") are used interchangeably and denote a mixture or solution comprising a therapeutically effective amount of an active pharmaceutical ingredient together with pharmaceutically acceptable excipients to be administered to a mammal, e.g., a human in need thereof.

The term "pharmaceutically acceptable" denotes an attribute of a material which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and is acceptable for veterinary as well as human pharmaceutical use.

The terms "pharmaceutically acceptable excipient", "pharmaceutically acceptable carrier" and "therapeutically inert excipient" can be used interchangeably and denote any pharmaceutically acceptable ingredient in a pharmaceutical composition having no therapeutic activity and being non-toxic to the subject administered, such as disintegrators, binders, fillers, solvents, buffers, tonicity agents, stabilizers, antioxidants, surfactants, carriers, diluents or lubricants used in formulating pharmaceutical products.

The terms "individual" or "subject" refer to a mammal. Mammals include, but are not limited to, domesticated animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats). In certain embodiments, the individual or subject is a human.

The term "therapeutically effective amount" denotes an amount of a compound or molecule of the present invention that, when administered to a subject, (i) treats or prevents the particular disease, condition or disorder, (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. The therapeutically effective amount will vary depending on the compound, the disease state being treated, the severity of the disease treated, the age and relative health of the subject, the route and form of administration, the judgement of the attending medical or veterinary practitioner, and other factors.

The terms "treating" or "treatment" of a disease state include inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, or relieving the disease state, i.e., causing temporary or permanent regression of the disease state or its clinical symptoms.

The term "spinal muscular atrophy" (or SMA) relates to a disease caused by an inactivating mutation or deletion in the SMN1 gene on both chromosomes, resulting in a loss of

SMN1 gene function.
Symptoms of SMA include muscle weakness, poor muscle tone, weak cry, weak cough, limpness or a tendency to flop, difficulty sucking or swallowing, difficulty breathing, accumulation of secretions in the lungs or throat, clenched fists with sweaty hand, flickering/vibrating of the tongue, head often tilted to one side, even when lying down, legs that tend to be weaker than the arms, legs frequently assuming a "frog legs" position, feeding difficulties, increased susceptibility to respiratory tract infections, bowel/bladder weakness, lower-than-normal weight, inability to sit without support, failure to walk, failure to crawl, and hypotonia, areflexia, and multiple congenital contractures (arthrogryposis) associated with loss of anterior hom cells.

The term "treating spinal muscular atrophy (SMA)" or "treatment of spinal muscular atrophy (SMA)" includes one or more of the following effects: (i) reduction or amelioration of the severity of SMA; (ii) delay of the onset of SMA; (iii) inhibition of the progression of SMA; (iv) reduction of hospitalization of a subject; (v) reduction of hospitalization length for a subject; (vi) increase of the survival of a subject; (vii) improvement of the quality of life of a subject; (viii) reduction of the number of symptoms associated with SMA; (ix) reduction of or amelioration of the severity of one or more symptoms associated with SMA; (x) reduction of the duration of a symptom associated with SMA; (xi) prevention of the recurrence of a symptom associated with SMA; (xii) inhibition of the development or onset of a symptom of SMA; and/or (xiii) inhibition of the progression of a symptom associated with SMA.
More particular, the term "treating SMA" denotes one or more of the following beneficial effects: (i) a reduction in the loss of muscle strength; (ii) an increase in muscle strength; (iii) a reduction in muscle atrophy; (iv) a reduction in the loss of motor function; (v) an increase in motor neurons; (vii) a reduction in the loss of motor neurons; (viii) protection of SMN deficient motor neurons from degeneration; (ix) an increase in motor function; (x) an increase in pulmonary function; and/or (xi) a reduction in the loss of pulmonary function.
In further detail, the term "treating SMA" refers to the functional ability or retention of the functional ability for a human infant or a human toddler to sit up unaided or for a human infant, a human toddler, a human child or a human adult to stand up unaided, to walk unaided, to run unaided, to breathe unaided, to turn during sleep unaided, or to swallow unaided.

The term "$EC_{1.5x}$ concentration for production of full length SMN2 minigene mRNA" (or "$EC_{1.5x}$ minigene") is defined as that concentration of test compound that is effective in increasing the amount of full length SMN2 minigene mRNA to a level 1.5-fold greater relative to that in vehicle-treated cells.

The term "$EC_{1.5x}$ concentration for SMN protein expression" (or "$EC_{1.5x}$ SMN protein") is defined as that concentration of test compound that is effective in producing 1.5 times the

amount of SMN protein in an SMA patient fibroblast cell compared to the amount produced from the vehicle control.

The term "neuromuscular disorders" encompasses diseases and ailments that either directly (via intrinsic muscle pathology) or indirectly (via nerve pathology) impair the functioning of muscle. Examples of neuromuscular disorders include but are not limited to:

- Motor Neuron Diseases like ALS (also known as Lou Gehrig's Disease), Spinal Muscular Atrophy Type 1 (SMA1, Werdnig-Hoffmann Disease), Spinal Muscular Atrophy Type 2 (SMA2), Spinal Muscular Atrophy Type 3 (SMA3, Kugelberg-Welander Disease), Spinal Bulbar Muscular Atrophy (SBMA, also known as Kennedy Disease and X-Linked SBMA),
- Muscular Dystrophies like Duchenne Muscular Dystrophy (DMD, also known as Pseudohypertrophic), Becker Muscular Dystrophy (BMD), Emery-Dreifuss Muscular Dystrophy (EDMD), Limb-Girdle Muscular Dystrophy (LGMD), Facioscapulohumeral Muscular Dystrophy (FSH or FSHD, also known as Landouzy-Dejerine), Myotonic Dystrophy (MMD, also known as Steinert Disease), Oculopharyngeal Muscular Dystrophy (OPMD), Distal Muscular Dystrophy (DD, Miyoshi), Congenital Muscular Dystrophy (CMD),
- Metabolic diseases of muscle like Phosphorylase Deficiency (MPD or PYGM, also known as McArdle Disease), Acid Maltase Deficiency (AMD, also known as Pompe Disease), Phosphofructokinase Deficiency (also known as Tarui Disease), Debrancher Enzyme Deficiency (DBD, also known as Cori or Forbes Disease), Mitochondrial Myopathy (MITO), Carnitine Deficiency (CD), Carnitine Palmityl Transferase Deficiency (CPT), Phosphoglycerate Kinase Deficiency, Phosphoglycerate Mutase Deficiency, Lactate Dehydrogenase Deficiency, Myoadenylate Deaminase Deficiency ne Palmityl Transferase Deficiency (CPT), Phosphoglycerate Kinase Deficiency, Phosphoglycerate Mutase Deficiency , Lactate Dehydrogenase Deficiency, Myoadenylate Deaminase Deficiency;
- Diseases of peripheral nerve like Charcot-Marie-Tooth Disease (CMT, also known as Hereditary Motor and Sensory Neuropathy (HMSN) or Peroneal Muscular Atrophy (PMA), Friedreich's Ataxia (FA), Dejerine-Sottas Disease (DS),
- Inflammatory myopathies like Dermatomyositis (DM), Polymyositis (PM), Inclusion Body Myositis (IBM),
- Diseases of the neuromuscular junction like Myasthenia Gravis (MG), Lambert-Eaton Syndrome (LES), Congenital Myasthenic Syndrome (CMS),
- Myopathies due endocrine abnormalities like Hyperthyroid Myopathy (HYPTM), Hypothyroid Myopathy (HYPOTM)
- Other myopathies like Myotonia Congenita (MC, also Thomsen and Becker Disease), Paramyotonia Congenita (PC), Central Core Disease (CCD), Nemaline Myopathy (NM)

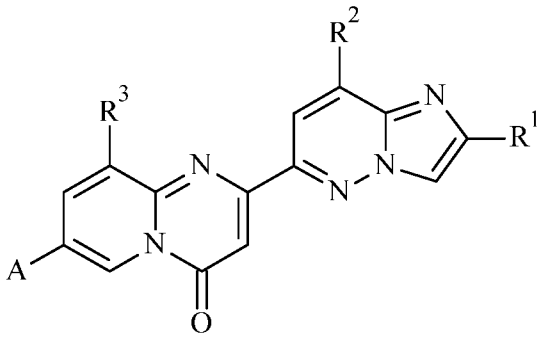
- Myotubular Myopathy/Centronuclear Myopathy (MTM or CNM), Periodic Paralysis (PP, two forms: Hypokalemic and Hyperkalemic).

By "MND" is meant a disease affecting a neuron with motor function, i. e. , a neuron that conveys motor impulses. Such neurons are also termed "motor neurons". These neurons include, without limitation, alpha neurons of the anterior spinal cord that give rise to the alpha fibers which innervate the skeletal muscle fibers; beta neurons of the anterior spinal cord that give rise to the beta fibers which innervate the extrafusal and intrafusal muscle fibers; gamma neurons of the anterior spinal cord that give rise to the gamma (fusimotor) fibers which innervate the intrafusal fibers of the muscle spindle; heteronymous neurons that supply muscles other than those from which afferent impulses originate; homonymous neurons that supply muscles from which afferent impulses originate; lower peripheral neurons whose cell bodies lie in the ventral gray columns of the spinal cord and whose terminations are in skeletal muscles; peripheral neurons that receive impulses from interneurons; and upper neurons in the cerebral cortex that conduct impulses from the motor cortex to motor nuclei of the cerebral nerves or to the ventral gray columns of the spinal cord.
Nonlimiting examples of motoneuron disorders include the various amyotrophies such as hereditary amyotrophies including hereditary spinal muscular atrophy, acute infantile spinal muscular atrophy such as Werdnig-Hoffman disease, progressive muscular atrophy in children such as the proximal, distal type and bulbar types, spinal muscular atrophy of adolescent or adult onset including the proximal, scapuloperoneal, facioscapulohumeral and distal types, amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS). Also included within the term is motoneuron injury.

The term "Amyotrophic Lateral Sclerosis" (or "ALS"), also called Lou Gehrig's disease, is a fatal disease affecting motor neurons of the cortex, brain stem and spinal cord. Although the etiology of the disease is unknown, one theory is that neuronal cell death in ALS is the result of over-excitement of neuronal cells due to excess extracellular glutamate. Glutamate is a neurotransmitter that is released by glutaminergic neurons, and is taken up into glial cells where it is converted into glutamine by the enzyme glutamine synthetase, glutamine then re-enters the neurons and is hydrolyzed by glutaminase to form glutamate, thus replenishing the neurotransmitter pool. In a normal spinal cord and brain stem, the level of extracellular glutamate is kept at low micromolar levels in the extracellular fluid because glial cells, which function in part to support neurons, use the excitatory amino acid transporter type 2 (EAAT2) protein to absorb glutamate immediately. A deficiency in the normal EAAT2 protein in patients with ALS, was identified as being important in the pathology of the disease. One explanation for the reduced levels of EAAT2 is that EAAT2 is spliced aberrantly. The aberrant splicing produces a splice variant with a deletion of 45 to 107 amino acids located in the C-terminal region of the EAAT2 protein. Due to the lack of, or defectiveness of EAAT2, extracellular glutamate

accumulates, causing neurons to fire continuously. The accumulation of glutamate has a toxic effect on neuronal cells because continual firing of the neurons leads to early cell death. Although a great deal is known about the pathology of ALS little is known about the pathogenesis of the sporadic form and about the causative properties of mutant SOD protein in familial ALS. Many models have been speculated, including glutamate toxicity, hypoxia, oxidative stress, protein aggregates, neurofilament and mitochondrial dysfunction. Presently, there is no cure for ALS, nor is there a therapy that has been proven effective to prevent or reverse the course of the disease. Several drugs have recently been approved by the Food and Drug Administration (FDA). To date, attempts to treat ALS have involved treating neuronal degeneration with long-chain fatty alcohols which have cytoprotective effects (See U.S. Pat. No. 5,135,956); or with a salt of pyruvic acid (See U.S. Pat. No. 5,395,822); and using a glutamine synthetase to block the glutamate cascade (See U.S. patent 5,906,976). For example, Riluzole, a glutamate release inhibitor, has been approved in the U.S. for the treatment of ALS, and appears to extend the life of at least some patients with ALS by three months. However, some reports have indicated that even though Riluzole therapy marginally prolongs survival time, it does not appear to provide any improvement of muscular strength in the patients. Therefore, the effect of Riluzole is limited in that the therapy does not modify the quality of life for the patient (Borras-Blasco etal. (1998) Rev. Neurol, 27: 1021-1027).

In detail, the present invention relates to compounds of formula (I)



(I)

wherein

R^1 is hydrogen or C_{1-7}-alkyl;

R^2 is hydrogen, cyano, C_{1-7}-alkyl, C_{1-7}-haloalkyl or C_{3-8}-cycloalkyl;

R^3 is hydrogen, C_{1-7}-alkyl, or C_{3-8}-cycloalkyl;

A is N-heterocycloalkyl or $NR^{12}R^{13}$, wherein N-heterocycloalkyl comprises 1 or 2 nitrogen ring atoms and is optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14};

R^{12} is heterocycloalkyl comprising 1 nitrogen ring atom, wherein heterocycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14};

R^{13} is hydrogen, C_{1-7}-alkyl or C_{3-8}-cycloalkyl;

R^{14} is independently selected from hydrogen, C_{1-7}-alkyl, amino, amino-C_{1-7}-alkyl, C_{3-8}-cycloalkyl and heterocycloalkyl or two R^{14} together form C_{1-7}-alkylene;

with the proviso that if A is N-heterocycloalkyl comprising only 1 nitrogen ring atom, then at least one R^{14} substituent is amino or amino-C_{1-7}-alkyl;

and pharmaceutically acceptable salts thereof

for use in the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS).

Particular embodiments of the present invention are compounds of formula (I) and pharmaceutically acceptable salts thereof for use in the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS).

Further, it is to be understood that every embodiment relating to a specific A, R^1, R^2 or R^3 as disclosed herein may be combined with any other embodiment relating to another A, R^1, R^2 or R^3 as disclosed herein.

A particular embodiment of the present invention relates to compounds of formula (I) wherein

R^1 is hydrogen or C_{1-7}-alkyl;

R^2 is hydrogen, cyano, C_{1-7}-alkyl, C_{1-7}-haloalkyl or C_{3-8}-cycloalkyl;

R^3 is hydrogen, C_{1-7}-alkyl, or C_{3-8}-cycloalkyl;

A is N-heterocycloalkyl comprising 1 or 2 nitrogen ring atoms, wherein N-heterocycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14};

R^{14} is independently selected from hydrogen, C_{1-7}-alkyl, amino, amino-C_{1-7}-alkyl, C_{3-8}-cycloalkyl and heterocycloalkyl or two R^{14} together form C_{1-7}-alkylene;

with the proviso that if A is N-heterocycloalkyl comprising only 1 nitrogen ring atom, then at least one R^{14} substituent is amino or amino-C_{1-7}-alkyl;

and pharmaceutically acceptable salts thereof,

for use in the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS).

