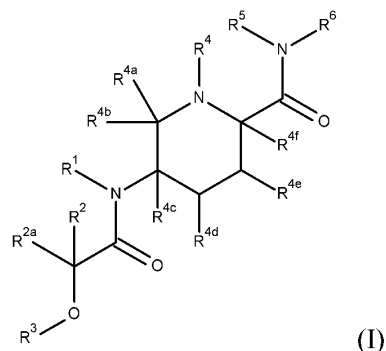


Modulators of the integrated stress response pathway

The present invention relates to compounds of formula (I)

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10 or pharmaceutically acceptable salts, solvates, hydrates, tautomers or stereoisomers 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 and R^6 have the meaning as indicated in the description and claims. The invention further relates to pharmaceutical compositions comprising said compounds, their use as medicament and in a method for treating or preventing of one or more diseases or disorders associated with integrated stress response.

15

The Integrated Stress Response (ISR) is a cellular stress response common to all eukaryotes (1). Dysregulation of ISR signaling has important pathological consequences linked inter alia to inflammation, viral infection, diabetes, cancer and neurodegenerative diseases.

20 ISR is a common denominator of different types of cellular stresses resulting in phosphorylation of the alpha subunit of eukaryotic translation initiation factor 2 (eIF2alpha) on serine 51 leading to the suppression of normal protein synthesis and expression of stress response genes (2). In mammalian cells the phosphorylation is carried out by a family of four eIF2alpha kinases, namely: PKR-like ER kinase (PERK), double-stranded RNA-dependent protein kinase (PKR),
 25 heme-regulated eIF2alpha kinase (HRI), and general control non-derepressible 2 (GCN2), each responding to distinct environmental and physiological stresses (3).

eIF2alpha together with eIF2beta and eIF2gamma form the eIF2 complex, a key player of the initiation of normal mRNA translation (4). The eIF2 complex binds GTP and Met-tRNA_i forming a ternary complex (eIF2-GTP-Met-tRNA_i), which is recruited by ribosomes for translation initiation (5, 6).

5

eIF2B is a heterodecameric complex consisting of 5 subunits (alpha, beta, gamma, delta, epsilon) which in duplicate form a GEF-active decamer (7).

In response to ISR activation, phosphorylated eIF2alpha inhibits the eIF2B-mediated exchange of GDP for GTP, resulting in reduced ternary complex formation and hence in the inhibition of translation of normal mRNAs characterized by ribosomes binding to the 5' AUG start codon (8). Under these conditions of reduced ternary complex abundance the translation of several specific mRNAs including the mRNA coding for the transcription factor ATF4 is activated via a mechanism involving altered translation of upstream ORFs (uORFs) (7, 9, 10). These mRNAs typically contain one or more uORFs that normally function in unstressed cells to limit the flow of ribosomes to the main coding ORF. For example, during normal conditions, uORFs in the 5' UTR of ATF occupy the ribosomes and prevent translation of the coding sequence of ATF4. However, during stress conditions, i.e. under conditions of reduced ternary complex formation, the probability for ribosomes to scan past these upstream ORFs and initiate translation at the ATF4 coding ORF is increased. ATF4 and other stress response factors expressed in this way subsequently govern the expression of an array of further stress response genes. The acute phase consists in expression of proteins that aim to restore homeostasis, while the chronic phase leads to expression of pro-apoptotic factors (1, 11, 12, 13).

Upregulation of markers of ISR signaling has been demonstrated in a variety of conditions, among these cancer and neurodegenerative diseases. In cancer, ER stress-regulated translation increases tolerance to hypoxic conditions and promotes tumor growth (14, 15, 16), and deletion of PERK by gene targeting has been shown to slow growth of tumours derived from transformed PERK^{-/-} mouse embryonic fibroblasts (14, 17). Further, a recent report has provided proof of concept using patient derived xenograft modeling in mice for activators of eIF2B to be effective in treating a form of aggressive metastatic prostate cancer (28). Taken together, prevention of cytoprotective ISR signaling may represent an effective anti-proliferation strategy for the treatment of at least some forms of cancer.

Further, modulation of ISR signaling could prove effective in preserving synaptic function and reducing neuronal decline, also in neurodegenerative diseases that are characterized by misfolded proteins and activation of the unfolded protein response (UPR), such as amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD),
5 Parkinson's disease (PD) and Jakob Creutzfeld (prion) diseases (18, 19, 20). With prion disease an example of a neurodegenerative disease exists where it has been shown that pharmacological as well as genetic inhibition of ISR signaling can normalize protein translation levels, rescue synaptic function and prevent neuronal loss (21). Specifically, reduction of levels of phosphorylated eIF2alpha by overexpression of the phosphatase controlling phosphorylated
10 eIF2alpha levels increased survival of prion-infected mice whereas sustained eIF2alpha phosphorylation decreased survival (22).

Further, direct evidence for the importance of control of protein expression levels for proper brain function exists in the form of rare genetic diseases affecting functions of eIF2 and eIF2B.
15 A mutation in eIF2gamma that disrupts complex integrity of eIF2 and hence results in reduced normal protein expression levels is linked to intellectual disability syndrome (ID) (23). Partial loss of function mutations in subunits of eIF2B have been shown to be causal for the rare leukodystrophy Vanishing White Matter Disease (VWMD) (24, 25). Specifically, stabilization of eIF2B partial loss of function in a VWMD mouse model by a small molecule related to
20 ISRIB has been shown to reduce ISR markers and improve functional as well as pathological end points (26, 27).

Modulators of the eIF2 alpha pathway are described in WO 2014/144952 A2. WO 2017/193030 A1, WO 2017/193034 A1, WO 2017/193041 A1 and WO 2017/193063 A1 describe modulators
25 of the integrated stress pathway. WO 2017/212423 A1, WO 2017/212425 A1, WO 2018/225093 A1, WO 2019/008506 A1 and WO 2019/008507 A1 describe inhibitors of the ATF4 pathway. WO 2019/032743 A1, WO 2019/046779 A1, WO 2020/167994 A1, WO 2020/168011 A1 and WO 2020/181247 A1 relate to eukaryotic initiation factor 2B modulators. In WO 2020/77217 A1 compounds, compositions, and methods useful for modulating the
30 integrated stress response (ISR) and for treating related diseases, disorders and conditions are described.

Further documents describing modulators of the integrated stress pathway are WO 2019/090069 A1, WO 2019/090074 A1, WO 2019/090076 A1, WO 2019/090078 A1, WO

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.

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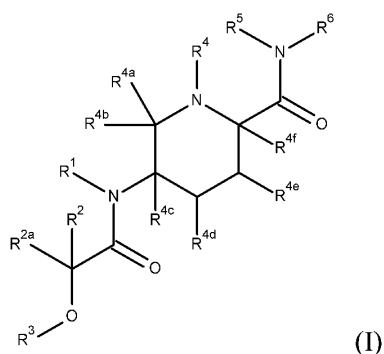
Modulators of eukaryotic initiation factors are described in WO 2019/183589 A1. WO 2019/118785 A2, WO 2019/236710 A1 and WO 2020/176428 A1 describe inhibitors of the integrated stress response pathway. Heteroaryl derivatives as ATF4 inhibitors are described in WO 2019/193540 A1. Bicyclic aromatic ring derivatives as ATF4 inhibitors are described in
10 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.

15

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
20 side effects.

Accordingly, the present invention provides a compound of formula (I)



25

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

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

R² is H, F or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more halogen,
5 which are the same or different;

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

R³ is phenyl or 6 membered aromatic heterocyclyl, wherein R³ is optionally substituted with
10 one or more R⁷, which are the same or different;

R⁷ is halogen, CN, C(O)OR⁸, OR⁸, C(O)R⁸, C(O)N(R⁸R^{8a}), S(O)₂N(R⁸R^{8a}), S(O)N(R⁸R^{8a}),
S(O)₂R⁸, S(O)R⁸, N(R⁸)S(O)₂N(R^{8a}R^{8b}), SR⁸, N(R⁸R^{8a}), NO₂, OC(O)R⁸, N(R⁸)C(O)R^{8a},
N(R⁸)S(O)₂R^{8a}, N(R⁸)S(O)R^{8a}, N(R⁸)C(O)OR^{8a}, N(R⁸)C(O)N(R^{8a}R^{8b}), OC(O)N(R⁸R^{8a}), C₁₋₆
15 alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are
optionally substituted with one or more R⁹, which are the same or different;

R⁸, R^{8a}, R^{8b} are independently selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl
and C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are optionally substituted
20 with one or more halogen, which are the same or different;

R⁹ is halogen, CN, C(O)OR¹⁰, OR¹⁰, C(O)R¹⁰, C(O)N(R¹⁰R^{10a}), S(O)₂N(R¹⁰R^{10a}),
S(O)N(R¹⁰R^{10a}), S(O)₂R¹⁰, S(O)R¹⁰, N(R¹⁰)S(O)₂N(R^{10a}R^{10b}), SR¹⁰, N(R¹⁰R^{10a}), NO₂,
OC(O)R¹⁰, N(R¹⁰)C(O)R^{10a}, N(R¹⁰)SO₂R^{10a}, N(R¹⁰)S(O)R^{10a}, N(R¹⁰)C(O)N(R^{10a}R^{10b}),
25 N(R¹⁰)C(O)OR^{10a} or OC(O)N(R¹⁰R^{10a});

R¹⁰, R^{10a}, R^{10b} are independently selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl
and C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are optionally substituted
30 with one or more halogen, which are the same or different.

R⁴ is H, C(O)OC₁₋₄ alkyl or C₁₋₄ alkyl, wherein C(O)OC₁₋₄ alkyl and C₁₋₄ alkyl are optionally
substituted with one or more substituents selected from the group consisting of halogen, OH
and O-C₁₋₃ 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;

- 5 or R^4 and one of R^{4d} and R^{4e} form a methylene or ethylene group;
or R^4 and R^{4e} 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,
10 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 ;

- 15 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
20 with one or more R^{15} , which are the same or different;

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

- 25 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 ;

- 30 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;

A² is phenyl, naphthyl, C₃₋₇ cycloalkyl, C₄₋₁₂ bicycloalkyl, 3 to 7 membered heterocyclyl or 7 to 12 membered heterobicyclyl, wherein A² is optionally substituted with one or more R^{16a}, which are the same or different;

- 5 R¹⁶, R^{16a} are independently selected from the group consisting of R¹⁷, OH, OR¹⁷, halogen and CN;

R¹⁷ is cyclopropyl, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein R¹⁷ is optionally substituted with one or more R¹⁸, which are the same or different;

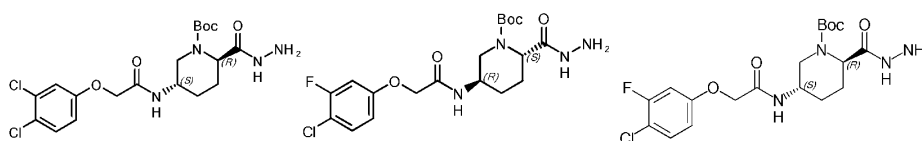
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R¹⁸ is halogen, CN or OR¹⁹;

R¹⁹ is H or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more halogen, which are the same or different.

15

Preferably, the following compounds are excluded:



- 20 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 invention insofar compounds as such of the present invention are concerned.

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

- 30 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,
5 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.

10 “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
15 carbon-carbon triple bond. Each hydrogen of an alkynyl carbon may be replaced by a substituent as further specified.

“C₁₋₄ 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. -
20 CH₂-, -CH₂-CH₂-, -CH(CH₃)-, -CH₂-CH₂-CH₂-, -CH(C₂H₅)-, -C(CH₃)₂-, when two moieties of a molecule are linked by the alkyl group. Each hydrogen of a C₁₋₄ alkyl carbon may be replaced by a substituent as further specified. The term “C₁₋₃ alkyl” is defined accordingly.

“C₁₋₆ alkyl” means an alkyl chain having 1 - 6 carbon atoms, e.g. if present at the end of a
25 molecule: C₁₋₄ alkyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, n-pentyl, n-hexyl, or e.g. -CH₂-, -CH₂-CH₂-, -CH(CH₃)-, -CH₂-CH₂-CH₂-, -CH(C₂H₅)-, -C(CH₃)₂-, when two moieties of a molecule are linked by the alkyl group. Each hydrogen of a C₁₋₆ alkyl carbon may be replaced by a substituent as further specified.

30 “C₂₋₆ alkenyl” means an alkenyl chain having 2 to 6 carbon atoms, e.g. if present at the end of a molecule: -CH=CH₂, -CH=CH-CH₃, -CH₂-CH=CH₂, -CH=CH-CH₂-CH₃, -CH=CH-CH=CH₂, or e.g. -CH=CH-, when two moieties of a molecule are linked by the alkenyl group. Each hydrogen of a C₂₋₆ alkenyl carbon may be replaced by a substituent as further specified.

“C₂₋₆ alkynyl” means an alkynyl chain having 2 to 6 carbon atoms, e.g. if present at the end of a molecule: -C≡CH, -CH₂-C≡CH, CH₂-CH₂-C≡CH, CH₂-C≡C-CH₃, or e.g. -C≡C- when two moieties of a molecule are linked by the alkynyl group. Each hydrogen of a C₂₋₆ alkynyl carbon may be replaced by a substituent as further specified.

5

“C₃₋₇ cycloalkyl” or “C₃₋₇ cycloalkyl ring” means a cyclic alkyl chain having 3 - 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl. Preferably, cycloalkyl refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl. Each hydrogen of a cycloalkyl carbon may be replaced by a substituent as further specified herein. The term “C₃₋₅ cycloalkyl” or “C₃₋₅ cycloalkyl ring” is defined accordingly.

10

“C₅ cycloalkylene” refers to a bivalent cycloalkyl with five carbon atoms, i.e. a bivalent cyclopentyl ring.

15

“C₅ cycloalkenylene” refers to a bivalent cycloalkenylene, i.e. a bivalent cyclopentene or cyclopentadiene.

“C₄₋₁₂ bicycloalkyl” or “C₄₋₁₂ bicycloalkyl ring” means a bicyclic fused, bridged or spiro alkyl chain having 4 to 12 carbon atoms, e.g. hexahydroindane, Octahydropentalen, bicycle[2.2.1]heptane or spiro(3.2)hexane. Each hydrogen of a bicycloalkyl carbon may be replaced by a substituent as further specified herein.

20

“Halogen” means fluoro, chloro, bromo or iodo. It is generally preferred that halogen is fluoro or chloro.

25

“3 to 7 membered heterocyclyl” or “3 to 7 membered heterocycle” means a ring with 3, 4, 5, 6 or 7 ring atoms that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one ring atom up to 4 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a 3 to 7 membered heterocycle are aziridine, azetidine, oxetane, thietane, furan, thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran,

30

tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine, piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, diazepane, azepine or homopiperazine. The term
5 “5 to 6 membered heterocyclyl” or “5 to 6 membered heterocycle” is defined accordingly and includes 5 to 6 membered aromatic heterocyclyl or heterocycle. The term “5 membered heterocyclyl” or “5 membered heterocycle” is defined accordingly and includes 5 membered aromatic heterocyclyl or heterocycle.

10 The term “nitrogen ring atom containing 5-membered heterocyclene” refers to a bivalent 5-membered heterocycle, wherein at least one of the five ring atoms is a nitrogen atom and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom.

“Saturated 4 to 7 membered heterocyclyl” or “saturated 4 to 7 membered heterocycle” means
15 fully saturated “4 to 7 membered heterocyclyl” or “4 to 7 membered heterocycle”.

“4 to 7 membered at least partly saturated heterocyclyl” or “4 to 7 membered at least partly saturated heterocycle” means an at least partly saturated “4 to 7 membered heterocyclyl” or “4 to 7 membered heterocycle”.

20

“5 to 6 membered aromatic heterocyclyl” or “5 to 6 membered aromatic heterocycle” means a heterocycle derived from cyclopentadienyl or benzene, where at least one carbon atom is replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-). Examples for such heterocycles are furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, thiadiazole, triazole, tetrazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine.
25

“5 membered aromatic heterocyclyl” or “5 membered aromatic heterocycle” means a heterocycle derived from cyclopentadienyl, where at least one carbon atom is replaced by a
30 heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-). Examples for such heterocycles are furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, thiadiazole, triazole, tetrazole.

“6 membered aromatic heterocyclyl” or “6 membered aromatic heterocycle” means a heterocycle derived from benzene, where at least one carbon atom is replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-). Examples for such heterocycles are pyridine, pyrimidine, pyridazine, pyrazine, triazine.

