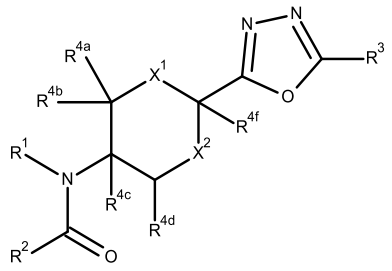
Modulators of eukaryotic initiation factors are described in WO 2019/183589 A1. WO 2019/118785 A2, WO 2019/236710 A1, WO 2020/176428 A1 and WO 2020/252205 A1 describe inhibitors of the integrated stress response pathway. Heteroaryl derivatives as ATF4 inhibitors are described in WO 2019/193540 A1. Bicyclic 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 aspet, the present disclosure provides a compound of formula (I)



(I)

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

$X^1$ is $N(R^4)$ and $X^2$ is $CH(R^{4e})$; or $X^1$ and $X^2$ are O.

$R^1$ 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;

or $R^4$ and $R^{4c}$ form an ethylene group;
or $R^{4b}$ and $R^{4d}$ form a covalent single bond.

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 as defined above or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament.

In another aspect, there is provided the use of a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof 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 the use of a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof 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.

Surprisingly, the disclosed example compounds according to the present disclosure have favourable physico-chemical properties and/or selectivity, which combine to help to achieve beneficial therapeutic efficacy whilst limiting unintended liabilities.

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:

The term “optionally substituted” means unsubstituted or substituted. Generally -but not limited to-, “one or more substituents” means one, two or three, preferably one or two substituents and more preferably one substituent. Generally these substituents can be the same or different. The term “one or more substituents” also means by way of example one, two, three, four or five, preferably by way of example one, two, three or four.

“Alkyl” means a straight-chain or branched hydrocarbon chain. Each hydrogen of an alkyl carbon may be replaced by a substituent as further specified.

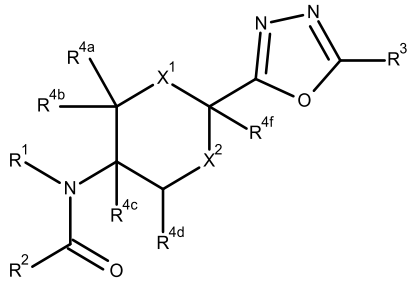
“Alkenyl” means a straight-chain or branched hydrocarbon chain that contains at least one carbon-carbon double bond. Each hydrogen of an alkenyl carbon may be replaced by a substituent as further specified.

“Alkynyl” means a straight-chain or branched hydrocarbon chain that contains at least one carbon-carbon triple bond. Each hydrogen of an alkynyl carbon may be replaced by a substituent as further specified.

“$C_{1-4}$ alkyl” means an alkyl chain having 1 - 4 carbon atoms, e.g. if present at the end of a molecule: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, or e.g. -$CH_2$-, -$CH_2$-$CH_2$-, -$CH(CH_3)$-, -$CH_2$-$CH_2$-$CH_2$-, -$CH(C_2H_5)$-, -$C(CH_3)_2$-, when two moieties of a molecule are linked by the alkyl group. Each hydrogen of a $C_{1-4}$ alkyl carbon may be replaced by a substituent as further specified. The term “$C_{1-3}$ alkyl” is defined accordingly.

**Claims**

1. A compound of formula (I)



(I)

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

$X^1$ is $N(R^4)$ and $X^2$ is $CH(R^{4e})$; or $X^1$ and $X^2$ are O.

$R^1$ 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 phenyl, naphthyl, $C_{3-7}$ cycloalkyl, 3 to 7 membered heterocyclyl or 7 to 12 membered heterobicyclyl, wherein $R^2$ is optionally substituted with one or more $R^5$, which are the same or different, provided that, if a ring atom of $R^2$ bound to the ring atom attaching $R^2$ to the carbon atom of the amide group shown in formula (I) is an oxygen, then the ring atom attaching $R^2$ to the carbon atom of the amide group is not substituted with H or F;