In a particular embodiment of the present invention R^1 is C_{1-7}-alkyl, particularly methyl.

In a particular embodiment of the present invention R^2 is hydrogen or C_{1-7}-alkyl, particularly hydrogen or methyl.

In a particular embodiment of the present invention R^3 is hydrogen or C_{1-7}-alkyl, particularly hydrogen or methyl.

In a particular embodiment of the present invention R^{12} is piperidinyl optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14}.

In a particular embodiment of the present invention R^{13} is hydrogen or C_{1-7}-alkyl, particularly hydrogen or methyl.

In a particular embodiment of the present invention R^{14} is independently selected from C_{1-7}-alkyl and heterocycloalkyl or two R^{14} together form C_{1-7}-alkylene.

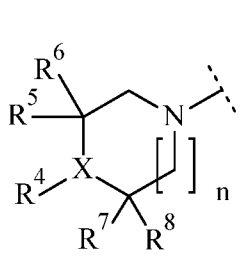
In a particular embodiment of the present invention R^{14} is independently selected from methyl, ethyl and pyrrolidinyl or two R^{14} together form ethylene.

In a particular embodiment of the present invention A is a saturated mono- or bicyclic N-heterocycloalkyl comprising 1 or 2 nitrogen atoms and is optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14}.

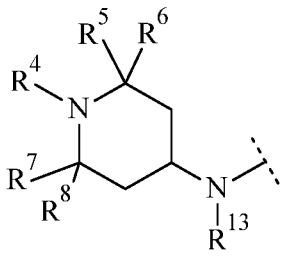
In a particular embodiment of the present invention the N-heterocycloalkyl in A or the heterocycloalkyl in R^{12} as defined herein are substituted with 1 or 2 substituents selected from R^{14}.

In a particular embodiment of the present invention the N-heterocycloalkyl in A as defined herein is further characterized in that one ring nitrogen atoms is basic.

In a particular embodiment of the present invention A is



or



, wherein

X is N or CH;

R^4 is hydrogen, C_{1-7}-alkyl or $-(CH_2)_m-NR^9R^{10}$;

R^5 is hydrogen or C_{1-7}-alkyl;

R^6 is hydrogen or C_{1-7}-alkyl;

R^7 is hydrogen or C_{1-7}-alkyl;

R^8 is hydrogen or C_{1-7}-alkyl;

R^9 and R^{10} are independently selected from hydrogen, C_{1-7}-alkyl and C_{3-8}-cycloalkyl;

R^{13} is hydrogen, C_{1-7}-alkyl or C_{3-8}-cycloalkyl;

n is 0, 1 or 2;

m is 0, 1, 2 or 3;

or R^4 and R^5 together form a C_{1-7}-alkylene;

or R^4 and R^7 together form a C_{1-7}-alkylene;

or R^5 and R^6 together form a C_{2-7}-alkylene;

or R^5 and R^7 together form a C_{1-7}-alkylene;

or R^5 and R^9 together form a C_{1-7}-alkylene;

or R^7 and R^8 together form a C_{2-7}-alkylene;

or R^7 and R^9 together form a C_{1-7}-alkylene;

or R^9 and R^{10} together form a C_{2-7}-alkylene;

with the proviso that if X is CH then R^4 is $-(CH_2)_m-NR^9R^{10}$; and

with the proviso that if X is N and R^4 is $-(CH_2)_m-NR^9R^{10}$ then m is 2 or 3.

It has been found that brain penetration is improved when at least one of R^4, R^5, R^6, R^7 and R^8 is not hydrogen.

In a particular embodiment of the invention at least one of R^4, R^5, R^6, R^7 and R^8 is other than hydrogen.

In a particular embodiment of the present invention X is N.

In a particular embodiment of the present invention n is 1.

In a particular embodiment of the present invention R^4 is hydrogen, methyl or $-(CH_2)_m-NR^9R^{10}$, more particularly hydrogen.

In a particular embodiment of the present invention R^5 is hydrogen, methyl or ethyl, more particularly methyl.

In a particular embodiment of the present invention R^6 is hydrogen or methyl, more particularly hydrogen.

In a particular embodiment of the present invention R^7 is hydrogen or methyl.

In a particular embodiment of the present invention R^8 is hydrogen.

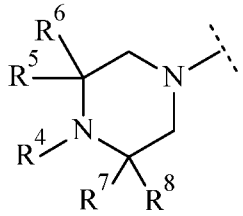
In a particular embodiment of the present invention m is 0.

In a particular embodiment of the present invention R^4 and R^5 together form propylene.

In a particular embodiment of the present invention R^5 and R^6 together form ethylene;

In a particular embodiment of the present invention R^9 and R^{10} together form butylene.

In a particular embodiment of the present invention A is selected from the group of:



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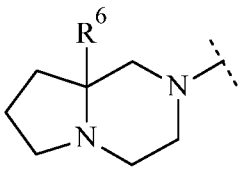

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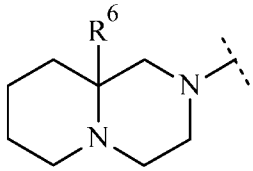

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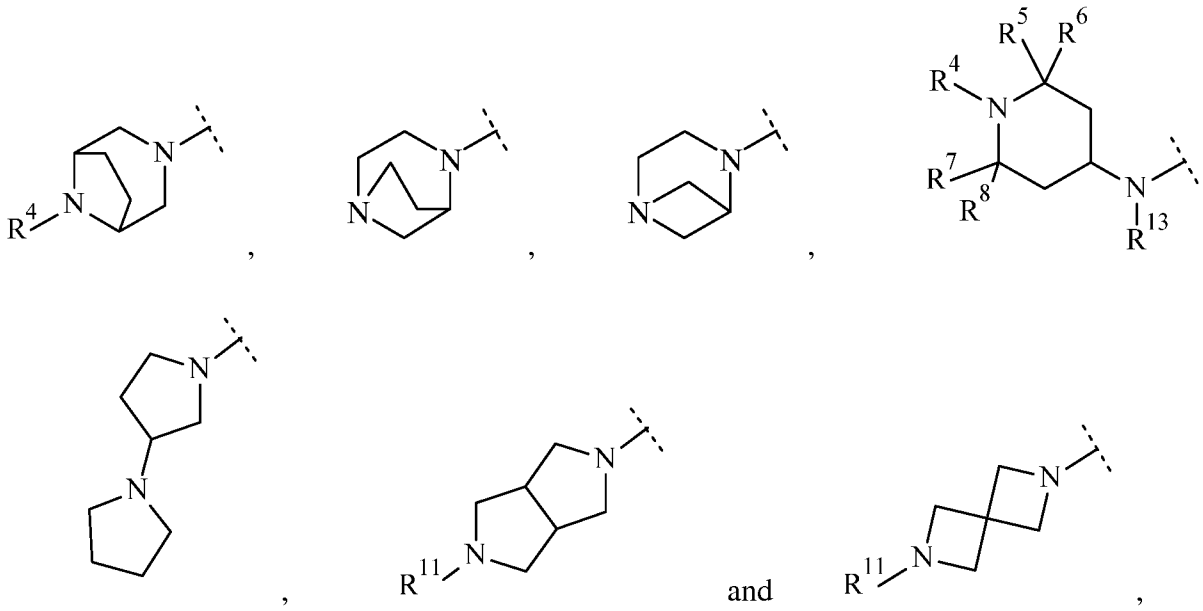


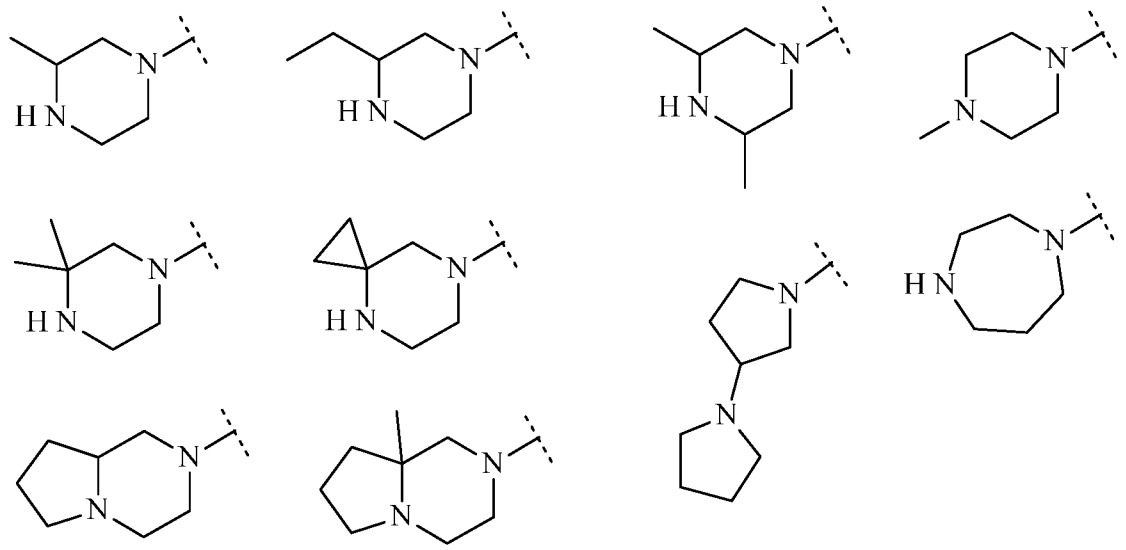
wherein R^4, R^5, R^6, R^7, R^8 and R^{13} are as defined herein and wherein R^{11} is hydrogen or C_{1-7}-alkyl.

In a particular embodiment of the present invention A is selected from the group of piperazinyl, diazepanyl, pyrrolidinyl and hexahydropyrrolo[1,2-a]pyrazinyl, each optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14} as defined herein.

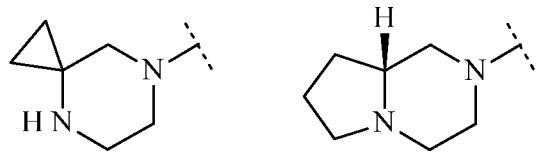
In a particular embodiment of the present invention A is selected from the group of piperazin-1-yl, 1,4-diazepan-1-yl, pyrrolidin-1-yl and hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, each optionally substituted with 1 or 2 substituents selected from R^{14} as defined herein.

In a particular embodiment of the present invention A is $NR^{12}R^{13}$, wherein R^{12} and R^{13} are as described herein.

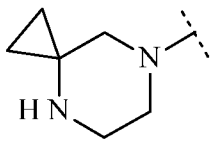
In a particular embodiment of the present invention A is selected from the group of:



In a particular embodiment of the present invention R^1 is methyl, R^2 is hydrogen or methyl, R^3 is hydrogen, and A is



In a particular embodiment of the present invention R^1 is methyl, R^2 is methyl, R^3 is hydrogen, and A is



Particular compounds of formula (I) of the present invention are those selected from the group consisting of:

2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-(4-methylpiperazin-1-yl)pyrido[1,2-a]pyrimidin-4-one;

7-[(8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;

7-[(8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;

7-[(8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;

7-[(8aS)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;

7-[(8aR)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;

2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S,5R)-3,5-dimethylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;

2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;

2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;

7-(1,4-diazepan-1-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;

2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;

2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;

7-(1,4-diazepan-1-yl)-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;

7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;

7-[(8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;

7-[(8aS)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;

7-[(8aR)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;

2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-pyrrolidin-1-ylpyrrolidin-1-yl]pyrido[1,2-a]pyrimidin-4-one;

7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-

a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-pyrrolidin-1-ylpyrrolidin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-(3,3-dimethylpiperazin-1-yl)pyrido[1,2-a]pyrimidin-4-one;
7-(3,3-dimethylpiperazin-1-yl)-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-9-methyl-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-9-methyl-7-[(3R)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-9-methyl-pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-(3,3-dimethylpiperazin-1-yl)-9-methyl-pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-9-methyl-pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S,5S)-3,5-dimethylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-pyrrolidin-1-ylpyrrolidin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-pyrrolidin-1-ylpyrrolidin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
7-[(3S,5S)-3,5-dimethylpiperazin-1-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-(3,3-dimethylpiperazin-1-yl)-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(3S,5S)-3,5-dimethylpiperazin-1-yl]-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-

yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(3R)-3-ethylpiperazin-1-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
and pharmaceutically acceptable salts thereof.

Particular compounds of formula (I) of the present invention are those selected from the group consisting of:
7-[(8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S,5R)-3,5-dimethylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-9-methyl-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-9-methyl-pyrido[1,2-a]pyrimidin-4-one;
7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
and pharmaceutically acceptable salts thereof.

A particular compound of formula (I) of the present invention is 7-[(8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one or pharmaceutically acceptable salts thereof.

A particular embodiment of the present invention relates to 7-[(8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-

a]pyrimidin-4-one or a pharmaceutically acceptable salt thereof for use in the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS).

A particular compound of formula (I) of the present invention is 7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one or pharmaceutically acceptable salts thereof.

A particular embodiment of the present invention relates to 7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one or a pharmaceutically acceptable salt thereof for use in the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS).

