profile of these drugs prohibits long-term use in SMA patients. Some drugs under clinical investigation for the treatment of SMA include transcription activators such as histone deacetylase ("HDAC") inhibitors (*e.g.*, butyrates, valproic acid, and hydroxyurea), and mRNA stabilizers (mRNA decapping inhibitor RG3039 from Repligen), intended to increase the amount of total RNA transcribed from the SMN2 gene. However, the use of HDAC inhibitors or mRNA stabilizers does not address the underlying cause of SMA and may result in a global increase in transcription and gene expression with potential safety problems in humans.

[0023] In an alternative approach, neuroprotective agents such as olesoxime have been chosen for investigation. Such strategies are not aimed at increasing the production of functional Smn for the treatment of SMA, but instead are being explored to protect the Smn-deficient motor neurons from neurodegeneration.

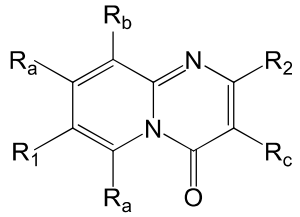
[0024] A system designed to identify compounds that increase the inclusion of exon 7 of SMN into RNA transcribed from the SMN2 gene and certain benzooxazole and benzoisoxazole compounds identified thereby have been described in International Application PCT/US2009/003238 filed May 27, 2009 (published as International Publication Number WO2009/151546 and United States Publication Number US2011/0086833). A system designed to identify compounds that produce a stabilized Smn protein from SMN2 Δ7 mRNA and certain isoindolinone compounds identified thereby have been described in International Application PCT/US2009/004625 filed August 13, 2009 (published as International Publication Number WO2010/019236 and United States Publication Number US2011/0172284). Each of the foregoing documents is herein incorporated in their entirety and for all purposes.

[0025] All other documents referred to herein are incorporated by reference into the present application as though fully set forth herein.

[0026] Despite the progress made in understanding the genetic basis and pathophysiology of SMA, there remains a need to identify compounds that alter the course of spinal muscular atrophy, one of the most devastating childhood neurological diseases.

SUMMARY

[0027] In one aspect, the present disclosure refers to a compound of Formula (IIa1):



(IIa1)

or a free acid, free base, salt, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof, wherein:

R_1 is heterocyclyl;

wherein, heterocyclyl is optionally substituted with one, two or three R_3 substituents and optionally, with one additional R_4 substituent; or,

wherein, heterocyclyl is optionally substituted with one, two, three or four R_3 substituents;

R_2 is phenyl;

wherein, R_2 is optionally substituted with one, two or three R_6 substituents and optionally, with one additional R_7 substituent;

R_a is, in each instance, independently selected from hydrogen, halogen or $C_{1\text{-}8}$alkyl;

R_b is hydrogen, halogen, $C_{1\text{-}8}$alkyl or $C_{1\text{-}8}$alkoxy;

R_c is hydrogen, halogen or $C_{1\text{-}8}$alkyl;

R_3 is, in each instance, independently selected from cyano, halogen, hydroxy, oxo, $C_{1\text{-}8}$alkyl, halo-$C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkyl-carbonyl, $C_{1\text{-}8}$alkoxy, halo-$C_{1\text{-}8}$alkoxy, $C_{1\text{-}8}$alkoxy-$C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkoxy-carbonyl, amino, $C_{1\text{-}8}$alkyl-amino, $(C_{1\text{-}8}\text{alkyl})_2$-amino, amino-$C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkyl-amino-$C_{1\text{-}8}$alkyl, $(C_{1\text{-}8}\text{alkyl})_2$-amino-$C_{1\text{-}8}$alkyl, amino-$C_{1\text{-}8}$alkyl-amino, $C_{1\text{-}8}$alkyl-amino-$C_{1\text{-}8}$alkyl-amino, $(C_{1\text{-}8}\text{alkyl-amino-}C_{1\text{-}8}\text{alkyl})_2$-amino, $(C_{1\text{-}8}\text{alkyl})_2$-amino-$C_{1\text{-}8}$alkyl-amino, $[(C_{1\text{-}8}\text{alkyl})_2\text{-amino-}C_{1\text{-}8}\text{alkyl}]_2$-amino, $(C_{1\text{-}8}\text{alkyl-amino-}C_{1\text{-}8}\text{alkyl})(C_{1\text{-}8}\text{alkyl})$amino,

$[(C_{1\text{-}8}\text{alkyl})_2\text{-amino-}C_{1\text{-}8}\text{alkyl}](C_{1\text{-}8}\text{alkyl})$amino, $C_{1\text{-}8}\text{alkoxy-}C_{1\text{-}8}\text{alkyl-amino}$, $(C_{1\text{-}8}\text{alkoxy-}C_{1\text{-}8}\text{alkyl})_2$-amino, $(C_{1\text{-}8}\text{alkoxy-}C_{1\text{-}8}\text{alkyl})(C_{1\text{-}8}\text{alkyl})$amino

C_{1-8}alkyl-carbonyl-amino, C_{1-8}alkoxy-carbonyl-amino, hydroxy-C_{1-8}alkyl, hydroxy-C_{1-8}alkoxy-C_{1-8}alkyl, hydroxy-C_{1-8}alkyl-amino, (hydroxy-C_{1-8}alkyl)$_2$-amino or (hydroxy-C_{1-8}alkyl)(C_{1-8}alkyl)amino;