$R^5$ is independently halogen, CN, $C(O)OR^6$, $OR^6$, $C(O)R^6$, $C(O)N(R^6R^{6a})$, $S(O)_2N(R^6R^{6a})$, $S(O)N(R^6R^{6a})$, $S(O)_2R^6$, $S(O)R^6$, $N(R^6)S(O)_2N(R^{6a}R^{6b})$, $SR^6$, $N(R^6R^{6a})$, $NO_2$, $OC(O)R^6$, $N(R^6)C(O)R^{6a}$, $N(R^6)S(O)_2R^{6a}$, $N(R^6)S(O)R^{6a}$, $N(R^6)C(O)OR^{6a}$, $N(R^6)C(O)N(R^{6a}R^{6b})$, $OC(O)N(R^6R^{6a})$, 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 $R^7$, which are the same or different;

$R^6$, $R^{6a}$, $R^{6b}$ 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;

$R^7$ is halogen, CN, $C(O)OR^8$, $OR^8$, $C(O)R^8$, $C(O)N(R^8R^{8a})$, $S(O)_2N(R^8R^{8a})$, $S(O)N(R^8R^{8a})$, $S(O)_2R^8$, $S(O)R^8$, $N(R^8)S(O)_2N(R^{8a}R^{8b})$, $SR^8$, $N(R^8R^{8a})$, $NO_2$, $OC(O)R^8$, $N(R^8)C(O)R^{8a}$, $N(R^8)SO_2R^{8a}$, $N(R^8)S(O)R^{8a}$, $N(R^8)C(O)N(R^{8a}R^{8b})$, $N(R^8)C(O)OR^{8a}$ or $OC(O)N(R^8R^{8a})$;

$R^8$, $R^{8a}$, $R^{8b}$ 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;

$R^3$ is $OR^9$, $SR^{9a}$, $N(R^9R^{9a})$, $A^1$, $C_{1-6}$ 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;

$R^9$, $R^{9a}$ are independently selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl and $A^1$, wherein $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl and $C_{2-6}$ alkynyl are optionally substituted with one or more $R^{11}$, which are the same or different;

$R^{10}$ is halogen, $OR^{12}$, CN or $A^1$;

$R^{11}$ is halogen, CN, $OR^{12}$, $OA^1$ or $A^1$;

$R^{12}$ 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;

$A^1$ is phenyl, $C_{3-7}$ cycloalkyl, $C_{4-12}$ bicycloalkyl or 3- to 7-membered heterocyclyl, wherein $A^1$ is optionally substituted with one or more $R^{13}$, which are the same or different;

$R^{13}$ is $R^{14}$, OH, $OR^{14}$, halogen, or CN; and

$R^{14}$ is cyclopropyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl or $C_{2-6}$ alkynyl, wherein $R^{14}$ is optionally substituted with one or more $R^{15}$, which are the same or different; or

two $R^{13}$ are joined to form together with the atoms to which they are attached a ring $A^2$;

$R^{15}$ is halogen, CN or $OR^{16}$;

$R^{16}$ 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;

$A^2$ is phenyl, $C_{3-7}$ cycloalkyl or 3 to 7 membered heterocyclyl, wherein $A^2$ is optionally substituted with one or more $R^{17}$, which are the same or different;

$R^{17}$ is $C_{1-6}$ 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;

$R^4$ is H, $C(O)OC_{1-4}$ alkyl or $C_{1-4}$ alkyl, wherein $C(O)OC_{1-4}$ alkyl and $C_{1-4}$ alkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, OH and $O\text{-}C_{1-3}$ alkyl, wherein the substituents are the same or different;

$R^{4a}$, $R^{4b}$, $R^{4c}$, $R^{4f}$ are independently selected from the group consisting of H, halogen and $C_{1-4}$ alkyl; and

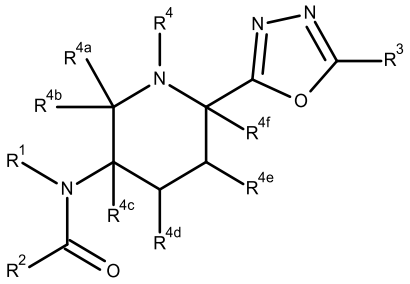
$R^{4d}$, $R^{4e}$ are independently selected from the group consisting of H, OH, $OC_{1-4}$ alkyl, halogen and $C_{1-4}$ alkyl,

or $R^4$ and one of $R^{4d}$ and $R^{4e}$ form a methylene or ethylene group;

or $R^4$ and $R^{4c}$ form an ethylene group;

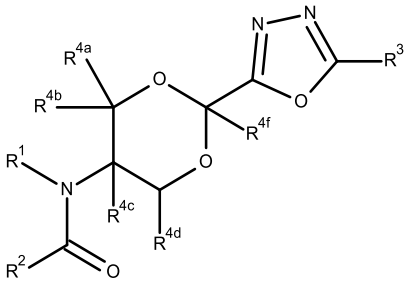
or $R^{4b}$ and $R^{4d}$ form a covalent single bond.