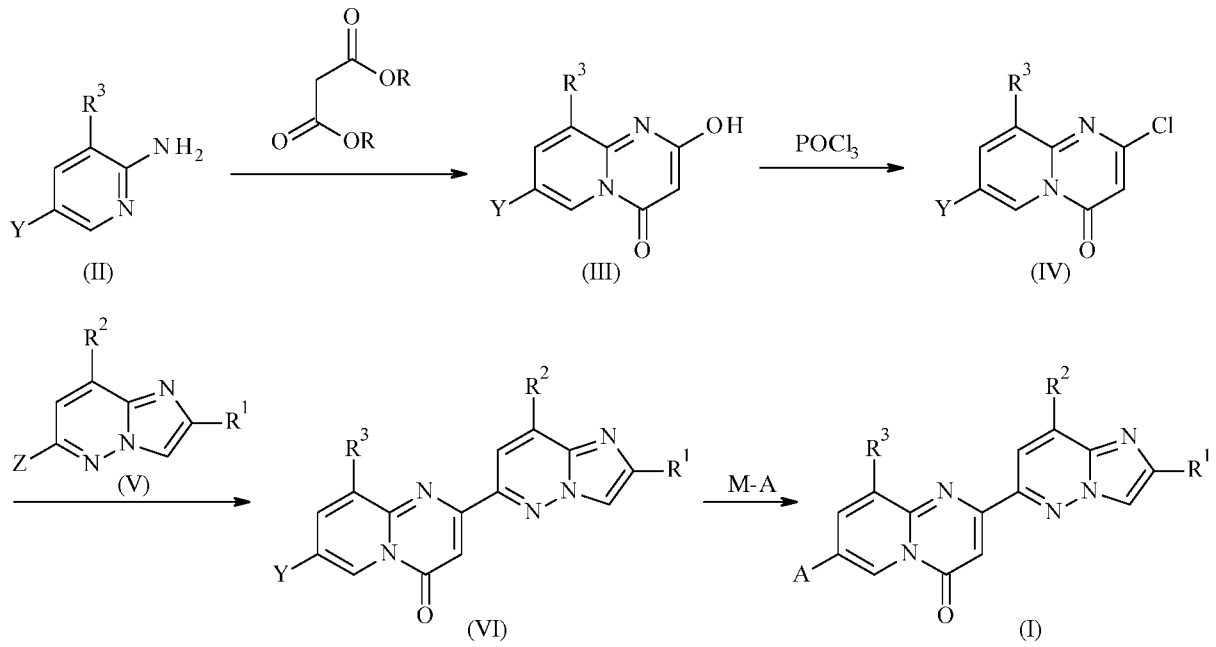
Manufacturing Processes

Compounds of formula (I) and pharmaceutically acceptable salts thereof as defined above can be prepared following standard methods known in the art.

As illustrated in Scheme 1, the commercially available amino-pyridine of formula (II) can be reacted with a malonic ester to afford the intermediate of formula (III), wherein Y and R^3 are as described herein and R is C_{1-2}-alkyl, particularly methyl. The compound of formula (III) is then treated with a chlorinating reagent (such as $POCl_3$ and the like) to provide a compound of formula (IV). The compound of formula (IV) is then reacted in a Suzuki cross-coupling reaction with a compound of formula (V), wherein R^1 and R^2 are as described herein and Z is $B(OH)_2$ or an C_{1-7}-alkyl boronic acid ester such as 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl, in the presence of a catalyst (such as (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride ($Pd(dppf)Cl_2$) and the like) and a base (such as K_2CO_3 and the like) in a suitable solvent (such as DMF and the like), to afford the compound of formula (VI). Finally, the compound of formula (VI) is reacted with a compound M-A either in:

a) an aromatic nucleophilic substitution reaction (particularly if Y is fluoro) by heating at a temperature from 80°C to 200°C; or
b) a Buchwald-Hartwig amination reaction in the presence of a palladium catalyst (e.g. tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) or bis(dibenzylideneacetone)palladium ($Pd(dba)_2$) by heating at a temperature from 20°C to 100°C;

in a solvent (e.g. dimethyl sulfoxide (DMSO), N-methylpyrrolidone (NMP), or dimethylformamide (DMF)) to give a compound of formula (I), wherein A is as defined herein, M is hydrogen, sodium or potassium, particularly hydrogen, and wherein M is linked to A via a nitrogen atom of A.



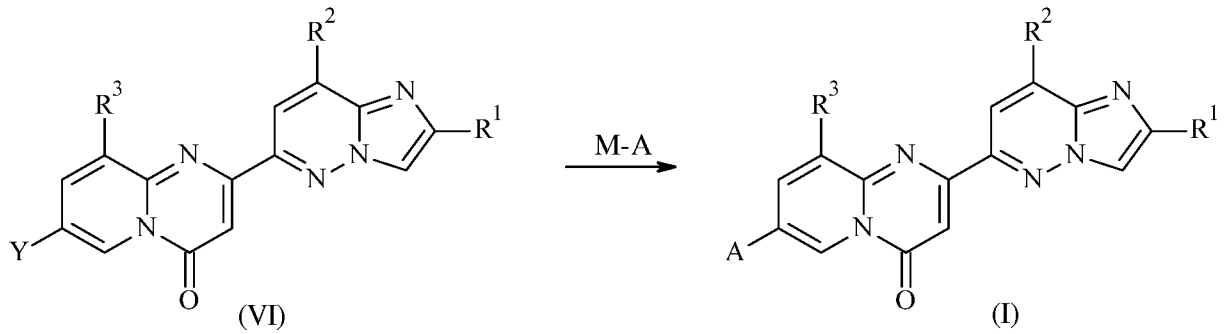
Scheme 1.

In one embodiment, the invention relates to a process for the manufacture of compounds of formula (I) and pharmaceutically acceptable salts thereof as defined above, comprising the reaction of a compound of formula (VI) with a compound M-A either in:

a) an aromatic nucleophilic substitution reaction (particularly if Y is fluoro) by heating at a temperature from 80°C to 200°C; or

b) a Buchwald-Hartwig amination reaction in the presence of a palladium catalyst (e.g. tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) or bis(dibenzylideneacetone)palladium $Pd(dba)_2$) by heating at a temperature from 20°C to 100°C;

in a solvent (e.g. dimethyl sulfoxide (DMSO), N-methylpyrrolidone (NMP), or dimethylformamide (DMF)), wherein A, Y, R^1, R^2 and R^3 are as defined herein, M is hydrogen, sodium or potassium, particularly hydrogen, and wherein M is linked to A via a nitrogen atom of A.



(VI) (I)

A particular embodiment of the invention relates to a process for the preparation of compounds of formula (I) and pharmaceutically acceptable salts thereof as defined above, comprising an aromatic nucleophilic substitution reaction between a compound of formula (VI) as described above with a compound of formula M-A by heating in a solvent, wherein A, R^1, R^2, R^3 and Y are as defined above, M is hydrogen, sodium or potassium, and wherein M is linked to A via a nitrogen atom of A.

A particular embodiment of the invention relates to a process for the preparation of compounds of formula (I) and pharmaceutically acceptable salts thereof as defined above, wherein the aromatic nucleophilic substitution reaction is performed at a temperature from 80°C to 200°C.

A particular embodiment of the invention relates to a process for the preparation of compounds of formula (I) and pharmaceutically acceptable salts thereof as defined above, wherein the solvent of the aromatic nucleophilic substitution reaction is selected from dimethyl sulfoxide (DMSO), N-methylpyrrolidone (NMP), and dimethylformamide (DMF).

A particular embodiment of the invention relates to a process for the preparation of compounds of formula (I) and pharmaceutically acceptable salts thereof as defined above, wherein M is hydrogen.

Particularly, compounds of formula (I) and pharmaceutically acceptable salts thereof can be prepared in accordance to the methods described in the examples herein.

Pharmaceutical Compositions

Another embodiment provides pharmaceutical compositions or medicaments comprising the compounds of the invention and a therapeutically inert carrier, diluent or pharmaceutically acceptable excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners.

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

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may comprise components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents, antioxidants, and further active agents. They can also comprise still other therapeutically valuable substances.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., *Ansel H.C. et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (2004) Lippincott, Williams & Wilkins, Philadelphia; Gennaro A.R. et al., Remington: The Science and Practice of Pharmacy (2000) Lippincott, Williams & Wilkins, Philadelphia; and Rowe R.C, Handbook of Pharmaceutical Excipients (2005) Pharmaceutical Press, Chicago*. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The dosage at which compounds of the invention can be administered can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.01 to 1000 mg per person of a compound of general formula (I) should be appropriate, although the above upper limit can also be exceeded when necessary.

An example of a suitable oral dosage form is a tablet comprising about 100 mg to 500 mg of the compound of the invention compounded with about 30 to 90 mg anhydrous lactose, about 5 to 40 mg sodium croscarmellose, about 5 to 30 mg polyvinylpyrrolidone (PVP) K30, and about 1 to 10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment.

An example of an aerosol formulation can be prepared by dissolving the compound, for example 10 to 100 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such as sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 μm filter, to remove impurities and contaminants.

Uses

As described above, the compounds of formula (I) and their pharmaceutically acceptable salts possess valuable pharmacological properties and have been found to enhance inclusion of exon 7 of SMN1 and/or SMN2 into mRNA transcribed from the SMN1 and/or SMN2 gene, thereby increasing expression of SMN protein in a human subject in need thereof.

The compounds of the present invention can be used, either alone or in combination with other drugs, for the treatment, prevention and/or delay of progression of neuromuscular disorders, in particular of amyotrophic lateral sclerosis (ALS).

A particular embodiment of the present invention relates to pharmaceutical compositions comprising compounds of formula (I) or their pharmaceutically acceptable salts as defined above and one or more pharmaceutically acceptable excipients for use in the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS).

A particular embodiment of the present invention relates to compounds of formula (I) or their pharmaceutically acceptable salts as defined above for use as therapeutically active substances for use in the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS).

A particular embodiment of the present invention relates to compounds of formula (I) or their pharmaceutically acceptable salts as defined above for use in the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS).

A particular embodiment of the present invention relates to a method for the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS), which method

comprises administering compounds of formula (I) or their pharmaceutically acceptable salts as defined above to a subject.

A particular embodiment of the present invention relates to the use of compounds of formula (I) or their pharmaceutically acceptable salts as defined above for the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS).

A particular embodiment of the present invention relates to the use of compounds of formula (I) or their pharmaceutically acceptable salts as defined above for the preparation of medicaments for the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS). Such medicaments comprise compounds of formula (I) or their pharmaceutically acceptable salts as defined above.

Examples

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

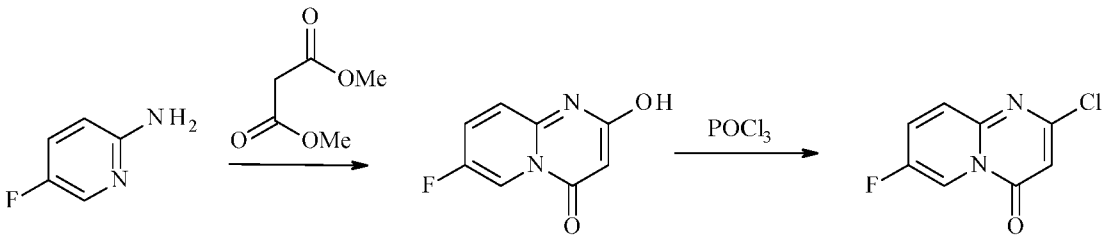
Abbreviations used

ACN: Acetonitrile; CH_2Cl_2: dichloromethane (DCM); DIPEA: diisopropyl ethylamine; DMA: dimethyl acetamide; TEA: triethylamine; RT: room temperature; $B_2(pin)_2$: bis(pinacolato)diboron; $Pd(dppf)Cl_2$: (1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) dichloride; PPTS: Pyridinium p-toluenesulfonate.

Intermediate 1

7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one

a) 2-chloro-7-fluoro-pyrido[1,2-a]pyrimidin-4-one

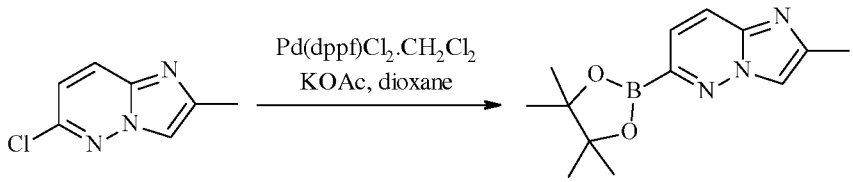


A mixture of 2-amino-5-fluoropyridine (11.20 g, 0.10 mol) and dimethyl malonate (57.0 mL, 0.50 mol) was heated at 230 °C for 1.5 h. After cooling to room temperature, the precipitate was filtered and washed with ACN (3x) to give 7-fluoro-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-

4-one as a dark solid (14 g), which was used directly in the next step. MS *m/z* 181.3 $[M+H]^+$.

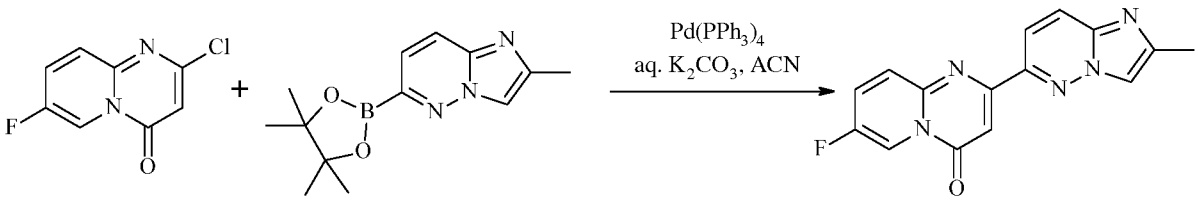
A dark mixture of crude 7-fluoro-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (14g, ~77 mmol) in $POCl_3$ (50 mL) and DIPEA (13.3 mL, 77 mmol) was heated at 110 °C for 15 hours. The solvent was removed and the dark residue was treated with ice-water, washed with water (3x) and dried to give a brown solid. The crude brown solid was chromatographed (5% MeOH in CH_2Cl_2) to give 2-chloro-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one as a yellow solid (9.84 g, 50%, 2 steps), MS *m/z* 199.2 $[M+H]^+$.

b) 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-b]pyridazine



A mixture of 6-chloro-2-methylimidazo[1,2-b]pyridazine (900 mg, 5.37 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.36 g, 5.37 mmol, 1.0 eq.), KOAc (1.05 g, 10.7 mmol) and $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (393 mg, 0.54 mmol) in dioxane (50 mL) was degassed and heated under N_2 at 95 °C. After 15 hours, the mixture was diluted with EtOAc, filtered through celite and concentrated under vacuum to give 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-b]pyridazine which was used directly in the next step.

c) 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one

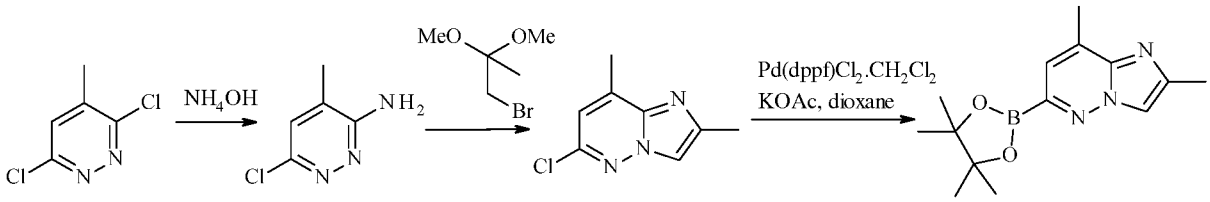


To a solution of 2-chloro-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one (750 mg, 3.78 mmol) in ACN (36 mL) was added 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-b]pyridazine (1.17 g, 4.53 mmol, Eq: 1.2), $Pd(Ph_3P)_4$ (218 mg, 0.189 mmol, 0.05 eq.) and an aqueous solution of K_2CO_3 (3.78 mL, 7.55 mmol, 2.0 eq.). The mixture was degassed and heated under argon at 105 °C overnight. The reaction was cooled to RT, and filtered. The precipitate was washed with Et_2O and then water, dried *in vacuo* to give 250 mg (22%) of 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one as a light brown solid. MS *m/z* 296.1 $[M+H]^+$.

