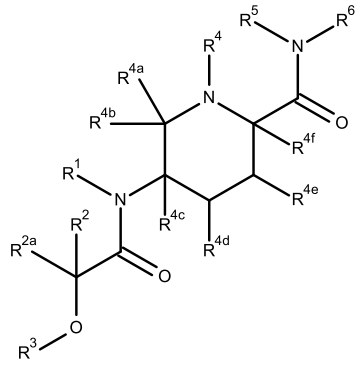
2019/090081 A1, WO 2019/090082 A1, WO 2019/090085 A1, WO 2019/090088 A1, WO 2019/090090 A1, WO 2020/223536 A1, WO 2020/223538 A1, WO 2020/252207 A1, WO 2020/252205 A1, WO 2021/180774 A1, WO 2021/151865 A1, WO 2020/216764 A1, WO 2020/216766 A1, and European patent applications 20203311.4, 21192154.9 and 20203309.8.

Modulators of eukaryotic initiation factors are described in WO 2019/183589 A1. WO 2019/118785 A2, WO 2019/236710 A1 and WO 2020/176428 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, the present disclosure provides a compound of formula (I)



(I)

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

$A^2$ is phenyl, naphthyl, $C_{3-7}$ cycloalkyl, $C_{4-12}$ bicycloalkyl, 3 to 7 membered heterocyclyl or 7 to 12 membered heterobicyclyl, wherein $A^2$ is optionally substituted with one or more $R^{16a}$, which are the same or different;

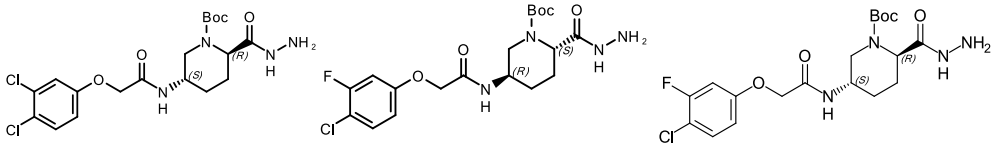
$R^{16}$, $R^{16a}$ are independently selected from the group consisting of $R^{17}$, OH, $OR^{17}$, halogen and CN;

$R^{17}$ is cyclopropyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl or $C_{2-6}$ alkynyl, wherein $R^{17}$ is optionally substituted with one or more $R^{18}$, which are the same or different;

$R^{18}$ is halogen, CN or $OR^{19}$;

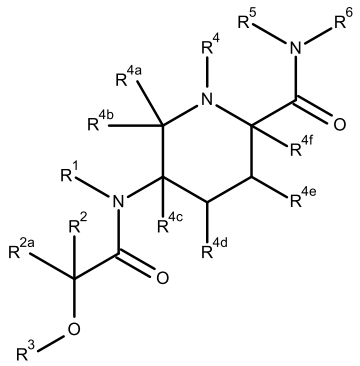
$R^{19}$ is H or $C_{1-4}$ alkyl, wherein $C_{1-4}$ alkyl is optionally substituted with one or more halogen, which are the same or different.

Preferably, the following compounds are excluded:



These compounds are known as intermediates 27, 28 and 26 on pages 71 and 72 of WO 2020/216766 A1 and are preferably excluded from the present scope of the disclosure inasfar compounds as such of the present disclosure are concerned.

In an aspect, there is provided a compound of formula (I)



(I)

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

$R^1$ 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;

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

$R^3$ is phenyl or 6 membered aromatic heterocyclyl, wherein $R^3$ is optionally substituted with one or more $R^7$, which are the same or different;

$R^7$ is halogen, CN, $C(O)OR^8$, $OR^8$, $C(O)R^8$, $C(O)N(R^8R^{8a})$, $S(O)_2N(R^8R^{8a})$, $S(O)N(R^8R^{8a})$, $S(O)_2R^8$, $S(O)R^8$, $N(R^8)S(O)_2N(R^{8a}R^{8b})$, $SR^8$, $N(R^8R^{8a})$, $NO_2$, $OC(O)R^8$, $N(R^8)C(O)R^{8a}$, $N(R^8)S(O)_2R^{8a}$, $N(R^8)S(O)R^{8a}$, $N(R^8)C(O)OR^{8a}$, $N(R^8)C(O)N(R^{8a}R^{8b})$, $OC(O)N(R^8R^{8a})$, $C_{1-6}$ 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 $R^9$, which are the same or different;