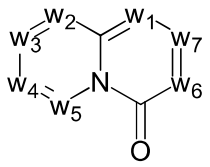
R_4 is C_{3-14}cycloalkyl, C_{3-14}cycloalkyl-C_{1-8}alkyl, C_{3-14}cycloalkyl-amino, aryl-C_{1-8}alkyl, aryl-C_{1-8}alkoxy-carbonyl, aryl-sulfonyloxy-C_{1-8}alkyl, heterocyclyl or heterocyclyl-C_{1-8}alkyl; wherein, each instance of C_{3-14}cycloalkyl, aryl and heterocyclyl is optionally substituted with one, two or three R_5 substituents;

R_5 is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C_{1-8}alkyl, halo-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, amino, C_{1-8}alkyl-amino, (C_{1-8}alkyl)$_2$-amino or C_{1-8}alkyl-thio;

R_6 is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C_{1-8}alkyl, C_{2-8}alkenyl, halo-C_{1-8}alkyl, hydroxy-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, C_{1-8}alkoxy-C_{1-8}alkyl, amino, C_{1-8}alkyl-amino, (C_{1-8}alkyl)$_2$-amino or C_{1-8}alkyl-thio; and,

R_7 is C_{3-14}cycloalkyl, C_{3-14}cycloalkyl-oxy, aryl, heterocyclyl or heteroaryl.

In one example, provided herein are compounds of Formula (I):



(I)

[0028] or a form thereof, wherein w_1, w_2, w_3, w_4, w_5, w_6 and w_7 are as defined herein. In one example, provided herein is a pharmaceutical composition comprising a compound of Formula (I) or a form thereof, and a pharmaceutically acceptable carrier, excipient or diluent. In a specific example, provided herein is a compound of Formula (I) or a form thereof, or a pharmaceutical composition thereof for treating spinal muscular atrophy (SMA).

[0029] SMA is caused by deletion or mutation of the SMN1 gene, resulting in selective degeneration of Smn-deficient motor neurons. Although human subjects retain several copies of the SMN2 gene, the small amount of functional Smn protein expressed from SMN2 does not fully compensate for the loss of Smn that would have been expressed from the SMN1 gene. The compounds, compositions thereof and uses therewith described herein are based, in part, on the

Applicants discovery that a compound of Formula (I) increases the inclusion of exon 7 of SMN2 into mRNA that is transcribed from an SMN2 minigene. The minigene reproduces the alternative splicing reaction of exon 7 of SMN2 which results in exon 7 skipping in the majority of SMN2 transcripts. Thus, compounds of Formula (I) or a form thereof may be used to modulate inclusion of exon 7 of SMN2 into mRNA that is transcribed from the SMN2 gene. Applicants have also discovered that a compound of Formula (I) increases the inclusion of exon 7 of SMN1 into mRNA that is transcribed from an SMN1 minigene. Thus, compounds of Formula (I) or a form thereof may be used to modulate inclusion of exon 7 of SMN1 into mRNA that is transcribed from the SMN1 gene.

[0030] In a specific example, provided herein are compounds of Formula (I) or a form thereof that may be used to modulate the inclusion of exon 7 of SMN2 into mRNA that is transcribed from the SMN2 gene. In another specific example, provided herein are compounds of Formula (I) or a form thereof that may be used to modulate the inclusion of exon 7 of SMN1 into mRNA that is transcribed from the SMN1 gene. In yet another example, provided herein are compounds of Formula (I) or a form thereof that may be used to modulate the inclusion of exon 7 of SMN1 and SMN2 into mRNA that is transcribed from the SMN1 and SMN2 genes, respectively.

[0031] In another example, provided herein is the use of a compound of Formula (I) or a form thereof for treating SMA. In a specific example, provided herein is a method for treating SMA in a human subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula (I) or a form thereof. The compound of Formula (I) or a form thereof is preferably administered to a human subject in a pharmaceutical composition. In another specific example, provided herein is the use of a compound of Formula (I) for treating SMA, wherein the compound enhances the inclusion of exon 7 of SMN2 into mRNA that is transcribed from the SMN2 gene. Without being limited by theory, compounds of Formula (I) enhance inclusion of exon 7 of SMN2 into mRNA that is 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.

[0032] In another example, provided herein are primers and/or probes described below in the Biological Examples (*e.g.*, SMN primers such as SEQ ID NO. 1, 7, 8, 11 or 13, and/or SEQ ID NO. 2, 9 or 12, and/or SMN probes such as a SEQ ID NO. 3 or 10) and the use of those primers

and/or probes. In a specific example, provided herein is an isolated nucleotide sequence comprising SEQ ID NO. 1, 2, 3, 7, 8, 9, 10, 11, 12 or 13. In another specific example, provided herein is an isolated nucleotide sequence consisting essentially of SEQ ID NO. 1, 2, 3, 7, 8, 9, 10, 11, 12 or 13. In another specific example, provided herein is an isolated nucleotide sequence consisting of SEQ ID NO. 1, 2, 3, 7, 8, 9, 10, 11, 12 or 13.