2. The compound of claim 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein in formula (I) $X^1$ is $N(R^4)$ and $X^2$ is $CH(R^{4e})$ to give formula (I-1)



(I-1).

3. The compound of claim 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $X^1$ and $X^2$ in formula (I) are O to give formula (I-2)



(I-2).

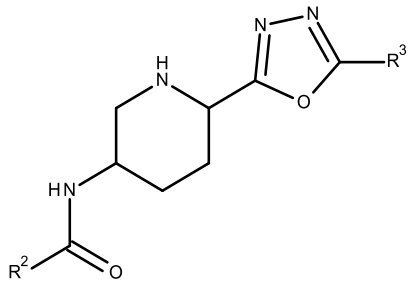
4. The compound of claim 1 or 2 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^4$ is H, $CH_3$, $CH_2CH_3$, or $CH_2CH_2OCH_3$; preferably, H or $CH_3$; more preferably H.

5. The compound of any one of claims 1 to 4 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^{4a}$, $R^{4b}$, $R^{4c}$, $R^{4f}$ are independently selected from the group consisting of H, halogen and $C_{1-4}$ alkyl and $R^{4d}$, $R^{4e}$ are independently selected from the group consisting of H, OH, $OC_{1-4}$ alkyl, halogen and $C_{1-4}$ alkyl; preferably $R^{4a}$, $R^{4b}$, $R^{4c}$, $R^{4f}$, $R^{4d}$, $R^{4e}$ are independently selected from the group consisting of H, F and $CH_3$; more preferably $R^{4a}$, $R^{4b}$, $R^{4c}$, $R^{4f}$, $R^{4d}$, $R^{4e}$ are H.

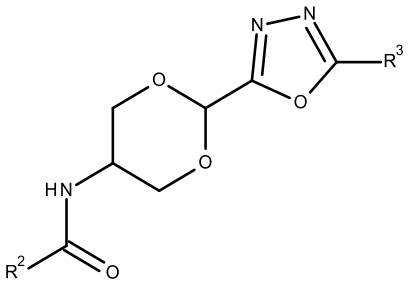
6. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^1$ is H or $CH_3$; preferably H.

7. The compound of any one of claims 1 to 6 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^1$, $R^4$, $R^{4a}$, $R^{4b}$, $R^{4c}$, $R^{4f}$, $R^{4d}$, $R^{4e}$ in

formula (I-1) are H to give formula (Ia-1) or wherein $R^1$, $R^{4a}$, $R^{4b}$, $R^{4c}$, $R^{4f}$, $R^{4d}$ in formula (I-2) are H to give formula (Ia-2),



(Ia-1)



(Ia-2)

8. The compound of any one of claims 1 to 7 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^2$ is phenyl, pyridyl, thiophenyl, 1H-indolyl, quinolinyl, isoquinolinyl, quinazolinyl, pyrazolo[1,5-a]pyridinyl, pyrrolo[1,2-a]pyrazinyl, indolizinyl, chromenyl, benzofuranyl or 2*H*-1,3-benzodioxolyl; preferably phenyl, pyridin-2-yl, pyridin-3-yl, thiophen-2-yl, 1H-indol-2-yl, quinolin-2-yl, quinolin-3-yl, quinolin-6-yl, quinolin-7-yl, isoquinolin-3-yl, quinazolin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrrolo[1,2-a]pyrazin-3-yl, indolizin-2-yl, chromen-3-yl, benzofuran-2-yl or 2*H*-1,3-benzodioxol-5-yl; and wherein $R^2$ is optionally substituted with one or more $R^5$, which are the same or different, provided that, if a ring atom of $R^2$ bound to the ring atom attaching $R^2$ to the carbon atom of the amide group shown in formula (I) is an oxygen, then the ring atom attaching $R^2$ to the carbon atom of the amide group is not substituted with H or F.