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

$R^9$ is halogen, CN, $C(O)OR^{10}$, $OR^{10}$, $C(O)R^{10}$, $C(O)N(R^{10}R^{10a})$, $S(O)_2N(R^{10}R^{10a})$, $S(O)N(R^{10}R^{10a})$, $S(O)_2R^{10}$, $S(O)R^{10}$, $N(R^{10})S(O)_2N(R^{10a}R^{10b})$, $SR^{10}$, $N(R^{10}R^{10a})$, $NO_2$, $OC(O)R^{10}$, $N(R^{10})C(O)R^{10a}$, $N(R^{10})SO_2R^{10a}$, $N(R^{10})S(O)R^{10a}$, $N(R^{10})C(O)N(R^{10a}R^{10b})$, $N(R^{10})C(O)OR^{10a}$ or $OC(O)N(R^{10}R^{10a})$;

$R^{10}$, $R^{10a}$, $R^{10b}$ 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.

$R^4$ 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;

$R^5$ 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; and

$R^6$ is $R^{11}$; or

$R^5$ and $R^6$ are joined to form together with the nitrogen atom to which they are attached a ring $A^1$;

$R^{11}$ is $OR^{12}$, $SR^{12a}$, $N(R^{12}R^{12a})$, $A^2$, $C_{1-6}$ 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 $R^{13}$, which are the same or different;

$R^{12}$, $R^{12a}$ are independently selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl and $A^2$, wherein $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl and $C_{2-6}$ alkynyl are optionally substituted with one or more $R^{15}$, which are the same or different;

$R^{13}$ is halogen, $OR^{14}$, CN or $A^2$;

$R^{14}$ 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;

$R^{15}$ is halogen, CN, $OR^{14}$, $OA^2$ or $A^2$;

$A^1$ is 3 to 7 membered heterocyclyl or 7 to 12 membered heterobicyclyl, wherein $A^1$ is optionally substituted with one or more $R^{16}$, which are the same or different;

$A^2$ is phenyl, naphthyl, $C_{3-7}$ cycloalkyl, $C_{4-12}$ bicycloalkyl, 3 to 7 membered heterocyclyl or 7 to 12 membered heterobicyclyl, wherein $A^2$ is optionally substituted with one or more $R^{16a}$, which are the same or different;

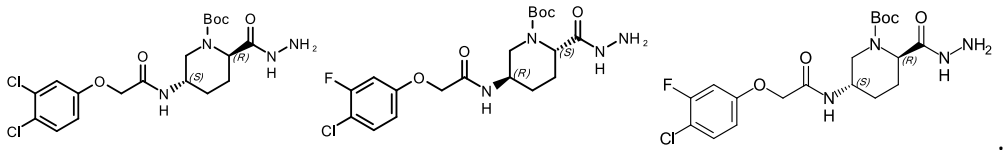
$R^{16}$, $R^{16a}$ are independently selected from the group consisting of $R^{17}$, OH, $OR^{17}$, halogen and CN;

$R^{17}$ is cyclopropyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl or $C_{2-6}$ alkynyl, wherein $R^{17}$ is optionally substituted with one or more $R^{18}$, which are the same or different;

$R^{18}$ is halogen, CN or $OR^{19}$;

$R^{19}$ 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;

provided that the following compounds are excluded:




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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 th 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.

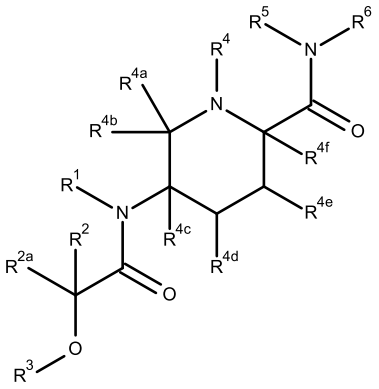
Surprisingly, the disclosed example compounds according to the present disclosure have favourable physico-chemical properties and/or selectivity, which combine to help to achieve beneficial therapeutic efficacy whilst limiting unintended liabilities.