[0033] In certain examples, the amount of mRNA that is transcribed from the SMN1 gene and/or SMN2 gene and does not include exon 7 of SMN1 and/or SMN2 may be used as a biomarker for SMA, such as disclosed herein. In other examples, the amount of mRNA that is transcribed from the SMN1 and/or SMN2 gene and includes exon 7 of SMN1 and/or SMN2 may be used as a biomarker for treating a patient with a compound, such as disclosed herein. In a specific example, the patient is an SMA patient. In another specific example, the patient is not an SMA patient.

[0034] In certain examples, the amount of mRNA that is transcribed from the SMN1 and/or SMN2 gene and includes exon 7 of SMN1 and/or SMN2 as well as the amount of mRNA that is transcribed from the SMN1 and/or SMN2 gene and does not include exon 7 of SMN1 and/or SMN2 may be used as biomarkers for treating a patient with a compound, such as disclosed herein. In a specific example, the patient is an SMA patient. In another specific example, the patient is not an SMA patient.

[0035] In accordance with these examples, an SMN primer(s) and/or an SMN probe described below may be used in assays, such as PCR (*e.g.*, qPCR), rolling circle amplification, and RT-PCR (*e.g.*, endpoint RT-PCR and/or RT-qPCR) to assess and/or quantify the amount of mRNA that is transcribed from the SMN1 gene and/or SMN2 gene and does or does not include exon 7 of SMN1 and/or SMN2.

[0036] In a specific example, a primer and/or probe described below in the Biological Examples (*e.g.*, SMN primers such as SEQ ID NO. 1, 7, 8, 11 or 13 and/or SEQ ID NO. 2, 9 or 12, and/or SMN probes such as a SEQ ID NO. 3 or 10) is used in an assay, such as RT-PCR, RT-qPCR, endpoint RT-PCR, PCR, qPCR, rolling circle amplification, Northern blot or Southern blot (*e.g.*, an assay such as described below in the Biological Examples), to determine whether a compound (*e.g.*, a compound of Formula (I) or a form thereof) enhances the inclusion of exon 7 of SMN2 into mRNA that is transcribed from an SMN2 gene.

[0037] In a specific example, a primer and/or probe described below in the Biological Examples (*e.g.*, SMN primers such as SEQ ID NO. 1, 7, 8, 11 or 13 and/or SEQ ID NO. 2, 9 or 12, and/or SMN probes such as a SEQ ID NO. 3 or 10) is used in an assay, such as RT-PCR, RT-qPCR, endpoint RT-PCR, PCR, qPCR, rolling circle amplification, Northern blot or Southern blot (*e.g.*, an assay such as described below in the Biological Examples), to determine whether a compound (*e.g.*, a compound of Formula (I) or a form thereof) enhances the inclusion of exon 7 of SMN1 into mRNA that is transcribed from an SMN1 gene.

[0038] In a specific example, a primer and/or probe described below in the Biological Examples (*e.g.*, SMN primers such as SEQ ID NO. 1, 7, 8, 11 or 13 and/or SEQ ID NO. 2, 9 or 12, and/or SMN probes such as a SEQ ID NO. 3 or 10) is used in an assay, such as RT-PCR, RT-qPCR, endpoint RT-PCR, PCR, qPCR, rolling circle amplification, Northern blot or Southern blot (*e.g.*, an assay such as described below in the Biological Examples), to determine whether a compound (*e.g.*, a compound of Formula (I) or a form thereof) enhances the inclusion of exon 7 of SMN1 and/or SMN2 into mRNA that is transcribed from an SMN1 and/or SMN2 gene.

[0039] In another example, a primer and/or probe described below in the Biological Examples (*e.g.*, SMN primers such as SEQ ID NO. 7, 11 or 13 and/or SEQ ID NO. 9 or 12, and/or SMN probes such as a SEQ ID NO. 3 or 10) is used in an assay, such as RT-PCR, RT-qPCR, endpoint RT-PCR, PCR, qPCR, rolling circle amplification, Northern blot or Southern blot (*e.g.*, an assay such as described below in the Biological Examples), to monitor the amount of mRNA that is transcribed from the SMN2 gene and includes exon 7 of SMN2 in a patient sample. In a specific example, the patient is an SMA patient. In another specific example, the patient is not an SMA patient.

[0040] In another example, a primer and/or probe described below in the Biological Examples (*e.g.*, SMN primers such as SEQ ID NO. 7, 11 or 13 and/or SEQ ID NO. 9 or 12, and/or SMN probes such as a SEQ ID NO. 3 or 10) is used in an assay, such as RT-PCR, RT-qPCR, endpoint RT-PCR, PCR, qPCR, rolling circle amplification, Northern blot or Southern blot (*e.g.*, an assay such as described below in the Biological Examples), to monitor the amount of mRNA that is transcribed from the SMN1 gene and includes exon 7 of SMN1 in a patient sample. In a specific example, the patient is an SMA patient. In another specific example, the patient is not an SMA patient.

[0041] In another example, a primer and/or probe described below in the Biological Examples (*e.g.*, SMN primers such as SEQ ID NO. 7, 11 or 13 and/or SEQ ID NO. 9 or 12, and/or SMN probes such as a SEQ ID NO. 3 or 10) is used in an assay, such as RT-PCR, RT-qPCR, endpoint RT-PCR, PCR, qPCR, rolling circle amplification, Northern blot or Southern blot (*e.g.*, an assay such as described below in the Biological Examples), to monitor the amount of mRNA that is transcribed from the SMN1 and/or SMN2 gene and includes exon 7 of SMN1 and/or SMN2 in a patient sample. In a specific example, the patient is an SMA patient. In another specific example, the patient is not an SMA patient.