“7 to 12 membered heterobicyclyl” or “7 to 12 membered heterobicycle” means a heterocyclic system of two rings with 7 to 12 ring atoms, where at least one ring atom is shared by both rings and that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one ring atom up to 6 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a 7 to 12 membered heterobicycle are indole, isoindole, indoline, benzofuran, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzodioxole, benzisothiazole, benzimidazole, benzimidazoline, quinoline, quinazoline, dihydroquinazoline, quinoline, dihydroquinoline, tetrahydroquinoline, decahydroquinoline, isoquinoline, decahydroisoquinoline, tetrahydroisoquinoline, dihydroisoquinoline, benzazepine, purine or pteridine. The term 7 to 12 membered heterobicycle also includes spiro structures of two rings like 6-oxa-2-azaspiro[3,4]octane, 2-oxa-6-azaspiro[3.3]heptan-6-yl or 2,6-diazaspiro[3.3]heptan-6-yl or bridged heterocycles like 8-aza-bicyclo[3.2.1]octane or 2,5-diazabicyclo[2.2.2]octan-2-yl or 3,8-diazabicyclo[3.2.1]octane.

“Saturated 7 to 12 membered heterobicyclyl” or “saturated 7 to 12 membered heterobicycle” means fully saturated “7 to 12 membered heterobicyclyl” or “7 to 12 membered heterobicycle”.

“7 to 12 membered at least partly saturated heterobicyclyl” or “7 to 12 membered at least partly saturated heterobicycle” means an at least partly saturated “7 to 12 membered heterobicyclyl” or “7 to 12 membered heterobicycle”.

“9 to 11 membered aromatic heterobicyclyl” or “9 to 11 membered aromatic heterobicycle” means a heterocyclic system of two rings, wherein at least one ring is aromatic and wherein the heterocyclic ring system has 9 to 11 ring atoms, where two ring atoms are shared by both rings and that may contain up to the maximum number of double bonds (fully or partially aromatic)

wherein at least one ring atom up to 6 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for an 9 to 11 membered aromatic heterobicycle are indole, indoline, benzofuran, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzimidazole, benzimidazoline, quinoline, quinazoline, dihydroquinazoline, dihydroquinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, dihydro-isoquinoline, benzazepine, purine or pteridine. The terms “9 to 10 membered aromatic heterobicycyl” or “9 to 10 membered aromatic heterobicycle” are defined accordingly.

Preferred compounds of formula (I) are those compounds in which one or more of the residues contained therein have the meanings given above or below, with all combinations of preferred substituent definitions being a subject of the present invention. With respect to all preferred compounds of the formula (I) the present invention also includes all tautomeric and stereoisomeric forms and mixtures thereof in all ratios, and their pharmaceutically acceptable salts.

In preferred embodiments of the present invention, the substituents mentioned below independently have the following meaning. Hence, one or more of these substituents can have the preferred or more preferred meanings given below.

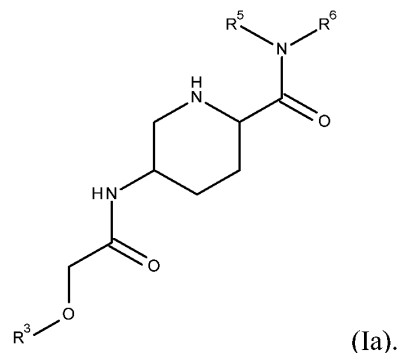
Preferably, R⁴ is H, CH₃, CH₂CH₃, or CH₂CH₂OCH₃; more preferably, H or CH₃; even more preferably H.

Preferably, R^{4a}, R^{4b}, R^{4c}, R^{4f} are independently selected from the group consisting of H, halogen and C₁₋₄ alkyl and R^{4d}, R^{4e} are independently selected from the group consisting of H, OH, OC₁₋₄ alkyl, halogen and C₁₋₄ alkyl; more preferably R^{4a}, R^{4b}, R^{4c}, R^{4f}, R^{4d}, R^{4e} are independently selected from the group consisting of H, F and CH₃; even more preferably R^{4a}, R^{4b}, R^{4c}, R^{4f}, R^{4d}, R^{4e} are H.

Preferably, R¹ is H or CH₃; more preferably H.

Preferably, R² is H, F or CH₃, more preferably H.

Preferably, 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)

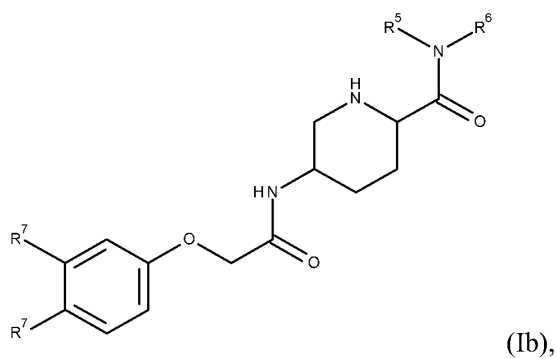


Preferably, R^3 is phenyl or pyridyl, more preferably phenyl, wherein R^3 is optionally substituted
5 with one or more R^7 , which are the same or different.

Preferably, R^3 is substituted with one, two or three, more preferably one or two, even more preferably two, R^7 , which are the same or different.

10 Preferably, R^7 is F, Cl, Br, CN, CHF_2 , CF_3 , OCH_3 , OCF_3 , $\text{CH}=\text{O}$, CH_2OH or CH_3 ; more preferably R^7 is CF_3 , F or Cl; even more preferably F or Cl.

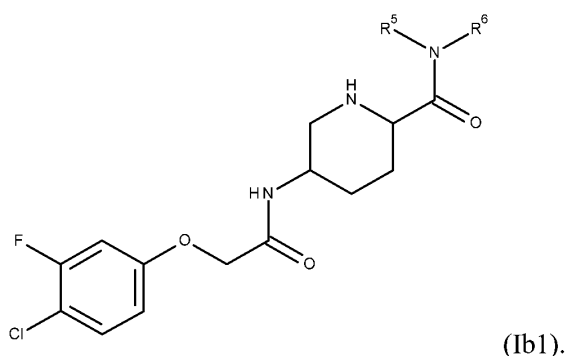
Preferably, R^1 , R^2 , R^{2a} , R^4 , R^{4a} , R^{4b} , R^{4c} , R^{4f} , R^{4d} , R^{4e} , R^3 in formula (I) are selected to give formula (Ib)



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

Preferably R^7 groups are selected in formula (Ib) to give formula (Ib1)



Preferably, R⁵ is H or CH₃, more preferably H.

- 5 Preferably, R⁶ is R¹¹ and R¹¹ is C₁₋₆ alkyl or C₁₋₆ alkenyl, wherein C₁₋₆ alkyl and C₁₋₆ alkenyl are substituted with one or more R¹³, which are the same or different.

Preferably, R⁶ is R¹¹ and R¹¹ is C₁₋₆ alkyl, more preferably ethyl or n-propyl, wherein C₁₋₆ alkyl is substituted with one R¹³.

10

Preferably, R⁶ is R¹¹ and R¹¹ is ethyl or n-propyl, each substituted with one R¹³, wherein R¹³ is OR¹⁴, preferably OCF₃.

15

Preferably, R⁶ is R¹¹ and R¹¹ is C₁₋₆ alkyl, more preferably n-propyl or n-pentyl, wherein C₁₋₆ alkyl is substituted with three F; more preferably R¹¹ is 3,3,3-trifluoropropyl or 5,5,5-trifluoropentyl.

20

Preferably, R⁶ is R¹¹ and R¹¹ is C₁₋₆ alkyl, preferably methyl, wherein C₁₋₆ alkyl is substituted with one R¹³, wherein R¹³ is A², preferably phenyl, pyridyl, pyrazolyl, oxazolyl, cyclobutyl, cyclohexyl, furanyl, bicyclo[3.1.0]hexan-3-yl or 6-oxaspiro[3.4]octan-7-yl. Preferably, R⁶ is R¹¹ and R¹¹ is C₁₋₆ alkyl, preferably methyl, wherein C₁₋₆ alkyl is substituted with one R¹³, wherein R¹³ is A², preferably phenyl, pyridyl, cyclobutyl, cyclohexyl, furanyl, bicyclo[3.1.0]hexan-3-yl or 6-oxaspiro[3.4]octan-7-yl.

25

Preferably, R⁶ is R¹¹ and R¹¹ is A², preferably phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzodioxolyl, cyclohexyl, cyclopentyl, cyclobutyl, pyrazolyl, oxazolyl or

oxolanyl. Preferably, R⁶ is R¹¹ and R¹¹ is A², preferably phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, cyclohexyl, cyclobutyl, pyrazolyl, oxazolyl or oxolanyl.

- 5 Preferably, A² is unsubstituted or substituted with one or two R^{16a}.

Preferably, R^{16a} is CH₃, CHF₂, CF₃, CH₂CF₃, OCHF₂, OCH₂CF₃, OCF₃, OCH₃, F or Cl.

- 10 Preferably, R⁵ and R⁶ are joined to form together with the nitrogen atom to which they are attached a ring A¹.

Preferably, A¹ is azetidine, piperidine, oxazepane, indoline, isoindoline, tetrahydroisoquinoline azabicyclo[3.1.0]hexane or azaspiro[3.3]heptane, wherein A¹ is optionally substituted with one or more R¹⁶, which are the same or different.

15

Preferably, A¹ is unsubstituted or substituted with one R¹⁶.

Preferably, R¹⁶ is CF₃, OCF₃ or OCH₂CH₂OCF₃.

- 20 Compounds of the formula (I) in which some or all of the above-mentioned groups have the preferred or more preferred meanings are also an object of the present invention.

For preferred specific compounds or pharmaceutically acceptable salts, solvates, hydrates, tautomers or stereoisomers thereof of the present invention R¹, R², R^{2a}, R³, R⁴, R^{4a}, R^{4b}, R^{4c},

- 25 R^{4d}, R^{4e}, R^{4f}, R⁵, R⁶ 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-

- 30 (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;
5 *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-
10 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-
15 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;
20 (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-
25 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;
30 (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*,5*S*)-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;
- 5 (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;
- 10 (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;
- 15 (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-
- 20 2-carboxamide;
- tert*-butyl (2*R*,5*S*)-2-[[3,5-bis(trifluoromethyl)phenyl]carbonyl]-5-[[2-(4-chloro-3-fluorophenoxy)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;
- 25 (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;
- 30 (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*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-{[2-(trifluoromethoxy)ethoxy]carbamoyl}piperidine-1-carboxylate;
- 5 *tert*-butyl (2*S*,5*R*)-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;
- 10 *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;
- 15 *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;
- 20 *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;
- 25 *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;
- 30 *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;
- 5 *tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2- {[5-methyl-1-(2,2,2-trifluoroethyl)-1*H*-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;
- 10 *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;
- 15 *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;
- 20 *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;
- 25 *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;
- 30 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;
- 5 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-
- 10 (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;
- 15 *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-
- 20 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;
- 25 *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-
- 30 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;
 5 *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.

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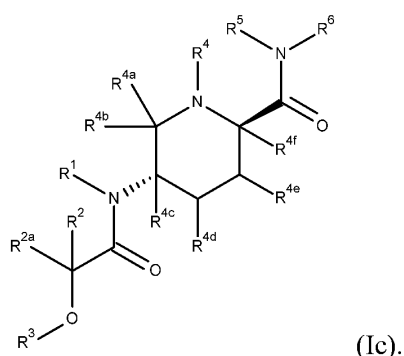
Where tautomerism, like e.g. keto-enol tautomerism, of compounds of formula (I) may occur, the individual forms, like e.g. the keto and enol form, are comprised separately and together as mixtures in any ratio. Same applies to stereoisomers, like e.g. enantiomers, cis/trans isomers, conformers and the like.

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Especially, when enantiomeric or diastereomeric forms are given in a compound according to formula (I) each pure form separately and any mixture of at least two of the pure forms in any ratio is comprised by formula (I) and is a subject of the present invention.

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A preferred compound is a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of formula (I) with a relative configuration as shown in formula (Ic)



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Isotopic labeled compounds of formula (I) are also within the scope of the present invention. Methods for isotope labeling are known in the art. Preferred isotopes are those of the elements

H, C, N, O and S. Solvates and hydrates of compounds of formula (I) are also within the scope of the present invention.

If desired, isomers can be separated by methods well known in the art, e.g. by liquid chromatography. Same applies for enantiomers by using e.g. chiral stationary phases. Additionally, enantiomers may be isolated by converting them into diastereomers, i.e. coupling with an enantiomerically pure auxiliary compound, subsequent separation of the resulting diastereomers and cleavage of the auxiliary residue. Alternatively, any enantiomer of a compound of formula (I) may be obtained from stereoselective synthesis using optically pure starting materials, reagents and/or catalysts.

In case the compounds according to formula (I) contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the formula (I) which contain acidic groups can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula (I) which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formula (I) simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts according to the formula (I) can be obtained by customary methods which are known to the person skilled in the art like, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the formula (I) which, owing to low physiological compatibility, are not directly suitable for

use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

As shown below compounds of the present invention are believed to be suitable for modulating the integrated stress response pathway.

The Integrated Stress Response (ISR) is a cellular stress response common to all eukaryotes (1). Dysregulation of ISR signaling has important pathological consequences linked inter alia to inflammation, viral infection, diabetes, cancer and neurodegenerative diseases.

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ISR is a common denominator of different types of cellular stresses resulting in phosphorylation of the alpha subunit of eukaryotic translation initiation factor 2 (eIF2alpha) on serine 51 leading to the suppression of normal protein synthesis and expression of stress response genes (2). In mammalian cells the phosphorylation is carried out by a family of four eIF2alpha kinases, namely: PKR-like ER kinase (PERK), double-stranded RNA-dependent protein kinase (PKR), heme-regulated eIF2alpha kinase (HRI), and general control non-derepressible 2 (GCN2), each responding to distinct environmental and physiological stresses (3).

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eIF2alpha together with eIF2beta and eIF2gamma form the eIF2 complex, a key player of the initiation of normal mRNA translation (4). The eIF2 complex binds GTP and Met-tRNA_i forming a ternary complex (eIF2-GTP-Met-tRNA_i), which is recruited by ribosomes for translation initiation (5, 6).

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eIF2B is a heterodecameric complex consisting of 5 subunits (alpha, beta, gamma, delta, epsilon) which in duplicate form a GEF-active decamer (7).

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In response to ISR activation, phosphorylated eIF2alpha inhibits the eIF2B-mediated exchange of GDP for GTP, resulting in reduced ternary complex formation and hence in the inhibition of translation of normal mRNAs characterized by ribosomes binding to the 5' AUG start codon (8). Under these conditions of reduced ternary complex abundance the translation of several specific mRNAs including the mRNA coding for the transcription factor ATF4 is activated via a mechanism involving altered translation of upstream ORFs (uORFs) (7, 9, 10). These mRNAs typically contain one or more uORFs that normally function in unstressed cells to limit the flow of ribosomes to the main coding ORF. For example, during normal conditions, uORFs in the 5'

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UTR of ATF occupy the ribosomes and prevent translation of the coding sequence of ATF4. However, during stress conditions, i.e. under conditions of reduced ternary complex formation, the probability for ribosomes to scan past these upstream ORFs and initiate translation at the ATF4 coding ORF is increased. ATF4 and other stress response factors expressed in this way subsequently govern the expression of an array of further stress response genes. The acute phase consists in expression of proteins that aim to restore homeostasis, while the chronic phase leads to expression of pro-apoptotic factors (1, 11, 12, 13).

Upregulation of markers of ISR signaling has been demonstrated in a variety of conditions, among these cancer and neurodegenerative diseases. In cancer, ER stress-regulated translation increases tolerance to hypoxic conditions and promotes tumor growth (14, 15, 16), and deletion of PERK by gene targeting has been shown to slow growth of tumours derived from transformed PERK^{-/-} mouse embryonic fibroblasts (14, 17). Further, a recent report has provided proof of concept using patient derived xenograft modeling in mice for activators of eIF2B to be effective in treating a form of aggressive metastatic prostate cancer (28). Taken together, prevention of cytoprotective ISR signaling may represent an effective anti-proliferation strategy for the treatment of at least some forms of cancer.

Further, modulation of ISR signaling could prove effective in preserving synaptic function and reducing neuronal decline, also in neurodegenerative diseases that are characterized by misfolded proteins and activation of the unfolded protein response (UPR), such as amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD) and Jakob Creutzfeld (prion) diseases (18, 19, 20). With prion disease an example of a neurodegenerative disease exists where it has been shown that pharmacological as well as genetic inhibition of ISR signaling can normalize protein translation levels, rescue synaptic function and prevent neuronal loss (21). Specifically, reduction of levels of phosphorylated eIF2alpha by overexpression of the phosphatase controlling phosphorylated eIF2alpha levels increased survival of prion-infected mice whereas sustained eIF2alpha phosphorylation decreased survival (22).