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:

**Patent Claims**

1. A compound of formula (I)



(I)

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

$R^1$ 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;

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

$R^3$ is phenyl or 6 membered aromatic heterocyclyl, wherein $R^3$ is optionally substituted with one or more $R^7$, which are the same or different;

$R^7$ is halogen, CN, $C(O)OR^8$, $OR^8$, $C(O)R^8$, $C(O)N(R^8R^{8a})$, $S(O)_2N(R^8R^{8a})$, $S(O)N(R^8R^{8a})$, $S(O)_2R^8$, $S(O)R^8$, $N(R^8)S(O)_2N(R^{8a}R^{8b})$, $SR^8$, $N(R^8R^{8a})$, $NO_2$, $OC(O)R^8$, $N(R^8)C(O)R^{8a}$, $N(R^8)S(O)_2R^{8a}$, $N(R^8)S(O)R^{8a}$, $N(R^8)C(O)OR^{8a}$, $N(R^8)C(O)N(R^{8a}R^{8b})$, $OC(O)N(R^8R^{8a})$, $C_{1-6}$ 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 $R^9$, which are the same or different;

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

$R^9$ is halogen, CN, $C(O)OR^{10}$, $OR^{10}$, $C(O)R^{10}$, $C(O)N(R^{10}R^{10a})$, $S(O)_2N(R^{10}R^{10a})$, $S(O)N(R^{10}R^{10a})$, $S(O)_2R^{10}$, $S(O)R^{10}$, $N(R^{10})S(O)_2N(R^{10a}R^{10b})$, $SR^{10}$, $N(R^{10}R^{10a})$, $NO_2$, $OC(O)R^{10}$, $N(R^{10})C(O)R^{10a}$, $N(R^{10})SO_2R^{10a}$, $N(R^{10})S(O)R^{10a}$, $N(R^{10})C(O)N(R^{10a}R^{10b})$, $N(R^{10})C(O)OR^{10a}$ or $OC(O)N(R^{10}R^{10a})$;

$R^{10}$, $R^{10a}$, $R^{10b}$ 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.

$R^4$ 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;

$R^5$ 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; and
$R^6$ is $R^{11}$; or
$R^5$ and $R^6$ are joined to form together with the nitrogen atom to which they are attached a ring $A^1$;

$R^{11}$ is $OR^{12}$, $SR^{12a}$, $N(R^{12}R^{12a})$, $A^2$, $C_{1-6}$ 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 $R^{13}$, which are the same or different;

$R^{12}$, $R^{12a}$ are independently selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl and $A^2$, wherein $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl and $C_{2-6}$ alkynyl are optionally substituted with one or more $R^{15}$, which are the same or different;

$R^{13}$ is halogen, $OR^{14}$, CN or $A^2$;

$R^{14}$ 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;

$R^{15}$ is halogen, CN, $OR^{14}$, $OA^2$ or $A^2$;

$A^1$ is 3 to 7 membered heterocyclyl or 7 to 12 membered heterobicyclyl, wherein $A^1$ is optionally substituted with one or more $R^{16}$, which are the same or different;

$A^2$ is phenyl, naphthyl, $C_{3-7}$ cycloalkyl, $C_{4-12}$ bicycloalkyl, 3 to 7 membered heterocyclyl or 7 to 12 membered heterobicyclyl, wherein $A^2$ is optionally substituted with one or more $R^{16a}$, which are the same or different;

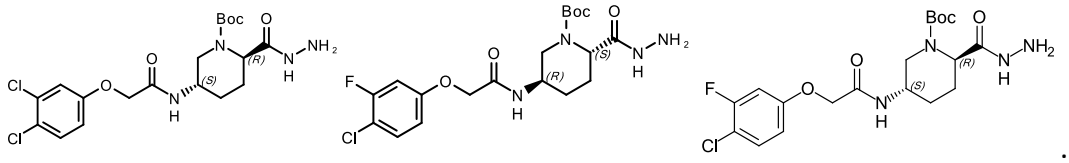
$R^{16}$, $R^{16a}$ are independently selected from the group consisting of $R^{17}$, OH, $OR^{17}$, halogen and CN;