9. The compound of any one of claims 1 to 8 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^2$ is substituted with one, two or three $R^5$, 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 $R^5$ is F, Cl, $CH_3$, $CF_3$, $OCF_3$ or $OCH_2CF_3$.

11. The compound of any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^3$ is $OR^9$ and $R^9$ is $C_{1-6}$

alkyl or $C_{2-6}$ alkenyl, wherein $C_{1-6}$ alkyl and $C_{2-6}$ alkenyl are substituted with one or more $R^{11}$, which are the same or different.

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 $OR^9$ and $R^9$ is $C_{1-6}$ alkyl, preferably ethyl, wherein $C_{1-6}$ alkyl is substituted with one $R^{11}$.

13. The compound of any one of claims 1 to 12 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^3$ is $OCH_2CH_2OCF_3$.

14. 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 $OR^9$ and $R^9$ is $C_{1-6}$ alkyl or $C_{2-6}$ alkenyl, preferably but-2-enyl, wherein $C_{1-6}$ alkyl and $C_{2-6}$ alkenyl are each substituted with three F; more preferably $R^3$ is $OCH_2CH=CHCF_3$.

15. The compound of any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^3$ is $A^1$, preferably phenyl or cyclobutyl, wherein $A^1$ is optionally substituted with one or more $R^{13}$, which are the same or different.

16. The compound of any one of claims 1 to 10 and 15 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $A^1$ is substituted with one or two, preferably one $R^{13}$.

17. The compound of any one of claims 1 to 10, 15 and 16 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^{13}$ is $CH_3$, $CHF_2$, $CF_3$, $CH_2CF_3$, $OCHF_2$, $OCH_2CF_3$, $OCF_3$, $OCH_3$, F or Cl, preferably Cl or $OCF_3$.

18. The compound of any one of claims 1 to 17 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^1$, $R^2$, $R^{4a}$, $R^{4b}$, $R^{4c}$, $R^{4f}$, $R^{4d}$, $R^3$, $X^1$, $X^2$ in formula (I) are selected to give

*tert*-butyl (2*R*,5*S*)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}-5-[6-(trifluoromethyl)quinoline-2-amido]piperidine-1-carboxylate;

*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]-6-(trifluoromethyl)quinoline-2-carboxamide;

7-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]quinoline-3-carboxamide;

7-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]-2H-chromene-3-carboxamide;

7-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]isoquinoline-3-carboxamide;

6-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]quinazoline-2-carboxamide;

*tert*-butyl (2*R*,5*S*)-5-(6-chloroquinoline-3-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

6-chloro-*N*-[(3S,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]quinoline-3-carboxamide;

5-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]-1-benzofuran-2-carboxamide;

3-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]quinoline-7-carboxamide;

7-chloro-6-fluoro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]quinoline-3-carboxamide;

5-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]pyrazolo[1,5-a]pyridine-2-carboxamide;

6-(2,2,2-trifluoroethoxy)-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]pyridine-3-carboxamide;

*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]-2-(trifluoromethyl)quinoline-6-carboxamide;

7-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]pyrrolo[1,2-a]pyrazine-3-carboxamide;

6-(trifluoromethoxy)-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]pyridine-3-carboxamide;

3,4-dichloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]benzamide;

4-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]benzamide;

7-chloro-8-fluoro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]quinoline-3-carboxamide;

7-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]indolizine-2-carboxamide;

6-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]indolizine-2-carboxamide;

1-methyl-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]-5-(trifluoromethyl)-1*H*-indole-2-carboxamide;

3-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]benzamide;

3,5-dimethyl-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]benzamide;

3,4-dimethyl-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]benzamide;

4,5-dimethyl-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]thiophene-2-carboxamide;

4-methyl-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]benzamide;

*tert*-butyl (2*R*,5*S*)-5-[4-(trifluoromethoxy)benzamido]-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

4-(trifluoromethoxy)-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]benzamide;

2,2-difluoro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]-2*H*-1,3-benzodioxole-5-carboxamide;