Further, direct evidence for the importance of control of protein expression levels for proper brain function exists in the form of rare genetic diseases affecting functions of eIF2 and eIF2B. A mutation in eIF2gamma that disrupts complex integrity of eIF2 and hence results in reduced normal protein expression levels is linked to intellectual disability syndrome (ID) (23). Partial

loss of function mutations in subunits of eIF2B have been shown to be causal for the rare leukodystrophy Vanishing White Matter Disease (VWMD) (24, 25). Specifically, stabilization of eIF2B partial loss of function in a VWMD mouse model by a small molecule related to ISRIB has been shown to reduce ISR markers and improve functional as well as pathological end points (26, 27).

The present invention provides compounds of the present invention in free or pharmaceutically acceptable salt form or in the form of solvates, hydrates, tautomers or stereoisomers to be used in the treatment of diseases or disorders mentioned herein. The same applies to a pharmaceutical composition of the present invention.

Thus an aspect of the present invention is a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of the present invention for use as a medicament. The same applies to a pharmaceutical composition of the present invention.

The therapeutic method described may be applied to mammals such as dogs, cats, cows, horses, rabbits, monkeys and humans. Preferably, the mammalian patient is a human patient.

Accordingly, the present invention provides a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof or a pharmaceutical composition of the present invention to be used in the treatment or prevention of one or more diseases or disorders associated with integrated stress response.

A further aspect of the present invention is a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof or a pharmaceutical composition of the present invention for use in a method of treating or preventing one or more disorders or diseases associated with integrated stress response.

A further aspect of the present invention is the use of a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof or a pharmaceutical composition of the present invention for the manufacture of a medicament for the treatment or prophylaxis of one or more disorders or diseases associated with integrated stress response.

Yet another aspect of the present invention is a method for treating, controlling, delaying or preventing in a mammalian patient in need of the treatment of one or more diseases or disorders associated with integrated stress response, wherein the method comprises administering to said patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof or a pharmaceutical composition of the present invention.

The present invention provides a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof or a pharmaceutical composition of the present invention to be used in the treatment or prevention of one or more diseases or disorders mentioned below.

A further aspect of the present invention is a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof or a pharmaceutical composition of the present invention for use in a method of treating or preventing one or more disorders or diseases mentioned below.

A further aspect of the present invention is the use of a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof or a pharmaceutical composition of the present invention for the manufacture of a medicament for the treatment or prophylaxis of one or more disorders or diseases mentioned below.

Yet another aspect of the present invention is a method for treating, controlling, delaying or preventing in a mammalian patient in need of the treatment of one or more diseases or disorders mentioned below, wherein the method comprises administering to said patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof or a pharmaceutical composition of the present invention.

Diseases or disorders include but are not limited to 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.

Leukodystrophies

- 5 Examples of leukodystrophies include, but are not limited to, Vanishing White Matter Disease (VWMD) and childhood ataxia with CNS hypo-myelination (e.g. associated with impaired function of eIF2 or components in a signal transduction or signaling pathway including eIF2).

Intellectual disability syndrome

- 10 Intellectual disability in particular refers to a condition in which a person has certain limitations in intellectual functions like communicating, taking care of him- or herself, and/or has impaired social skills. Intellectual disability syndromes include, but are not limited to, intellectual disability conditions associated with impaired function of eIF2 or components in a signal transduction or signaling pathway including eIF2.

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Neurodegenerative diseases / disorders

- Examples of neurodegenerative diseases and disorders include, but are not limited to, Alexander's disease, Alper's disease, Alzheimer's disease, Amyotrophic lateral sclerosis, Ataxia telangiectasia, Batten disease (also known as Spielmeyer-Vogt-Sjogren-Batten disease),
- 20 Bovine spongiform encephalopathy (BSE), Canavan disease, Cockayne syndrome, Corticobasal degeneration, Creutzfeldt-Jakob disease, frontotemporal dementia, Gerstmann-Straussler-Scheinker syndrome, Huntington's disease, HIV-associated dementia, Kennedy's disease, Krabbe's disease, Kuru, Lewy body dementia, Machado-Joseph disease (Spinocerebellar ataxia type 3), Multiple sclerosis, Multiple System Atrophy, Narcolepsy,
- 25 Neuroborreliosis, Parkinson's disease, Pelizaeus-Merzbacher Disease, Pick's disease, Primary lateral sclerosis, Prion diseases, Progressive supranuclear palsy, Refsum's disease, Sandhoffs disease, Schilder's disease, Subacute combined degeneration of spinal cord secondary to Pernicious Anaemia, Schizophrenia, Spinocerebellar ataxia (multiple types with varying characteristics), Spinal muscular atrophy, Steele-Richardson-Olszewski disease, Tabes
- 30 dorsalis, and tauopathies.

In particular, the neurodegenerative disease or and disorder is selected from the group consisting of Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis.

Neoplastic diseases

A neoplastic disease may be understood in the broadest sense as any tissue resulting from miss-controlled cell growth. In many cases a neoplasm leads to at least bulky tissue mass optionally innervated by blood vessels. It may or may not comprise the formation of one or more metastasis/metastases. A neoplastic disease of the present invention may be any neoplasm as
5 classified by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) classes C00-D48.

Exemplarily, a neoplastic disease according to the present invention may be the presence of one or more malignant neoplasm(s) (tumors) (ICD-10 classes C00-C97), may be the presence of
10 one or more *in situ* neoplasm(s) (ICD-10 classes D00-D09), may be the presence of one or more benign neoplasm(s) (ICD-10 classes D10-D36), or may be the presence of one or more neoplasm(s) of uncertain or unknown behavior (ICD-10 classes D37-D48). Preferably, a neoplastic disease according to the present invention refers to the presence of one or more malignant neoplasm(s), i.e., is malignant neoplasia (ICD-10 classes C00-C97).

15 In a more preferred embodiment, the neoplastic disease is cancer.

Cancer may be understood in the broadest sense as any malignant neoplastic disease, i.e., the presence of one or more malignant neoplasm(s) in the patient. Cancer may be solid or hematologic malignancy. Contemplated herein are without limitation leukemia, lymphoma,
20 carcinomas and sarcomas.

In particular, neoplastic diseases, such as cancers, characterized by upregulated ISR markers are included herein.

Exemplary cancers include, but are not limited to, thyroid cancer, cancers of the endocrine system, pancreatic cancer, brain cancer (e.g. glioblastoma multiforme, glioma), breast cancer
25 (e.g. ER positive, ER negative, chemotherapy resistant, herceptin resistant, HER2 positive, doxorubicin resistant, tamoxifen resistant, ductal carcinoma, lobular carcinoma, primary, metastatic), cervix cancer, ovarian cancer, uterus cancer, colon cancer, head & neck cancer, liver cancer (e.g. hepatocellular carcinoma), kidney cancer, lung cancer (e.g. non-small cell lung carcinoma, squamous cell lung carcinoma, adenocarcinoma, large cell lung carcinoma,
30 small cell lung carcinoma, carcinoid, sarcoma), colon cancer, esophageal cancer, stomach cancer, bladder cancer, bone cancer, gastric cancer, prostate cancer and skin cancer (e.g. melanoma).

Further examples include, but are not limited to, myeloma, leukemia, mesothelioma, and sarcoma.

5 Additional examples include, but are not limited to, Medulloblastoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, malignant pancreatic insuloma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, genitourinary tract cancer, malignant
 10 hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, Paget's Disease of the Nipple, Phyllodes Tumors, Lobular Carcinoma, Ductal Carcinoma, cancer of the pancreatic stellate cells, and cancer of the hepatic stellate cells.

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Exemplary leukemias include, but are not limited to, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemiac leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic
 20 leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocyte leukemia,
 25 micromyeloblastic leukemia, monocytic leukemia, myeloblasts leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, and undifferentiated cell leukemia.

30 Exemplary sarcomas include, but are not limited to, chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell

sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, and telangiectatic sarcoma.

Exemplary melanomas include, but are not limited to, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungual melanoma, and superficial spreading melanoma.

Exemplary carcinomas include, but are not limited to, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, ductal carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniformi carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lobular carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell

carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tubular carcinoma, tuberos carcinoma, verrucous carcinoma, and carcinoma villosum.

5

Infectious diseases

Examples include, but are not limited to, infections caused by viruses (such as infections by HIV-1: human immunodeficiency virus type 1; IAV: influenza A virus; HCV: hepatitis C virus; DENV: dengue virus; ASFV: African swine fever virus; EBV: Epstein-Barr virus; HSV1: herpes simplex virus 1; CHIKV: chikungunya virus; HCMV: human cytomegalovirus; SARS-CoV: severe acute respiratory syndrome coronavirus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2) and infections caused by bacteria (such as infections by Legionella, Brucella, Simkania, Chlamydia, Helicobacter and *Campylobacter*).

10

Inflammatory diseases

Examples of inflammatory diseases include, but are not limited to, postoperative cognitive dysfunction (decline in cognitive function after surgery), traumatic brain injury, arthritis, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, multiple sclerosis, systemic lupus erythematosus (SLE), myasthenia gravis, juvenile onset diabetes, diabetes mellitus type 1, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, ankylosing spondylitis, psoriasis, Sjogren's syndrome, vasculitis, glomerulonephritis, auto-immune thyroiditis, Behcet's disease, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, ichthyosis, Graves ophthalmopathy, inflammatory bowel disease, Addison's disease, Vitiligo, asthma, allergic asthma, acne vulgaris, celiac disease, chronic prostatitis, inflammatory bowel disease, pelvic inflammatory disease, reperfusion injury, sarcoidosis, transplant rejection, interstitial cystitis, atherosclerosis, and atopic dermatitis.

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Musculoskeletal diseases

Examples of musculoskeletal diseases include, but are not limited to, muscular dystrophy, multiple sclerosis, Freidrich's ataxia, a muscle wasting disorder (e.g., muscle atrophy, sarcopenia, cachexia), inclusion body myopathy, progressive muscular atrophy, motor neuron disease, carpal tunnel syndrome, epicondylitis, tendinitis, back pain, muscle pain, muscle soreness, repetitive strain disorders, and paralysis.

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Metabolic diseases

Examples of metabolic diseases include, but are not limited to, diabetes (in particular diabetes Type II), non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), Niemann-Pick disease, liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, phenylketonuria, proliferative retinopathy, and Kearns-Sayre disease.

Ocular diseases

Examples of ocular diseases include, but are not limited to, edema or neovascularization for any occlusive or inflammatory retinal vascular disease, such as rubeosis irides, neovascular glaucoma, pterygium, vascularized glaucoma filtering blebs, conjunctival papilloma; choroidal neovascularization, such as neovascular age-related macular degeneration (AMD), myopia, prior uveitis, trauma, or idiopathic; macular edema, such as post surgical macular edema, macular edema secondary to uveitis including retinal and/or choroidal inflammation, macular edema secondary to diabetes, and macular edema secondary to retinovascular occlusive disease (i.e. branch and central retinal vein occlusion); retinal neovascularization due to diabetes, such as retinal vein occlusion, uveitis, ocular ischemic syndrome from carotid artery disease, ophthalmic or retinal artery occlusion, sickle cell retinopathy, other ischemic or occlusive neovascular retinopathies, retinopathy of prematurity, or Eale's Disease; and genetic disorders, such as VonHippel-Lindau syndrome.

Further diseases

Further diseases include, but are not limited to, organ fibrosis (such as liver fibrosis, lung fibrosis, or kidney fibrosis), chronic and acute diseases of the liver (such as fatty liver disease, or liver steatosis), 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.

Yet another aspect of the present invention is a pharmaceutical composition comprising at least one compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof of the present invention together with a pharmaceutically acceptable carrier, optionally in combination with one or more other bioactive compounds or pharmaceutical compositions.

Preferably, the one or more bioactive compounds are modulators of the integrated stress response pathway other than compounds of formula (I).

"Pharmaceutical composition" means one or more active ingredients, and one or more inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the present invention may comprise one or more additional compounds as active ingredients like a mixture of compounds of formula (I) in the composition or other modulators of the integrated stress response pathway.

The active ingredients may be comprised in one or more different pharmaceutical compositions (combination of pharmaceutical compositions).

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids, including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of formula (I) can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.*, oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents,

granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

5 Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may
10 conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally, for example, as liquid drops or spray.

15 The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

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Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

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Compounds of formula (I) may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these
30 preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form should be sterile and should be fluid to the extent

that easy syringability exists. It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of formula (I) are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

Starting materials for the synthesis of preferred embodiments of the invention may be purchased from commercially available sources such as Array, Sigma Aldrich, Acros, Fisher, Fluka, ABCR or can be synthesized using known methods by one skilled in the art.

In general, several methods are applicable to prepare compounds of the present invention. In some cases various strategies can be combined. Sequential or convergent routes may be used. Exemplary synthetic routes are described below.

Examples

I Chemical Synthesis

Experimental procedures:

The following Abbreviations and Acronyms are used:

aq	aqueous
ACN	acetonitrile
AgSO ₃ CF ₃	silver trifluoromethanesulfonate

	Brine	saturated solution of NaCl in water
	Bn	benzyl
	BnONH ₂ ·HCl	<i>O</i> -benzylhydroxylamine hydrochloride
	Boc	<i>tert</i> -butoxycarbonyl
5	Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
	^t BuOK	potassium <i>tert</i> -butoxide
	CDCl ₃	deuterated chloroform
	DCM	dichloromethane
	DMSO	dimethylsulfoxide
10	DMSO- <i>d</i> ₆	deuterated dimethylsulfoxide
	DIAD	diisopropyl azodicarboxylate
	DIPEA	diisopropylethylamine
	DMF	dimethyl formamide
	DMAP	<i>N,N</i> -dimethylpyridin-4-amine
15	ESI ⁺	positive ionisation mode
	ESI ⁻	negative ionisation mode
	EtOAc	ethyl acetate
	EtOH	ethanol
	Et ₂ O	diethyl ether
20	H ₂ SO ₄	sulfuric acid
	HATU	1-[bis(dimethylamino)methylidene]-1 <i>H</i> -[1,2,3]triazolo[4,5- <i>b</i>]pyridin-1-ium 3-oxide hexafluorophosphate
	HCl	hydrochloric acid
	HPLC	high-performance liquid chromatography
25	h	hour(s)
	IPA	isopropyl alcohol
	Josiphos SL-J009-1	{(<i>R</i>)-1-[(<i>Sp</i>)-2-(dicyclohexylphosphino)ferrocenyl]ethyl-di- <i>tert</i> -butylphosphine}[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate
30	KHCO ₃	potassium bicarbonate
	KF	potassium fluoride
	LiOH	lithium hydroxide
	m	multiplet
	MeI	iodomethane

	MeNHNH ₂	methylhydrazine
	MeOH	methanol
	MgSO ₄	magnesium sulphate
	min	minutes
5	MsCl	mesyl chloride
	MsOH	methanesulfonic acid
	mL	millilitre (s)
	N ₂	nitrogen atmosphere
	Na ₂ SO ₄	sodium sulphate
10	NaHCO ₃	sodium bicarbonate
	NH ₄ Cl	ammonium chloride
	NMM	4-methylmorpholine
	NMR	Nuclear Magnetic Resonance
	Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
15	prep.	preparative
	POCl ₃	phosphoric trichloride
	PPh ₃	triphenylphosphine
	r.t.	room temperature
	RT	retention time
20	satd	saturated
	Selectfluor	1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane-1,4-diium ditetrafluoroborate
	T3P	propanephosphonic acid anhydride
	THF	tetrahydrofuran
25	TFA	2,2,2-trifluoroacetic acid
	TMSOI	trimethylsulfoxonium iodide
	XPhos	dicyclohexyl[2',4',6'-tris(propan-2-yl)[1,1'-biphenyl]-2-yl]phosphane
	ZnBr ₂	zinc dibromide

Analytical LCMS conditions are as follows:

30

System 1 (S1): ACIDIC IPC METHOD (MS18 and MS19)

Analytical (MET/CR/1410) HPLC-MS were performed on a Shimadzu LCMS systems using a Kinetex Core shell C18 column (2.1 mm × 50 mm, 5 µm; temperature: 40 °C) and a gradient of 5-100% B (A= 0.1% formic acid in H₂O; B= 0.1% formic acid in ACN) over 1.2 min then

100% B for 0.1 min. A second gradient of 100-5% B was then applied over 0.01 min with an injection volume of 3 μ L at a flow rate of 1.2 mL/min. UV spectra were recorded at 215 nm using a SPD-M20A photo diode array detector spectrum range: 200-400 nm. Mass spectra were obtained using a 2010EV detector. Data were integrated and reported using Shimadzu LCMS-
5 Solutions and PsiPort software.