$R^{17}$ is cyclopropyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl or $C_{2-6}$ alkynyl, wherein $R^{17}$ is optionally substituted with one or more $R^{18}$, which are the same or different;

$R^{18}$ is halogen, CN or $OR^{19}$;

$R^{19}$ 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;

provided that the following compounds are excluded:



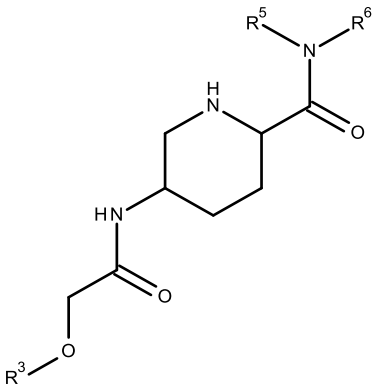
2. The compound of claim 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^4$ is H, $CH_3$, $CH_2CH_3$, or $CH_2CH_2OCH_3$; preferably, H or $CH_3$; more preferably H.

3. The compound of claim 1 or 2 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.

4. The compound of any one of claims 1 to 3 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^1$ is H or $CH_3$; 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 $R^2$ is H, F or $CH_3$, preferably H.

6. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^1$, $R^2$, $R^{2a}$, $R^4$, $R^{4a}$, $R^{4b}$, $R^{4c}$, $R^{4f}$, $R^{4d}$, $R^{4e}$ in formula (I) are H to give formula (Ia)



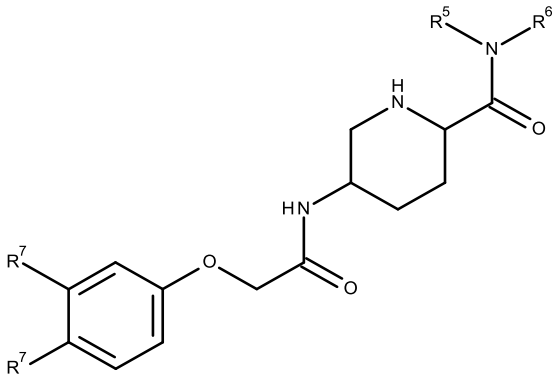
(Ia).

7. The compound of any one of claims 1 to 6 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^3$ is phenyl or pyridyl, preferably phenyl, wherein $R^3$ is optionally substituted with one or more $R^7$, 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 $R^3$ is substituted with one, two or three, preferably one or two, more preferably two, $R^7$, 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 $R^7$ is F, Cl, Br, CN, $CHF_2$, $CF_3$, $OCH_3$, $OCF_3$, CH=O, $CH_2OH$ or $CH_3$; preferably $R^7$ is $CF_3$, F or Cl, more preferably F or Cl.

10. The compound of any one of claims 1 to 9 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^1$, $R^2$, $R^{2a}$, $R^4$, $R^{4a}$, $R^{4b}$, $R^{4c}$, $R^{4f}$, $R^{4d}$, $R^{4e}$, $R^3$ in formula (I) are selected to give formula (Ib)



(Ib),

wherein each $R^7$ is independently selected from the group consisting of halogen and $CF_3$.

11. The compound of any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^5$ is H or $CH_3$, preferably H.

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

or $C_{1-6}$ alkenyl, wherein $C_{1-6}$ alkyl and $C_{1-6}$ alkenyl are substituted with one or more $R^{13}$, which are the same or different.

13. The compound of any one of claims 1 to 12 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^6$ is $R^{11}$ and $R^{11}$ is $C_{1-6}$ alkyl, preferably ethyl or n-propyl, wherein $C_{1-6}$ alkyl is substituted with one $R^{13}$.

14. The compound of any one of claims 1 to 13 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^6$ is $R^{11}$ and $R^{11}$ is ethyl or n-propyl, each substitiuted with one $R^{13}$, wherein $R^{13}$ is $OR^{14}$, preferably $OCF_3$.

