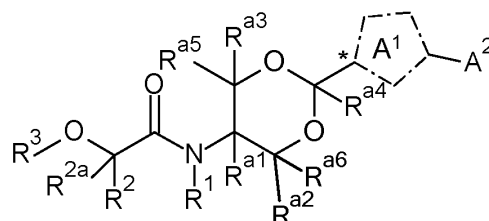


Patent Claims

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein

R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , R^{a6} are independently selected from the group consisting of H; halogen; C_{1-4} alkyl; and A^{2a} , wherein C_{1-4} alkyl is optionally substituted with one or more substituents selected from the group consisting of halogen, OH, and $O-C_{1-3}$ alkyl, wherein the substituents are the same or different, and provided that only one of R^{a1} , R^{a2} , R^{a3} , R^{a4} , R^{a5} , R^{a6} is A^{2a} ,

A^1 is C_5 cycloalkylene, C_5 cycloalkenylene, or a nitrogen ring atom containing 5-membered heterocyclene, provided that the ring atom of ring A^1 marked with an asterisk is a carbon atom, wherein A^1 is optionally substituted with one or more R^4 , which are the same or different;

each R^4 is independently oxo ($=O$) where the ring is at least partially saturated, thiooxo ($=S$) where the ring is at least partially saturated, halogen, CN, OR^5 , or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^5 is H or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

A² is R^{6a} or A^{2a};

5 R^{6a} is OR^{6a1}, SR^{6a1}, N(R^{6a1}R^{6a2}); C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; OR^{6a3}; CN; and A^{2a}, wherein the substituents are the same or different;

10 R^{6a1}, R^{6a2} are independently selected from the group consisting of H; C₁₋₆ alkyl; C₂₋₆ alkenyl; C₂₋₆ alkynyl; and A^{2a}, wherein C₁₋₆ alkyl; C₂₋₆ alkenyl; and C₂₋₆ alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; A^{2a}; and OA^{2a}, wherein the substituents are the same or different;

15 R^{6a3} is H; or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more halogen, which are the same or different;

A^{2a} is phenyl; C₃₋₇ cycloalkyl; C₄₋₁₂ bicycloalkyl; or 3- to 7-membered heterocyclyl, wherein A^{2a} is optionally substituted with one or more R⁶, which are the same or different;

20 each R⁶ is independently R^{6b}, OH; OR^{6b}; halogen; or CN, wherein R^{6b} is cyclopropyl, C₁₋₆ alkyl; C₂₋₆ alkenyl; or C₂₋₆ alkynyl, wherein R^{6b} is optionally substituted with one or more halogen, which are the same or different; or two R⁶ are joined to form together with the atoms to which they are attached a ring A^{2b};

25 A^{2b} is phenyl; C₃₋₇ cycloalkyl; or 3 to 7 membered heterocyclyl, wherein A^{2b} is optionally substituted with one or more R⁷, which are the same or different;

30 each R⁷ is independently C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are optionally substituted with one or more halogen, which are the same or different;

R¹ is H or C₁₋₄ alkyl, preferably H, wherein C₁₋₄ alkyl is optionally substituted with one or more halogen, which are the same or different;

R^2 is H; F; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different; and

R^3 is A^3 , C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^8 , which are the same or different; or

R^2 and R^3 are joined to form together with the oxygen atom and carbon atom to which they are attached a ring A^{3a} , wherein A^{3a} is a 7 to 12 membered heterobicycyl, wherein 7 to 12 membered heterobicycyl is optionally substituted with one or more R^{10} , which are the same or different;

R^{2a} is H or F, preferably H;

each R^8 is independently halogen; CN, $C(O)OR^9$, OR^9 , $C(O)R^9$, $C(O)N(R^9R^{9a})$, $S(O)_2N(R^9R^{9a})$, $S(O)N(R^9R^{9a})$, $S(O)_2R^9$, $S(O)R^9$, $N(R^9)S(O)_2N(R^{9a}R^{9b})$, SR^9 , $N(R^9R^{9a})$, NO_2 , $OC(O)R^9$, $N(R^9)C(O)R^{9a}$, $N(R^9)SO_2R^{9a}$, $N(R^9)S(O)R^{9a}$, $N(R^9)C(O)N(R^{9a}R^{9b})$, $N(R^9)C(O)OR^{9a}$, $OC(O)N(R^9R^{9a})$, or A^3 ;