System 2 (S2): ACIDIC IPC METHOD (MSQ1, MSQ2 and MSQ4)

Analytical (MET/uPLC/1704) uHPLC-MS were performed on a Waters Acquity uPLC system using a Waters UPLC® BEH™ C18 column (2.1 mm $\times$ 50 mm, 1.7 μ m; temperature 40 °C) and a gradient of 5-100% B (A= 0.1% formic acid in H₂O; B= 0.1% formic acid in ACN) over
10 1.1 min then 100% B for 0.25 min. A second gradient of 100-5% B was then applied over 0.05 min and held for 0.1 min with an injection volume of 1 μ L at a flow rate of 0.9 mL/min. UV spectra were recorded at 215 nm on a Waters Acquity PDA with a spectrum range of 200-400 nm. Mass spectra were obtained using a Waters QDa. Data were integrated and reported using
15 Waters MassLynx and OpenLynx software.

System 3 (S3): BASIC IPC METHOD (MS16)

Analytical (MET/CR/1602) uHPLC-MS were performed on a Waters Acquity uPLC system using Waters UPLC® BEH™ C18 column (2.1 mm $\times$ 30 mm, 1.7 μ m; temperature 40 °C) and
20 a gradient of 5-100% B (A: 2 mM ammonium bicarbonate, buffered to pH 10, B: ACN) over 0.75 min, then 100% B for 0.1 min. A second gradient of 100-5% B was then applied over 0.05 min and held for 0.1 min with an injection volume of 1 μ L at a flow rate of 1 mL/min. UV spectra were recorded at 215 nm on a Waters Acquity PDA with a spectrum range of 200-400 nm. Mass spectra were obtained using a Waters Quattro Premier XE. Data were integrated and
25 reported using Waters MassLynx and OpenLynx software.

System 4 (S4): ACIDIC FINAL METHOD (MSQ1 and MSQ2)

Analytical (MET/uPLC/AB101) uHPLC-MS were performed on a Waters Acquity uPLC system using a Phenomenex Kinetex-XB C18 column (2.1 mm $\times$ 100 mm, 1.7 μ m; temperature:
30 40 °C) and a gradient of 5-100% B (A = 0.1% formic acid in H₂O; B = 0.1% formic acid in ACN) over 5.3 min then 100% B for 0.5 min. A second gradient of 100-5% B was then applied over 0.02 min and held for 1.18 min with an injection volume of 1 μ L at flow rate of 0.6 mL/min. UV spectra were recorded at 215 nm using a Waters Acquity PDA detector spectrum range: 200-400 nm. Mass spectra were obtained using a Waters SQD (MSQ1) or Waters

Acquity QDA (MSQ2). Data were integrated and reported using Waters MassLynx and OpenLynx software.

System 5 (S5): ACIDIC FINAL METHOD (MS18, MS19)

- 5 Analytical (MET/CR/1416) HPLC-MS were performed on Shimadzu LCMS systems using a Waters Atlantis dC18 column (2.1 mm × 100 mm, 3 µm; temperature: 40 °C) and a gradient of 5-100% B (A= 0.1% formic acid in H₂O; B= 0.1% formic acid in ACN) over 5 min then 100% B for 0.4 min. A second gradient of 100-5% B was then applied over 0.02 min and held for 1.58 min with an injection volume of 3 µL at flow rate of 0.6 mL/min. UV spectra were recorded
- 10 at 215 nm using a SPD-M20A photo diode array detector spectrum range: 200-400 nm. Mass spectra were obtained using a 2010EV detector. Data were integrated and reported using Shimadzu LCMS-Solutions and PsiPort software.

System 6 (S6): BASIC FINAL METHOD (MS16)

- 15 Analytical (MET/uHPLC/AB105) uPLC-MS were performed on a Waters Acquity uPLC system using a Waters UPLC® BEH™ C18 column (2.1 mm × 100 mm, 1.7 µm column; temperature: 40 °C) and a gradient of 5-100% (A= 2 mM ammonium bicarbonate, buffered to pH 10; B = ACN) over 5.3 min then 100% B for 0.5 min. A second gradient of 100-5% B was then applied over 0.02 min and held for 1.18 min with an injection volume of 1 µL and at flow
- 20 rate of 0.6 mL/min. UV spectra were recorded at 215 nm using a Waters Acquity photo diode array detector Spectrum range: 200-400 nm. Mass spectra were obtained using a Waters Quattro Premier XE mass detector. Data were integrated and reported using Waters MassLynx and OpenLynx software.

- 25 **Purification methods are as follows:**

Method 1: ACIDIC EARLY METHOD

- Purifications (P1) LC were performed on a Gilson LC system using a Waters Sunfire C18 column (30 mm × 100 mm, 10 µm; temperature: r.t.) and a gradient of 10-95% B (A= 0.1% formic acid in H₂O; B= 0.1% formic acid in ACN) over 14.44 min then 95% B for 2.11 min. A
- 30 second gradient of 95-10% B was then applied over 0.2 min with an injection volume of 1500 µL at flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Method 2: ACIDIC STANDARD METHOD

Purifications (P2) LC were performed on a Gilson LC system using a Waters Sunfire C18 column (30 mm × 10 mm, 10 µM; temperature: r.t.) and a gradient of 30-95% B (A= 0.1% formic acid in water; B= 0.1% formic acid in ACN) over 11.00 min then 95% B for 2.10 min. A second gradient of 95-30% B was then applied over 0.2 min with an injection volume of 1500 µL at flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Method 3: BASIC EARLY METHOD

Purifications (P3) LC were performed on a Gilson LC system using a Waters X-Bridge C18 column (30 mm × 100 mm, 10 µM; temperature: r.t.) and a gradient of 10-95% B (A= 0.2% NH₄OH in H₂O; B= 0.2% NH₄OH in ACN) over 14.44 min then 95% B for 2.11 min. A second gradient of 95-10% B was then applied over 0.2 min with an injection volume of 1500 µL at flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Method 4: BASIC STANDARD METHOD

Purifications (P4) LC were performed on a Gilson LC system using a Waters X-Bridge C18 column (30 mm × 10 mm, 10 µM; temperature: r.t.) and a gradient of 30-95% B (A= 0.2% NH₄OH in water; B= 0.2% NH₄OH in ACN) over 11.00 min then 95% B for 2.10 min. A second gradient of 95-30% B was then applied over 0.21 min with an injection volume of 1500 µL at flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Chiral Separation Methods:

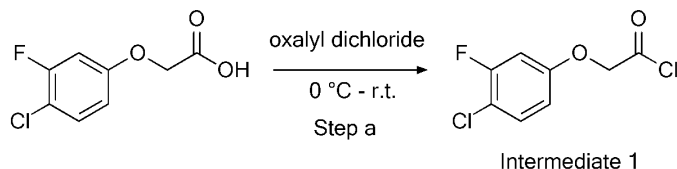
NMR Conditions

Unless otherwise stated, ¹H NMR spectra were recorded at 500 MHz, 400 MHz or 250 MHz on either a Bruker Avance III HD 500 MHz spectrometer, Bruker Avance III HD 400 MHz spectrometer or Bruker Avance III HD 250 MHz spectrometer respectively. Chemical shifts, δ, are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used to denote the multiplicities and general assignments: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), hep (heptet), m (multiplet), pent (pentet), td (triplet of doublets), qd (quartet of doublets), app. (apparent) and br. (broad). Coupling constants, *J*, are quoted to the nearest 0.1 Hz.

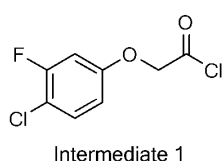
General synthesis:

All the compounds have been synthesised with a purity > 95% unless otherwise specified.

Scheme for route 1

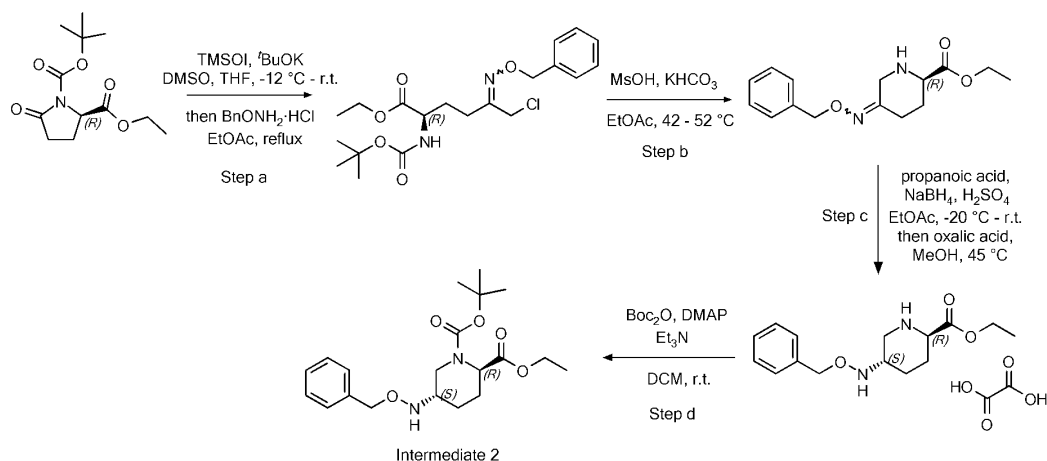


5 Intermediate 1: 2-(4-chloro-3-fluorophenoxy)acetyl chloride

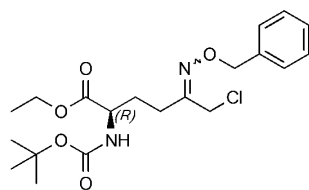


To a solution of 2-(4-chloro-3-fluorophenoxy)acetic acid (5.16 g, 22.7 mmol) in DCM (45 mL) at 0 °C was added oxalyl dichloride (10 mL, 0.115 mol) followed by DMF (81 μ L, 1.11 mmol) and the mixture was stirred at r.t. for 17 h. The reaction mixture was concentrated *in vacuo* to afford the title compound (90% purity, 5.30 g, 21.4 mmol, 94% yield) as an orange oil; ^1H NMR (400 MHz, CDCl_3) δ 7.31 (t, J = 8.6 Hz, 1H), 6.75 (dt, J = 10.2, 2.9 Hz, 1H), 6.66 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 4.96 (s, 2H).

Scheme for route 2

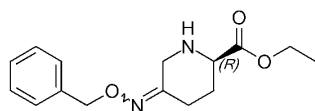


Step 2.a: ethyl (2R)-5-[(benzyloxy)imino]-2-[(*tert*-butoxy)carbonyl]amino}-6-chlorohexanoate



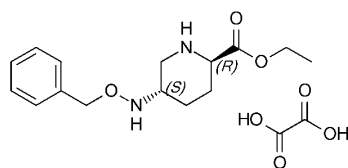
DMSO (75 mL) was added to a solution of TMSOI (12.89 g, 58.3 mmol) and ^tBuOK (6.27 g, 55.9 mmol) in anhydrous THF (60 mL) and the mixture was stirred at r.t. for 1 h. The reaction mixture was cooled to -12 °C and a solution of ethyl Boc-D-Pyroglutamate (12.5 g, 48.6 mmol) in anhydrous THF (38 mL) was added and stirred at r.t. for 16 h. The reaction mixture was diluted with satd aq NH₄Cl solution (80 mL), H₂O (15 mL) and EtOAc (200 mL), and the organic layer was isolated, washed with brine, and concentrated *in vacuo* to approximately 100 mL. A solution of BnONH₂·HCl (8.14 g, 51.0 mmol) in EtOAc (62 mL), was added and the mixture was stirred at reflux for 2 h. The reaction mixture was cooled to r.t., washed with H₂O and brine, and the organic layer was concentrated *in vacuo* to afford the title compound (85% purity, 19.5 g, 40.1 mmol, 83% yield) as a colourless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.16 – 7.33 (m, 5H), 5.01 – 5.06 (m, 2H), 3.95 – 4.30 (m, 5H), 2.32 – 2.50 (m, 2H), 1.98 – 2.13 (m, 1H), 1.75 – 1.92 (m, 1H), 1.30 – 1.40 (m, 9H), 1.12 – 1.24 (m, 3H).

Step 2.b: ethyl (2R)-5-[(benzyloxy)imino]piperidine-2-carboxylate



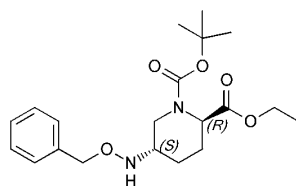
To a solution of ethyl (2R)-5-[(benzyloxy)imino]-2-[[*tert*-butoxy]carbonyl]amino}-6-chlorohexanoate (85% purity, 19.5 g, 40.1 mmol) in EtOAc (157 mL) was added MsOH (7.8 mL, 0.12 mol) and the mixture was stirred at 42 °C for 2 h. The resultant mixture was added to a solution of KHCO₃ (20.1 g, 0.201 mol) in H₂O (100 mL) and stirred at 52 °C for 2 h. The reaction mixture was cooled to r.t. and the organic layer was isolated, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to afford the title compound (85% purity, 13.0 g, 40.0 mmol) in quantitative yield as a dark orange oil; ¹H NMR (400 MHz, CDCl₃) δ 7.20 – 7.34 (m, 5H), 4.99 (d, *J* = 4.8 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.45 – 3.56 (m, 1H), 3.25 (dd, *J* = 14.9, 9.8 Hz, 1H), 3.08 (dt, *J* = 14.5, 4.3 Hz, 1H), 2.01 – 2.32 (m, 3H), 1.55 – 1.80 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H).

Step 2.c: ethyl (2R,5S)-5-[(benzyloxy)amino]piperidine-2-carboxylate oxalic acid



Propanoic acid (23 mL, 0.240 mol) was added to a suspension of NaBH₄ (3.03 g, 80.0 mmol) in EtOAc (95 mL) and the mixture was stirred at r.t. for 1 h. The resultant mixture was added to a solution of ethyl (2R)-5-[(benzyloxy)imino]piperidine-2-carboxylate (85% purity, 13.0 g, 40.0 mmol) in EtOAc (95 mL) and H₂SO₄ (11 mL, 0.20 mol) at -20 °C and stirred at r.t. for 60 h. The reaction mixture was diluted with H₂O (75 mL) and neutralised with aq NH₄OH solution. The organic layer was isolated, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to ~75 mL volume. The solution was warmed to 45 °C, and MeOH (30 mL), followed by a solution of oxalic acid (3.60 g, 40.0 mmol) in MeOH (15 mL) was added. The mixture was cooled to 0 °C, and the resultant precipitate was isolated *via* vacuum filtration, washing with MeOH:EtOH (1:4) and EtOAc to afford the title compound (7.17 g, 19.1 mmol, 48% yield); ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.25 – 7.42 (m, 5H), 4.59 (s, 2H), 4.17 – 4.24 (m, 2H), 3.92 (dd, *J* = 12.3, 3.2 Hz, 1H), 3.34 – 3.40 (m, 1H), 3.10 (ddd, *J* = 15.1, 7.6, 3.9 Hz, 1H), 2.64 (t, *J* = 11.5 Hz, 1H), 2.13 (dt, *J* = 10.2, 3.4 Hz, 1H), 1.87 (dd, *J* = 9.0, 3.8 Hz, 1H), 1.65 (qd, *J* = 13.2, 3.6 Hz, 1H), 1.40 (qd, *J* = 12.8, 3.9 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H); *M/Z*: 279, [M+H]⁺, ESI⁺, RT = 0.81 (S1).

