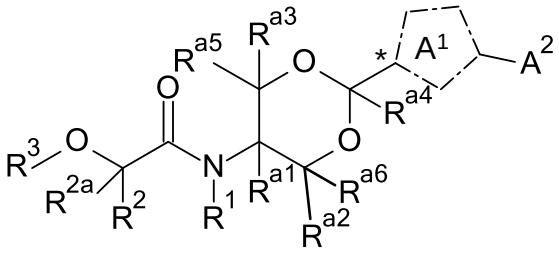
2019/236710 A1, WO 2020/176428 A1 and WO 2020/252205 A1 describe inhibitors of the integrated stress response pathway. Heteroaryl derivatives as ATF4 inhibitors are described in WO 2019/193540 A1. Bicyclic aromatic ring derivatives as ATF4 inhibitors are described in WO 2019/193541 A1. WO 2020/031107 A1 and WO 2020/012339 A1 describe inhibitors of the ATF4 pathway.

However, there is a continuing need for new compounds useful as modulators of the integrated stress response pathway with good pharmacokinetic properties.

Thus, an object of the present invention is to provide a new class of compounds as modulators of the integrated stress response pathway, which may be effective in the treatment of integrated stress response pathway related diseases and which may show improved pharmaceutically relevant properties including activity, solubility, selectivity, ADMET properties and/or reduced side effects.

~~Accordingly~~In an aspect, the present ~~invention~~ disclosure provides 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};

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, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{12}, which are the same or different;

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;

each R^{12} is independently halogen, CN, $C(O)OR^{13}$, OR^{13}, $C(O)R^{13}$, $C(O)N(R^{13}R^{13a})$, $S(O)_2N(R^{13}R^{13a})$, $S(O)N(R^{13}R^{13a})$, $S(O)_2R^{13}$, $S(O)R^{13}$, $N(R^{13})S(O)_2N(R^{13a}R^{13b})$, SR^{13}, $N(R^{13}R^{13a})$, NO_2, $OC(O)R^{13}$, $N(R^{13})C(O)R^{13a}$, $N(R^{13})SO_2R^{13a}$, $N(R^{13})S(O)R^{13a}$, $N(R^{13})C(O)N(R^{13a}R^{13b})$, $N(R^{13})C(O)OR^{13a}$, or $OC(O)N(R^{13}R^{13a})$;

R^{13}, R^{13a}, R^{13b} 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, there is provided 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 or more other bioactive compounds or pharmaceutical compositions.

In another aspect, there is provided a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of as defined above for use as a medicament.

In another aspect, there is provided an use of a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament for treating or preventing of one or more diseases or disorders associated with integrated stress response.

In another aspect, there is provided an use of a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of as defined above or a pharmaceutical composition as defined above 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.

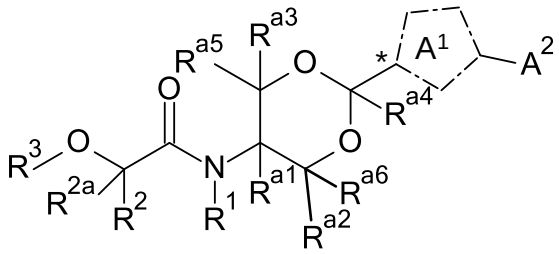
The compounds of the present ~~invention~~ disclosure represent 1,3-dioxane derivatives, which can be prepared according to the routes and methods described herein or elsewhere, e.g. in WO 98/56788 A2.

In case a variable or substituent can be selected from a group of different variants and such variable or substituent occurs more than once the respective variants can be the same or different.

Within the meaning of the present invention the terms are used as follows:

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;

A^2 is R^{6a} or A^{2a};

R^{6a} is OR^{6a1}, SR^{6a1}, $N(R^{6a1}R^{6a2})$; 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 substituents selected from the group consisting of halogen; OR^{6a3}; CN; and A^{2a}, wherein the substituents are the same or different;

R^{6a1}, R^{6a2} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; and A^{2a}, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} 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;

R^{6a3} 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;

A^{2a} is phenyl; C_{3-7} cycloalkyl; C_{4-12} bicycloalkyl; or 3- to 7-membered heterocyclyl, wherein A^{2a} is optionally substituted with one or more R^6, which are the same or different;

each R^6 is independently R^{6b}; OH; OR^{6b}; halogen; or CN, wherein R^{6b} is cyclopropyl, C_{1-6} alkyl; C_{2-6} alkenyl; or C_{2-6} alkynyl, wherein R^{6b} is optionally substituted with one or more halogen, which are the same or different; or
two R^6 are joined to form together with the atoms to which they are attached a ring A^{2b};