Intermediate 2

2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one

a) 2,8-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-b]pyridazine

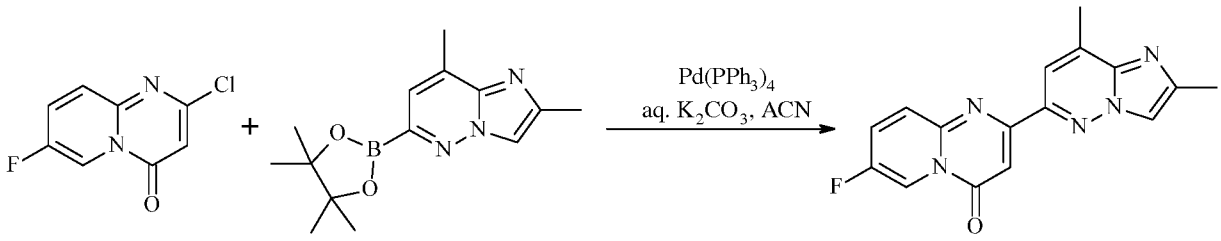


In a sealed flask, 3,6-dichloro-4-methylpyridazine (27 g, 161 mmol) was suspended in aqueous ammonia (25%, 300 mL). The reaction mixture was heated at 110 °C for 48 hours (turned into solution after 1 hour). After cooling to room temperature, the reaction was poured into CH_2Cl_2, and the organic phase was separated, dried over Na_2SO_4, and concentrated under vacuum, to give 22.4 g of 6-chloro-4-methyl-pyridazin-3-amine and 6-chloro-5-methyl-pyridazin-3-amine as a mixture of regioisomers which were used directly in the next step.

The mixture of regioisomers 6-chloro-4-methyl-pyridazin-3-amine and 6-chloro-5-methyl-pyridazin-3-amine (22.4 g) was suspended in 2-propanol (300 mL). 1-bromo-2,2-dimethoxypropane (36.0 g, 26.6 mL, 193 mmol, 1.2 eq.) and PPTS (2.96 g, 11.6 mmol, 0.0725 eq.) were added, and the resulting solution was heated at 105°C overnight. The solvent was removed *in vacuo* and the residue was taken up in CH_2Cl_2 and washed with $NaHCO_3$. The organic phases were dried over Na_2SO_4, concentrated *in vacuo* and the crude light brown solid was chromatographed (EtOAc / Heptane 1/2 -1/1) to give separately 6.1 g of 6-chloro-2,8-dimethyl-imidazo[1,2-b]pyridazine MS *m/z* 182.1 $[M+H]^+$ (21%) as a white solid and 5.9 g of 6-chloro-2,7-dimethyl-imidazo[1,2-b]pyridazine MS *m/z* 182.1 $[M+H]^+$ (20%) as a white solid.

A mixture of 6-chloro-2,8-dimethylimidazo[1,2-b]pyridazine (0.9 g, 4.96 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.26 g, 4.96 mmol, 1.0 eq.), KOAc (0.97 g, 9.91 mmol) and $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (363 mg, 0.49 mmol) in dioxane (50 mL) was degassed and heated under N_2 at 110 °C. After 15 hours, the mixture was diluted with EtOAc, filtered through celite and concentrated under vacuum to give 2,8-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-b]pyridazine which was used directly in the next step.

b) 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one

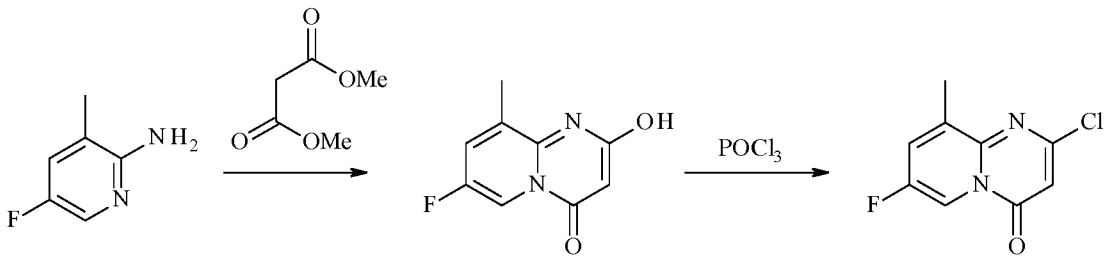


To a solution of 2-chloro-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one (750 mg, 3.78 mmol, described herein above) in ACN (36 mL) was added 2,8-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-b]pyridazine (1.24 g, 4.53 mmol, 1.2 eq.), $Pd(Ph_3P)_4$ (218 mg, 0.189 mmol, 0.05 eq.) and an aqueous solution of K_2CO_3 (3.78 mL, 7.55 mmol, 2.0 eq.). The mixture was degassed and heated under argon at 100 °C for 6 hours. The reaction was cooled to RT, and filtered. The precipitate was washed with Et_2O and then water, dried *in vacuo* to give 700 mg (60%) of 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one as a light brown solid. MS *m/z* 310.1 $[M+H]^+$.

Intermediate 3

7-fluoro-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one

a) 2-chloro-7-fluoro-9-methyl-pyrido[1,2-a]pyrimidin-4-one

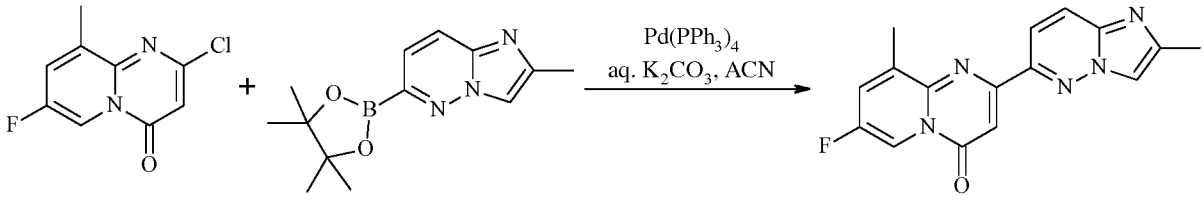


A mixture of 5-fluoro-3-methylpyridin-2-amine (3.3 g, 26.2 mmol) and dimethyl malonate (15.0 mL, 0.13 mol, 5.0 eq.) was heated at 210 °C for 1.5 hours. After cooling to room temperature, the precipitate was filtered and washed with ACN (3x) to give 7-fluoro-2-hydroxy-9-methyl-pyrido[1,2-a]pyrimidin-4-one as a dark solid (2.3 g), which was used directly in the next step. MS *m/z* 195.1 $[M+H]^+$.

A mixture of crude 7-fluoro-2-hydroxy-9-methyl-pyrido[1,2-a]pyrimidin-4-one (2.3 g, 11.8 mmol) in $POCl_3$ (7.7 mL, 82.9 mmol) and DIEA (2.07 mL, 11.8 mmol) was heated at 110 °C for 15 hours. The solvent was removed and the residue was treated with ice-water, washed with water (3x) and dried to give a brown solid. The crude brown solid was

chromatographed (5% MeOH in CH_2Cl_2) to give 2-chloro-7-fluoro-9-methyl-pyrido[1,2-a]pyrimidin-4-one as a yellow solid (1.77 g, 70% over 2 steps), MS *m/z* 213.1 $[M+H]^+$.

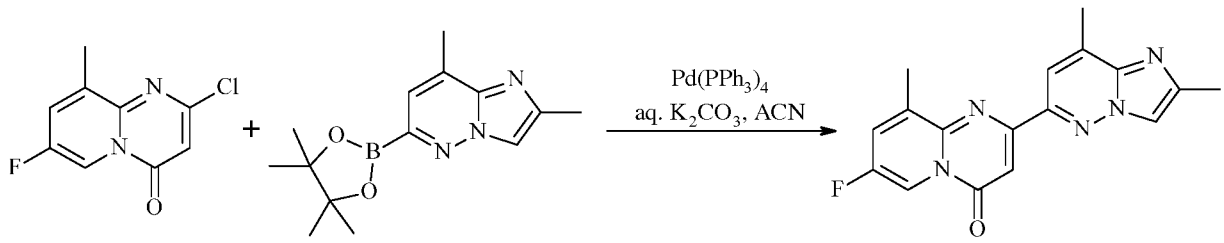
b) 7-fluoro-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one



To a solution of 2-chloro-7-fluoro-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (2.2 g, 10.3 mmol) in ACN (80 mL) was added 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-b]pyridazine (3.22 g, 12.4 mmol, 1.2 eq., described herein above), $Pd(Ph_3P)_4$ (1.20 g, 1.03 mmol, 0.1 eq.) and an aqueous solution of K_2CO_3 (10.3 mL, 20.7 mmol, 2.0 eq.). The mixture was degassed and heated under argon at 100 °C for 6 hours. The reaction was cooled to RT, and filtered. The precipitate was washed with Et_2O and then water, dried *in vacuo* to give 1.80 g (56%) of 7-fluoro-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one as a light brown solid. MS *m/z* 310.1 $[M+H]^+$.

Intermediate 4

2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-9-methyl-pyrido[1,2-a]pyrimidin-4-one

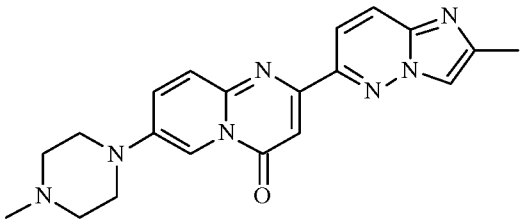


To a solution of 2-chloro-7-fluoro-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (0.98 g, 4.61 mmol, described herein above) in ACN (50 mL) was added 2,8-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-b]pyridazine (1.51 g, 5.53 mmol, 1.2 eq., described herein above), $Pd(Ph_3P)_4$ (0.32 g, 0.277 mmol, 0.06 eq.) and an aqueous solution of K_2CO_3 (4.61 mL, 9.22 mmol, 2.0 eq.). The mixture was degassed and heated under argon at 100 °C for 6 hours. The reaction was cooled to RT, and filtered. The precipitate was washed with Et_2O and water, then dried *in vacuo* to give 0.89 g (60%) of 2-(2,8-dimethylimidazo[1,2-

b]pyridazin-6-yl)-7-fluoro-9-methyl-pyrido[1,2-a]pyrimidin-4-one as a light brown solid. MS *m/z* 324.4 $[M+H]^+$.

Example 1

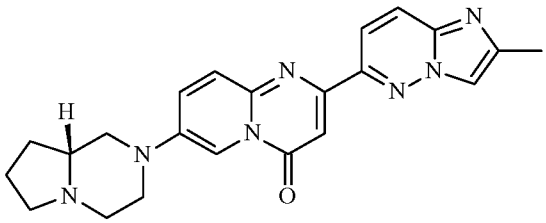
2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-(4-methylpiperazin-1-yl)pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 35 mg, 0.119 mmol) and 1-methylpiperazine (47.5 mg, 0.474 mmol, 4 eq.) were stirred in DMSO (1 mL) at 120°C overnight. LC-MS showed total convertion. The solvent was removed under high vacuum. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 9/1) to afford the title product (25 mg, 56%) as a light yellow solid. MS *m/z* 376.3 $[M+H^+]$.

Example 2

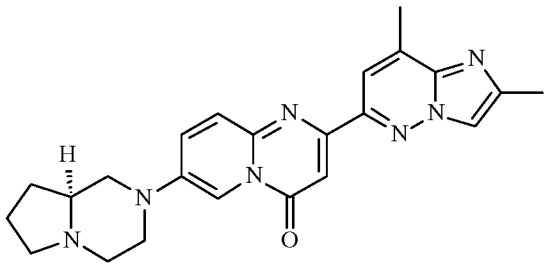
7-[(8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 125 mg, 0.426 mmol) and (R)-octahydropyrrolo-[1,2-a]pyrazine (160 mg, 1.27 mmol, 3 eq.) were stirred in DMSO (5 mL) at 125°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=98/2 to 95/5) to afford the title product (65 mg, 38%) as a light yellow solid. MS *m/z* 402.5 $[M+H^+]$.

Example 3

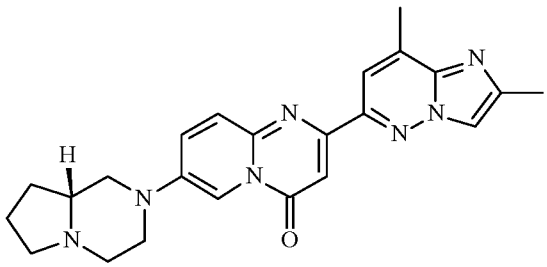
7-[(8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 2**; 200 mg, 0.647 mmol) and (S)-octahydropyrrolo-[1,2-a]pyrazine (286 mg, 2.26 mmol, 3.5 eq.) were stirred in DMSO (5 mL) at 125°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=98/2 to 95/5) to afford the title product (115 mg, 43%) as a light yellow solid. MS *m/z* 416.3 [M+H^+].

Example 4

7-[(8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one

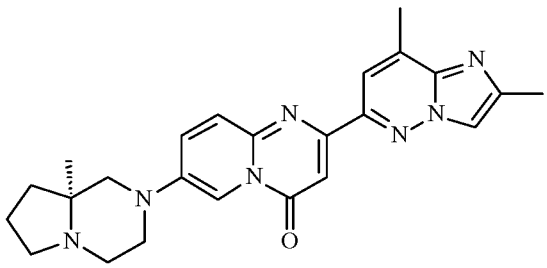


In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 2**; 200 mg, 0.647 mmol), DIPEA (0.113 mL, 0.67 mmol, 1eq.) and (R)-octahydropyrrolo-[1,2-a]pyrazine (245 mg, 1.95 mmol, 3.0 eq.) were stirred in DMSO (2.5 mL) at 125°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic

layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=98/2 to 95/5) to afford the title product (132 mg, 49%) as a light yellow solid. MS *m/z* 416.3 [M+H$^+$].