15. The compound of any one of claims 1 to 12 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^6$ is $R^{11}$ and $R^{11}$ is $C_{1-6}$ alkyl, preferably n- propyl or n-pentyl, wherein $C_{1-6}$ alkyl is substituted with three F; more preferably $R^{11}$ is 3,3,3-trifluoropropyl or 5,5,5-trifluoropentyl.

16. The compound of any one of claims 1 to 12 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^6$ is $R^{11}$ and $R^{11}$ is $C_{1-6}$ alkyl, preferably methyl, wherein $C_{1-6}$ alkyl is substituted with one $R^{13}$, wherein $R^{13}$ is $A^2$, preferably phenyl, pyridyl, pyrazolyl, oxazolyl, cyclobutyl, cyclohexyl, furanyl, bicyclo[3.1.0]hexan-3-yl or 6-oxaspiro[3.4]octan-7-yl.

17. The compound of any one of claims 1 to 11 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^6$ is $R^{11}$ and $R^{11}$ is $A^2$, preferably phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzodioxolyl, cyclohexyl, cyclopentyl, cyclobutyl, pyrazolyl, oxazolyl or oxolanyl.

18. The compound of any one of claims 1 to 14, 16 and 17 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $A^2$ is unsubstituted or substituted with one or two $R^{16a}$.

19. The compound of any one of claims 1 to 14, and 16 to 18 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^{16a}$ is $CH_3$, $CHF_2$, $CF_3$, $CH_2CF_3$, $OCHF_2$, $OCH_2CF_3$, $OCF_3$, $OCH_3$, F or Cl.

20. The compound of any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^5$ and $R^6$ are joined to form together with the nitrogen atom to which they are attached a ring $A^1$.

21. The compound of claim 20, wherein $A^1$ is azetidine, piperidine, oxazepane, indoline, isoindoline, tetrahydroisoquioline azabicyclo[3.1.0]hexane or azaspiro[3.3]heptane and wherein $A^1$ is optionally substituted with one or more $R^{16}$, which are the same or different.

22. The compound of claim 20 or 21 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $A^1$ is unsubstituted or substituted with one $R^{16}$.

23. The compound of any one of claims 20 to 22 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^{16}$ is $CF_3$, $OCF_3$ or $OCH_2CH_2OCF_3$.

24. The compound of any one of claims 1 to 23 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein $R^1$, $R^2$, $R^{2a}$, $R^3$, $R^4$, $R^{4a}$, $R^{4b}$, $R^{4c}$, $R^{4d}$, $R^{4e}$, $R^{4f}$, $R^5$, $R^6$ in formula (I) are selected to give

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[3-(trifluoromethoxy)propyl]carbamoyl}piperidine-1-carboxylate;
(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[3-(trifluoromethoxy)propyl]piperidine-2-carboxamide hydrochloride;
tert-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-({[4-(trifluoromethyl)phenyl]methyl}carbamoyl)piperidine-1-carboxylate;
(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-{[4-(trifluoromethyl)phenyl]methyl}piperidine-2-carboxamide;
2-(4-chloro-3-fluorophenoxy)-*N*-[(3*S*,6*R*)-6-{3-[2-(trifluoromethoxy)ethoxy]azetidine-1-carbonyl}piperidin-3-yl]acetamide;
(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[2-(trifluoromethoxy)ethoxy]piperidine-2-carboxamide;

tert-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[(4-chlorophenyl)carbamoyl]piperidine-1-carboxylate;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(4-chlorophenyl)piperidine-2-carboxamide;

(2*S*,5*R*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(4-chlorophenyl)piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-phenylpiperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(3-chlorophenyl)piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[3-(trifluoromethyl)phenyl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[3-(trifluoromethoxy)phenyl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(5-chloropyridin-2-yl)methyl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(1*s*,4*s*)-4-(trifluoromethoxy)cyclohexyl]piperidine-2-carboxamide;