[0042] In another example, a primer and/or probe described below in the Biological Examples (*e.g.*, SMN primers such as SEQ ID NO. 7, 8, 11 or 13 and/or SEQ ID NO. 9 or 12, and/or SMN probes such as a SEQ ID NO. 3 or 10) is used in an assay, such as RT-PCR, RT-qPCR, endpoint RT-PCR, PCR, qPCR, rolling circle amplification, Northern blot or Southern blot (*e.g.*, an assay such as described below in the Biological Examples), to monitor a patient's response to a compound (*e.g.*, a compound of Formula (I) or a form thereof). In a specific example, the patient is an SMA patient. In another specific example, the patient is not an SMA patient.

[0043] In another example, provided herein is a method for determining whether a compound (*e.g.*, a compound of Formula (I) disclosed herein) enhances the inclusion of exon 7 of SMN2 into mRNA that is transcribed from the SMN2 gene, comprising (a) contacting mRNA that is transcribed from an SMN2 minigene described herein or in International Application PCT/US2009/004625, filed August 13, 2009 (published as International Publication Number WO2010/019236) or United States Publication Number US2011/0172284 in the presence of a compound (*e.g.*, a compound of Formula (I) disclosed herein) with a primer(s) described herein (*e.g.*, SEQ ID NO. 1 and/or 2) along with applicable components for, *e.g.*, RT-PCR, RT-qPCR, PCR, endpoint RT-PCR, qPCR or rolling circle amplification; and (b) detecting the amount of mRNA that is transcribed from the minigene and includes exon 7 of the SMN2, wherein (1) an increase in the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN2 in the presence of the compound relative to the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN2 in the absence of the compound indicates that the compound enhances inclusion of exon 7 of SMN2 into mRNA that is transcribed from the SMN2 gene; and (2) no change or no substantial change in the amount of mRNA that is transcribed

from the minigene and includes exon 7 of SMN2 in the presence of the compound relative to the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN2 in the absence of the compound indicates that the compound does not enhance the inclusion of exon 7 of SMN2 into mRNA that is transcribed from the SMN2 gene.

[0044] In another example, provided herein is a method for determining whether a compound (*e.g.*, a compound of Formula (I) disclosed herein) enhances the inclusion of exon 7 of SMN1 into mRNA that is transcribed from the SMN1 gene, comprising (a) contacting mRNA that is transcribed from an SMN1 minigene described in International Application PCT/US2009/004625, filed August 13, 2009 (published as International Publication Number WO2010/019236) or United States Publication Number US2011/0172284 in the presence of a compound (*e.g.*, a compound of Formula (I) disclosed herein) with a primer(s) described herein (*e.g.*, SEQ ID NO. 1 and/or 2) along with applicable components for, *e.g.*, RT-PCR, RT-qPCR, PCR, endpoint RT-PCR, qPCR or rolling circle amplification; and (b) detecting the amount of mRNA that is transcribed from the minigene and includes exon 7 of the SMN1, wherein (1) an increase in the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN1 in the presence of the compound relative to the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN1 in the absence of the compound indicates that the compound enhances inclusion of exon 7 of SMN1 into mRNA that is transcribed from the SMN1 gene; and (2) no change or no substantial change in the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN1 in the presence of the compound relative to the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN1 in the absence of the compound indicates that the compound does not enhance the inclusion of exon 7 of SMN1 into mRNA that is transcribed from the SMN1 gene.

[0045] In another example, provided herein is a method for determining whether a compound (*e.g.*, a compound of Formula (I) disclosed herein) enhances the inclusion of exon 7 of SMN2 into mRNA that is transcribed from the SMN2 gene, comprising (a) contacting mRNA that is transcribed from an SMN2 minigene described herein or in International Application PCT/US2009/004625, filed August 13, 2009 (published as International Publication Number WO2010/019236) or United States Publication Number US2011/0172284 in the presence of a compound (*e.g.*, a compound of Formula (I) disclosed herein) with a probe described herein (*e.g.*, SEQ ID NO. 3 or 10) along with applicable components for, *e.g.*, RT-PCR, RT-qPCR,

endpoint RT-PCR, PCR, qPCR, rolling circle amplification and, as applicable, Northern blot or Southern blot; and (b) detecting the amount of mRNA that is transcribed from the minigene and includes exon 7 of the SMN2, wherein (1) an increase in the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN2 in the presence of the compound relative to the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN2 in the absence of the compound indicates that the compound enhances inclusion of exon 7 of SMN2 into mRNA that is transcribed from the SMN2 gene; and (2) no change or no substantial change in the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN2 in the presence of the compound relative to the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN2 in the absence of the compound indicates that the compound does not enhance the inclusion of exon 7 of SMN2 into mRNA that is transcribed from the SMN2 gene.