Example 5

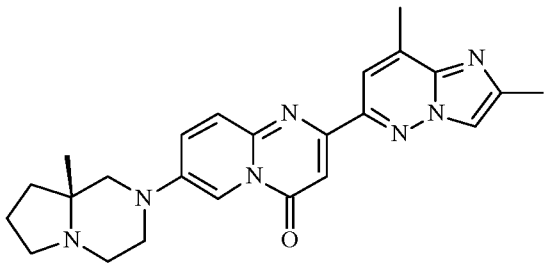
7-[(8aS)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 2**; 90 mg, 0.291 mmol), DIPEA (0.05 mL, 0.29 mmol, 1eq.) and (S)-8a-methyloctahydropyrrolo[1,2-a]pyrazine (81 mg, 0.58 mmol, 2.0 eq.) were stirred in DMSO (2.5 mL) at 125°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (55 mg, 44%) as a light yellow solid. MS *m/z* 430.3 [M+H$^+$].

Example 6

7-[(8aR)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one

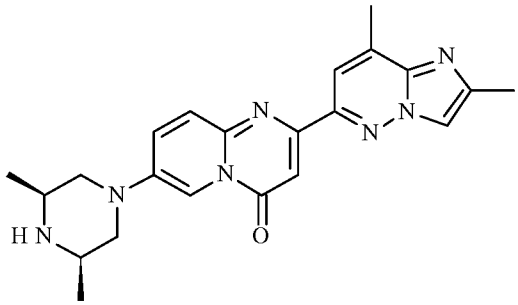


In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 2**; 90 mg, 0.291 mmol), DIPEA (0.05 mL, 0.29 mmol, 1eq.)

and (R)-8a-methyloctahydropyrrolo[1,2-a]pyrazine (81 mg, 0.58 mmol, 2.0 eq.) were stirred in DMSO (2.5 mL) at 125°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (50 mg, 40%) as a light yellow solid. MS *m/z* 430.4 [M+H$^+$].

Example 7

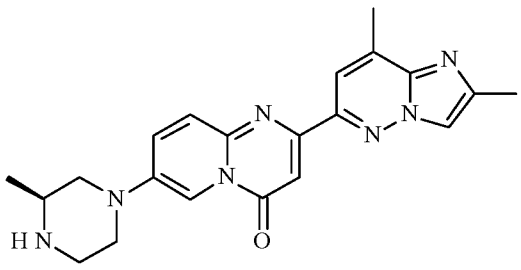
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S,5R)-3,5-dimethylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 2**; 50 mg, 0.162 mmol), and cis-2,6-dimethylpiperazine (74 mg, 0.647 mmol, 4.0 eq.) were stirred in DMSO (1.5 mL) at 110°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (32 mg, 49%) as a light yellow solid. MS *m/z* 404.4 [M+H$^+$].

Example 8

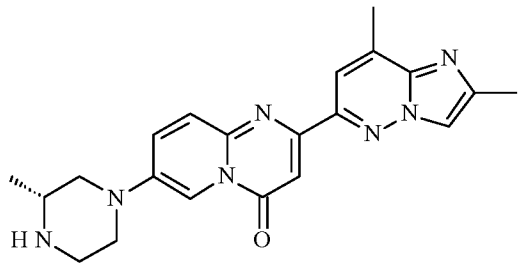
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 2**; 33 mg, 0.107 mmol), and (S)-2-methylpiperazine (43 mg, 0.427 mmol, 4.0 eq.) were stirred in DMSO (2 mL) at 120°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (18 mg, 43%) as a light yellow solid. MS *m/z* 390.3 [$M+H^+$].

Example 9

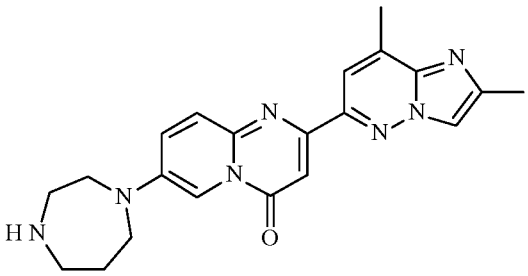
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 2**; 85 mg, 0.275 mmol), and (R)-2-methylpiperazine (110 mg, 1.10 mmol, 4.0 eq.) were stirred in DMSO (5 mL) at 120°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (35 mg, 33%) as a light yellow solid. MS *m/z* 390.3 [$M+H^+$].

Example 10

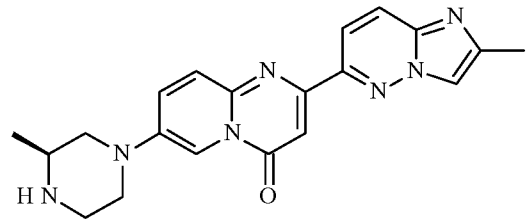
7-(1,4-diazepan-1-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 2**; 33 mg, 0.107 mmol), and 1,4-diazepane (32 mg, 0.320 mmol, 3.0 eq.) were stirred in DMSO (2 mL) at 120°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (20 mg, 48%) as a light yellow solid. MS *m/z* 390.3 [$M+H^+$].

Example 11

2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one

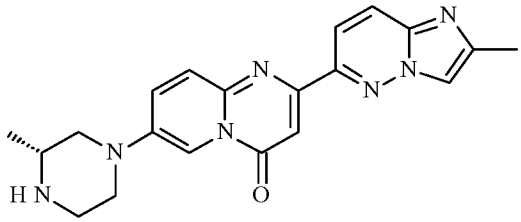


In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 50 mg, 0.169 mmol), and (S)-2-methylpiperazine (68 mg, 0.677 mmol, 4.0 eq.) were stirred in DMSO (2 mL) at 110°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (40 mg, 63%) as a light yellow solid.

MS *m/z* 376.2 [M+H$^+$].

Example 12

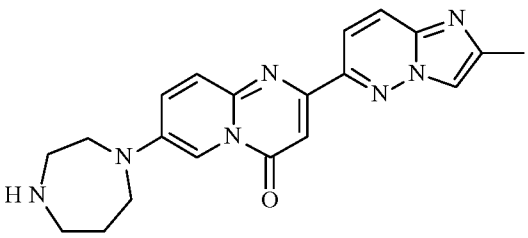
2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 50 mg, 0.169 mmol), and (R)-2-methylpiperazine (68 mg, 0.677 mmol, 4.0 eq.) were stirred in DMSO (2 mL) at 110°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (48 mg, 75%) as a light yellow solid. MS *m/z* 376.3 [M+H$^+$].

Example 13

7-(1,4-diazepan-1-yl)-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one

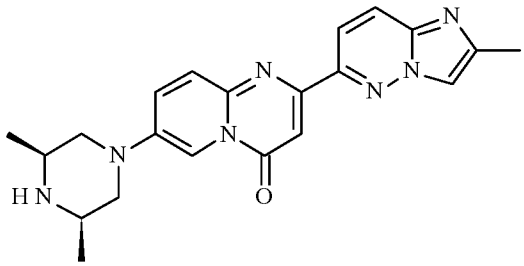


In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 50 mg, 0.169 mmol), and 1,4-diazepane (68 mg, 0.677 mmol, 4.0 eq.) were stirred in DMSO (2 mL) at 110°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated

in vacuo. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (41 mg, 65%) as a light yellow solid. MS *m/z* 376.2 [M+H$^+$].

Example 14

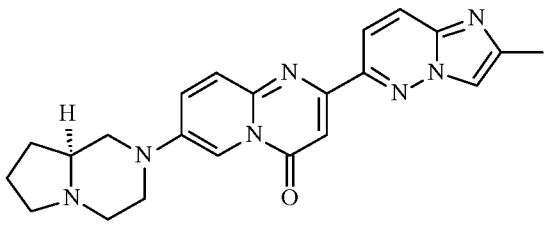
7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 50 mg, 0.169 mmol), and cis-2,6-dimethylpiperazine (77 mg, 0.677 mmol, 4.0 eq.) were stirred in DMSO (2 mL) at 110°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (41 mg, 62%) as a light yellow solid. MS *m/z* 390.3 [M+H$^+$].

Example 15

7-[(8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one

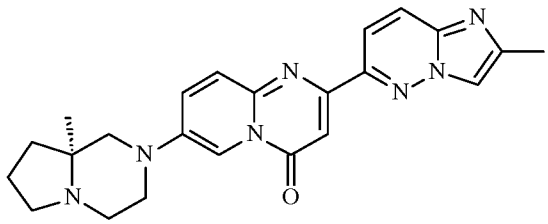


In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 50 mg, 0.169 mmol), and (S)-octahydropyrrolo[1,2-a]pyrazine (85 mg, 0.677 mmol, 4.0 eq.) were stirred in DMSO (2 mL) at 125°C overnight. The

solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (36 mg, 53%) as a light yellow solid. MS *m/z* 402.3 [M+H$^+$].

Example 16

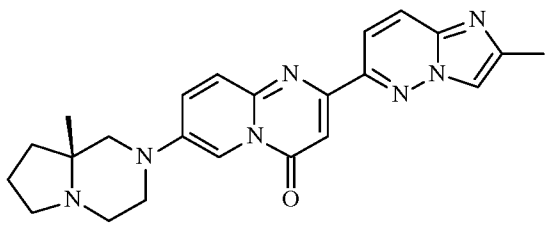
7-[(8aS)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 50 mg, 0.169 mmol) and (S)-8a-methyloctahydropyrrolo[1,2-a]pyrazine (95 mg, 0.677 mmol, 4.0 eq.) were stirred in DMSO (2 mL) at 125°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (45 mg, 64%) as a light yellow solid. MS *m/z* 416.3 [M+H$^+$].

Example 17

7-[(8aR)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one

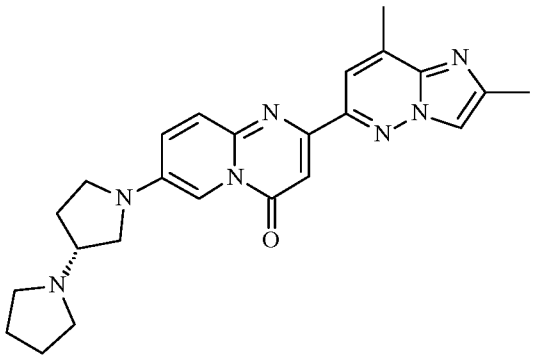


In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-

a]pyrimidin-4-one (**Intermediate 1**; 100 mg, 0.339 mmol) and (R)-8a-methyloctahydropyrrolo[1,2-a]pyrazine (190 mg, 1.35 mmol, 4.0 eq.) were stirred in DMSO (4 mL) at 125°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (45 mg, 64%) as a light yellow solid. MS *m/z* 416.3 [M+H$^+$].

Example 18

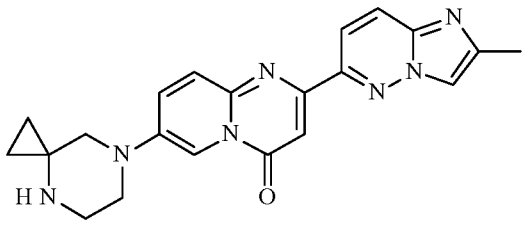
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-pyrrolidin-1-ylpyrrolidin-1-yl]pyrido[1,2-a]pyrimidin-4-one



In a microwave reactor, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 2**; 45 mg, 0.145 mmol), (R)-1,3'-bipyrrolidine dihydrochloride (62 mg, 0.291 mmol, 2.0 eq.) and DIPEA (0.20 mL, 1.16 mmol, 8 eq.) were stirred in NMP (3 mL) at 220°C for 1 hour. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=98/2 to 90/10) to afford the title product (25 mg, 40%) as a light yellow solid. MS *m/z* 430.3 [M+H$^+$].

Example 19

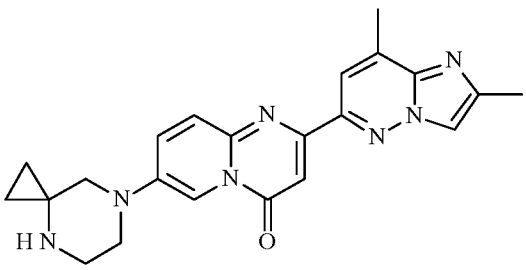
7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 50 mg, 0.169 mmol), DIPEA (0.24 mL, 1.35 mmol, 8 eq.) and 4,7-diazaspiro[2.5]octane dihydrochloride (62.7 mg, 0.339 mmol, 2.0 eq.) were stirred in DMSO (2 mL) at 125°C for 2 days. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (22 mg, 33%) as a light yellow solid. MS *m/z* 388.3 [$M+H^+$].

Example 20

7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one

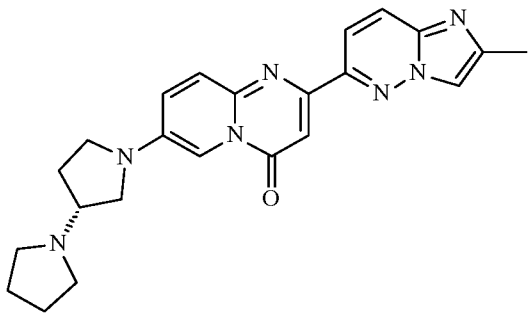


In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 2**; 50 mg, 0.162 mmol), DIPEA (0.22 mL, 1.29 mmol, 4 eq.) and 4,7-diazaspiro[2.5]octane dihydrochloride (32 mg, 0.320 mmol, 3.0 eq.) were stirred in DMSO (2 mL) at 130°C for 48 hours. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=98/2 to 95/5) to afford the title product (12 mg,

18%) as a light yellow solid. MS *m/z* 402.3 [M+H$^+$].

Example 21

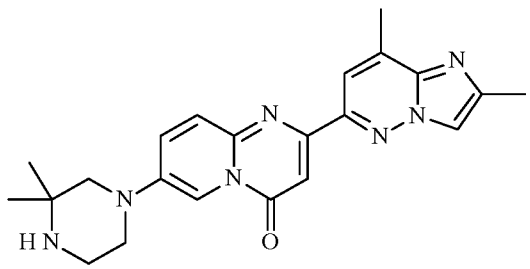
2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-pyrrolidin-1-ylpyrrolidin-1-yl]pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 40 mg, 0.135 mmol), DIPEA (0.19 mL, 1.08 mmol, 8 eq.) and (R)-1,3'-bipyrrolidine dihydrochloride (58 mg, 0.271 mmol, 2.0 eq.) were stirred in DMSO (4 mL) and heated at 220°C for 40 minutes in a microwave. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=98/2 to 90/10) to afford the title product (30 mg, 53%) as a light yellow solid. MS *m/z* 416.3 [M+H$^+$].

