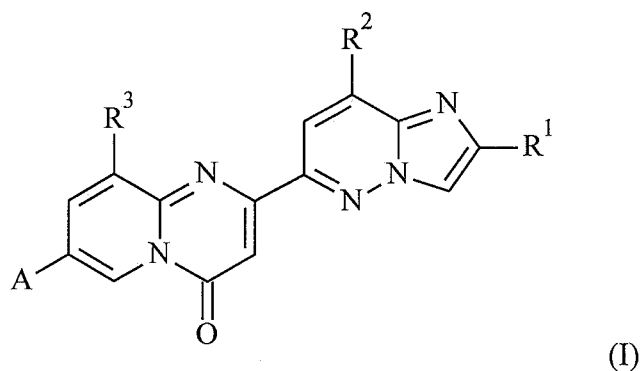


Summary

In one aspect, the present disclosure relates to the compound of formula (I)



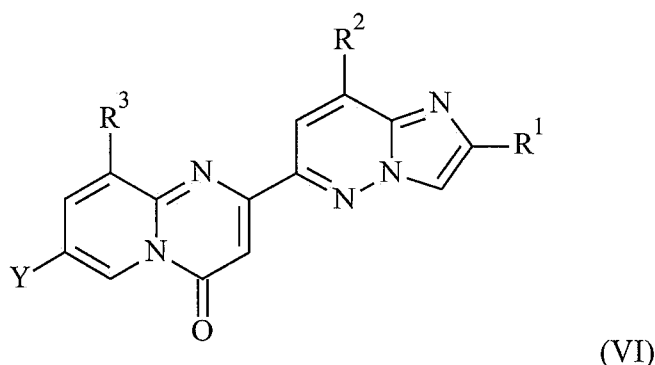
wherein

- 5 R¹ is hydrogen or C₁₋₇-alkyl;
- R² is hydrogen, cyano, C₁₋₇-alkyl, C₁₋₇-haloalkyl or C₃₋₈-cycloalkyl;
- R³ is hydrogen, C₁₋₇-alkyl, or C₃₋₈-cycloalkyl;
- A is N-heterocycloalkyl, wherein N-heterocycloalkyl comprises 1 or 2 nitrogen ring atoms and is optionally substituted with 1, 2, 3 or 4 substituents selected from R¹⁴;
- 10 R¹⁴ is independently selected from hydrogen, C₁₋₇-alkyl, amino, amino-C₁₋₇-alkyl, C₃₋₈-cycloalkyl and heterocycloalkyl or two R¹⁴ together form C₁₋₇-alkylene;

with the proviso that if A is N-heterocycloalkyl comprising only 1 nitrogen ring atom, then at least one R¹⁴ substituent is amino or amino-C₁₋₇-alkyl;

and pharmaceutically acceptable salts thereof.

In another aspect, the present disclosure relates to the compound of formula (VI)



wherein R^1 , R^2 and R^3 are as described herein;

Y is halogen or trifluoromethanesulfonate;

5 and salts thereof.

In another aspect, the present disclosure relates to a process for the preparation of compounds of formula (I) as disclosed herein, comprising an aromatic nucleophilic substitution reaction between a compound of formula (VI) as described herein with a compound of formula M-A by heating in a solvent, wherein A, R^1 , R^2 and R^3 are as defined herein, Y is as defined
10 herein, M is hydrogen, sodium or potassium, and wherein M is linked to A via a nitrogen atom of A.

In another aspect, the present disclosure relates to pharmaceutical compositions comprising compounds of formula (I) as disclosed herein or their pharmaceutically acceptable salts and one or more pharmaceutically acceptable excipients.

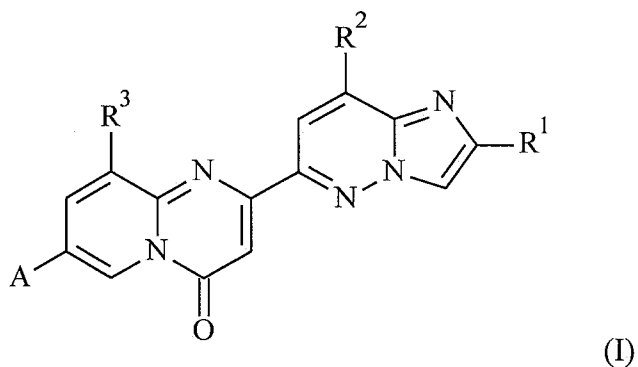
15 In another aspect, the present disclosure relates to compounds of formula (I) as disclosed herein or their pharmaceutically acceptable salts above for use as therapeutically active substances.

