each R^6 is independently OH, O(C_{1-6} alkyl), halogen, CN, cyclopropyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein cyclopropyl, 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
two R^6 are joined to form together with atoms to which they are attached a ring A^{2a};

A^{2a} is phenyl~~;~~, C_{3-7} cycloalkyl~~;~~, or 3 to 7 membered heterocyclyl, wherein A^{2a} is optionally substituted with one or more R^7, which are the same or different;

each R^7 is independently 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 halogen, which are the same or different;

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

R^2 is H 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; or
R^2 and R^3 are joined to form a 3,4-dihydro-2H-1-benzopyran ring, which is optionally substituted with one or more R^8, which are the same or different;

A^3 is phenyl or 5- to 6-membered aromatic heterocyclyl, preferably, phenyl or 6-membered aromatic heterocyclyl, wherein A^3 is optionally substituted with one or more R^8, which are the same or different;

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, $OC(O)R^9$, $N(R^9)C(O)R^{9a}$, $N(R^9)S(O)_2R^{9a}$, $N(R^9)S(O)R^{9a}$, $N(R^9)C(O)OR^{9a}$, $N(R^9)C(O)N(R^{9a}R^{9b})$, $OC(O)N(R^9R^{9a})$, 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, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{10}, which are the same or different;

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;

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, $OC(O)R^{11}$, $N(R^{11})C(O)R^{11a}$, $N(R^{11})SO_2R^{11a}$, $N(R^{11})S(O)R^{11a}$, $N(R^{11})C(O)N(R^{11a}R^{11b})$, $N(R^{11})C(O)OR^{11a}$, or $OC(O)N(R^{11}R^{11a})$;

R^{11}, R^{11a}, R^{11b} 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.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising at least one compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof as defined above together with a pharmaceutically acceptable carrier, optionally in combination with one of more other bioactive compounds or pharmaceutical compositions.

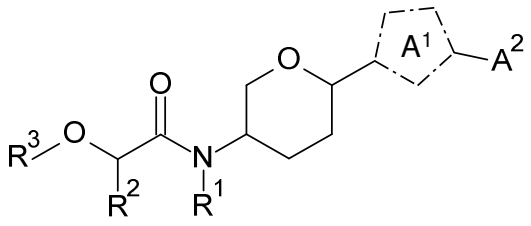
In yet another aspect, the present disclosure refers to a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof as defined above for the use as a medicament.

~~In yet another aspect, the present disclosure refers to a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof as defined above for use in treating or preventing of one or more diseases or disorders associated with integrated stress response.~~

~~In yet another aspect, the present disclosure refers to a use of a compound of a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof as defined above in the manufacture of a medicament for the treatment or prevention of one or more diseases or disorders associated with integrated stress response.~~

Patent Claims

1. A compound of formula (I)



(I)

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

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

each R^4 is independently halogen, CN, OR^5, oxo (=O) where the ring is at least partially saturated 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;

A^2 is phenyl or 5- to 6-membered aromatic heterocyclyl, wherein A^2 is optionally substituted with one or more R^6, which are the same or different;

each R^6 is independently OH, O(C_{1-6} alkyl), halogen, CN, cyclopropyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein cyclopropyl, 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

two R^6 are joined to form together with atoms to which they are attached a ring A^{2a};

A^{2a} is phenyl~~;~~, C_{3-7} cycloalkyl~~;~~, or 3 to 7 membered heterocyclyl, wherein A^{2a} is optionally substituted with one or more R^7, which are the same or different;

each R^7 is independently 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 halogen, which are the same or different;

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

R^2 is H 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; or
R^2 and R^3 are joined to form a 3,4-dihydro-2H-1-benzopyran ring, which is optionally substituted with one or more R^8, which are the same or different;

A^3 is phenyl or 5- to 6-membered aromatic heterocyclyl, wherein A^3 is optionally substituted with one or more R^8, which are the same or different;