(2*R*,5*S*)-*N*-(4-chloro-2-methoxyphenyl)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-{[5-(trifluoromethyl)furan-2-yl]methyl}piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-{[4-(trifluoromethyl)furan-2-yl]methyl}piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-{[(1*s*,4*s*)-4-(trifluoromethyl)cyclohexyl]methyl}piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(3-methoxyphenyl)piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[4-fluoro-3-(trifluoromethyl)phenyl]piperidine-2-carboxamide;

(2*R*,5S)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[5-(trifluoromethyl)pyridin-3-yl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(3-fluorophenyl)piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[3-(difluoromethyl)phenyl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(5-chloropyridin-2-yl)piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[5-methyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(1*s*,3*s*)-3-(trifluoromethoxy)cyclobutyl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(3,5-dimethylphenyl)piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(5,5,5-trifluoropentyl)piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[3-(difluoromethoxy)phenyl]piperidine-2-carboxamide;

(2*S*,5*R*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[3-(trifluoromethyl)phenyl]piperidine-2-carboxamide;

*tert*-butyl (2*R*,5*S*)-2-[[3,5-bis(trifluoromethyl)phenyl]carbamoyl]-5-[[2-(4-chloro-3-fluoro-phenoxy)acetyl]amino]piperidine-1-carboxylate;

(2*R*,5*S*)-*N*-[3,5-bis(trifluoromethyl)phenyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[1-(trifluoromethyl)-1*H*-pyrazol-3-yl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[2-fluoro-5-(trifluoromethyl)phenyl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[2-fluoro-3-(trifluoromethyl)phenyl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[6-(trifluoromethoxy)pyridin-2-yl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[4-(trifluoromethyl)pyridin-2-yl]piperidine-2-carboxamide;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{3-[2-(trifluoromethoxy)ethoxy]azetidine-1-carbonyl}piperidine-1-carboxylate;

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

*tert*-butyl (2S,5R)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[(4-chlorophenyl)carbamoyl]piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-(phenylcarbamoyl)piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[(3-chlorophenyl)carbamoyl]piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[3-(trifluoromethyl)phenyl]carbamoyl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[3-(trifluoromethoxy)phenyl]carbamoyl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[(5-chloropyridin-2-yl)methyl]carbamoyl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[(1*s*,4*s*)-4-(trifluoromethoxy)cyclohexyl]carbamoyl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-2-[(4-chloro-2-methoxyphenyl)carbamoyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-({[5-(trifluoromethyl)furan-2-yl]methyl}carbamoyl)piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-({[4-(trifluoromethyl)furan-2-yl]methyl}carbamoyl)piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-({[(1*s*,4*s*)-4-(trifluoromethyl)cyclohexyl]methyl}carbamoyl)piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[(3-methoxyphenyl)carbamoyl]piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[4-fluoro-3-(trifluoromethyl)phenyl]carbamoyl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[5-(trifluoromethyl)pyridin-3-yl]carbamoyl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[(3-fluorophenyl)carbamoyl]piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[3-(difluoromethyl)phenyl]carbamoyl}piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[(5-chloropyridin-2-yl)carbamoyl]piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[5-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl]carbamoyl}piperidine-1-carboxylate;
*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[(1*s*,3*s*)-3-(trifluoromethoxy)cyclobutyl]carbamoyl}piperidine-1-carboxylate;
*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[(3,5-dimethylphenyl)carbamoyl]piperidine-1-carboxylate;
*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[(5,5,5-trifluoropentyl)carbamoyl]piperidine-1-carboxylate;
*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[3-(difluoromethoxy)phenyl]carbamoyl}piperidine-1-carboxylate;
*tert*-butyl (2*S*,5*R*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[3-(trifluoromethyl)phenyl]carbamoyl}piperidine-1-carboxylate;
*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[1-(trifluoromethyl)-1*H*-pyrazol-3-yl]carbamoyl}piperidine-1-carboxylate;
*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[2-fluoro-5-(trifluoromethyl)phenyl]carbamoyl}piperidine-1-carboxylate;
*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[2-fluoro-3-(trifluoromethyl)phenyl]carbamoyl}piperidine-1-carboxylate;
*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[6-(trifluoromethoxy)pyridin-2-yl]carbamoyl}piperidine-1-carboxylate or
*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[4-(trifluoromethyl)pyridin-2-yl]carbamoyl}piperidine-1-carboxylate;
(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(2,2-difluoro-2*H*-1,3-benzodioxol-5-yl)piperidine-2-carboxamide;
2-(4-chloro-3-fluorophenoxy)-*N*-[(3*S*,6*R*)-6-[5-(trifluoromethyl)-2,3-dihydro-1*H*-isoindole-2-carbonyl]piperidin-3-yl]acetamide;
2-(4-chloro-3-fluorophenoxy)-*N*-[(3*S*,6*R*)-6-[5-(trifluoromethoxy)-2,3-dihydro-1*H*-isoindole-2-carbonyl]piperidin-3-yl]acetamide;
(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-{[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]methyl}piperidine-2-carboxamide;
(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-{[5-(trifluoromethyl)-1,2-oxazol-3-yl]methyl}piperidine-2-carboxamide;
(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-{[4-(trifluoromethyl)pyridin-2-yl]methyl}piperidine-2-carboxamide;