Example 22

2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-(3,3-dimethylpiperazin-1-yl)pyrido[1,2-a]pyrimidin-4-one

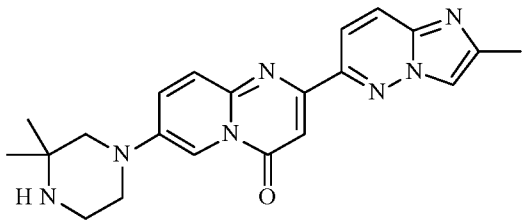


In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 2**; 40 mg, 0.129 mmol) and 2,2-dimethylpiperazine (59 mg, 0.517 mmol, 4.0 eq.) were stirred in DMSO (1.6 mL) at 130°C overnight. The solvent was

removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 9/1) to afford the title product (29 mg, 55%) as a light yellow solid. MS *m/z* 404.3 [M+H$^+$].

Example 23

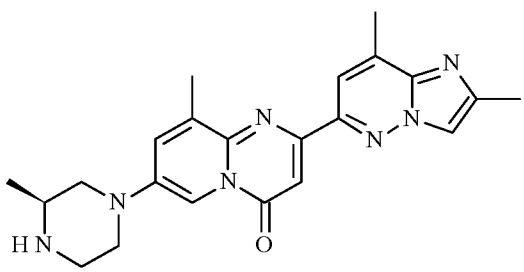
7-(3,3-dimethylpiperazin-1-yl)-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 40 mg, 0.135 mmol) and 2,2-dimethylpiperazine (62 mg, 0.542 mmol, 4.0 eq.) were stirred in DMSO (2 mL) at 130°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (26 mg, 49%) as a light yellow solid. MS *m/z* 390.3 [M+H$^+$].

Example 24

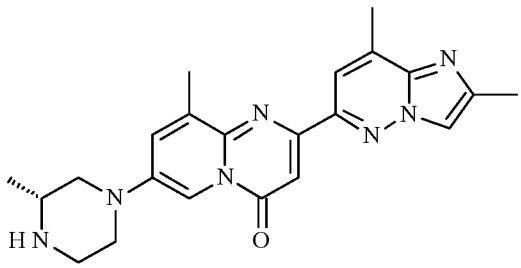
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-9-methyl-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-9-methyl-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 4**; 50 mg, 0.155 mmol) and (S)-2-methylpiperazine (62 mg, 0.619 mmol, 4.0 eq.) were stirred in DMSO (2 mL) at 125°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (45 mg, 72%) as a light yellow solid. MS *m/z* 404.3 [M+H$^+$].

Example 25

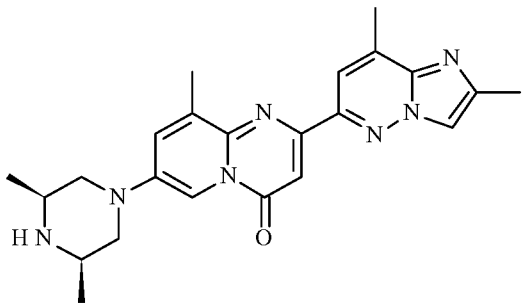
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-9-methyl-7-[(3R)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-9-methyl-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 4**; 50 mg, 0.155 mmol) and (R)-2-methylpiperazine (62 mg, 0.619 mmol, 4.0 eq.) were stirred in DMSO (2 mL) at 125°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (40 mg, 70%) as a light yellow solid. MS *m/z* 404.3 [M+H$^+$].

Example 26

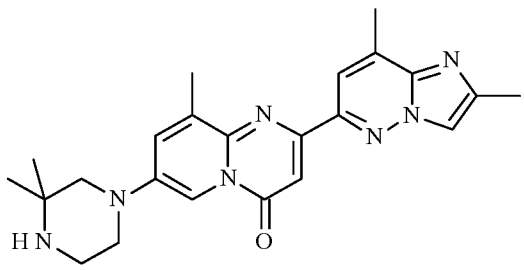
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-9-methyl-pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-9-methyl-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 4**; 50 mg, 0.155 mmol) and cis-2,6-dimethylpiperazine (70 mg, 0.619 mmol, 4.0 eq.) were stirred in DMSO (2 mL) at 125°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (26 mg, 40%) as a light yellow solid. MS *m/z* 418.3 [M+H$^+$].

Example 27

2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-(3,3-dimethylpiperazin-1-yl)-9-methyl-pyrido[1,2-a]pyrimidin-4-one

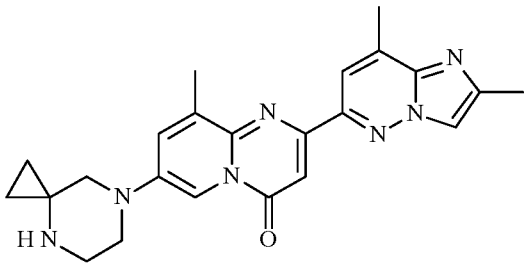


In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-9-methyl-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 4**; 50 mg, 0.155 mmol) and 2,2-dimethylpiperazine (35 mg, 0.309 mmol, 2.0 eq.) were stirred in DMSO (2 mL) at 125°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2,

CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (36 mg, 56%) as a light yellow solid. MS *m/z* 418.3 [M+H^+].

Example 28

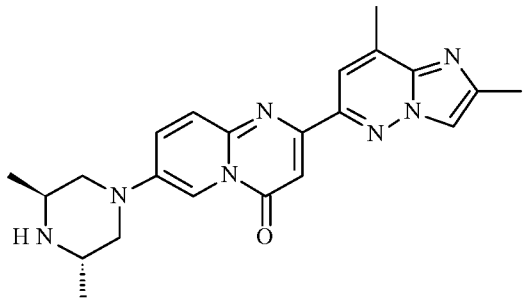
7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-9-methyl-pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-9-methyl-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 4**; 50 mg, 0.155 mmol), DIPEA (0.21 mL, 1.24 mmol, 8 eq.) and 4,7-diazaspiro[2.5]octane dihydrochloride (57 mg, 0.309 mmol, 2.0 eq.) were stirred in DMSO (2 mL) at 125°C for 2 days. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (17 mg, 26%) as a light yellow solid. MS *m/z* 416.3 [M+H^+].

Example 29

2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S,5S)-3,5-dimethylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one

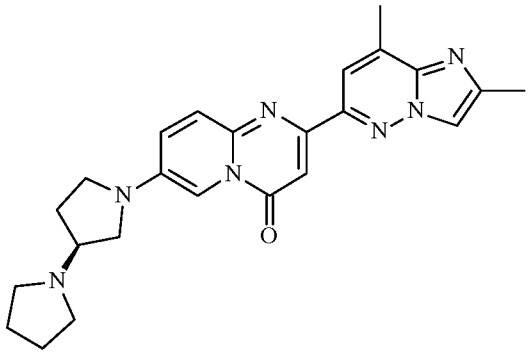


In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 2**; 50 mg, 0.162 mmol), TEA (0.18 mL, 1.29 mmol, 8 eq.) and

(2S,6S)-2,6-dimethylpiperazine dihydrochloride (90 mg, 0.485 mmol, 3.0 eq.) were stirred in DMSO (2 mL) at 140°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 9/1) to afford the title product (20 mg, 30%) as a light yellow solid. MS *m/z* 404.3 [M+H$^+$].

Example 30

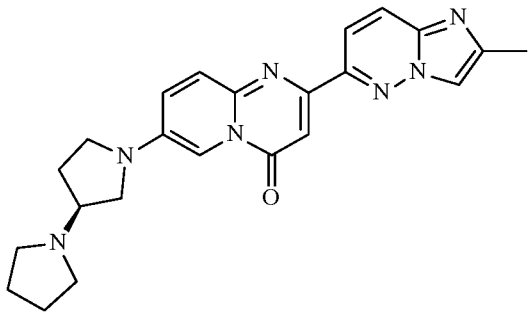
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-pyrrolidin-1-ylpyrrolidin-1-yl]pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-fluoro-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 2**; 50 mg, 0.162 mmol), DIPEA (0.22 mL, 1.29 mmol, 8 eq.) and (S)-1,3'-bipyrrolidine dihydrochloride (103 mg, 0.485 mmol, 3.0 eq.) were stirred in NMP (2 mL) at 140°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 9/1) to afford the title product (22 mg, 32%) as a light yellow solid. MS *m/z* 430.3 [M+H$^+$].

Example 31

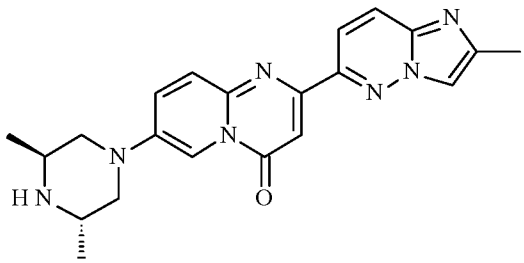
2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-pyrrolidin-1-ylpyrrolidin-1-yl]pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 75 mg, 0.254 mmol), TEA (0.28 mL, 2.03 mmol, 8 eq.) and (S)-1,3'-bipyrrolidine dihydrochloride (162 mg, 0.762 mmol, 3.0 eq.) were stirred in NMP (4 mL) and heated at 220°C for 1 hour in a microwave. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (12 mg, 11%) as a light yellow solid. MS *m/z* 416.2 [M+H$^+$].

Example 32

7-[(3S,5S)-3,5-dimethylpiperazin-1-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one

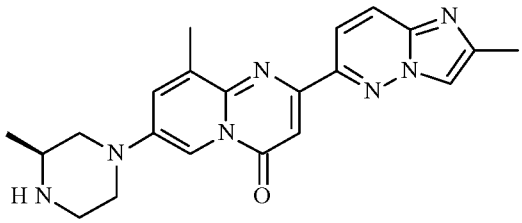


In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 75 mg, 0.254 mmol), TEA (0.28 mL, 2.03 mmol, 8 eq.) and (2S,6S)-2,6-dimethylpiperazine dihydrochloride (143 mg, 0.762 mmol, 3.0 eq.) were stirred in DMSO (3 mL) and heated at 140°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude

was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (10 mg, 10%) as a light yellow solid. MS *m/z* 390.3 [M+H$^+$].

Example 33

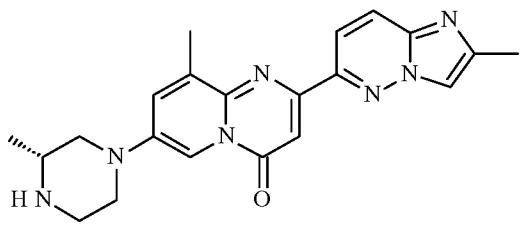
9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one (**Intermediate 3**; 250 mg, 0.808 mmol), and (S)-2-methylpiperazine (405 mg, 4.04 mmol, 5.0 eq.) were stirred in DMSO (6 mL) and heated at 130°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 85/15) to afford the title product (135 mg, 43%) as a light yellow solid. MS *m/z* 390.3 [M+H$^+$].

Example 34

9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one

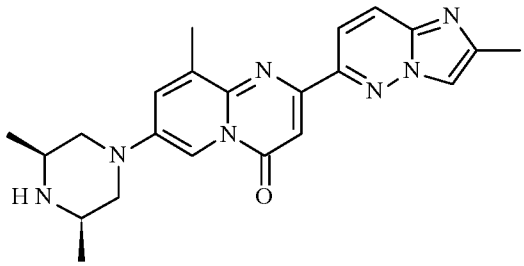


In a sealed tube, 7-fluoro-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one (**Intermediate 3**; 250 mg, 0.808 mmol), and (R)-2-methylpiperazine (405 mg, 4.04 mmol, 5.0 eq.) were stirred in DMSO (6 mL) and heated at 130°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an

aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 85/15) to afford the title product (100 mg, 32%) as a light yellow solid. MS *m/z* 390.3 [M+H$^+$].

Example 35

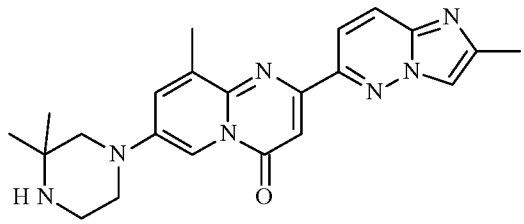
7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one (**Intermediate 3**; 250 mg, 0.808 mmol), and (2S,6R)-2,6-dimethylpiperazine (461 mg, 4.04 mmol, 5.0 eq.) were stirred in DMSO (6 mL) and heated at 130°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 85/15) to afford the title product (101 mg, 31%) as a light yellow solid. MS *m/z* 404.3 [M+H$^+$].

Example 36

7-(3,3-dimethylpiperazin-1-yl)-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one

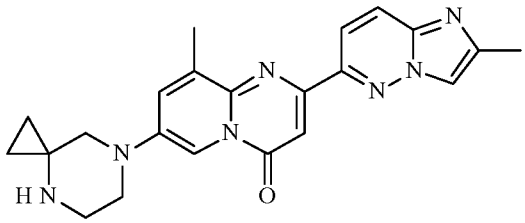


In a sealed tube, 7-fluoro-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-

a]pyrimidin-4-one (**Intermediate 3**; 250 mg, 0.808 mmol), and 2,2-dimethylpiperazine (461 mg, 4.04 mmol, 5.0 eq.) were stirred in DMSO (6 mL) and heated at 130°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 85/15) to afford the title product (120 mg, 36%) as a light yellow solid. MS *m/z* 404.3 [M+H$^+$].

Example 37

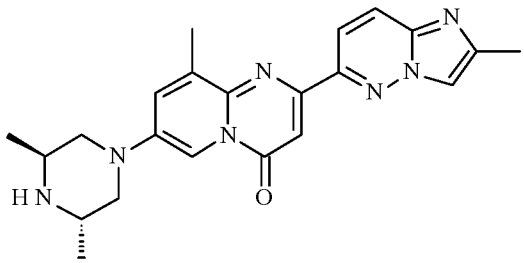
7-(4,7-diazaspiro[2.5]octan-7-yl)-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one (**Intermediate 3**; 125 mg, 0.404 mmol), K_2CO_3 (223 mg, 1.62 mmol, 4 eq.) and 4,7-diazaspiro[2.5]octane dihydrochloride (112 mg, 0.606 mmol, 1.5 eq.) were stirred in DMA (2 mL) and heated at 130°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (75 mg, 46%) as a light yellow solid. MS *m/z* 402.2 [M+H$^+$].