4-chloro-3-methyl-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]benzamide;

4-chloro-3,5-difluoro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]benzamide;

3-fluoro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]-4-(trifluoromethyl)benzamide;

3-chloro-4-(trifluoromethoxy)-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]benzamide;

4-fluoro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]-3-(trifluoromethyl)benzamide;

3-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]-4-(trifluoromethyl)benzamide;

4-chloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]-3-(trifluoromethyl)benzamide;

4,5-dichloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]pyridine-2-carboxamide;

5,6-dichloro-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]pyridine-2-carboxamide;

4-chloro-3-(trifluoromethoxy)-*N*-[(3*S*,6*R*)-6-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]benzamide;

*tert*-butyl (2*R*,5*S*)-5-[[1-methyl-6-(trifluoromethyl)indole-2-carbonyl]amino]-2-[5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl]piperidine-1-carboxylate;

1-methyl-*N*-[(3*S*,6*R*)-6-[5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl]-3-piperidyl]-6-(trifluoromethyl)indole-2-carboxamide;

*tert*-butyl (2*R*,5*S*)-5-[(3-chloro-4-methyl-benzoyl)amino]-2-[5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl]piperidine-1-carboxylate;

3-chloro-4-methyl-*N*-[(3*S*,6*R*)-6-[5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl]-3-piperidyl]benzamide;

*tert*-butyl (2*R*,5*S*)-2-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-5-[(7-chloroquinoline-3-carbonyl)amino]piperidine-1-carboxylate;

7-chloro-*N*-[(3*S*,6*R*)-6-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-3-piperidyl]quinoline-3-carboxamide;

*tert*-butyl (2*R*,5*S*)-5-[(7-chloroquinoline-3-carbonyl)amino]-2-[5-[(*E*)-4,4,4-trifluorobut-2-enoxy]-1,3,4-oxadiazol-2-yl]piperidine-1-carboxylate;

7-chloro-*N*-[(3*S*,6*R*)-6-[5-[(*E*)-4,4,4-trifluorobut-2-enoxy]-1,3,4-oxadiazol-2-yl]-3-piperidyl]quinoline-3-carboxamide;

7-chloro-*N*-[(3*R*,6*S*)-6-[5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl]-3-piperidyl]quinoline-3-carboxamide;

*tert*-butyl (2*R*,5*S*)-5-(7-chloroquinoline-3-amido)-2-{5-[(1*s*,3*s*)-3-(trifluoromethoxy)cyclobutyl]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

7-chloro-*N*-[(3*S*,6*R*)-6-{5-[(1*s*,3*s*)-3-(trifluoromethoxy)cyclobutyl]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]quinoline-3-carboxamide;

7-chloro-*N*-[(3*R*,6*S*)-6-{5-[(1s,3s)-3-(trifluoromethoxy)cyclobutyl]-1,3,4-oxadiazol-2-yl}piperidin-3-yl]quinoline-3-carboxamide;

*tert*-butyl (2*S*,5*R*)-5-[(3,4-dichlorobenzoyl)amino]-2-[5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl]piperidine-1-carboxylate;

3,4-dichloro-*N*-[(3*R*,6*S*)-6-[5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl]-3-piperidyl]benzamide;

*tert*-butyl (2*S*,5*R*)-5-(7-chloroquinoline-3-amido)-2-{5-[(1*s*,3*s*)-3-(trifluoromethoxy)cyclobutyl]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*S*,5*R*)-5-(7-chloroquinoline-3-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[4-chloro-3-(trifluoromethoxy)benzamido]-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(5,6-dichloropyridine-2-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(4,5-dichloropyridine-2-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[4-chloro-3-(trifluoromethyl)benzamido]-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[3-chloro-4-(trifluoromethoxy)benzamido]-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[4-fluoro-3-(trifluoromethyl)benzamido]-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[3-chloro-4-(trifluoromethyl)benzamido]-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[3-fluoro-4-(trifluoromethyl)benzamido]-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(4-chloro-3,5-difluorobenzamido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(4-chloro-3-methylbenzamido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(2,2-difluoro-2H-1,3-benzodioxole-5-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(4-methylbenzamido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(4,5-dimethylthiophene-2-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(3,4-dimethylbenzamido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(3,5-dimethylbenzamido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(3-chlorobenzamido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[1-methyl-5-(trifluoromethyl)-1*H*-indole-2-amido]-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(6-chloroindolizine-2-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(7-chloroindolizine-2-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(7-chloro-8-fluoroquinoline-3-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(4-chlorobenzamido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(3,4-dichlorobenzamido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}-5-[6-(trifluoromethoxy)pyridine-3-amido]piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-{7-chloropyrrolo[1,2-a]pyrazine-3-amido}-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}-5-[2-(trifluoromethyl)quinoline-6-amido]piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[6-(2,2,2-trifluoroethoxy)pyridine-3-amido]-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-{5-chloropyrazolo[1,5-a]pyridine-2-amido}-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