[0046] In another example, provided herein is a method for determining whether a compound (*e.g.*, a compound of Formula (I) disclosed herein) enhances the inclusion of exon 7 of SMN1 into mRNA that is transcribed from the SMN1 gene, comprising (a) contacting mRNA that is transcribed from an SMN1 minigene described in International Application PCT/US2009/004625, filed August 13, 2009 (published as International Publication Number WO2010/019236) or United States Publication Number US2011/0172284 in the presence of a compound (*e.g.*, a compound of Formula (I) disclosed herein) with a probe described herein (*e.g.*, SEQ ID NO. 3 or 10) along with applicable components for, *e.g.*, RT-PCR, RT-qPCR, endpoint RT-PCR, PCR, qPCR, rolling circle amplification and, as applicable, Northern blot or Southern blot; and (b) detecting the amount of mRNA that is transcribed from the minigene and includes exon 7 of the SMN1, wherein (1) an increase in the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN1 in the presence of the compound relative to the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN1 in the absence of the compound indicates that the compound enhances inclusion of exon 7 of SMN1 into mRNA that is transcribed from the SMN1 gene; and (2) no change or no substantial change in the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN1 in the presence of the compound relative to the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN1 in the absence of the compound indicates that the

compound does not enhance the inclusion of exon 7 of SMN2 into mRNA that is transcribed from the SMN2 gene.

[0047] In another example, provided herein is a method for determining whether a compound (*e.g.*, a compound of Formula (I) disclosed herein) enhances the inclusion of exon 7 of SMN2 into mRNA that is transcribed from the SMN2 gene, comprising (a) contacting mRNA that is transcribed from an SMN2 minigene described herein or in International Application PCT/US2009/004625, filed August 13, 2009 (published as International Publication Number WO2010/019236) or United States Publication Number US2011/0172284 in the presence of a compound (*e.g.*, a compound of Formula (I) disclosed herein) with a primer(s) (*e.g.*, SEQ ID NO. 1 or 2) and/or a probe described herein (*e.g.*, SEQ ID NO. 3 or 10) along with applicable components for, *e.g*, RT-PCR, RT-qPCR, endpoint RT-PCR, PCR, qPCR, rolling circle amplification and, as applicable, Northern blot or Southern blot; and (b) detecting the amount of mRNA that is transcribed from the minigene and includes exon 7 of the SMN2, wherein (1) an increase in the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN2 in the presence of the compound relative to the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN2 in the absence of the compound indicates that the compound enhances inclusion of exon 7 of SMN2 into mRNA that is transcribed from the SMN2 gene; and (2) no change or no substantial change in the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN2 in the presence of the compound relative to the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN2 in the absence of the compound indicates that the compound does not enhance the inclusion of exon 7 of SMN2 into mRNA that is transcribed from the SMN2 gene.

[0048] In another example, provided herein is a method for determining whether a compound (*e.g.*, a compound of Formula (I) disclosed herein) enhances the inclusion of exon 7 of SMN1 into mRNA that is transcribed from the SMN1 gene, comprising (a) contacting mRNA that is transcribed from an SMN1 minigene described in International Application PCT/US2009/004625, filed August 13, 2009 (published as International Publication Number WO2010/019236) or United States Publication Number US2011/0172284 in the presence of a compound (*e.g.*, a compound of Formula (I) disclosed herein) with a primer(s) (*e.g.*, SEQ ID NO. 1 or 2) and/or a probe described herein (*e.g.*, SEQ ID NO. 3 or 10) along with applicable components for, *e.g*, RT-PCR, RT-qPCR, endpoint RT-PCR, PCR, qPCR, rolling circle

amplification and, as applicable, Northern blot or Southern blot; and (b) detecting the amount of mRNA that is transcribed from the minigene and includes exon 7 of the SMN1, wherein (1) an increase in the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN1 in the presence of the compound relative to the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN1 in the absence of the compound indicates that the compound enhances inclusion of exon 7 of SMN1 into mRNA that is transcribed from the SMN1 gene; and (2) no change or no substantial change in the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN1 in the presence of the compound relative to the amount of mRNA that is transcribed from the minigene and includes exon 7 of SMN1 in the absence of the compound indicates that the compound does not enhance the inclusion of exon 7 of SMN1 into mRNA that is transcribed from the SMN1 gene.

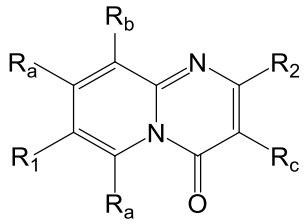
[0049] In another example, provided herein are kits comprising a primer and/or probe described below in the Biological Examples (*e.g.*, SMN primers such as SEQ ID NO. 1, 7, 8, 11 or 13 and/or SEQ ID NO. 2, 9 or 12, and/or SMN probes such as a SEQ ID NO. 3 or 10) and the use thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0050] Figure 1, referenced in Biological Example 1, is a schematic drawing of the SMN2-A minigene construct, which produces two alternatively spliced mRNA transcripts: a full length

What is claimed is:

1. A compound of Formula (IIa1):



(IIa1)

or a free acid, free base, salt, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof, wherein:

R_1 is heterocyclyl;

wherein, heterocyclyl is optionally substituted with one, two or three R_3 substituents and optionally, with one additional R_4 substituent; or,

wherein, heterocyclyl is optionally substituted with one, two, three or four R_3 substituents;

R_2 is phenyl;

wherein, R_2 is optionally substituted with one, two or three R_6 substituents and optionally, with one additional R_7 substituent;

R_a is, in each instance, independently selected from hydrogen, halogen or $C_{1\text{-}8}$alkyl;