R^9 , R^{9a} , R^{9b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different, or one OH, or one OC_{1-4} alkyl, or one A^3 ;

each A^3 is independently phenyl, naphthyl, C_{3-7} cycloalkyl, 3 to 7 membered heterocyclyl, or 7 to 12 membered heterobicycyl, wherein A^3 is optionally substituted with one or more R^{10} , which are the same or different;

each R^{10} is independently halogen, CN, $C(O)OR^{11}$, OR^{11} , $C(O)R^{11}$, $C(O)N(R^{11}R^{11a})$, $S(O)_2N(R^{11}R^{11a})$, $S(O)N(R^{11}R^{11a})$, $S(O)_2R^{11}$, $S(O)R^{11}$, $N(R^{11})S(O)_2N(R^{11a}R^{11b})$, SR^{11} , $N(R^{11}R^{11a})$, NO_2 , $OC(O)R^{11}$, $N(R^{11})C(O)R^{11a}$, $N(R^{11})S(O)_2R^{11a}$, $N(R^{11})S(O)R^{11a}$, $N(R^{11})C(O)OR^{11a}$, $N(R^{11})C(O)N(R^{11a}R^{11b})$, $OC(O)N(R^{11}R^{11a})$, oxo (=O) where the ring is at least partially saturated, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl,

C₂₋₆ alkenyl, and C₂₋₆ alkynyl are optionally substituted with one or more R¹², which are the same or different;

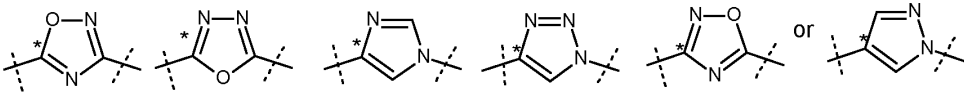
5 R¹¹, R^{11a}, R^{11b} are independently selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are optionally substituted with one or more halogen, which are the same or different;

10 each R¹² is independently halogen, CN, C(O)OR¹³, OR¹³, C(O)R¹³, C(O)N(R¹³R^{13a}), S(O)₂N(R¹³R^{13a}), S(O)N(R¹³R^{13a}), S(O)₂R¹³, S(O)R¹³, N(R¹³)S(O)₂N(R^{13a}R^{13b}), SR¹³, N(R¹³R^{13a}), NO₂, OC(O)R¹³, N(R¹³)C(O)R^{13a}, N(R¹³)SO₂R^{13a}, N(R¹³)S(O)R^{13a}, N(R¹³)C(O)N(R^{13a}R^{13b}), N(R¹³)C(O)OR^{13a}, or OC(O)N(R¹³R^{13a});

15 R¹³, R^{13a}, R^{13b} are independently selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are optionally substituted with one or more halogen, which are the same or different.

2. The compound of claim 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} are H.
- 20 3. The compound of claim 1 or 2 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A¹ is a nitrogen ring atom containing 5-membered heterocyclene and wherein A¹ is optionally substituted with one or more R⁴, which are the same or different.
- 25 4. The compound of any one of claims 1 to 3 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A¹ is a nitrogen ring atom containing 5-membered heterocyclene selected from the group of bivalent heterocycles consisting of oxadiazole, imidazole, imidazolidine, pyrazole and triazole, preferably triazole or oxadiazole, more preferably oxadiazole, and wherein A¹ is optionally substituted with

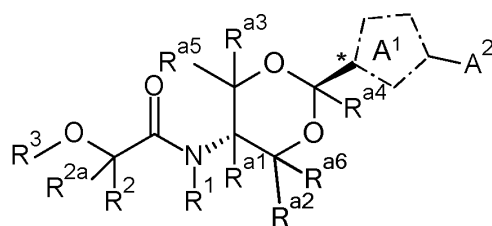
30 one or more R⁴, which are the same or different.

5. The compound of any one of claims 1 to 4 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^1 is unsubstituted or substituted with one or two R^4 , which are the same or different, preferably A^1 is unsubstituted.
- 5 6. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^4 is oxo, where the ring is at least partly saturated.
7. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^1 is
- 10
- 
8. The compound of any one of claims 1 to 7 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^2 is R^{6a} .
- 15
9. The compound of claim 8 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^{6a} is OR^{6a1} and R^{6a1} is preferably A^{2a} or C_{1-6} alkyl, optionally substituted with one or more halogen and/or one A^{2a} and/or one OR^{6a3} ; or R^{6a} is C_{1-6} alkyl, optionally substituted with one or more halogen and/or one A^{2a} and/or one OR^{6a3} .
- 20
10. The compound of claim 8 or 9 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^{6a} is OR^{6a1} and R^{6a1} is preferably C_{1-6} alkyl, optionally substituted with one or more F and/or one OR^{6a3} ; or R^{6a} is C_{1-6} alkyl, optionally substituted with one or more halogen and/or one OR^{6a3} .
- 25
11. The compound of any one of claims 1 to 7 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^2 is A^{2a} .
- 30 12. The compound of claim 11 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^{2a} is phenyl, cyclobutyl, azetidiny, or 5- to

6-membered aromatic heterocyclyl, and wherein A^{2a} is optionally substituted with one or more R⁶, which are the same or different.