Example 38

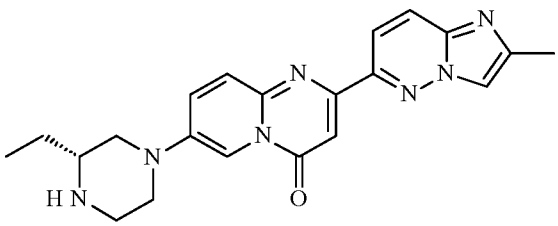
7-[(3S,5S)-3,5-dimethylpiperazin-1-yl]-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one (**Intermediate 3**; 125 mg, 0.404 mmol), K_2CO_3 (223 mg, 1.62 mmol, 4 eq.) and (2S,6S)-2,6-dimethylpiperazine dihydrochloride (113 mg, 0.606 mmol, 1.5 eq.) were stirred in DMA (2 mL) and heated at 130°C overnight. The solvent was removed under high vacuum. The residue was taken up in CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 90/10) to afford the title product (50 mg, 31%) as a light yellow solid. MS *m/z* 404.3 [M+H$^+$].

Example 39

7-[(3R)-3-ethylpiperazin-1-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one



In a sealed tube, 7-fluoro-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (**Intermediate 1**; 200 mg, 0.677 mmol), K_2CO_3 (374 mg, 2.71 mmol, 4 eq.) and (R)-2-ethylpiperazine dihydrochloride (238 mg, 0.606 mmol, 1.5 eq.) were stirred in DMA (3 mL) at 100°C for 4 days. The solvent was removed under high vacuum. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=95/5 to 8/2) to afford the title product (168 mg, 64%) as a light yellow solid. MS *m/z* 390.2 [M+H$^+$].

Biological Assays

To describe in more detail and assist in understanding the present description, the following non-limiting biological examples are offered to more fully illustrate the scope of the description and are not to be construed as specifically limiting the scope thereof. Such variations of the present description that may be now known or later developed, which would be within the purview of one skilled in the art to ascertain, are considered to fall within the scope of the present description and as hereinafter claimed. These examples illustrate the testing of certain compounds described herein in vitro and/or in vivo and demonstrate the usefulness of the compounds for treating of SMA by enhancing the inclusion of exon 7 of SMN2 into mRNA transcribed from the SMN2 gene. Compounds of formula (I) enhance inclusion of exon 7 of SMN2 into mRNA transcribed from the SMN2 gene and increase levels of SMN protein produced from the SMN2 gene, and thus can be used to treat SMA in a human subject in need thereof. These examples further illustrate the testing of certain compounds described herein in vitro and/or in vivo and demonstrate the usefulness of the compounds for enhancing the inclusion of exon 7 of SMNI into mRNA transcribed from the SMN1 gene. Accordingly, compounds of formula (I) also enhance the inclusion of exon 7 of SMN1 into mRNA transcribed from the SMN1 gene and increase levels of SMN protein produced from the SMN1 gene.

Assay 1

SMN2 minigene mRNA splicing RT-qPCR assay in cultured cells

The reverse transcription-quantitative PCR-based (RT-qPCR) assay is used to quantify the level of the full length SMN2 minigene (referred to herein by the term "FL SMN2mini") mRNA containing SMN2 exon 7 in a HEK293H cell line stably transfected with said minigene and treated with a test compound. Materials used and respective sources are listed below in Table 1.

Material	**Source**
HEK293H cells	Life Technologies, Inc. (formerly Invitrogen) Catalog No. 11631-017
Cells-To-Ct lysis buffer	Life Technologies, Inc. (formerly Applied Biosystems) part No. 4399002
DMEM	Life Technologies, Inc. (formerly Invitrogen) Catalog No. 11960-044
96-well flat-bottom plates	Becton Dickinson Catalog No. 353072

RT-PCR Enzyme Mix	Life Technologies, Inc. (formerly Applied Biosystems) part No. 4388520
RT-PCR buffer	Life Technologies, Inc. (formerly Applied Biosystems) part No. 4388519
AgPath-ID One-Step RT-PCR kit	Life Technologies, Inc. (formerly Applied Biosystems) part No. 4387391
Thermocycler	Life Technologies, Inc. (formerly Applied Biosystems) 7900HT

Table 1. Materials and their respective sources used in the SMN2 minigene mRNA splicing RT-qPCR assay in cultured cells.

The SMN2-A minigene construct was prepared as described in International Patent Application WO2009/151546A1 page 145 paragraph [00400] to page 147 paragraph [00412] (incl. Figure 1 and Figure 3 therein).

HEK293H cells stably transfected with the SMN2-A minigene construct (10,000 cells/well) are seeded in 200 µL of cell culture medium (DMEM plus 10% FBS, with 200 µg/mL hygromycin) in 96-well flat-bottom plates and the plate is immediately swirled to ensure proper dispersal of cells and the formation of an even monolayer of cells. Cells are allowed to attach for 6 hours. Test compounds are serially diluted 3.16-fold in 100% DMSO to generate a 7-point concentration curve. A solution of test compound (1 µL, 200x in DMSO) is added to each cell-containing well and the plate is incubated for 24 hours in a cell culture incubator (37°C, 5% $C0_2$, 100% relative humidity). 2 replicates are prepared for each test compound concentration. The cells are then lysed in the Cells-To-Ct lysis buffer and the lysate is stored at -80°C.

Full length SMN2-A minigene and GAPDH mRNA are quantified using the primers and probes referenced in WO2014/209841A2 on page 80 in Table 1. Primer SMN Forward A (SEQ ID NO.1) hybridizes to a nucleotide sequence in exon 7 (nucleotide 22 to nucleotide 40), primer SMN Reverse A (SEQ ID NO.2) hybridizes to a nucleotide sequence in the coding sequence of Firefly luciferase, SMN Probe A (SEQ ID NO.3) hybridizes to a nucleotide sequence in exon 7 (nucleotide 50 to nucleotide 54) and exon 8 (nucleotide 1 to nucleotide 21). The combination of these three oligonucleotides detects only SMN1 or SMN2 minigenes (RT-qPCR) and will not detect endogenous SMN1 or SMN2 genes.

The SMN forward and reverse primers are used at final concentrations of 0.4 µM. The SMN probe is used at a final concentration of 0.15 µM. The GAPDH primers are used at final concentrations of 0.2 µM and the probe at 0.15 µM.

The SMN2-minigene GAPDH mix (15 µL total volume) is prepared by combining 7.5 µL of 2x RT-PCR buffer, 0.4 µL of 25x RT-PCR enzyme mix, 0.75 µL of 20x GAPDH primer-probe mix, 4.0075 µL of water, 2 µL of 10-fold diluted cell lysate, 0.06 µL of 100 µM SMN forward primer, 0.06 µL of 100 µM SMN reverse primer, and 0.225 µL of 100 µM SMN probe.

PCR is carried out at the following temperatures for the indicated time: Step 1: 48°C (15 min); Step 2: 95°C (10 min); Step 3: 95°C (15 sec); Step 4: 60°C (1 min); then repeat Steps 3 and 4 for a total of 40 cycles.

Each reaction mixture contains both SMN2-A minigene and GAPDH primers/probe sets (multiplex design), allowing simultaneous measurement of the levels of two transcripts.

The increase in the abundance of the FL SMN2mini mRNA relative to that in cells treated with vehicle control is determined from real-time PCR data using a modified ΔΔCt method (as described in *Livak and Schmittgen, Methods, 2001, 25:402-8*). The amplification efficiency E is calculated from the slope of the amplification curve for FL SMN2mini and GAPDH individually. The abundance of FL SMN2mini and GAPDH mRNA are then calculated as $(1 + E)^{-Ct}$, where Ct is the threshold value for each amplicon. The abundance of FL SMN2mini mRNA is normalized to GAPDH mRNA abundance. The normalized FL SMN2mini mRNA abundance from test compound-treated samples is then divided by normalized FL SMN2mini mRNA abundance from vehicle-treated cells to determine the level of FL SMN2mini mRNA relative to vehicle control.

Table 2 provides $EC_{1.5x}$ concentrations for production of full length SMN2 minigene mRNA that was obtained from the 7-point concentration data generated according to the above procedure for particular compounds of the present invention.

Particular compounds of the present invention exhibit an $EC_{1.5x}$ concentration for production of full length SMN2 minigene mRNA $\leq$ 1 µM.

More particular compounds of the present invention exhibit an $EC_{1.5x}$ concentration for production of full length SMN2 minigene mRNA $\leq$ 0.1 µM.

Most particular compounds of the present invention exhibit an EC1.5x concentration for production of full length SMN2 minigene mRNA $\leq$ 0.02 µM.

Example	$EC_{1.5x}$ minigene (nM)	Example	$EC_{1.5x}$ minigene (nM)	Example	$EC_{1.5x}$ minigene (nM)
1	3.5	14	4.1	27	39.9
2	3.8	15	4	28	5
3	3.2	16	1.1	29	0.3
4	1.8	17	6.4	30	3
5	0.6	18	3.6	31	6.7
6	2.8	19	10.2	32	1.6
7	3.7	20	4.3	33	0.5
8	0.3	21	9.6	34	0.9
9	0.1	22	0.9	35	4.7
10	6.4	23	3.4	36	5
11	1.4	24	0.4	37	4.4
12	1.2	25	0.5	38	0.3
13	5	26	327	39	0.9

Table 2. $EC_{1.5x}$ concentrations for production of full length SMN2 minigene mRNA.

Assay 2

SMN protein assay in cultured cells

The SMN HTRF (homogeneous time resolved fluorescence) assay is used to quantify the level of SMN protein in SMA patient fibroblast cells treated with test compounds. Materials used and respective sources are listed below in Table 3.

Material	**Source**
SMA Type 1 human cells	GM03813 (Coriell Institute)
Protease inhibitor cocktail	Roche Applied Science Catalog No. 11836145001
Anti-SMN d2	Blue cap Cisbio Catalog No. 63IDC002-SMN
Anti-SMN kryptate	Red cap Cisbio Catalog No. 63IDC002-SMN
SMN reconstitution buffer	Cisbio Catalog No. 63IDC002-SMN-Buffer
DMEM	Life Technologies (formerly Invitrogen) Catalog No. 11960-044
RIPA Lysis Buffer	20 mM Tris-HCl pH 7.5, 150 mM NaCl, 1 mM EDTA, 1% Thermo Scientific NP-40 Surfact-Amps Detergent Solution (Fisher Scientific, Pittsburgh/PA), 1% Sodium deoxycholate
Diluent Buffer	20 mM Tris-HCl pH 7.5, 150 mM NaCl
Envision Plate Reader	Perkin Elmer Model # 2103

Table 3. Materials and their respective sources used in the SMN protein assay in cultured cells.

Cells are thawed and cultured in DMEM-10% FBS for 72 hours. Cells are trypsinized, counted and re-suspended to a concentration of 25,000 cells/mL in DMEM-10% FBS. The cell suspensions are plated at 5,000 cells per well in a 96 well microtiter plate and incubated for 3 to 5 hours. Test compounds are serially diluted 3.16-fold in 100% DMSO to generate a 7-point concentration curve. 1 µL of test compound solution is transferred to cell-containing wells and cells are incubated for 48 hours in a cell culture incubator (37°C, 5% CO_2, 100% relative humidity). Triplicate samples are set up for each test compound concentration. After 48 hours, the supernatant is removed from the wells and 25 µL of the RIPA lysis buffer, containing protease inhibitors, is added to the wells and incubated with shaking at room temperature for 1 hour. 25 µL of the diluent is added and then 35 µL of the resulting lysate is transferred to a 384-

well plate, where each well contains 5 μL of the antibody solution (1:100 dilution of anti-SMN d2 and anti-SMN kryptate in SMN reconstitution buffer). The plate is centrifuged for 1 minute to bring the solution to the bottom of the wells, then incubated overnight at room temperature. Fluorescence for each well of the plate at 665 nm and 620 nm is measured on an EnVision multilabel plate reader (Perkin-Elmer).

The normalized fluorescence signal is calculated for each sample, Blank and vehicle control well by dividing the signal at 665 nm by the signal at 620 nm. Normalizing the signal accounts for possible fluorescence quenching due to the matrix effect of the lysate. The ΔF value (a measurement of SMN protein abundance as a percent value) for each sample well is calculated by subtracting the normalized average fluorescence for the Blank control wells from the normalized fluorescence for each sample well, then dividing this difference by the normalized average fluorescence for the Blank control wells and multiplying the resulting value by 100. The ΔF value for each sample well represents the SMN protein abundance from test compound-treated samples. The ΔF value for each sample well is divided by the ΔF value for the vehicle control wells to calculate the fold increase in SMN protein abundance relative to the vehicle control. Table 4 provides $EC_{1.5x}$ concentrations for SMN protein expression that was obtained from the 7-point concentration data generated according to the above procedure for particular compounds of the present invention.

Particular compounds of the present invention exhibit an $EC_{1.5x}$ concentration for SMN protein expression ≤ 1 μM.

More particular compounds of the present invention exhibit an $EC_{1.5x}$ concentration for SMN protein expression ≤ 100 nM.

Most particular compounds of the present invention exhibit an $EC_{1.5x}$ concentration for SMN protein expression ≤ 30 nM.

Table 5 provides the maximum fold increase of SMN protein that was obtained from the 7-point concentration data generated according to the above procedure for particular compounds of the present invention

Particular compounds of the present invention exhibit a maximum fold increase > 1.5.

More particular compounds of the present invention exhibit a maximum fold increase > 1.7.

Most particular compounds of the present invention exhibit a maximum fold increase > 1.8.

Example	EC1.5x SMN protein (nM)	Example	EC1.5x SMN protein (nM)	Example	EC1.5x SMN protein (nM)
1	10.8	14	17.6	27	126.5
2	19.8	15	21.2	28	49.7
3	25.6	16	3	29	2.1
4	15.7	17	20.2	30	13.6
5	4.1	18	25	31	27.7
6	11	19	29.8	32	4
7	15.5	20	37	33	4
8	5.9	21	68.7	34	4.4
9	2.5	22	13.8	35	19.5
10	22.8	23	23.9	36	34.4
11	7	24	4.7	37	45
12	7.5	25	11.9	38	3.1
13	3	26	1230	39	15.8

Table 4. $EC_{1.5x}$ concentrations for SMN protein expression.