R_b is hydrogen, halogen, $C_{1\text{-}8}$alkyl or $C_{1\text{-}8}$alkoxy;

R_c is hydrogen, halogen or $C_{1\text{-}8}$alkyl;

R_3 is, in each instance, independently selected from cyano, halogen, hydroxy, oxo, $C_{1\text{-}8}$alkyl, halo-$C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkyl-carbonyl, $C_{1\text{-}8}$alkoxy, halo-$C_{1\text{-}8}$alkoxy, $C_{1\text{-}8}$alkoxy-$C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkoxy-carbonyl, amino, $C_{1\text{-}8}$alkyl-amino, $(C_{1\text{-}8}\text{alkyl})_2$-amino, amino-$C_{1\text{-}8}$alkyl, $C_{1\text{-}8}$alkyl-amino-$C_{1\text{-}8}$alkyl, $(C_{1\text{-}8}\text{alkyl})_2$-amino-$C_{1\text{-}8}$alkyl, amino-$C_{1\text{-}8}$alkyl-amino, $C_{1\text{-}8}$alkyl-amino-$C_{1\text{-}8}$alkyl-amino, $(C_{1\text{-}8}\text{alkyl-amino-}C_{1\text{-}8}\text{alkyl})_2$-amino, $(C_{1\text{-}8}\text{alkyl})_2$-amino-$C_{1\text{-}8}$alkyl-amino, $[(C_{1\text{-}8}\text{alkyl})_2\text{-amino-}C_{1\text{-}8}\text{alkyl}]_2$-amino, $(C_{1\text{-}8}\text{alkyl-amino-}C_{1\text{-}8}\text{alkyl})(C_{1\text{-}8}\text{alkyl})$amino, $[(C_{1\text{-}8}\text{alkyl})_2\text{-amino-}C_{1\text{-}8}\text{alkyl}](C_{1\text{-}8}\text{alkyl})$amino, $C_{1\text{-}8}$alkoxy-$C_{1\text{-}8}$alkyl-amino, $(C_{1\text{-}8}\text{alkoxy-}C_{1\text{-}8}\text{alkyl})_2$-amino, $(C_{1\text{-}8}\text{alkoxy-}C_{1\text{-}8}\text{alkyl})(C_{1\text{-}8}\text{alkyl})$amino,

C_{1-8}alkyl-carbonyl-amino, C_{1-8}alkoxy-carbonyl-amino, hydroxy-C_{1-8}alkyl, hydroxy-C_{1-8}alkoxy-C_{1-8}alkyl, hydroxy-C_{1-8}alkyl-amino, (hydroxy-C_{1-8}alkyl)$_2$-amino or (hydroxy-C_{1-8}alkyl)(C_{1-8}alkyl)amino;

R_4 is C_{3-14}cycloalkyl, C_{3-14}cycloalkyl-C_{1-8}alkyl, C_{3-14}cycloalkyl-amino, aryl-C_{1-8}alkyl, aryl-C_{1-8}alkoxy-carbonyl, aryl-sulfonyloxy-C_{1-8}alkyl, heterocyclyl or heterocyclyl-C_{1-8}alkyl; wherein, each instance of C_{3-14}cycloalkyl, aryl and heterocyclyl is optionally substituted with one, two or three R_5 substituents;

R_5 is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C_{1-8}alkyl, halo-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, amino, C_{1-8}alkyl-amino, (C_{1-8}alkyl)$_2$-amino or C_{1-8}alkyl-thio;

R_6 is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C_{1-8}alkyl, C_{2-8}alkenyl, halo-C_{1-8}alkyl, hydroxy-C_{1-8}alkyl, C_{1-8}alkoxy, halo-C_{1-8}alkoxy, C_{1-8}alkoxy-C_{1-8}alkyl, amino, C_{1-8}alkyl-amino, (C_{1-8}alkyl)$_2$-amino or C_{1-8}alkyl-thio; and,

R_7 is C_{3-14}cycloalkyl, C_{3-14}cycloalkyl-oxy, aryl, heterocyclyl or heteroaryl.

2. The compound of claim 1, wherein R_1 is heterocyclyl selected from azetidinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, 1,4-diazepanyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (7R,8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aS)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, 3-azabicyclo[3.1.0]hexyl, (1R,5S)-3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl, (1R,5S)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, (1R,5S)-8-azabicyclo[3.2.1]oct-2-enyl, 9-azabicyclo[3.3.1]nonyl,

(1R,5S)-9-azabicyclo[3.3.1]nonyl, 2,5-diazabicyclo[2.2.1]heptyl, (1S,4S)-2,5-diazabicyclo[2.2.1]heptyl, 2,5-diazabicyclo[2.2.2]octyl, 3,8-diazabicyclo[3.2.1]octyl, (1R,5S)-3,8-diazabicyclo[3.2.1]octyl, 1,4-diazabicyclo[3.2.2]nonyl, azaspiro[3.3]heptyl, 2,6-diazaspiro[3.3]heptyl, 2,7-diazaspiro[3.5]nonyl, 5,8-diazaspiro[3.5]nonyl, 2,7-diazaspiro[4.4]nonyl and 6,9-diazaspiro[4.5]decyl; wherein, each instance of heterocyclyl is optionally substituted one, two or three R_3 substituents and optionally, with one additional R_4 substituent.