In another aspect, the present disclosure relates to compounds of formula (I) as disclosed herein or their pharmaceutically acceptable salts for the use in the treatment or prevention of
20 spinal muscular atrophy (SMA).

In another aspect, the present disclosure relates to the use of compounds of formula (I) as disclosed herein or their pharmaceutically acceptable salts for the preparation of medicaments for the treatment or prevention of spinal muscular atrophy (SMA).

Claims

1. The compound of formula (I)



wherein

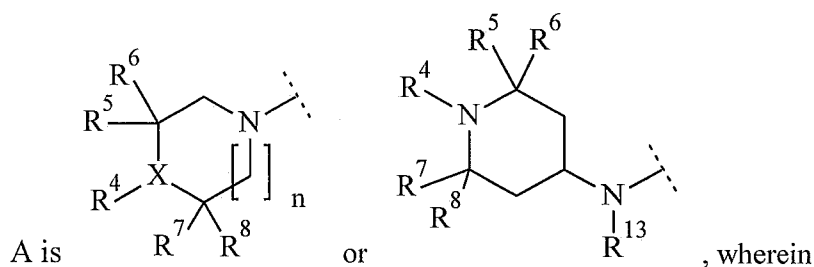
- R^1 is hydrogen or C_{1-7} -alkyl;
- R^2 is hydrogen, cyano, C_{1-7} -alkyl, C_{1-7} -haloalkyl or C_{3-8} -cycloalkyl;
- R^3 is hydrogen, C_{1-7} -alkyl, or C_{3-8} -cycloalkyl;
- A is N-heterocycloalkyl, wherein N-heterocycloalkyl comprises 1 or 2 nitrogen ring atoms and is optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14} ;
- R^{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.

2. A compound according to claim 1, wherein R^1 is C_{1-7} -alkyl.
3. A compound according to any of claims 1 to 2, wherein R^1 is methyl.
4. A compound according to any of claims 1 to 3, wherein R^2 is hydrogen or C_{1-7} -alkyl.
5. A compound according to any of claims 1 to 4, wherein R^2 is hydrogen or methyl.
6. A compound according to any of claims 1 to 5, wherein R^3 is hydrogen or C_{1-7} -alkyl.
7. A compound according to any of claims 1 to 6, wherein R^3 is hydrogen or methyl.
8. A compound according to any of claims 1 to 7, wherein R^{12} is piperidinyl optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14} .
9. A compound according to any of claims 1 to 8, wherein R^{13} is hydrogen or C_{1-7} -alkyl.
10. A compound according to any of claims 1 to 9, wherein R^{13} is hydrogen or methyl.
11. A compound according to any of claims 1 to 10, wherein R^{14} is independently selected from C_{1-7} -alkyl and heterocycloalkyl or two R^{14} together form C_{1-7} -alkylene.
12. A compound according to any of claims 1 to 11, wherein R^{14} is independently selected from methyl, ethyl and pyrrolidinyl or two R^{14} together form ethylene
13. A compound according to any of claims 1 to 12, wherein the N-heterocycloalkyl in A or the heterocycloalkyl in R^{12} as defined in Claim 1 are further characterized in that one ring nitrogen atom is basic.