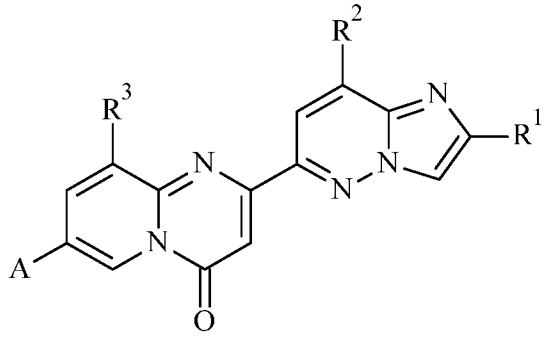
Example	max. fold increase	Example	max. fold increase	Example	max. fold increase
1	1.84	14	1.86	27	1.57
2	1.76	15	1.94	28	1.72
3	1.81	16	1.83	29	1.81
4	1.76	17	1.98	30	1.84
5	1.71	18	1.75	31	1.65
6	1.84	19	1.83	32	1.88
7	1.76	20	1.72	33	1.82
8	1.85	21	1.54	34	1.89
9	1.92	22	1.69	35	1.79
10	1.95	23	1.63	36	1.77
11	1.9	24	1.77	37	1.87
12	1.77	25	1.79	38	1.85
13	1.91	26	1.52	39	1.81

Table 5. Maximum fold increase of SMN protein.

5

Claims

1. The compound of formula (I)



(I)

wherein

R^1 is hydrogen or C_{1-7}-alkyl;

R^2 is hydrogen, cyano, C_{1-7}-alkyl, C_{1-7}-haloalkyl or C_{3-8}-cycloalkyl;

R^3 is hydrogen, C_{1-7}-alkyl, or C_{3-8}-cycloalkyl;

A is N-heterocycloalkyl or $NR^{12}R^{13}$, wherein N-heterocycloalkyl comprises 1 or 2 nitrogen ring atoms and is optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14};

R^{12} is heterocycloalkyl comprising 1 nitrogen ring atom, wherein heterocycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14};

R^{13} is hydrogen, C_{1-7}-alkyl or C_{3-8}-cycloalkyl;

R^{14} is independently selected from hydrogen, C_{1-7}-alkyl, amino, amino-C_{1-7}-alkyl, C_{3-8}-cycloalkyl and heterocycloalkyl or two R^{14} together form C_{1-7}-alkylene;

with the proviso that if A is N-heterocycloalkyl comprising only 1 nitrogen ring atom, then at least one R^{14} substituent is amino or amino-C_{1-7}-alkyl;

and pharmaceutically acceptable salts thereof,

for use in the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS).

2. A compound according to claim 1 for use according to claim 1, wherein

R^1 is hydrogen or C_{1-7}-alkyl;

R^2 is hydrogen, cyano, C_{1-7}-alkyl, C_{1-7}-haloalkyl or C_{3-8}-cycloalkyl;

R^3 is hydrogen, C_{1-7}-alkyl, or C_{3-8}-cycloalkyl;

A is N-heterocycloalkyl comprising 1 or 2 nitrogen ring atoms, wherein N-heterocycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14};

R^{14} is independently selected from hydrogen, C_{1-7}-alkyl, amino, amino-C_{1-7}-alkyl, C_{3-8}-cycloalkyl and heterocycloalkyl or two R^{14} together form C_{1-7}-alkylene;

with the proviso that if A is N-heterocycloalkyl comprising only 1 nitrogen ring atom, then at least one R^{14} substituent is amino or amino-C_{1-7}-alkyl;

and pharmaceutically acceptable salts thereof.

3. A compound according to any of claims 1 or 2 for use according to claim 1, wherein R^1 is C_{1-7}-alkyl.

4. A compound according to any of claims 1 to 3 for use according to claim 1, wherein R^1 is methyl.

5. A compound according to any of claims 1 to 4 for use according to claim 1, wherein R^2 is hydrogen or C_{1-7}-alkyl.

6. A compound according to any of claims 1 to 5 for use according to claim 1, wherein R^2 is hydrogen or methyl.

7. A compound according to any of claims 1 to 6 for use according to claim 1, wherein R^3 is hydrogen or C_{1-7}-alkyl.

8. A compound according to any of claims 1 to 7 for use according to claim 1, wherein R^3 is hydrogen or methyl.

9. A compound according to any of claims 1 to 8 for use according to claim 1, wherein R^{12} is piperidinyl optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14}.

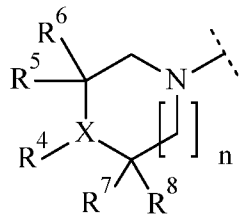
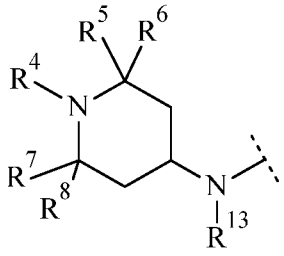
10. A compound according to any of claims 1 to 9 for use according to claim 1, wherein R^{13} is hydrogen or C_{1-7}-alkyl.

11. A compound according to any of claims 1 to 10 for use according to claim 1, wherein R^{13} is hydrogen or methyl.

12. A compound according to any of claims 1 to 11 for use according to claim 1, wherein R^{14} is independently selected from C_{1-7}-alkyl and heterocycloalkyl or two R^{14} together form C_{1-7}-alkylene.

13. A compound according to any of claims 1 to 12 for use according to claim 1, wherein R^{14} is independently selected from methyl, ethyl and pyrrolidinyl or two R^{14} together form ethylene

14. A compound according to any of claims 1 to 13 for use according to claim 1, wherein

A is  or  , wherein

X is N or CH;

R^4 is hydrogen, C_{1-7}-alkyl or $-(CH_2)_m-NR^9R^{10}$;

R^5 is hydrogen or C_{1-7}-alkyl;

R^6 is hydrogen or C_{1-7}-alkyl;

R^7 is hydrogen or C_{1-7}-alkyl;

R^8 is hydrogen or C_{1-7}-alkyl;

R^9 and R^{10} are independently selected from hydrogen, C_{1-7}-alkyl and C_{3-8}-cycloalkyl;

R^{13} is hydrogen, C_{1-7}-alkyl or C_{3-8}-cycloalkyl;

n is 0, 1 or 2;

m is 0, 1, 2 or 3;

or R^4 and R^5 together form C_{1-7}-alkylene;

or R^4 and R^7 together form C_{1-7}-alkylene;

or R^5 and R^6 together form C_{2-7}-alkylene;

or R^5 and R^7 together form C_{1-7}-alkylene;

or R^5 and R^9 together form C_{1-7}-alkylene;

or R^7 and R^8 together form C_{2-7}-alkylene;

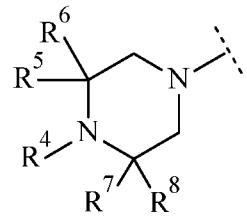
or R^7 and R^9 together form C_{1-7}-alkylene;

or R^9 and R^{10} together form C_{2-7}-alkylene;

with the proviso that if X is CH then R^4 is $-(CH_2)_m-NR^9R^{10}$; and

with the proviso that if X is N and R^4 is $-(CH_2)_m-NR^9R^{10}$ then m is 2 or 3.

15. A compound according to any of claims 1 to 14 for use according to claim 1, wherein A is selected from the group of: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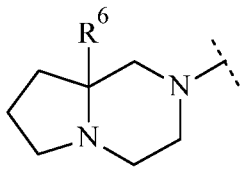
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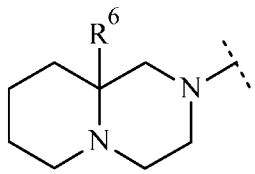
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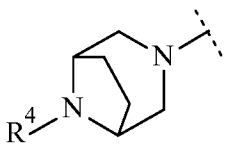
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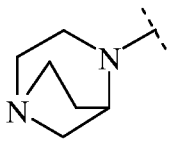
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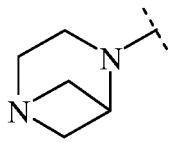
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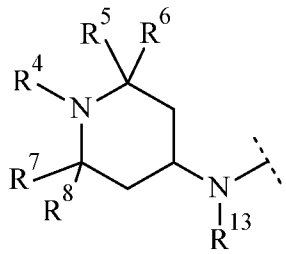
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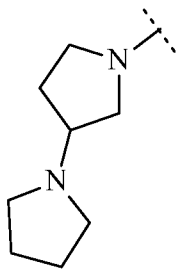
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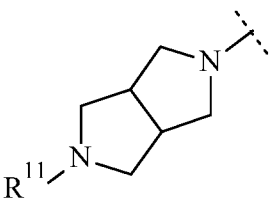
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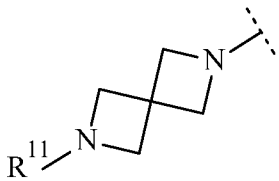
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wherein R^4, R^5, R^6, R^7, R^8 and R^{13} are as defined in any of claims 1 to 30 and wherein R^{11} is hydrogen or C_{1-7}-alkyl.

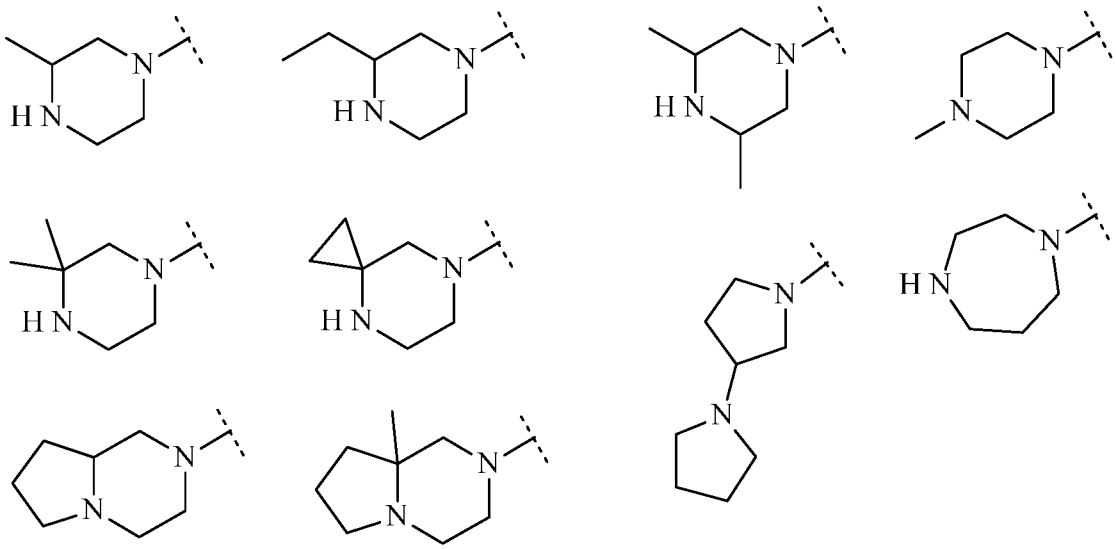
16. A compound according to any of claims 1 to 15 for use according to claim 1, wherein A is selected from the group of piperazinyl, diazepanyl, pyrrolidinyl and hexahydropyrrolo[1,2-

a]pyrazinyl, each optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14} as defined in any of claims 1 to 32.

17. A compound according to any of claims 1 to 16 for use according to claim 1, wherein A is selected from the group of piperazin-1-yl, 1,4-diazepan-1-yl, pyrrolidin-1-yl and hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, each optionally substituted with 1 or 2 substituents selected from R^{14} as defined in any of claims 1 to 16.

18. A compound according to any of claims 1 to 15 for use according to claim 1, wherein A is $NR^{12}R^{13}$, wherein R^{12} and R^{13} are as described in any of claims 1 to 15.

19. A compound according to any of claims 1 to 17 for use according to claim 1, wherein A is selected from the group of:



20. A compound according to any one of claims 1 to 19 for use according to claim 1, selected from the group consisting of:
2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-(4-methylpiperazin-1-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(8aS)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;

7-[(8aR)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S,5R)-3,5-dimethylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
7-(1,4-diazepan-1-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
7-(1,4-diazepan-1-yl)-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(8aS)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(8aR)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-pyrrolidin-1-ylpyrrolidin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-pyrrolidin-1-ylpyrrolidin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-(3,3-dimethylpiperazin-1-yl)pyrido[1,2-a]pyrimidin-4-one;
7-(3,3-dimethylpiperazin-1-yl)-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-9-methyl-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;

2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-9-methyl-7-[(3R)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-9-methyl-pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-(3,3-dimethylpiperazin-1-yl)-9-methyl-pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-9-methyl-pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S,5S)-3,5-dimethylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-pyrrolidin-1-ylpyrrolidin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-pyrrolidin-1-ylpyrrolidin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
7-[(3S,5S)-3,5-dimethylpiperazin-1-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-[(3R)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-(3,3-dimethylpiperazin-1-yl)-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(3S,5S)-3,5-dimethylpiperazin-1-yl]-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(3R)-3-ethylpiperazin-1-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
and pharmaceutically acceptable salts thereof.

21. A compound according to any one of claims 1 to 20 for use according to claim 1, selected from the group consisting of:
7-[(8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;

7-[(8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-7-[(3S,5R)-3,5-dimethylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-[(8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-9-methyl-7-[(3S)-3-methylpiperazin-1-yl]pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-9-methyl-pyrido[1,2-a]pyrimidin-4-one;
7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
7-(4,7-diazaspiro[2.5]octan-7-yl)-9-methyl-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
and pharmaceutically acceptable salts thereof.

22. Pharmaceutical compositions comprising compounds of formula (I) according to any of claims 1 - 21 or their pharmaceutically acceptable salts and one or more pharmaceutically acceptable excipients for use in the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS).

23. A method for the the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS), which method comprises administering compounds of formula (I) according to any of claims 1 - 21 or their pharmaceutically acceptable salts as defined above to a subject.

24. The use of compounds of formula (I) according to any of claims 1 - 21 or their pharmaceutically acceptable salts for the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS).

25. The use of compounds of formula (I) according to any of claims 1 - 21 or their pharmaceutically acceptable salts for the preparation of medicaments for the treatment, prevention and/or delay of progression of amyotrophic lateral sclerosis (ALS).

26. The invention as described hereinbefore.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/077190

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/5025 A61P21/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/119916 A2 (PTC THERAPEUTICS INC [US]; HOFFMANN LA ROCHE [CH]) 15 August 2013 (2013-08-15) page 85 - page 135; claims -----	1

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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