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, $OC(O)R^9$, $N(R^9)C(O)R^{9a}$, $N(R^9)S(O)_2R^{9a}$, $N(R^9)S(O)R^{9a}$, $N(R^9)C(O)OR^{9a}$, $N(R^9)C(O)N(R^{9a}R^{9b})$, $OC(O)N(R^9R^{9a})$, 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, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{10}, which are the same or different;

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;

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, $OC(O)R^{11}$, $N(R^{11})C(O)R^{11a}$, $N(R^{11})SO_2R^{11a}$, $N(R^{11})S(O)R^{11a}$, $N(R^{11})C(O)N(R^{11a}R^{11b})$, $N(R^{11})C(O)OR^{11a}$, or $OC(O)N(R^{11}R^{11a})$;

R^{11}, R^{11a}, R^{11b} 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.

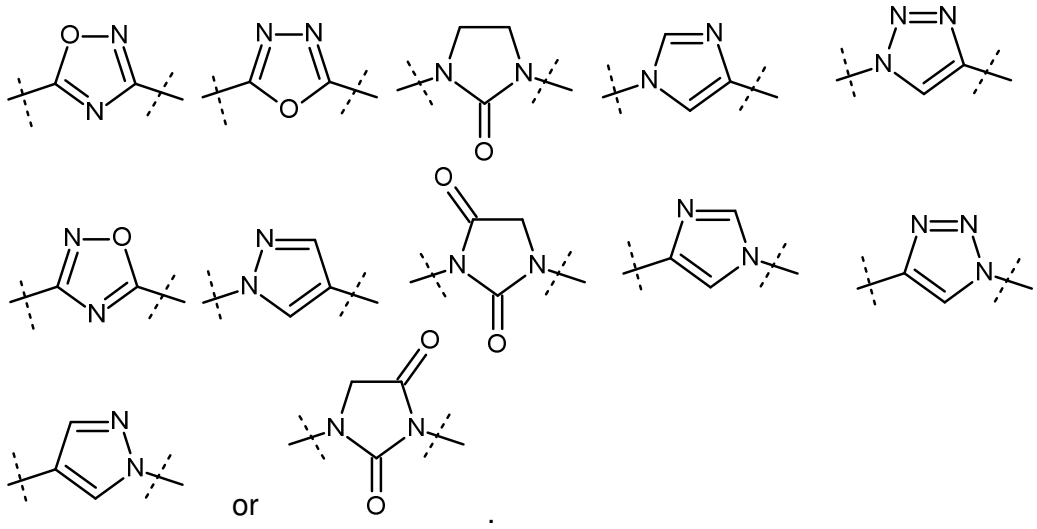
2. The compound of claim 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^1 is a nitrogen ring atom containing 5-membered heterocyclene and wherein A^1 is optionally substituted with one or more R^4, which are the same or different.

3. The compound of claim 1 or 2 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^1 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 oxadiazole, and wherein A^1 is optionally substituted with one or more R^4, which are the same or different.

4. The compound of any one of claims 1 to 3 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. The compound of any one of claims 1 to 4 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^4 is oxo, where the ring is at least partly saturated.

6. 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



7. The compound of any one of claims 1 to 6 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^2 is phenyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl or 1,2,4-oxadiazolyl, and wherein A^2 is optionally substituted with one or more R^6, which are the same or different.

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 phenyl, pyridyl, pyrazinyl or pyridazinyl, and wherein A^2 is optionally substituted with one or more R^6, which are the same or different.

9. The compound of any one of claims 1 to 8 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^2 is substituted with one or two R^6, which are the same or different.

10. The compound of any one of claims 1 to 9 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein each R^6 is independently F, Cl, CF_3, OCH_3, CH_3, CH_2CH_3, or cyclopropyl.

11. The compound of any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^2 is H.

12. The compound of any one of claims 1 to 11 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^3 is A^3.

13. The compound of any one of claims 1 to 12 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^3 is phenyl, pyridyl, pyrazinyl or pyrimidazyl, and wherein A^3 is optionally substituted with one or more R^8, which are the same or different.