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



X is N or CH;

R⁴ is hydrogen, C₁₋₇-alkyl or -(CH₂)_m-NR⁹R¹⁰;

R⁵ is hydrogen or C₁₋₇-alkyl;

R⁶ is hydrogen or C₁₋₇-alkyl;

R⁷ is hydrogen or C₁₋₇-alkyl;

R⁸ is hydrogen or C₁₋₇-alkyl;

R⁹ and R¹⁰ are independently selected from hydrogen, C₁₋₇-alkyl and C₃₋₈-cycloalkyl;

R¹³ is hydrogen, C₁₋₇-alkyl or C₃₋₈-cycloalkyl;

n is 0, 1 or 2;

m is 0, 1, 2 or 3;

or R⁴ and R⁵ together form C₁₋₇-alkylene;

or R⁴ and R⁷ together form C₁₋₇-alkylene;

or R⁵ and R⁶ together form C₂₋₇-alkylene;

or R⁵ and R⁷ together form C₁₋₇-alkylene;

or R⁵ and R⁹ together form C₁₋₇-alkylene;

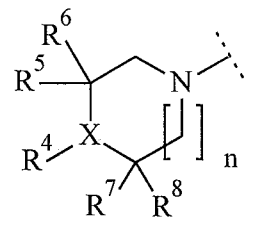
or R⁷ and R⁸ together form C₂₋₇-alkylene;

or R⁷ and R⁹ together form C₁₋₇-alkylene;

or R⁹ and R¹⁰ together form C₂₋₇-alkylene;

with the proviso that if X is CH then R⁴ is -(CH₂)_m-NR⁹R¹⁰; and

with the proviso that if X is N and R⁴ is $-(CH_2)_m-NR^9R^{10}$ then m is 2 or 3.



15. A compound according to any of claims 1 to 14, wherein A is wherein

X is N or CH;

R⁴ is hydrogen, C₁₋₇-alkyl or $-(CH_2)_m-NR^9R^{10}$;

R⁵ is hydrogen or C₁₋₇-alkyl;

R⁶ is hydrogen or C₁₋₇-alkyl;

R⁷ is hydrogen or C₁₋₇-alkyl;

R⁸ is hydrogen or C₁₋₇-alkyl;

R⁹ and R¹⁰ are independently selected from hydrogen, C₁₋₇-alkyl and C₃₋₈-cycloalkyl;

n is 0, 1 or 2;

m is 0, 1, 2 or 3;

or R⁴ and R⁵ together form C₁₋₇-alkylene;

or R⁴ and R⁷ together form C₁₋₇-alkylene;

or R⁵ and R⁶ together form C₂₋₇-alkylene;

or R⁵ and R⁷ together form C₁₋₇-alkylene;

or R⁵ and R⁹ together form C₁₋₇-alkylene;

or R⁷ and R⁸ together form C₂₋₇-alkylene;

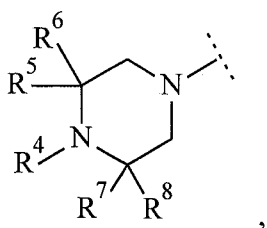
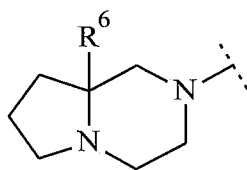
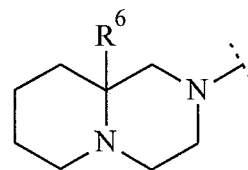
or R⁷ and R⁹ together form C₁₋₇-alkylene;

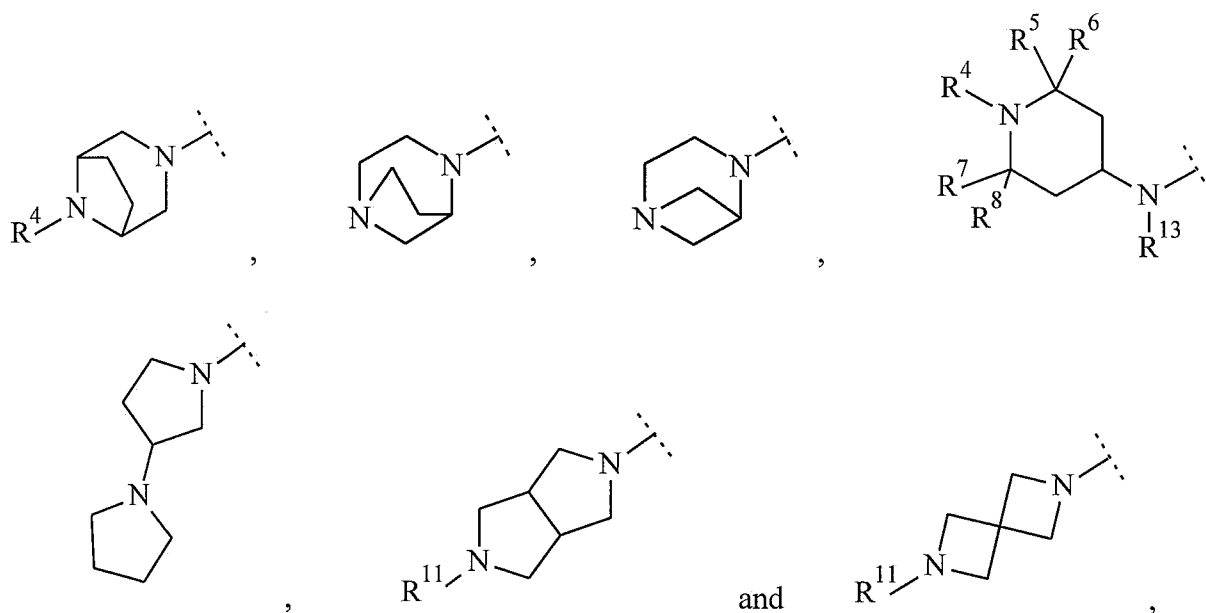
or R⁹ and R¹⁰ together form C₂₋₇-alkylene;