Intermediate 2 (step 2.d): 1-*tert*-butyl 2-ethyl (2R,5S)-5-[(benzyloxy)amino]piperidine-1,2-dicarboxylate



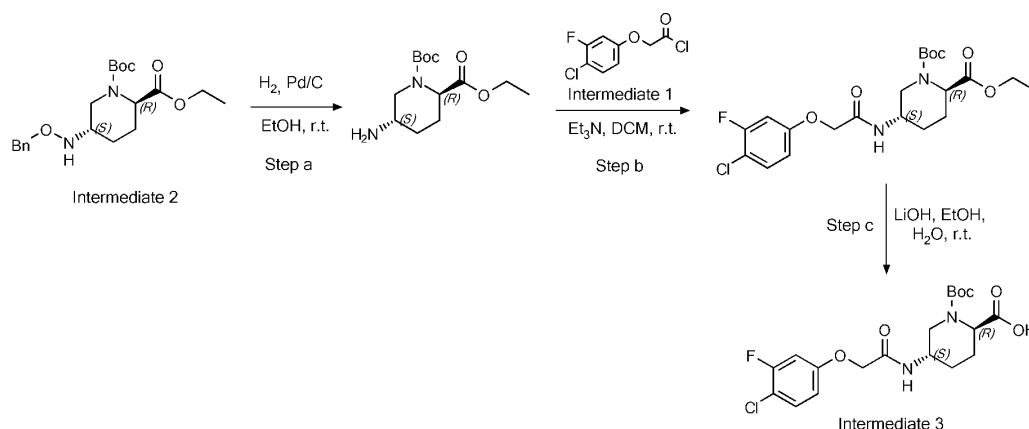
Intermediate 2

To a solution of ethyl (2R,5S)-5-[(benzyloxy)amino]piperidine-2-carboxylate oxalic acid (2.22 g, 6.03 mmol) in anhydrous DCM (30 mL) at 0 °C was added Et₃N (3.6 mL, 25.8 mmol), DMAP (76 mg, 0.622 mmol) and Boc₂O (4.2 mL, 18.3 mmol) and the mixture was stirred at r.t. for 17 h. The reaction mixture was diluted with satd aq NH₄Cl solution and DCM, and the organic layer was isolated, washed with H₂O and brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (0-20% EtOAc in heptane) to afford the title compound (86% purity, 1.40 g, 3.18 mmol, 53% yield) as a colourless oil; ¹H

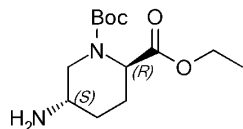
NMR (500 MHz, CDCl₃) δ 7.40 – 7.26 (m, 5H), 5.51 – 5.41 (m, 1H), 4.92 – 4.80 (m, 1H), 4.79 – 4.62 (m, 2H), 4.19 (q, J = 7.0 Hz, 3H), 3.11 (d, J = 45.4 Hz, 2H), 1.96 (s, 2H), 1.73 – 1.60 (m, 1H), 1.55 – 1.49 (m, 1H), 1.46 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H); M/Z : 379, $[M+H]^+$, ESI⁺, RT = 1.09 (S2).

5

Scheme for route 3

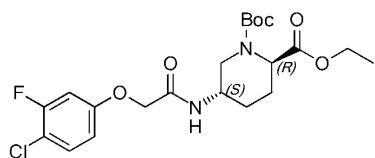


10 Step 3.a: 1-*tert*-butyl 2-ethyl (2*R*,5*S*)-5-aminopiperidine-1,2-dicarboxylate



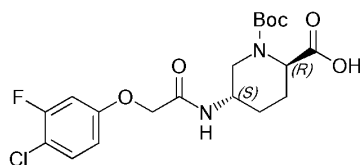
To a solution of 1-*tert*-butyl 2-ethyl (2*R*,5*S*)-5-[(benzyloxy)amino]piperidine-1,2-dicarboxylate (93% purity, 8.7 g, 21.3 mmol, Intermediate 2) in anhydrous EtOH (200 mL) under N₂ was added Pd/C (10%, 2.28 g, 2.14 mmol) and the mixture was stirred under H₂ at r.t. for 17 h. The reaction mixture was filtered through a pad of Celite and the filtrate concentrated *in vacuo*. The residue was purified using an SCX-2 cartridge, first flushing with MeOH and second eluting with 3 M NH₃ in MeOH to afford the title compound (4.88 g, 17.0 mmol, 80% yield) as a pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 4.98 – 4.57 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.87 – 3.64 (m, 1H), 3.35 – 2.99 (m, 2H), 2.14 – 1.92 (m, 2H), 1.64 – 1.52 (m, 2H), 1.45 (s, 11H), 1.26 (t, J = 7.1 Hz, 3H).

Step 3.b: 1-*tert*-butyl 2-ethyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-1,2-dicarboxylate



To a mixture of 1-*tert*-butyl 2-ethyl (2*R*,5*S*)-5-aminopiperidine-1,2-dicarboxylate (4.88 g, 17.0 mmol) and Et₃N (14 mL, 0.103 mol) in DCM (170 mL) at 0 °C was added dropwise a solution of 2-(4-chloro-3-fluorophenoxy)acetyl chloride (4.19 g, 18.8 mmol, Intermediate 1) in DCM (10 mL) and stirred at r.t. for 48 h. The reaction mixture was diluted with DCM (250 mL) and washed with satd aq NaHCO₃ solution (2 × 100 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (0-50% EtOAc in heptane) to afford the title compound (7.14 g, 15.6 mmol, 91% yield) as a colourless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.32 (t, *J* = 8.6 Hz, 1H), 6.86 – 6.72 (m, 2H), 6.69 – 6.63 (m, 1H), 4.98 – 4.66 (m, 1H), 4.45 (s, 2H), 4.29 – 4.13 (m, 3H), 4.09 – 3.87 (m, 1H), 3.33 – 3.10 (m, 1H), 2.23 – 2.02 (m, 1H), 2.00 – 1.71 (m, 2H), 1.56 (s, 1H), 1.44 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H); *M/Z*: 459, 461 [M+H]⁺, ESI⁺, RT = 3.83 (S4).

Intermediate 3 (step 3.c): (2*R*,5*S*)-1-[(*tert*-butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy) acetamido]piperidine-2-carboxylic acid



Intermediate 3

LiOH (0.78 g, 31.1 mmol) was added to a solution of 1-*tert*-butyl 2-ethyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido] piperidine-1,2-dicarboxylate (7.1 g, 15.6 mmol) in EtOH (80 mL) and H₂O (20 mL) and the mixture was stirred at r.t. for 3 h. The reaction mixture was concentrated *in vacuo*, dissolved in H₂O (50 mL), and extracted with DCM (2 × 100 mL). The aqueous layer was then acidified to pH 2 using 2 M aq HCl solution and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo* to afford the title compound (87% purity, 5.60 g, 11.3 mmol, 73% yield) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.02 (d, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 8.9 Hz, 1H), 7.03 (dd, *J* = 11.4, 2.8 Hz, 1H), 6.83 – 6.75 (m, 1H), 4.59 – 4.54 (m, 2H), 3.93 (s, 1H), 3.73 (d, *J* = 54.2 Hz, 1H), 3.13 – 2.94 (m, 1H), 2.06 – 1.87 (m, 2H), 1.61 (d, *J* = 12.2 Hz, 1H), 1.56 – 1.43 (m, 1H), 1.37 (s, 10H); *M/Z*: 429, 431 [M+H]⁺, ESI⁺, RT = 0.91 min (S1).

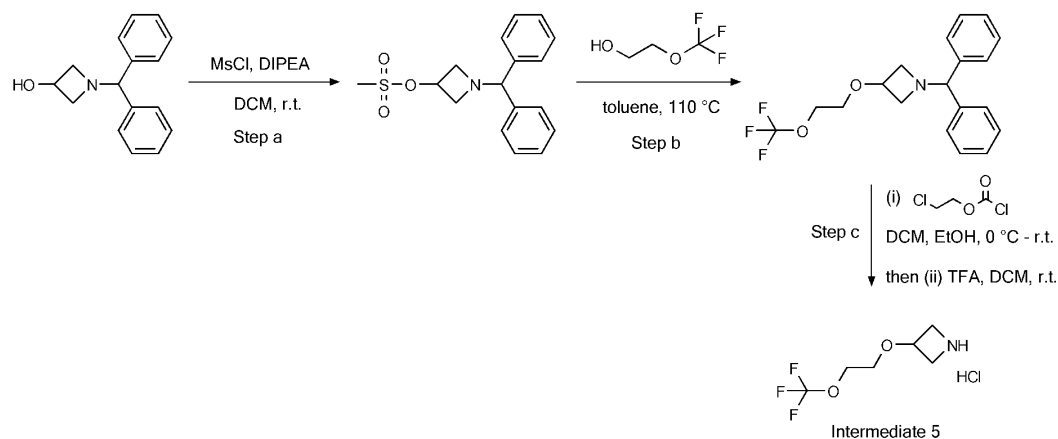
The intermediate in **Table 1** was synthesised according to general route 3 as exemplified by **Intermediate 3** using the corresponding starting materials.

Table 1

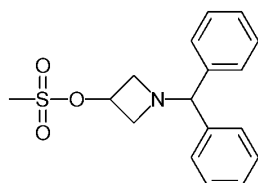
Intermediate	Structure	Name	Starting material	LCMS data	¹ H NMR data
4		(2 <i>S</i> ,5 <i>R</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid	1- <i>tert</i> -butyl 2-ethyl (2 <i>S</i> ,5 <i>R</i>)-5-aminopiperidine-1,2-dicarboxylate following steps 3.b and 3.c	<i>M/Z</i> : 375, 377 [M- ^t Butyl+H] ⁺ , ESI ⁺ , RT = 0.91 (S2).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 12.86 (s, 1H), 8.03 (d, <i>J</i> = 7.3 Hz, 1H), 7.47 (t, <i>J</i> = 8.9 Hz, 1H), 7.03 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.81 (d, <i>J</i> = 8.7 Hz, 1H), 4.70 – 4.45 (m, 3H), 4.00 – 3.70 (m, 2H), 3.06 (d, <i>J</i> = 32.9 Hz, 1H), 2.07 – 1.83 (m, 2H), 1.73 – 1.42 (m, 2H), 1.37 (s, 9H).

5

Scheme for route 4



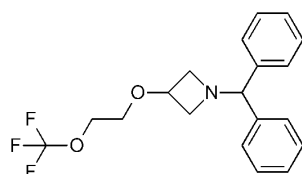
Step 4.a: (1-benzhydrylazetidin-3-yl) methanesulfonate



10

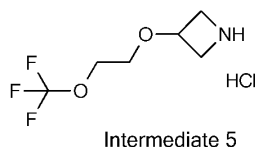
To a solution of 1-(diphenylmethyl)azetidin-3-ol (500 mg, 2.09 mmol) in anhydrous DCM (5 mL) was added MsCl (0.19 mL, 2.51 mmol) followed by DIPEA (0.55 mL, 3.13 mmol) and the mixture was stirred at r.t. for 30 min. The reaction mixture was diluted with H₂O (20 mL), the aqueous phase separated and extracted with DCM (2 × 20 mL). The organic phases were combined, washed with brine, dried using a phase separator cartridge and concentrated *in vacuo* to afford the title compound (738 mg, 2.05 mmol, 98% yield) as a yellow solid; ¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.39 (m, 4H), 7.33 – 7.27 (m, 4H), 7.24 – 7.19 (m, 2H), 5.18 – 5.09 (m, 1H), 4.52 – 4.44 (m, 1H), 3.80 – 3.68 (m, 2H), 3.35 – 3.20 (m, 2H), 2.99 (s, 3H). *M/Z*: 318 [M+H]⁺, ESI⁺, RT = 0.66 (S2).

Step 4.b: 1-benzhydryl-3-[2-(trifluoromethoxy)ethoxy]azetidine



A solution of (1-benzhydrylazetidin-3-yl) methanesulfonate (590 mg, 1.64 mmol) and 2-(trifluoromethoxy)ethanol (0.80 mL, 8.18 mmol) in anhydrous toluene (0.6 mL) was irradiated at 110 °C in a microwave vial for 30 min. The reaction mixture was diluted with EtOAc (10 mL) and the organic layer was washed with H₂O (10 mL) and satd aq NaHCO₃ solution (10 mL). The organic layer was dried over MgSO₄, concentrated *in vacuo*, and purified by chromatography on silica gel (5-100% EtOAc in heptane) to afford the title compound (140 mg, 0.319 mmol, 19% yield) as a viscous orange oil; *M/Z*: 352 [M+H]⁺, ESI⁺, RT = 0.70 (S2).

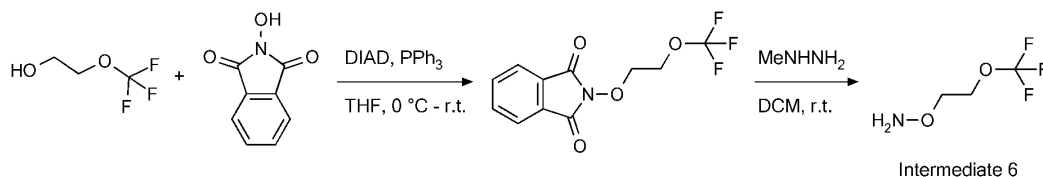
Intermediate 5 (step 4.c): 3-[2-(trifluoromethoxy)ethoxy]azetidine;hydrochloride



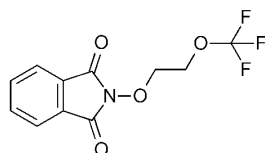
1-Chloroethyl chloroformate (0.038 mL, 0.351 mmol) was added to a solution of 1-benzhydryl-3-[2-(trifluoromethoxy)ethoxy]azetidine (140 mg, 0.319 mmol) in anhydrous DCM (2.5 mL) at 0° C and the mixture was stirred at r.t. for 1 h. Anhydrous EtOH (2.5 mL) was added and the resultant mixture was stirred at 45 °C for 1 h. The mixture was then cooled to r.t. and stirred overnight. A second portion of 1-chloroethyl chloroformate (0.017 mL, 0.159 mmol) was added

and the reaction mixture stirred at r.t. for 6 h. The solvent was removed *in vacuo* and the resultant residue was dissolved in anhydrous DCM (2.5 mL) and TFA (0.24 mL, 3.19 mmol) was added. The reaction was stirred at r.t. for 3 h and then concentrated *in vacuo* to afford the title compound (270 mg, 0.183 mmol, 57% yield) as an orange oil; *M/Z*: 186 [M+H]⁺, ESI⁺, RT = 0.33 (S2).

Scheme for route 5

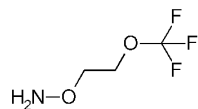


Step 5.a: 2-[2-(trifluoromethoxy)ethoxy]-2,3-dihydro-1H-isoindole-1,3-dione



To a solution of 2-(trifluoromethoxy)ethanol (350 mg, 2.69 mmol), 2-hydroxy-2,3-dihydro-1H-isoindole-1,3-dione (461 mg, 2.83 mmol) and PPh₃ (776 mg, 2.96 mmol) in anhydrous THF (17.5 mL) at 0 °C, was added DIAD (556 μL, 2.83 mmol) and the mixture was stirred at r.t. for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by chromatography on silica gel (10-100% EtOAc in heptane) to afford the title compound (770 mg, 2.66 mmol, 99% yield) as a white solid; ¹H NMR (500 MHz, CDCl₃) δ 7.88 – 7.84 (m, 2H), 7.79 – 7.75 (m, 2H), 4.48 – 4.44 (m, 2H), 4.36 – 4.31 (m, 2H); *M/Z*: 276 [M+H]⁺, ESI⁺, RT = 3.00 (S4).

Intermediate 6 (step 5.b): O-[2-(trifluoromethoxy)ethyl]hydroxylamine

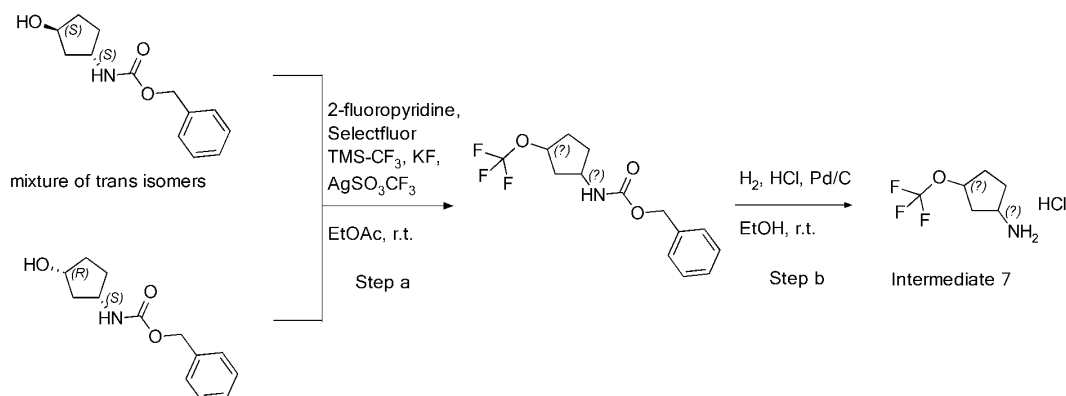


Intermediate 6

To solution of 2-[2-(trifluoromethoxy)ethoxy]-2,3-dihydro-1H-isoindole-1,3-dione (770 mg, 2.66 mmol) in DCM (15 mL) was added MeNHNH₂ (122 mg, 2.66 mmol) and the mixture was stirred at r.t. for 1 h. The resultant precipitate was removed *via* vacuum filtration and the filtrate was concentrated *in vacuo* (35 °C, 700 mbar) to afford the title compound (41% purity, 905

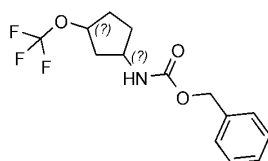
mg, 2.56 mmol, 96% yield) as a light yellow oil; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 6.12 (s, 2H), 4.22 – 4.17 (m, 2H), 3.76 – 3.69 (m, 2H).