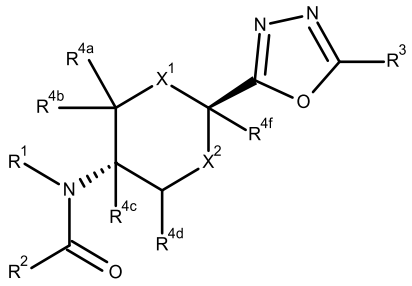
*tert*-butyl (2*R*,5*S*)-5-(7-chloro-6-fluoroquinoline-3-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(3-chloroquinoline-7-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-(5-chloro-1-benzofuran-2-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;

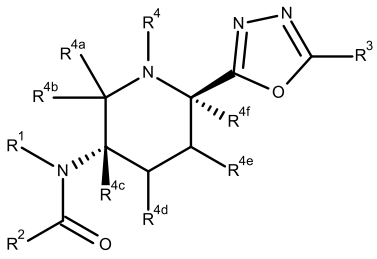
*tert*-butyl (2*R*,5*S*)-5-(6-chloroquinazoline-2-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;
*tert*-butyl (2*R*,5*S*)-5-(7-chloroisoquinoline-3-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;
*tert*-butyl (2*R*,5*S*)-5-(7-chloro-2H-chromene-3-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate;
*tert*-butyl (2*R*,5*S*)-5-(7-chloroquinoline-3-amido)-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidine-1-carboxylate or
7-chloro-*N*-[*trans*-2-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}-1,3-dioxan-5-yl]quinoline-3-carboxamide.

19. The compound of any one of claims 1 to 18 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein formula (I) has a stereochemistry as shown in formula (Ib)

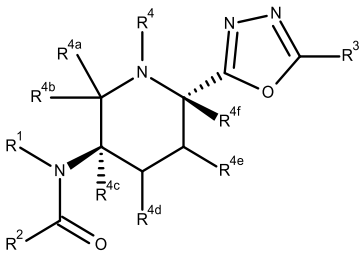


(Ib).

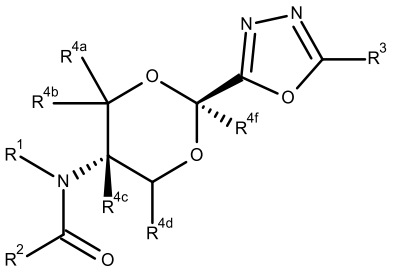
20. The compound of any one of claims 1 to 19 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein formula (I) has a stereochemistry as shown in formulas (Ib-1), (Ib-2), (Ib-3), (Ib-4)



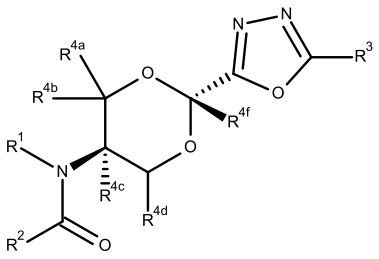
(Ib-1)



(Ib-2)



(Ib-3)



(Ib-4).

21. 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 20 together with a pharmaceutically acceptable carrier, optionally in combination with one or more other bioactive compounds or pharmaceutical compositions.

22. A compound of any one of claims 1 to 20 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament.

23. Use of a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of any one of claims 1 to 20 or a pharmaceutical composition of claim 21 in the manufacture of a medicament for treating or preventing of one or more diseases or disorders associated with integrated stress response.

24. Use of a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof as defined in any one of claims 1 to 20 or a pharmaceutical composition of claim 21 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.