14. The compound of any one of claims 1 to 13 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^3 is substituted with one or two R^8, which are the same or different.

15. The compound of any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^2 and R^3 are joined to form the dihydrobenzopyran ring, wherein the ring is optionally substituted with one or more R^8, which are the same or different, preferably the ring is substituted with one or two R^8.

16. The compound of any one of claims 1 to 15 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^8 is independently F, Cl, CF_3, CH=O, CH_2OH or CH_3.

17. The compound of any one of claims 1 to 16 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein the compound is

2-(4-chloro-3-fluorophenoxy)-N-[(3R,6S)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]acetamide,
2-(4-chlorophenoxy)-N-[(3R,6S)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]acetamide,
2-(4-chloro-3-fluorophenoxy)-N-[(3R,6S)-6-{5-[6-(trifluoromethyl)pyridin-3-yl]-1,3,4-oxadiazol-2-yl}oxan-3-yl]acetamide,
2-(4-chloro-3-fluorophenoxy)-N-[(3S,6R)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]acetamide,
2-(4-chloro-3-fluorophenoxy)-N-[(3R,6S)-6-[5-(6-cyclopropylpyridin-3-yl)-1,3,4-

oxadiazol-2-yl]oxan-3-yl]acetamide,
2-(4-chloro-3-fluorophenoxy)-N-[(3R,6S)-6-[5-(6-ethylpyridin-3-yl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]acetamide,
2-[(6-chloro-5-fluoropyridin-3-yl)oxy]-N-[(3R,6S)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]acetamide,
N-[(3R,6S)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]-2-{[2-(trifluoromethyl)pyridin-4-yl]oxy}acetamide,
N-[(3R,6S)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]-2-[(6-chloropyridin-3-yl)oxy]acetamide,
N-[(3R,6S)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]-2-[(5-fluoro-6-methylpyridin-3-yl)oxy]acetamide,
2-[(6-chloro-5-fluoropyridin-3-yl)oxy]-N-[(3R,6S)-6-[5-(6-chloropyridin-3-yl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]acetamide,
N-[(3R,6S)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]-2-[(6-methylpyridin-3-yl)oxy]acetamide,
N-[(3R,6S)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]-2-[(5-chloropyrazin-2-yl)oxy]acetamide,
N-[(3R,6S)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]-2-[(2-chloropyrimidin-5-yl)oxy]acetamide,
2-[(5-chloro-6-methylpyridin-3-yl)oxy]-N-[(3R,6S)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]acetamide,
2-(4-chloro-3-fluorophenoxy)-N-[(3R,6S)-6-{5-[5-(trifluoromethyl)pyridin-3-yl]-1,3,4-oxadiazol-2-yl}oxan-3-yl]acetamide,
2-(4-chloro-3-fluorophenoxy)-N-[(3R,6S)-6-{5-[2-(trifluoromethyl)pyridin-4-yl]-1,3,4-oxadiazol-2-yl}oxan-3-yl]acetamide,
N-[*3R,6S*)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl] tetrahydropyran-3-yl]-2-[[6-(trifluoromethyl)-3-pyridyl]oxy]acetamide, or
N-[(3R,6S)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]oxan-3-yl]-2-{[5-(trifluoromethyl)pyridin-3-yl]oxy}acetamide.

18. A pharmaceutical composition comprising at least one compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of any one of claims 1 to 17 together with a pharmaceutically acceptable carrier,

optionally in combination with one or more other bioactive compounds or pharmaceutical compositions.

19. A compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of any one of claims 1 to 17 for use as a medicament.

~~20. A compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of any one of claims 1 to 17 for use in treating or preventing of one or more diseases or disorders associated with integrated stress response.~~

~~21. Use of a compound of a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of any one of claims 1 to 17 in the manufacture of a medicament for the treatment or prevention of one or more diseases or disorders associated with integrated stress response.~~

~~22~~20. Use of a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of any one of claims 1 to 17 in the manufacture of a medicament for 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.