Scheme for route 6



5 mixture of cis isomers

Step 6.a: benzyl N-[3-(trifluoromethoxy)cyclopentyl]carbamate



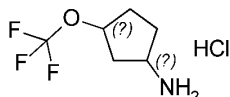
2-fluoropyridine (0.73 mL, 8.50 mmol) and TMS-CF₃ (1.3 mL, 8.50 mmol) were added to a solution of *rac*-benzyl N-[(1S*,3S*)-3-hydroxycyclopentyl]carbamate (1.00 g, 4.25 mmol),
 10 AgSO₃CF₃ (2.19 g, 8.50 mmol), Selectfluor (2.26 g, 6.38 mmol) and KF (0.74 g, 12.8 mmol) in EtOAc (20 mL) at r.t. under nitrogen in a foil-covered flask and the mixture was stirred at r.t. for 6 days. The reaction mixture was filtered through a pad of Celite and washed with EtOAc (100 mL) before concentrating *in vacuo* to give an orange-brown oil.

15 2-fluoropyridine (0.73 mL, 8.50 mmol) and TMS-CF₃ (1.3 mL, 8.50 mmol) were added to a solution of *rac*-benzyl N-[(1S*,3R*)-3-hydroxycyclopentyl]carbamate (1.00 g, 4.25 mmol), AgSO₃CF₃ (2.19 g, 8.50 mmol), Selectfluor (2.26 g, 6.38 mmol) and KF (0.74 g, 12.8 mmol) in EtOAc (20 mL) at r.t. under nitrogen in a foil-covered flask and the mixture was stirred at r.t. for 6 days. The reaction mixture was filtered through a pad of Celite and washed with EtOAc
 20 (100 mL) before concentrating *in vacuo* to give an orange-brown oil.

The crude materials from both reactions were combined and purified by FCC on silica gel (0 – 100% EtOAc in heptane) to afford the title compound as a mixture of four isomers (90% purity,

1.60 g, 4.75 mmol, 56% yield) as a colourless oil; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.43 (dd, $J = 18.2, 7.1$ Hz, 1H), 7.39 – 7.29 (m, 6H), 5.01 (s, 2H), 4.91 (tt, $J = 6.4, 3.4$ Hz, 1H), 4.83 – 4.76 (m, 1H), 4.05 – 3.96 (m, 1H), 3.83 (h, $J = 7.5$ Hz, 1H), 2.35 (dt, $J = 14.4, 7.4$ Hz, 1H), 2.16 – 1.79 (m, 7H), 1.78 – 1.53 (m, 3H), 1.47 (ddt, $J = 13.0, 8.9, 6.5$ Hz, 1H); M/Z : 304 $[\text{M}+\text{H}]^+$, ESI^+ , $\text{RT} = 0.97$ (S2).

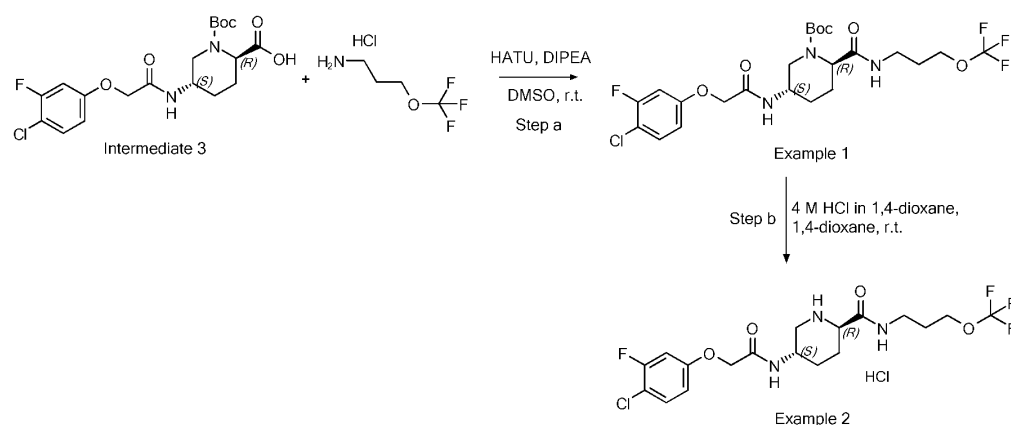
Intermediate 7 (step 6.b): 3-(trifluoromethoxy)cyclopentan-1-amine hydrochloride



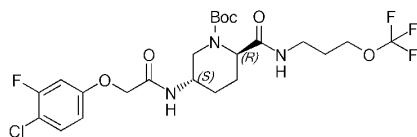
Intermediate 7

Pd/C (10%, 253 mg, 0.237 mmol) was added to a round-bottomed flask and the flask was evacuated and purged with nitrogen five times. Benzyl *N*-[3-(trifluoromethoxy)cyclopentyl]carbamate (90% purity, 1.60 g, 4.75 mmol) in EtOH (15 mL) was added, followed by 12 M HCl (0.40 mL, 4.75 mmol). The flask was evacuated and purged with nitrogen five times before purging with H_2 and evacuating five times. The reaction was placed under H_2 and stirred at r.t. for 20 h. The reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo* to afford title compound (75% purity, 0.42 g, 1.51 mmol, 32% yield) as a yellow oil; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 4.97 (tt, $J = 6.4, 3.6$ Hz, 1H), 4.81 (p, $J = 6.1, 5.5$ Hz, 1H), 3.55 (dt, $J = 13.4, 7.1$ Hz, 1H), 3.34 (p, $J = 7.2$ Hz, 1H), 2.38 (dt, $J = 14.2, 7.3$ Hz, 1H), 2.18 (dq, $J = 14.6, 6.7$ Hz, 1H), 2.11 – 1.82 (m, 2H), 1.82 – 1.71 (m, 1H), 1.69 – 1.45 (m, 1H); M/Z : 170 $[\text{M}+\text{H}]^+$, ESI^+ (S4).

Scheme for route 7



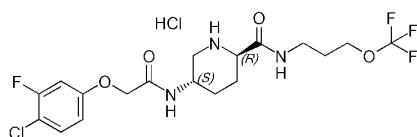
Example 1 (step 7.a): *tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[[3-(trifluoromethoxy)propyl]carbamoyl]piperidine-1-carboxylate



Example 1

- 5 To a solution of (2*R*,5*S*)-1-[(*tert*-butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (100 mg, 0.220 mmol, Intermediate 3) in DMSO (1.5 mL) was added DIPEA (120 μ L, 0.661 mmol) and HATU (101 mg, 0.265 mmol) and the mixture was stirred at r.t. for 10 min. 3-(Trifluoromethoxy)propan-1-amine hydrochloride (48 mg, 0.265 mmol) was then added and the mixture was stirred at r.t. for 1 h.
- 10 The reaction mixture was diluted with ACN/H₂O (3:2, 1.5 mL) and purified by prep. HPLC (Method 4) to afford the title compound (97 mg, 0.174 mmol, 79% yield) as a colourless glass; *M/Z*: 456.2, 458.3 [M-BOC+H]⁺, ESI⁺, RT = 1.01 (S2).

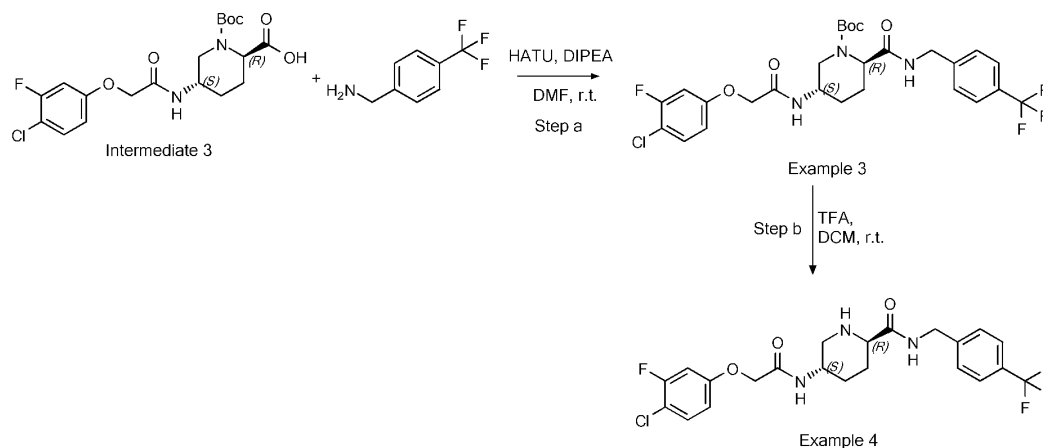
- Example 2 (step 7.b): (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[3-(trifluoromethoxy)propyl]piperidine-2-carboxamide hydrochloride**
- 15



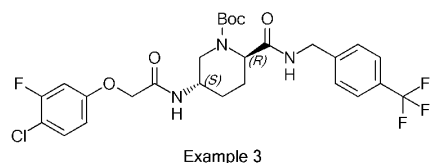
Example 2

- To a solution of *tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[[3-(trifluoromethoxy)propyl]carbamoyl]piperidine-1-carboxylate (97 mg, 0.174 mmol, Example 1) in anhydrous 1,4-dioxane (3 mL) was added 4 M HCl in 1,4-dioxane (1.0 mL, 4.00 mmol) and the mixture was stirred at r.t. for 16 h. The reaction mixture was concentrated *in vacuo* to afford the title compound (89 mg, 0.174 mmol, 99% yield) as a white powder; ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.42 – 8.89 (m, 2H), 8.58 (s, 1H), 8.24 (s, 1H), 7.51 (t, *J* = 8.9 Hz, 1H), 7.09 (dd, *J* = 11.3, 2.8 Hz, 1H), 6.92 – 6.82 (m, 1H), 4.55 (s, 2H), 4.15 – 4.09 (m, 2H), 4.08 – 4.01 (m, 1H), 3.77 – 3.68 (m, 1H), 3.27 – 3.18 (m, 3H), 2.89 – 2.76 (m, 1H), 2.22 – 2.13 (m, 1H),
- 20 1.97 – 1.88 (m, 1H), 1.88 – 1.80 (m, 2H), 1.70 – 1.50 (m, 2H); *M/Z*: 456.2, 458.2 [M+H]⁺, ESI⁺, RT = 2.03 (S4).
- 25

Scheme for route 8



Example 3 (step 8.a): *tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-([4-(trifluoromethyl)phenyl]methyl)carbamoyl]piperidine-1-carboxylate

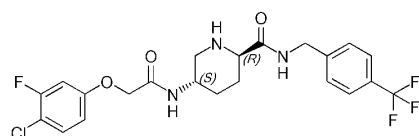


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To a solution of (2*R*,5*S*)-1-[(*tert*-butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (200 mg, 0.464 mmol, Intermediate 3) in anhydrous DMF (2.5 mL) was added DIPEA (163 μ L, 0.933 mmol) and HATU (194 mg, 0.510 mmol) and the mixture was stirred at r.t. for 10 min. 1-[4-(Trifluoromethyl)phenyl]methanamine (73 μ L, 0.512 mmol) was added and the mixture was stirred at r.t. for 4 h. The reaction mixture was diluted with EtOAc (20 mL) and H₂O (10 mL). The organic layer was isolated, washed with brine (2 $\times$ 10 mL), dried over MgSO₄, and concentrated *in vacuo* to afford the title compound (341 mg, 99% yield, 80% purity) as an orange solid; *M/Z*: 488, 490 [M+H]⁺, ESI⁺, RT = 1.13 (S2). The compound was taken forward without further purification.

15

Example 4 (step 8.b): (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-{[4-(trifluoromethyl)phenyl]methyl}piperidine-2-carboxamide



Example 4

To a solution of *tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-({[4-(trifluoromethyl)phenyl]methyl} carbamoyl)piperidine-1-carboxylate (80% purity, 341 mg, 0.464 mmol, Example 3) in DCM (3 mL) at 0 °C was added TFA (350 µL, 4.71 mmol) and the mixture was stirred at r.t. for 4 h. The reaction mixture was diluted with DCM (10 mL) and washed with satd aq NaHCO₃ solution (3 × 10 mL). The organic layer was dried using a phase separation cartridge and concentrated *in vacuo*. The residue was purified by prep. HPLC (Method 4) to afford the title compound (119 mg, 0.244 mmol, 53% yield) as a white powder; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.35 (t, *J* = 6.2 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.52 – 7.42 (m, 3H), 7.06 (dd, *J* = 11.4, 2.8 Hz, 1H), 6.85 (ddd, *J* = 9.0, 2.8, 1.1 Hz, 1H), 4.53 – 4.47 (m, 2H), 4.34 (d, *J* = 6.1 Hz, 2H), 3.70 – 3.60 (m, 1H), 3.08 – 3.00 (m, 1H), 3.00 – 2.91 (m, 1H), 2.47 – 2.41 (m, 1H), 2.38 – 2.30 (m, 1H), 1.93 – 1.79 (m, 2H), 1.48 – 1.32 (m, 2H); *M/Z*: 488, 490 [M+H]⁺, ESI⁺, RT = 2.18 (S4).

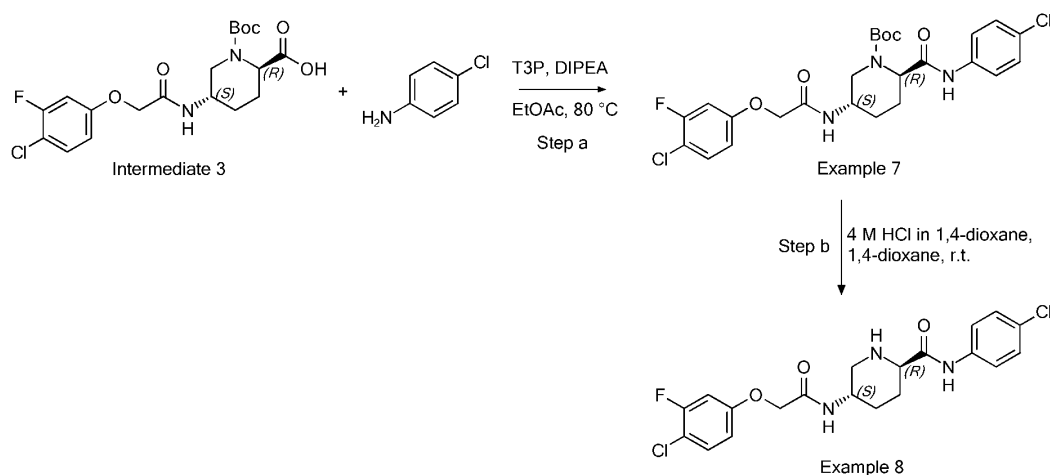
The example compounds in **Table 2** were synthesised according to general route 8 as exemplified by **Example 4** using the corresponding intermediates. The corresponding boc protected intermediates of the numbered examples are also examples of the invention.