13. The compound of any one of claims 1 to 9, 11 and 12 or a pharmaceutically acceptable
5 salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^{2a} is substituted with one or two R⁶, which are the same or different.
14. The compound of any one of claims 1 to 9, 11 to 13 or a pharmaceutically acceptable
10 salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein each R⁶ is independently F, Cl, CF₃, OCH₃, OCF₃, CH₃, CH₂CH₃, or cyclopropyl.
15. The compound of any one of claims 1 to 14 or a pharmaceutically acceptable salt,
solvate, hydrate, tautomer or stereoisomer thereof, wherein R² is H.
- 15 16. The compound of any one of claims 1 to 15 or a pharmaceutically acceptable salt,
solvate, hydrate, tautomer or stereoisomer thereof, wherein R³ is A³.
17. The compound of any one of claims 1 to 16 or a pharmaceutically acceptable salt,
solvate, hydrate, tautomer or stereoisomer thereof, wherein A³ is phenyl, pyridyl,
20 pyrazinyl, pyrimidazolyl, cyclopropyl, cyclobutyl or cyclohexyl and wherein A³ is optionally substituted with one or more R¹⁰, which are the same or different.
18. The compound of any one of claims 1 to 17 or a pharmaceutically acceptable salt,
solvate, hydrate, tautomer or stereoisomer thereof, wherein A³ is substituted with one
25 or two R¹⁰, which are the same or different.
19. The compound of any one of claims 1 to 14 or a pharmaceutically acceptable salt,
solvate, hydrate, tautomer or stereoisomer thereof, wherein R² and R³ are joined together
with the oxygen and carbon atom to which they are attached to form a
30 dihydrobenzopyran ring, wherein the ring is optionally substituted with one or more R¹⁰, which are the same or different, preferably the ring is substituted with one or two R¹⁰.

20. The compound of any one of claims 1 to 19 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R¹⁰ is independently F, Cl, Br, CHF₂, CF₃, OCF₃, CH=O, CH₂OH or CH₃.
- 5 21. The compound of any one of claims 1 to 20 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein the compound is
- 2-(4-chloro-3-fluorophenoxy)-*N*-[*trans*-2-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-1,3-dioxan-5-yl]acetamide;
- 10 2-(4-chloro-3-fluorophenoxy)-*N*-[*trans*-2-{5-[*cis*-3-(trifluoromethoxy)cyclobutyl]-1,3,4-oxadiazol-2-yl}-1,3-dioxan-5-yl]acetamide;
- 2-(4-chloro-3-fluorophenoxy)-*N*-[*cis*-2-[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]-1,3-dioxan-5-yl]acetamide;
- 15 2-(4-chloro-3-fluorophenoxy)-*N*-[*trans*-2-[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]-1,3-dioxan-5-yl]acetamide;
- 2-(4-chloro-3-fluorophenoxy)-*N*-[*trans*-2-[5-(4,4,4-trifluorobutoxy)-1,3,4-oxadiazol-2-yl]-1,3-dioxan-5-yl]acetamide;
- 2-(4-chloro-3-fluorophenoxy)-*N*-[*trans*-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}-1,3-dioxan-5-yl]acetamide;
- 20 2-(4-chloro-3-fluorophenoxy)-*N*-[*trans*-2-{5-[3-(trifluoromethoxy)azetidin-1-yl]-1,3,4-oxadiazol-2-yl}-1,3-dioxan-5-yl]acetamide;
- 2-[(6-chloro-5-fluoro-3-pyridyl)oxy]-*N*-[*trans*-2-[5-[*cis*-3-(trifluoromethoxy)cyclobutyl]-1,3,4-oxadiazol-2-yl]-1,3-dioxan-5-yl]acetamide;
- 25 2-[3-chloro-4-(difluoromethyl)phenoxy]-*N*-[*trans*-2-{5-[3-(trifluoromethoxy)azetidin-1-yl]-1,3,4-oxadiazol-2-yl}-1,3-dioxan-5-yl]acetamide; or
- 2-(3,4-dichlorophenoxy)-*N*-[*trans*-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}-1,3-dioxan-5-yl]acetamide.
22. The compound of any one of claims 1 to 21 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein the compound is of formula (Ia)
- 30



(Ia).

23. A pharmaceutical composition comprising at least one compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof as defined in any one of claims 1 to 22 together with a pharmaceutically acceptable carrier, optionally in combination with one or more other bioactive compounds or pharmaceutical compositions.
24. A compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of any one of claims 1 to 22 for use as a medicament.
25. A compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of any one of claims 1 to 22 or a pharmaceutical composition of claim 23 for use in a method of treating or preventing of one or more diseases or disorders associated with integrated stress response.
26. A compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of any one of claims 1 to 22 or a pharmaceutical composition of claim 23 for use in a method of treating or preventing of one or more diseases or disorders selected from the group consisting of leukodystrophies, intellectual disability syndrome, neurodegenerative diseases and disorders, neoplastic diseases, infectious diseases, inflammatory diseases, musculoskeletal diseases, metabolic diseases, ocular diseases as well as diseases selected from the group consisting of organ fibrosis, chronic and acute diseases of the liver, chronic and acute diseases of the lung, chronic and acute diseases of the kidney, myocardial infarction, cardiovascular disease, arrhythmias, atherosclerosis, spinal cord injury, ischemic stroke, and neuropathic pain.