A^{2b} is phenyl; C_{3-7} cycloalkyl; or 3 to 7 membered heterocyclyl, wherein A^{2b} 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; 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 heterobicyclyl, wherein 7 to 12 membered heterobicyclyl 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 heterobicyclyl, 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, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{12}, which are the same or different;

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;

each R^{12} is independently halogen, CN, $C(O)OR^{13}$, OR^{13}, $C(O)R^{13}$, $C(O)N(R^{13}R^{13a})$, $S(O)_2N(R^{13}R^{13a})$, $S(O)N(R^{13}R^{13a})$, $S(O)_2R^{13}$, $S(O)R^{13}$, $N(R^{13})S(O)_2N(R^{13a}R^{13b})$, SR^{13}, $N(R^{13}R^{13a})$, NO_2, $OC(O)R^{13}$, $N(R^{13})C(O)R^{13a}$, $N(R^{13})SO_2R^{13a}$, $N(R^{13})S(O)R^{13a}$, $N(R^{13})C(O)N(R^{13a}R^{13b})$, $N(R^{13})C(O)OR^{13a}$, or $OC(O)N(R^{13}R^{13a})$;

R^{13}, R^{13a}, R^{13b} 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 R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} are H.

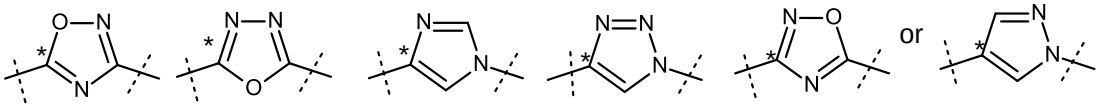
3. The compound of claim 1 or 2 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^1 is a nitrogen ring atom containing 5-membered heterocyclene and wherein A^1 is optionally substituted with one or more R^4, which are the same or different.

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 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 A^1 is optionally substituted with one or more R^4, 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.

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



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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}.

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}.

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}.

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}.

12. The compound of claim 11 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^{2a} is phenyl, cyclobutyl, azetidinyl, or 5- to 6-membered aromatic heterocyclyl, and wherein A^{2a} is optionally substituted with one or more R^6, which are the same or different.

13. The compound of any one of claims 1 to 9, 11 and 12 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^{2a} is substituted with one or two R^6, which are the same or different.

14. The compound of any one of claims 1 to 9, 11 to 13 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein each R^6 is independently F, Cl, CF_3, OCH_3, OCF_3, CH_3, CH_2CH_3, 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 R^2 is H.

16. The compound of any one of claims 1 to 15 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^3 is A^3.

17. The compound of any one of claims 1 to 16 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^3 is phenyl, pyridyl, pyrazinyl, pyrimidazyl, cyclopropyl, cyclobutyl or cyclohexyl and wherein A^3 is optionally substituted with one or more R^{10}, 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 A^3 is substituted with one or two R^{10}, which are the same or different.

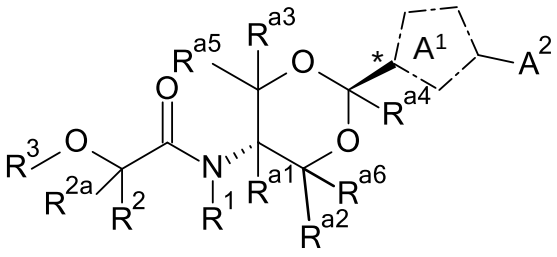
19. The compound of any one of claims 1 to 14 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^2 and R^3 are joined together with the oxygen and carbon atom to which they are attached to form a dihydrobenzopyran ring, wherein the ring is optionally substituted with one or more R^{10}, which are the same or different, preferably the ring is substituted with one or two R^{10}.

20. The compound of any one of claims 1 to 19 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^{10} is independently F, Cl, Br, CHF_2, CF_3, OCF_3, CH=O, CH_2OH or CH_3.

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;
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;
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;
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;
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)



(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. Use of ~~A~~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~~in the manufacture of a medicament for treating or preventing of one or more diseases or disorders associated with integrated stress response.

26. Use of ~~A~~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~~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.