with the proviso that if X is CH then R⁴ 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.

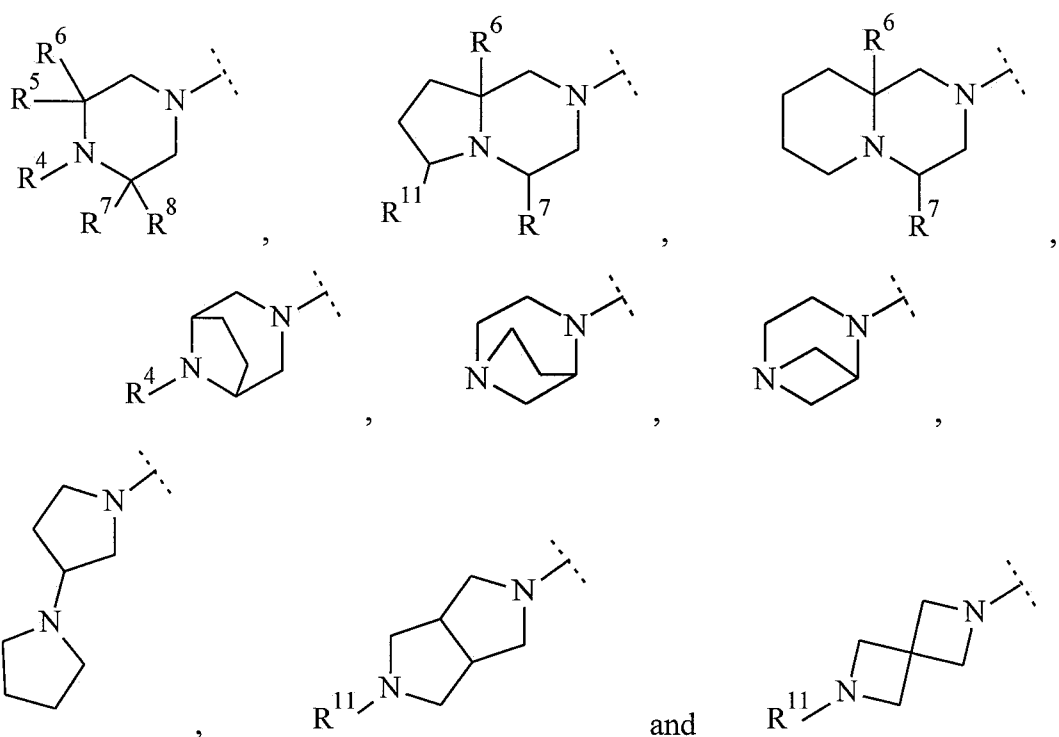
16. A compound according to any of claims 14 to 15, wherein X is N.
17. A compound according to any of claims 14 to 16, wherein n is 1.
18. A compound according to any of claims 14 to 17, wherein R^4 is hydrogen, methyl or $-(CH_2)_m-NR^9R^{10}$.
19. A compound according to any of claims 14 to 18, wherein R^4 is hydrogen.
20. A compound according to any of claims 14 to 19, wherein R^5 is hydrogen, methyl or ethyl.
21. A compound according to any of claims 14 to 20, wherein R^5 is methyl.
22. A compound according to any of claims 14 to 21, wherein R^6 is hydrogen or methyl.
23. A compound according to any of claims 14 to 22, wherein R^6 is hydrogen.
24. A compound according to any of claims 14 to 23, wherein R^7 is hydrogen or methyl.
25. A compound according to any of claims 14 to 24, wherein R^8 is hydrogen.
26. A compound according to any of claims 14 to 18, wherein m is 0.
27. A compound according to any of claims 14 to 17, wherein R^4 and R^5 together form propylene.
28. A compound according to any of claims 14 to 17, wherein R^5 and R^6 together form ethylene.
29. A compound according to any of claims 14 to 17, wherein R^9 and R^{10} together form butylene.
30. A compound according to any of claims 1 to 29, wherein A is selected from the group of:





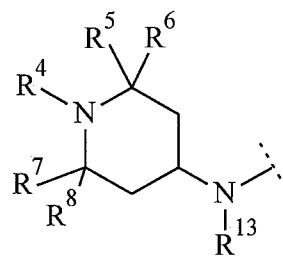
wherein R^4 , R^5 , R^6 , R^7 , R^8 and R^{13} are as defined in any of claims 1 to 29 and wherein R^{11} is hydrogen or C_{1-7} -alkyl.

31. A compound according to any of claims 1 to 30, wherein A is selected from the group of:

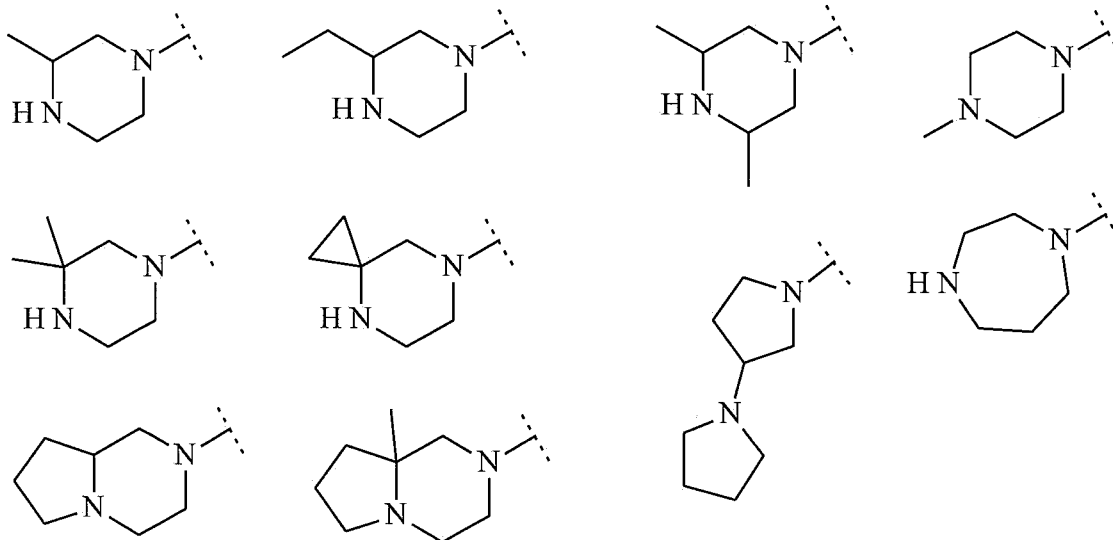


wherein R^4 , R^5 , R^6 , R^7 and R^8 are as defined in any of claims 1 to 30 and wherein R^{11} is hydrogen or C_{1-7} -alkyl.