3. The compound of claim 1, wherein the compound is selected from the group consisting of:

2-(4-methoxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(4-methoxyphenyl)-7-(4-methylpiperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(4-methoxyphenyl)-7-[(3R)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-2-(4-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(1,4-diazepan-1-yl)-2-(4-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(3,3-dimethylpiperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[(3R)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(4-ethylpiperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(1,4-diazepan-1-yl)-2-(3,4-dimethoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(4-methyl-1,4-diazepan-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(4-methoxyphenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(4-methylpiperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(4-propylpiperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(4-methoxyphenyl)-7-(4-methyl-1,4-diazepan-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(3,3-dimethylpiperazin-1-yl)-2-(4-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-methoxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-methoxyphenyl)-7-(4-methylpiperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,

2-(3-methoxyphenyl)-7-[(3R)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-2-(3-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(4-ethylpiperazin-1-yl)-2-(3-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(1,4-diazepan-1-yl)-2-(3-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-methoxyphenyl)-7-(4-methyl-1,4-diazepan-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-phenyl-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-[(3S)-3-methylpiperazin-1-yl]-2-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-fluoro-7-(4-methylpiperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-chlorophenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(4-chlorophenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(piperazin-1-yl)-2-[3-(trifluoromethyl)phenyl]-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(piperazin-1-yl)-2-[4-(trifluoromethyl)phenyl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-methylphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(4-fluorophenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(4-nitrophenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,

2-[4-(dimethylamino)phenyl]-9-fluoro-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[4-(dimethylamino)phenyl]-9-fluoro-7-[(3R)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(2-fluorophenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,

2-[4-(dimethylamino)phenyl]-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[4-(dimethylamino)phenyl]-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethylphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethylphenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[3-(dimethylamino)phenyl]-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,

2-[3-(dimethylamino)phenyl]-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[4-(difluoromethoxy)phenyl]-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[4-(difluoromethoxy)phenyl]-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluorophenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-nitrophenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(4-methylphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(2-fluoro-4,5-dimethoxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(2-fluoro-4,5-dimethoxyphenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(3,8-diazabicyclo[3.2.1]oct-3-yl)-2-(3,4-dimethoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[4-methoxy-3-(trifluoromethyl)phenyl]-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[4-methoxy-3-(trifluoromethyl)phenyl]-7-[(3R)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[4-methoxy-3-(trifluoromethyl)phenyl]-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methoxy-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,5-difluoro-4-hydroxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
4-[4-oxo-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-2-yl]benzonitrile
2-[3-fluoro-5-(trifluoromethyl)phenyl]-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[4-fluoro-3-(trifluoromethyl)phenyl]-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[2-methoxy-3-(trifluoromethyl)phenyl]-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,5-difluorophenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(piperazin-1-yl)-2-[3-(trifluoromethoxy)phenyl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[4-methoxy-3-(trifluoromethoxy)phenyl]-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[4-hydroxy-3-(trifluoromethoxy)phenyl]-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,

2-[4-methoxy-3-(trifluoromethoxy)phenyl]-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[4-hydroxy-3-(trifluoromethoxy)phenyl]-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-[(3R)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(2,4-dimethoxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(2,4-dimethoxyphenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[3-(difluoromethoxy)-4-methoxyphenyl]-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[3-(difluoromethoxy)-4-hydroxyphenyl]-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[3-(difluoromethoxy)-4-methoxyphenyl]-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[3-(difluoromethoxy)-4-hydroxyphenyl]-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,5-difluorophenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-chloro-4-methoxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-chloro-4-methoxyphenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-ethoxy-4-methoxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-ethoxy-4-methoxyphenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[(3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(4-aminopiperidin-1-yl)-2-(3,4-dimethoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-5-methoxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-5-methoxyphenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,

2-(3,4-dimethoxyphenyl)-9-methyl-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(piperidin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4,5-dimethoxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(4-hydroxypiperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[4-(dimethylamino)piperidin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(4-methoxy-3-methylphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
3-[4-oxo-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-2-yl]benzonitrile
2-methoxy-5-[4-oxo-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-2-yl]benzonitrile
2-(3-fluoro-4-hydroxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(4-ethoxy-3-fluorophenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[3-fluoro-4-(2,2,2-trifluoroethoxy)phenyl]-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methylphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methylphenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
7-[(3S)-3-aminopyrrolidin-1-yl]-2-(3,4-dimethoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(1-methylpiperidin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[(3S)-3-(propan-2-ylamino)pyrrolidin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-(4-methyl-1,4-diazepan-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(4-methoxy-3-nitrophenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-[3-fluoro-4-(methylsulfanyl)phenyl]-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,

2-(3,5-difluoro-4-methoxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,

2-(3,5-difluoro-4-methoxyphenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
7-[4-(dimethylamino)piperidin-1-yl]-2-(3-fluoro-4-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-(1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-chloro-5-fluorophenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-chloro-5-fluorophenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-2-(3-fluoro-4-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-[(3R,4R)-3-(dimethylamino)-4-hydroxypyrrolidin-1-yl]-2-(3-fluoro-4-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(4-aminopiperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-[4-(methylamino)piperidin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-[(3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-[(3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[1-(2-hydroxyethyl)piperidin-4-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(4-fluoro-3-methoxyphenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(4-fluoro-3-methoxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-difluoro-5-methoxyphenyl)-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,

2-(3,4-difluoro-5-methoxyphenyl)-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,