2-(4-chloro-3-fluorophenoxy)-*N*-[(3*S*,6*R*)-6-[4-(trifluoromethyl)-2,3-dihydro-1*H*-indole-1-carbonyl]piperidin-3-yl]acetamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[1-(2,2-difluorocyclopropyl)-1*H*-pyrazol-3-yl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[2-(trifluoromethyl)pyrimidin-4-yl]carbamoyl}piperidine-1-carboxylate;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[2-(trifluoromethyl)pyrimidin-4-yl]piperidine-2-carboxamide;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[6-(trifluoromethyl)pyrazin-2-yl]carbamoyl}piperidine-1-carboxylate;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[6-(trifluoromethyl)pyrazin-2-yl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-1-methyl-*N*-[6-(trifluoromethyl)pyrazin-2-yl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(1*S*,3*S*)-3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide;

(2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(1*R*,3*R*)-3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[(2,2-difluoro-2*H*-1,3-benzodioxol-5-yl)carbamoyl]piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[5-(trifluoromethyl)-2,3-dihydro-1*H*-isoindole-2-carbonyl]piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[5-(trifluoromethoxy)-2,3-dihydro-1*H*-isoindole-2-carbonyl]piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-({[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]methyl}carbamoyl)piperidine-1-carboxylate;

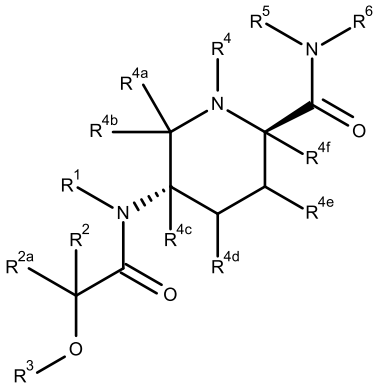
*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-({[5-(trifluoromethyl)-1,2-oxazol-3-yl]methyl}carbamoyl)piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-({[4-(trifluoromethyl)pyridin-2-yl]methyl}carbamoyl)piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[4-(trifluoromethyl)-2,3-dihydro-1*H*-indole-1-carbonyl]piperidine-1-carboxylate;

*tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[1-(2,2-difluorocyclopropyl)-1*H*-pyrazol-3-yl]carbamoyl}piperidine-1-carboxylate or *tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[3-(trifluoromethoxy)cyclopentyl]carbamoyl}piperidine-1-carboxylate.

25. The compound of any one of claims 1 to 24 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein formula (I) has a stereochemistry as shown in formula (Ic)




(Ic).

26. 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 25 together with a pharmaceutically acceptable carrier, optionally in combination with one or more other bioactive compounds or pharmaceutical compositions.

27. A compound of any one of claims 1 to 25 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament.

28. Use of a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of any one of claims 1 to 25 or a pharmaceutical composition of claim 26 in the manufacture of a medicament for treating or preventing of one or more diseases or disorders associated with integrated stress response.

29. Use of a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof as defined in any one of claims 1 to 25 or a pharmaceutical composition of claim 26 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.