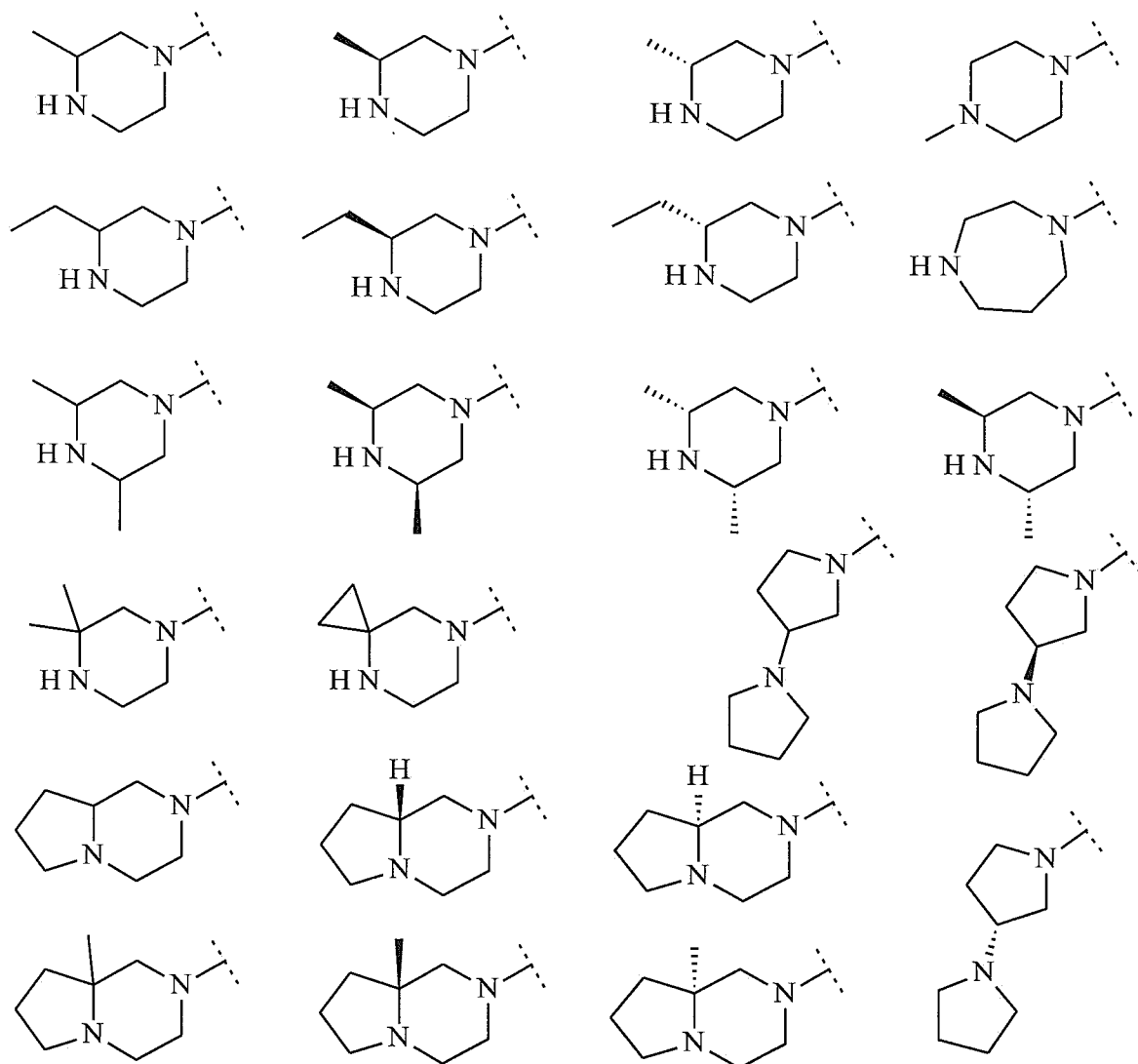
32. A compound according to any of claims 1 to 31, wherein A is selected from the group of piperazinyl, diazepanyl, pyrrolidinyl and hexahydropyrrolo[1,2-a]pyrazinyl, each optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14} as defined in any of claims 1 to 31.
33. A compound according to any of claims 1 to 32, 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 32.
34. A compound according to any of claims 1 to 30, wherein A is $NR^{12}R^{13}$, wherein R^{12} and R^{13} are as described in any of claims 1 to 30.