2-(3-fluoro-4-methoxyphenyl)-7-[(3S)-3-(methylamino)pyrrolidin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-{4-[(methylamino)methyl]piperidin-1-yl}-4H-pyrido[1,2-a]pyrimidin-4-one,
7-[(3S)-3-aminopyrrolidin-1-yl]-2-(3-fluoro-4-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-{4-[(dimethylamino)methyl]piperidin-1-yl}-2-(3-fluoro-4-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
3-fluoro-5-{7-[(3S)-3-methylpiperazin-1-yl]-4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl}benzonitrile
3-fluoro-5-[4-oxo-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-2-yl]benzonitrile
2-(3-fluoro-4-methoxyphenyl)-7-[(3'S,4'S)-4'-hydroxy-1,3'-bipyrrolidin-1'-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(1,4-diazepan-1-yl)-2-(3,4-dimethoxyphenyl)-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-[(3aR,6aR)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-(1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[1-(2-hydroxyethyl)-1,2,3,6-tetrahydropyridin-4-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-(piperidin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-(1-methylpiperidin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[(3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-[(3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,

2-(3,4-dimethoxyphenyl)-7-[4-(dimethylamino)piperidin-1-yl]-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
7-[(1R,5S)-8-azabicyclo[3.2.1]oct-2-en-3-yl]-2-(3,4-dimethoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(1,2,5,6-tetrahydropyridin-3-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-[(3aR,6aS)-5-(2-hydroxyethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-[(3aS,6aS)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-[(3aR,6aS)-5-(propan-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
7-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-2-(3-fluoro-4-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-[(4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
7-[(3aR,6aS)-5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-2-(3-fluoro-4-methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-9-methyl-7-(1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-[(4aR,7aR)-1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-[(3R)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-9-methyl-7-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[(1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[(2R)-2-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-9-methyl-7-[(3S)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,

7-[4-(dimethylamino)piperidin-1-yl]-2-(3-fluoro-4-methoxyphenyl)-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-9-methyl-7-(1-methylpiperidin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-[4-(cyclopropylamino)piperidin-1-yl]-2-(3,4-dimethoxyphenyl)-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[(3R)-3,4-dimethylpiperazin-1-yl]-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-(4-methylpiperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[4-(dimethylamino)piperidin-1-yl]-9-ethyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[1-(2-hydroxyethyl)-1,2,3,6-tetrahydropyridin-4-yl]-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrimido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-[4-(methylamino)piperidin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[4-(ethylamino)piperidin-1-yl]-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-8-methyl-7-(piperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[4-(propan-2-ylamino)piperidin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(1-cyclobutyl-1,2,3,6-tetrahydropyridin-4-yl)-2-(3,4-dimethoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[1-(propan-2-yl)-1,2,3,6-tetrahydropyridin-4-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,

2-(3,4-dimethoxyphenyl)-7-(1-propyl-1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-(1-propyl-1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(1-cyclobutyl-1,2,3,6-tetrahydropyridin-4-yl)-2-(3,4-dimethoxyphenyl)-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-[1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-[1-(propan-2-yl)-1,2,3,6-tetrahydropyridin-4-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-8-methyl-7-(1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-(1-cyclopropyl-1,2,3,6-tetrahydropyridin-4-yl)-2-(3,4-dimethoxyphenyl)-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-8-methyl-7-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrimido[1,2-b]pyridazin-4-one,
2-(3,4-dimethoxyphenyl)-7-(1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrazino[1,2-a]pyrimidin-4-one,
2-(3-fluoro-4-methoxyphenyl)-7-(piperidin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(1-ethylpiperidin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[cis-4-(methylamino)cyclohexyl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-(piperidin-3-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-[4-(propylamino)piperidin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,

2-(3,4-dimethoxyphenyl)-9-ethyl-7-(1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[(8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-ethyl-7-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-[4-(propan-2-ylamino)piperidin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-[(8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-ethyl-7-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-methyl-7-[4-(morpholin-4-yl)piperidin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-{4-[(2-hydroxyethyl)amino]piperidin-1-yl}-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-ethyl-7-(1-methylpiperidin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
7-[4-(diethylamino)piperidin-1-yl]-2-(3,4-dimethoxyphenyl)-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-ethyl-7-(1-ethylpiperidin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-{4-[(2-hydroxyethyl)(methyl)amino]piperidin-1-yl}-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-ethyl-7-[(3R)-3-methylpiperazin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-9-ethyl-7-[(8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-{4-[(2-methoxyethyl)amino]piperidin-1-yl}-9-methyl-4H-pyrido[1,2-a]pyrimidin-4-one,
2-(3,4-dimethoxyphenyl)-7-{4-[(dimethylamino)methyl]piperidin-1-yl}-4H-pyrido[1,2-a]pyrimidin-4-one,

2-(3,4-dimethoxyphenyl)-7-[4-(pyrrolidin-1-ylmethyl)piperidin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one, and

2-(3,4-dimethoxyphenyl)-7-[4-(piperidin-1-ylmethyl)piperidin-1-yl]-4H-pyrido[1,2-a]pyrimidin-4-one,

or a salt, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof.

4. The compound of claim 1, wherein the salt is a chloride, hydrobromide, hydrochloride, dihydrochloride, acetate, trifluoroacetate or trifluoroacetic acid salt.