Table 2

Ex	Structure	Name	Intermediates	LCMS data	¹ H NMR
5		2-(4-chloro-3-fluorophenoxy)- <i>N</i> -[(3 <i>S</i> ,6 <i>R</i>)-6-{3-[2-(trifluoromethoxy)ethoxy]azetidine-1-carbonyl}piperidin-3-yl]acetamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 3-[2-(trifluoromethoxy)ethoxy]azetidine; hydrochloride (Intermediate 5)	<i>M/Z</i> : 498.2, 500.2 [M+H] ⁺ , ESI ⁺ , RT = 2.18 (S4).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.87 (d, <i>J</i> = 8.1 Hz, 1H), 7.49 (t, <i>J</i> = 8.9 Hz, 1H), 7.05 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.84 (ddd, <i>J</i> = 9.0, 2.9, 1.1 Hz, 1H), 4.49 (s, 2H), 4.45 – 4.32 (m, 2H), 4.22 – 4.17 (m, 2H), 4.10 – 3.95 (m, 2H), 3.68 – 3.61 (m, 3H), 3.60 – 3.52 (m, 1H), 3.07 (s, 1H), 2.94 (dd, <i>J</i> = 9.2 Hz, 1H), 2.32 (s, 1H), 2.07 (s, 1H), 1.84 (d, 1H), 1.70 (d, <i>J</i> = 11.1 Hz, 1H),

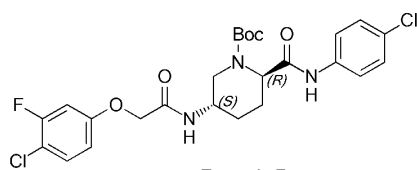
					1.37 (q, $J = 13.2, 12.7$ Hz, 2H).
6		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[2-(trifluoromethoxy)ethoxy]piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and <i>O</i> -[2-(trifluoromethoxy)ethyl]hydroxylamine (Intermediate 6)	M/Z : 458, 460 [$M+H$] ⁺ , ESI ⁺ , RT = 1.94 (S4).	¹ H NMR (400 MHz, DMSO- d_6) δ 11.13 (s, 1H), 7.89 (d, $J = 8.1$ Hz, 1H), 7.49 (t, $J = 8.9$ Hz, 1H), 7.06 (dd, $J = 11.4, 2.8$ Hz, 1H), 6.88 – 6.80 (m, 1H), 4.49 (s, 2H), 4.27 – 4.20 (m, 2H), 4.03 – 3.97 (m, 2H), 3.68 – 3.56 (m, 1H), 2.98 – 2.88 (m, 2H), 2.35 – 2.24 (m, 1H), 1.90 – 1.70 (m, 2H), 1.45 – 1.34 (m, 2H).
47		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide (mixture of four isomers)	2 <i>R</i> ,5 <i>S</i> -1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 3-(trifluoromethoxy)cyclopentan-1-amine hydrochloride (Intermediate 7)	M/Z : 482, 484 [$M+H$] ⁺ , ESI ⁺ , RT = 2.25, 2.29 (S4).	¹ H NMR (500 MHz, DMSO) δ 7.90 (d, $J = 8.1$ Hz, 1H), 7.76 – 7.69 (m, 1H), 7.49 (t, $J = 8.9$ Hz, 1H), 7.06 (dd, $J = 11.4, 2.8$ Hz, 1H), 6.84 (ddd, $J = 9.0, 2.8, 0.9$ Hz, 1H), 4.97 – 4.78 (m, 1H), 4.49 (s, 2H), 4.25 – 3.99 (m, 1H), 3.67 – 3.55 (m, 1H), 3.00 – 2.86 (m, 2H), 2.35 – 2.28 (m, 2H), 2.18 – 1.44 (m, 8H), 1.41 – 1.29 (m, 2H).

Scheme for route 9



Example 7 (step 9.a): *tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-

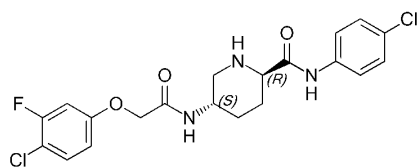
5 [(4-chlorophenyl)carbamoyl]piperidine-1-carboxylate



Example 7

To a solution of (2*R*,5*S*)-1-[(*tert*-butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (90% purity, 200 mg, 0.418 mmol, intermediate 3), T3P (50% in EtOAc, 0.30 mL, 0.501 mmol) and DIPEA (150 μ L, 0.836 mmol) in EtOAc (5 mL) was added 4-chloroaniline (53 mg, 0.418 mmol) and stirred at 80 °C for 1 h. Further portions of T3P (50% in EtOAc, 99 μ L, 0.167 mmol) and DIPEA (58 μ L, 0.334 mmol) were added and the mixture was stirred at 80 °C for 1.5 h. The reaction mixture was cooled to r.t., diluted with H₂O (20 mL), and extracted with EtOAc (3 $\times$ 20 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated *in vacuo* to afford the title compound (70% purity, 245 mg, 0.317 mmol, 76% yield) as a colourless oil; *M/Z*: 440, 442, 444 [M-Boc+H]⁺, ESI⁺, RT = 1.06 (S2). The product was taken on crude without further purification.

Example 8 (step 9.b): (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(4-chlorophenyl)piperidine-2-carboxamide



Example 8

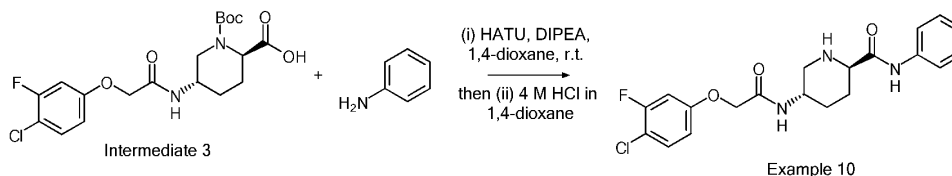
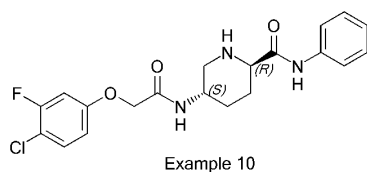
To a solution of *tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[(4-chlorophenyl)carbamoyl]piperidine-1-carboxylate (70% purity, 245 mg, 0.317 mmol, Example 7) in anhydrous 1,4-dioxane (1 mL) was added 4 M HCl in 1,4-dioxane (0.79 mL, 3.17 mmol) and the mixture was stirred at r.t. for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by prep. HPLC (Method 1), followed by prep. HPLC (Method 3) to afford the title compound (21 mg, 0.0471 mmol, 15% yield) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.70 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.48 (t, *J* = 8.9 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.06 (dd, *J* = 11.4, 2.8 Hz, 1H), 6.86 (ddd, *J* = 9.0, 2.8, 1.1 Hz, 1H), 4.51 (s, 2H), 3.73 – 3.63 (m, 1H), 3.08 – 3.00 (m, 1H), 2.46 – 2.36 (m, 2H), 1.99 – 1.85 (m, 2H), 1.55 – 1.41 (m, 2H); *M/Z*: 440, 442, 444 [M+H]⁺, ESI⁺, RT = 2.24 (S4).

The example compound in **Table 3** was synthesised according to general route 9 as exemplified by **Example 8** using the corresponding intermediates. The corresponding boc protected intermediate of the numbered example is also an example of the invention.

Table 3

Ex	Structure	Name	Intermediates	LCMS data	¹ H NMR
9		(2 <i>S</i> ,5 <i>R</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(4-chlorophenyl)piperidine-2-carboxamide	(2 <i>S</i> ,5 <i>R</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 4) and 4-chloroaniline	<i>M/Z</i> : 440, 442, 444 [<i>M</i> + <i>H</i>] ⁺ , ESI ⁺ , RT = 2.22 (S4).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.68 (s, 1H), 9.19 (s, 2H), 8.21 (d, <i>J</i> = 8.0 Hz, 1H), 7.64 (d, <i>J</i> = 8.9 Hz, 2H), 7.52 (t, <i>J</i> = 8.9 Hz, 1H), 7.44 (d, <i>J</i> = 8.9 Hz, 2H), 7.10 (dd, <i>J</i> = 11.3, 2.8 Hz, 1H), 6.94 – 6.81 (m, 1H), 4.57 (s, 2H), 4.18 – 4.07 (m, 1H), 3.95 – 3.87 (m, 1H), 3.30 – 3.25 (m, 1H), 2.92 – 2.84 (m, 1H), 2.65 – 2.57 (m, 1H), 2.02 – 1.94 (m, 1H), 1.78 – 1.59 (m, 2H).

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Scheme for route 10**Example 10: (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-phenylpiperidine-2-carboxamide**

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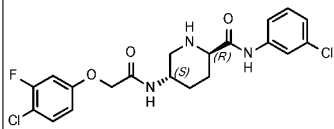
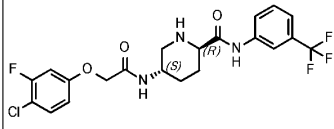
To a solution of (2*R*,5*S*)-1-[(*tert*-butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (100 mg, 0.232 mmol, intermediate 3) in anhydrous 1,4-dioxane (2.5 mL) was added HATU (88 mg, 0.232 mmol) and DIPEA (81 μL, 0.464 mmol) and stirred at r.t. for 45 min. Aniline (163 μL, 0.232 mmol) was added and the mixture was stirred at r.t. for 4 h. The reaction mixture was cooled to 0 °C and 4 M HCl in

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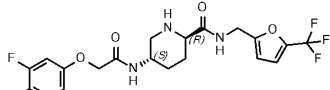
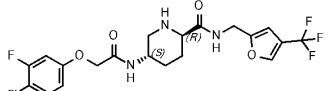
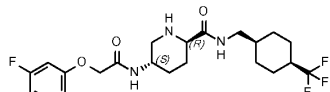
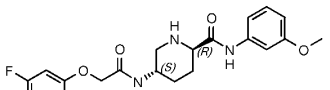
1,4-dioxane (1.0 mL, 4.00 mmol) was added dropwise under a flush of N₂. The mixture was stirred at r.t. for 2 h, diluted with EtOAc (10 mL) and washed with H₂O (5 mL). The organic extracts were washed with satd aq NaHCO₃ solution, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by prep. HPLC (Method 4) to afford the title compound (12 mg, 0.030 mmol, 13% yield) as a white solid; ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.66 (s, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 8.9 Hz, 1H), 7.36 – 7.24 (m, 2H), 7.14 – 6.97 (m, 2H), 6.90 – 6.79 (m, 1H), 4.52 (s, 2H), 3.78 – 3.60 (m, 1H), 3.23 – 3.14 (m, 1H), 3.12 – 2.94 (m, 1H), 2.45 – 2.38 (m, 2H), 2.00 – 1.86 (m, 2H), 1.47 (t, *J* = 10.0 Hz, 2H); *M/Z*: 406, 408 [M+H]⁺, ESI⁺, RT = 3.10 (S6).

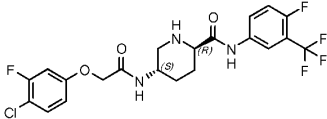
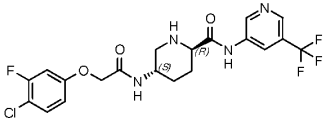
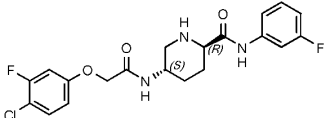
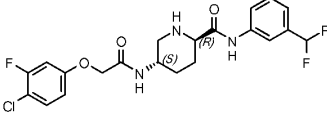
Example compounds in **Table 4** were synthesised according to general route 10 as exemplified by **Example 10** using the corresponding intermediates. The corresponding boc protected intermediates of the numbered examples are also examples of the invention.

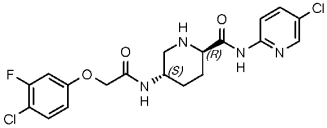
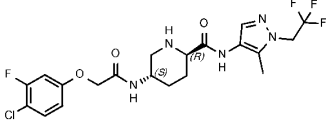
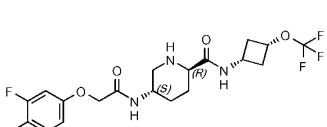
Table 4

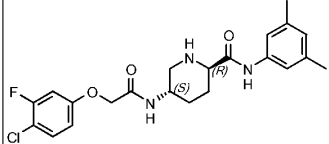
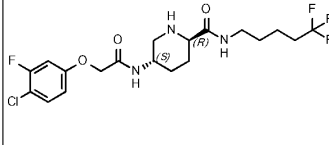
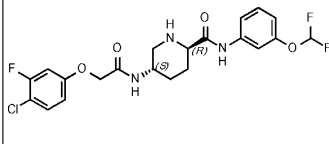
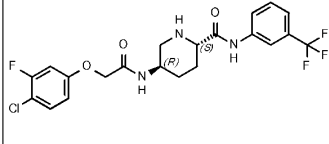
Ex	Structure	Name	Intermediates	LCMS data	¹ H NMR
11		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 3-chloroaniline	<i>M/Z</i> : 440, 442, 444 [M+H] ⁺ , ESI ⁺ , RT = 3.43 (S6).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.88 (s, 1H), 7.95 (d, <i>J</i> = 8.1 Hz, 1H), 7.88 (t, <i>J</i> = 2.0 Hz, 1H), 7.58 – 7.42 (m, 2H), 7.33 (t, <i>J</i> = 8.1 Hz, 1H), 7.16 – 7.03 (m, 2H), 6.96 – 6.81 (m, 1H), 4.52 (s, 2H), 3.76 – 3.64 (m, 1H), 3.22 – 3.13 (m, 1H), 3.11 – 2.95 (m, 1H), 2.42 – 2.37 (m, 2H), 2.01 – 1.78 (m, 2H), 1.59 – 1.42 (m, 2H).
12		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 3-(trifluoromethyl)aniline	<i>M/Z</i> : 474, 476 [M+H] ⁺ , ESI ⁺ , RT = 3.58 (S6).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.04 (s, 1H), 8.17 (s, 1H), 7.95 (d, <i>J</i> = 8.1 Hz, 1H), 7.88 (d, <i>J</i> = 8.3 Hz, 1H), 7.60 – 7.43 (m, 2H), 7.40 (d, <i>J</i> = 7.7 Hz, 1H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.90 – 6.81 (m, 1H), 4.52 (s, 2H), 3.80 – 3.64 (m, 1H), 3.27 – 3.16 (m, 1H), 3.10 – 2.97 (m, 1H), 2.45 – 2.40 (m, 2H), 2.06 – 1.83 (m, 2H), 1.61 – 1.39 (m, 2H).

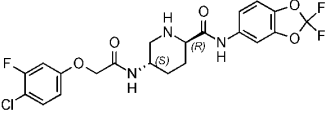
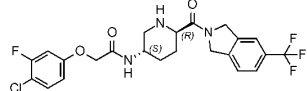
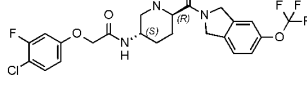
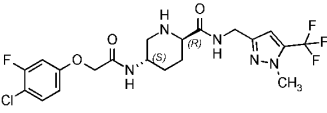
13		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(3-(trifluoromethoxy)phenyl)piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 3-(trifluoromethoxy)aniline	<i>M/Z</i> : 490, 492 [<i>M</i> + <i>H</i>] ⁺ , ESI ⁺ , RT = 3.66 (S6).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.99 (s, 1H), 7.95 (d, <i>J</i> = 8.1 Hz, 1H), 7.86 (s, 1H), 7.64 – 7.55 (m, 1H), 7.51 (t, <i>J</i> = 8.9 Hz, 1H), 7.43 (t, <i>J</i> = 8.2 Hz, 1H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 7.03 (d, <i>J</i> = 7.1 Hz, 1H), 6.91 – 6.83 (m, 1H), 4.52 (s, 2H), 3.78 – 3.64 (m, 1H), 3.24 – 3.15 (m, 1H), 3.06 – 2.98 (m, 1H), 2.43 – 2.39 (m, 2H), 1.98 – 1.85 (m, 2H), 1.53 – 1.43 (m, 2H).
14		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(5-chloropyridin-2-yl)methylpiperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 1-(5-chloropyridin-2-yl)methanamine	<i>M/Z</i> : 455, 457, 459 [<i>M</i> + <i>H</i>] ⁺ , ESI ⁺ , RT = 3.06 (S6).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.55 (d, <i>J</i> = 2.0 Hz, 1H), 8.35 (t, <i>J</i> = 6.0 Hz, 1H), 7.93 (d, <i>J</i> = 8.1 Hz, 1H), 7.89 (dd, <i>J</i> = 8.4, 2.5 Hz, 1H), 7.50 (t, <i>J</i> = 8.9 Hz, 1H), 7.32 (d, <i>J</i> = 8.4 Hz, 1H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.89 – 6.83 (m, 1H), 4.51 (s, 2H), 4.36 (d, <i>J</i> = 6.0 Hz, 2H), 3.73 – 3.60 (m, 1H), 3.12 – 3.03 (m, 1H), 3.01 – 2.95 (m, 1H), 2.53 – 2.52 (m, 1H), 2.39 – 2.34 (m, 1H), 1.94 – 1.81 (m, 2H), 1.51 – 1.34 (m, 2H).
15		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1 <i>s</i> ,4 <i>s</i>)-4-(trifluoromethoxycyclohexyl)piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and (1 <i>s</i> ,4 <i>s</i>)-4-(trifluoromethoxy)cyclohexan-1-amine	<i>M/Z</i> : 496, 498 [<i>M</i> + <i>H</i>] ⁺ , ESI ⁺ , RT = 3.60 (S6).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.90 (d, <i>J</i> = 8.1 Hz, 1H), 7.57 (d, <i>J</i> = 7.8 Hz, 1H), 7.50 (t, <i>J</i> = 8.9 Hz, 1H), 7.07 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.88 – 6.81 (m, 1H), 4.60 – 4.54 (m, 1H), 4.50 (s, 2H), 3.74 – 3.58 (m, 2H), 3.09 – 2.92 (m, 2H), 2.39 – 2.29 (m, 1H), 2.25 (s, 1H), 1.91 – 1.77 (m, 4H), 1.76 – 1.66 (m, 2H), 1.65 – 1.58 (m, 2H), 1.56 – 1.48 (m, 2H), 1.46 – 1.29 (m, 2H).
16		(2 <i>R</i> ,5 <i>S</i>)- <i>N</i> -(4-chloro-2-methoxyphenyl)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate	<i>M/Z</i> : 470, 472, 474 [<i>M</i> + <i>H</i>] ⁺ , ESI ⁺ , RT = 3.76 (S6).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.30 (s, 1H), 8.24 (d, <i>J</i> = 8.7 Hz, 1H), 7.98 (d, <i>J</i> = 8.1 Hz, 1H), 7.51 (t, <i>J</i> = 8.9 Hz, 1H), 7.15 (d, <i>J</i> = 2.3 Hz, 1H), 7.08 (m, 1H), 6.99 (dd, <i>J</i> = 8.7, 2.3 Hz, 1H), 6.86 (ddd, <i>J</i> = 9.0, 2.8, 1.1 Hz, 1H), 4.53 (s, 2H), 3.90 (s, 3H), 3.72 – 3.63