35. A compound according to any of claims 1 to 30, wherein A is $NR^{12}R^{13}$, wherein R^{12} and R^{13} are as described in any of claims 1 to 30.
36. A compound according to any of claims 1 to 33, wherein A is selected from the group of:



37. A compound according to any of claims 1 to 33, wherein A is selected from the group of:



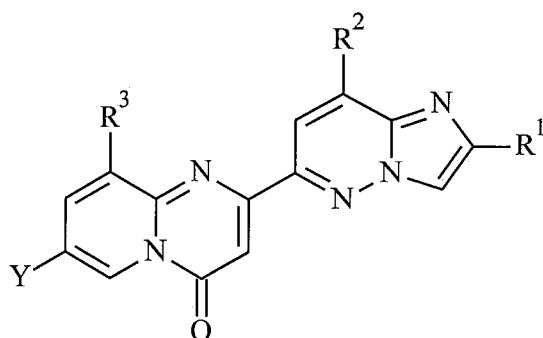
38. A compound according to any one of claims 1 to 37, selected from the group consisting of:
 2-(2-methylimidazo[1,2-b]pyridazin-6-yl)-7-(4-methylpiperazin-1-yl)pyrido[1,2-a]pyrimidin-4-one;
 7-[(8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-2-(2-methylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one;
 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;

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.

39. A compound according to any one of claims 1 to 38, 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-methylpyrido[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.

40. The compound of formula (VI)



(VI)

wherein R¹, R² and R³ are as described in any of claims 1 to 6;

Y is halogen or trifluoromethanesulfonate;

and salts thereof.

41. A compound of formula (VI) according to claim 40, wherein Y is fluoro, chloro, bromo, iodo or trifluoromethanesulfonate.

42. A compound of formula (VI) according to claim 40, wherein Y is fluoro.
43. A compound of formula (VI) according to any one of claims 40 to 42, selected from the group consisting of:
 7-fluoro-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-fluoro-pyrido[1,2-a]pyrimidin-4-one;
 7-fluoro-9-methyl-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-fluoro-9-methyl-pyrido[1,2-a]pyrimidin-4-one;
 and salts thereof.
44. A compound of claim 38 or 39, wherein the compound 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 a pharmaceutically acceptable salt thereof.
45. A compound of claim 38 or 39, wherein the compound is 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, or a pharmaceutically acceptable salt thereof.
46. A compound of claim 38 or 39, wherein the compound 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 a pharmaceutically acceptable salt thereof.
47. A compound of claim 38 or 39, wherein the compound is 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, or a pharmaceutically acceptable salt thereof.
48. A compound of claim 38 or 39, wherein the compound is 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, or a pharmaceutically acceptable salt thereof.
49. A process for the preparation of compounds of formula (I) according to any of claims 1 to 39, comprising an aromatic nucleophilic substitution reaction between a compound of formula (VI) as described in any of claims 40 to 43 with a compound of formula M-A by heating in a solvent, wherein A, R¹, R² and R³ are as defined in any of claims 1 to 39, Y is as defined in any of claims 40 to 43, M is hydrogen, sodium or potassium, and wherein M is linked to A via a nitrogen atom of A.
50. The process of claim 49, wherein the aromatic nucleophilic substitution reaction is performed at a temperature from 80°C to 200°C.

51. The process according to any of claims 49 or 50, wherein the solvent of the aromatic nucleophilic substitution reaction is selected from dimethyl sulfoxide, N-methylpyrrolidone, and dimethylformamide.
52. The process according to any of claims 49 to 50, wherein M is hydrogen.
53. Pharmaceutical compositions comprising compounds of formula (I) according to any of claims 1 - 39 or 44 to 48 or their pharmaceutically acceptable salts and one or more pharmaceutically acceptable excipients.
54. Compounds of formula (I) according to any of claims 1 - 39 or 44 to 48 or their pharmaceutically acceptable salts above for use as therapeutically active substances.
55. Compounds of formula (I) according to any of claims 1 - 39 or 44 to 48 or their pharmaceutically acceptable salts for the use in the treatment or prevention of spinal muscular atrophy (SMA).

56. The use of compounds of formula (I) according to any of claims 1 - 39 or 44 to 48 or their pharmaceutically acceptable salts for the preparation of medicaments for the treatment or prevention of spinal muscular atrophy (SMA).