			3) and 4-chloro-2-methoxyaniline		(m, 1H), 3.24 – 3.16 (m, 1H), 3.05 – 2.94 (m, 2H), 2.45 – 2.38 (m, 1H), 2.03 – 1.97 (m, 1H), 1.89 – 1.81 (m, 1H), 1.56 – 1.37 (m, 2H).
17		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[5-(trifluoromethyl)furan-2-yl)methyl]pi-peridine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]pi-peridine-2-carboxylic acid (Intermediate 3) and 1-[5-(trifluoromethyl)furan-2-yl]methanamine	<i>M/Z</i> : 478, 480 [M+H] ⁺ , ESI ⁺ , RT = 3.45 (S6).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.30 (t, <i>J</i> = 6.0 Hz, 1H), 7.92 (d, <i>J</i> = 8.1 Hz, 1H), 7.50 (t, <i>J</i> = 8.9 Hz, 1H), 7.18 – 7.12 (m, 1H), 7.07 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.90 – 6.81 (m, 1H), 6.44 (d, <i>J</i> = 2.8 Hz, 1H), 4.51 (s, 2H), 4.32 (d, <i>J</i> = 5.9 Hz, 2H), 3.73 – 3.59 (m, 1H), 3.09 – 2.99 (m, 1H), 2.99 – 2.92 (m, 1H), 2.44 – 2.39 (m, 1H), 2.37 – 2.30 (m, 1H), 1.90 – 1.79 (m, 2H), 1.51 – 1.31 (m, 2H).
18		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[4-(trifluoromethyl)furan-2-yl)methyl]pi-peridine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]pi-peridine-2-carboxylic acid (Intermediate 3) and 1-[4-(trifluoromethyl)furan-2-yl]methanamine hydrochloride	<i>M/Z</i> : 478, 480 [M+H] ⁺ , ESI ⁺ , RT = 2.14 (S4).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.32 – 8.29 (m, 1H), 8.27 – 8.20 (m, 1H), 7.91 (d, <i>J</i> = 8.1 Hz, 1H), 7.50 (t, <i>J</i> = 8.9 Hz, 1H), 7.07 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.85 (ddd, <i>J</i> = 9.0, 2.8, 1.1 Hz, 1H), 6.59 (s, 1H), 4.51 (s, 2H), 4.32 – 4.26 (m, 2H), 3.70 – 3.60 (m, 1H), 3.05 – 2.93 (m, 2H), 2.46 – 2.32 (m, 2H), 1.90 – 1.81 (m, 2H), 1.43 – 1.33 (m, 2H).
19		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[(1 <i>S</i> ,4 <i>S</i>)-4-(trifluoromethyl)cyclohexyl)methyl]pi-peridine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]pi-peridine-2-carboxylic acid (Intermediate 3) and 1-[4-(trifluoromethyl)cyclohexyl]methanamine	<i>M/Z</i> : 494, 496 [M+H] ⁺ , ESI ⁺ , RT = 3.43 (S6).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.03 (d, <i>J</i> = 8.0 Hz, 2H), 7.51 (t, <i>J</i> = 8.9 Hz, 1H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.91 – 6.71 (m, 1H), 4.52 (s, 2H), 4.02 – 3.70 (m, 1H), 3.32 – 3.31 (m, 2H), 3.16 – 3.03 (m, 3H), 2.58 – 2.54 (m, 1H), 2.31 – 2.21 (m, 1H), 2.06 – 1.95 (m, 1H), 1.90 – 1.83 (m, 1H), 1.82 – 1.69 (m, 1H), 1.66 – 1.36 (m, 10H).
20		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(3-methoxyphenyl)	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]pi	<i>M/Z</i> : 436, 438 [M+H] ⁺ , ESI ⁺ , RT = 3.15 (S6).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.64 (s, 1H), 7.94 (d, <i>J</i> = 8.1 Hz, 1H), 7.51 (t, <i>J</i> = 8.9 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.20 (dd, <i>J</i> = 4.9, 2.0 Hz, 2H), 7.08 (dd, <i>J</i> = 11.4,

		nyl)piperidine-2-carboxamide	peridine-2-carboxylic acid (Intermediate 3) and 3-methoxyaniline		¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.07 (s, 1H), 8.19 (dd, <i>J</i> = 6.6, 2.6 Hz, 1H), 7.95 (d, <i>J</i> = 8.1 Hz, 2H), 7.62 – 7.40 (m, 2H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.96 – 6.78 (m, 1H), 4.52 (s, 2H), 3.81 – 3.56 (m, 1H), 3.19 (s, 1H), 3.03 (dd, <i>J</i> = 11.6, 3.6 Hz, 1H), 2.60 (s, 1H), 2.45 – 2.36 (m, 1H), 2.01 – 1.87 (m, 2H), 1.55 – 1.42 (m, 2H).
21		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(4-fluoro-3-(trifluoromethyl)phenyl)piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 4-fluoro-3-(trifluoromethyl)aniline	<i>M/Z</i> : 492, 494 [M+H] ⁺ , ESI ⁺ , RT = 3.58 (S6).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.07 (s, 1H), 8.19 (dd, <i>J</i> = 6.6, 2.6 Hz, 1H), 7.95 (d, <i>J</i> = 8.1 Hz, 2H), 7.62 – 7.40 (m, 2H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.96 – 6.78 (m, 1H), 4.52 (s, 2H), 3.81 – 3.56 (m, 1H), 3.19 (s, 1H), 3.03 (dd, <i>J</i> = 11.6, 3.6 Hz, 1H), 2.60 (s, 1H), 2.45 – 2.36 (m, 1H), 2.01 – 1.87 (m, 2H), 1.55 – 1.42 (m, 2H).
22		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(5-(trifluoromethyl)pyridin-3-yl)piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 5-(trifluoromethyl)pyridin-3-amine	<i>M/Z</i> : 475, 477 [M+H] ⁺ , ESI ⁺ , RT = 3.15 (S6).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.08 (d, <i>J</i> = 2.2 Hz, 1H), 8.65 (s, 1H), 8.57 (s, 1H), 7.96 (d, <i>J</i> = 8.0 Hz, 1H), 7.51 (t, <i>J</i> = 8.9 Hz, 1H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.87 (dd, <i>J</i> = 9.0, 1.8 Hz, 1H), 4.53 (s, 2H), 3.71 (s, 1H), 3.29 – 3.21 (m, 2H), 3.08 – 3.00 (m, 1H), 2.46 – 2.38 (m, 2H), 2.00 – 1.88 (m, 2H), 1.54 – 1.44 (m, 2H).
23		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(3-fluorophenyl)piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 3-fluoroaniline	<i>M/Z</i> : 424, 426 [M+H] ⁺ , ESI ⁺ , RT = 2.03 (S4).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.89 (s, 1H), 7.95 (d, <i>J</i> = 8.1 Hz, 1H), 7.65 (dt, <i>J</i> = 11.8, 2.3 Hz, 1H), 7.51 (t, <i>J</i> = 8.9 Hz, 1H), 7.43 – 7.38 (m, 1H), 7.37 – 7.29 (m, 1H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.91 – 6.83 (m, 2H), 4.52 (s, 2H), 3.76 – 3.62 (m, 2H), 3.22 – 3.15 (m, 1H), 3.07 – 2.97 (m, 1H), 2.44 – 2.36 (m, 1H), 1.97 – 1.84 (m, 2H), 1.53 – 1.41 (m, 2H).
24		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(3-fluorophenyl)piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 3-fluoroaniline	<i>M/Z</i> : 456, 458 [M+H] ⁺ , ESI ⁺ , RT = 2.14 (S4).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.89 (s, 1H), 8.00 – 7.89 (m, 2H), 7.77 – 7.68 (m, 1H), 7.54 – 7.40 (m, 2H), 7.23 (d, <i>J</i> = 7.7 Hz, 1H), 7.17 –

		(difluoromethyl)phenyl]piperidine-2-carboxamide	acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 3-(difluoromethyl)aniline		6.80 (m, 3H), 4.51 (s, 2H), 3.77 – 3.62 (m, 1H), 3.21 – 3.17 (m, 1H), 3.05 – 2.98 (m, 1H), 2.44 – 2.37 (m, 1H), 1.97 – 1.85 (m, 2H), 1.47 (t, $J = 9.3$ Hz, 2H).
25		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(5-chloropyridin-2-yl)piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 2-amino-5-chloropyridine	M/Z : 441, 443, 445 [$M+H$] ⁺ , ESI ⁺ , RT = 1.80 (S4).	¹ H NMR (500 MHz, DMSO- d_6) δ 10.14 (s, 1H), 8.36 (dd, $J = 2.6$, 0.6 Hz, 1H), 8.13 – 8.10 (m, 1H), 7.97 – 7.89 (m, 2H), 7.50 (t, $J = 8.9$ Hz, 1H), 7.07 (dd, $J = 11.4$, 2.8 Hz, 1H), 6.85 (ddd, $J = 9.0$, 2.8, 1.1 Hz, 1H), 4.51 (s, 2H), 3.71 – 3.62 (m, 1H), 2.99 (d, $J = 15.9$ Hz, 1H), 2.60 (s, 1H), 2.43 – 2.37 (m, 1H), 1.97 – 1.83 (m, 2H), 1.50 – 1.41 (m, 2H).
26		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[5-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl]piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 5-methyl-1-(2,2,2-trifluoroethyl)pyrazol-4-amine;hydrochloride	M/Z : 492, 494 [$M+H$] ⁺ , ESI ⁺ , RT = 1.79 (S4).	¹ H NMR (500 MHz, DMSO- d_6) δ 9.13 (s, 1H), 7.94 (d, $J = 8.1$ Hz, 1H), 7.60 (s, 1H), 7.51 (t, $J = 8.9$ Hz, 1H), 7.08 (dd, $J = 11.4$, 2.8 Hz, 1H), 6.86 (ddd, $J = 9.0$, 2.8, 1.1 Hz, 1H), 5.04 (q, $J = 9.2$ Hz, 2H), 4.52 (s, 2H), 3.74 – 3.61 (m, 1H), 3.22 – 3.13 (m, 1H), 3.05 – 2.95 (m, 1H), 2.45 – 2.40 (m, 1H), 2.19 (s, 3H), 1.95 – 1.86 (m, 2H), 1.50 – 1.40 (m, 2H).
27		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1 <i>S</i> ,3 <i>S</i>)-3-(trifluoromethoxy)cyclobutyl]piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 3-(trifluoromethoxy)cyclobutanamine;hydrochloride	M/Z : 468, 470 [$M+H$] ⁺ , ESI ⁺ , RT = 3.20 (S6).	¹ H NMR (400 MHz, DMSO) δ 8.53 (s, 1H), 8.03 (d, $J = 8.3$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 7.50 (t, $J = 8.9$ Hz, 1H), 7.07 (dd, $J = 11.4$, 2.8 Hz, 1H), 6.85 (dd, $J = 9.0$, 1.7 Hz, 1H), 4.62 – 4.54 (m, 1H), 4.50 (s, 2H), 3.97 – 3.86 (m, 1H), 3.67 – 3.58 (m, 1H), 2.95 (s, 2H), 2.63 (s, 1H), 2.34 – 2.32 (m, 1H), 2.26 – 2.16 (m, 2H), 2.07 – 1.98 (m, 1H), 1.90 – 1.78 (m, 2H), 1.43 – 1.27 (m, 2H).

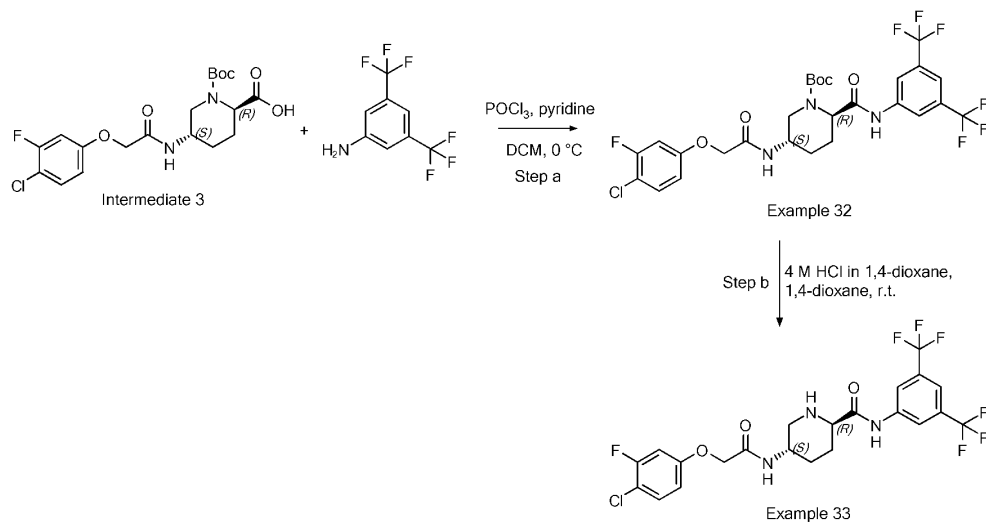
28		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(3,5-dimethylphenyl)piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 3,5-dimethylaniline	<i>M/Z</i> : 434, 436 [M+H] ⁺ , ESI ⁺ , RT = 2.29 (S4).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.47 (s, 1H), 7.93 (d, <i>J</i> = 8.1 Hz, 1H), 7.50 (t, <i>J</i> = 8.9 Hz, 1H), 7.24 (s, 2H), 7.07 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.85 (dd, <i>J</i> = 9.0, 2.8 Hz, 1H), 6.68 (s, 1H), 4.51 (s, 2H), 3.73 – 3.61 (m, 1H), 3.18 – 3.09 (m, 1H), 3.04 – 2.96 (m, 1H), 2.43 – 2.35 (m, 1H), 2.22 (s, 6H), 1.94 – 1.85 (m, 2H), 1.49 – 1.41 (m, 2H).
29		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(5,5,5-trifluoropentyl)piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 5,5,5-trifluoropentylamine; hydrochloride	<i>M/Z</i> : 454, 456 [M+H] ⁺ , ESI ⁺ , RT = 2.13 (S4).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.89 (d, <i>J</i> = 8.1 Hz, 1H), 7.69 (t, <i>J</i> = 5.8 Hz, 1H), 7.49 (t, <i>J</i> = 8.9 Hz, 1H), 7.06 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.84 (ddd, <i>J</i> = 9.0, 2.8, 1.1 Hz, 1H), 4.50 (s, 2H), 3.67 – 3.57 (m, 1H), 3.11 – 3.03 (m, 2H), 2.98 – 2.90 (m, 2H), 2.32 – 2.17 (m, 3H), 1.87 – 1.78 (m, 2H), 1.50 – 1.43 (m, 4H), 1.41 – 1.27 (m, 2H).
30		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(3-(difluoromethoxy)phenyl)piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 3-(difluoromethoxy)aniline	<i>M/Z</i> : 472, 474 [M+H] ⁺ , ESI ⁺ , RT = 2.21 (S4).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.86 (s, 1H), 7.94 (d, <i>J</i> = 8.1 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.55 – 7.42 (m, 2H), 7.39 – 6.97 (m, 3H), 6.92 – 6.81 (m, 2H), 4.51 (s, 2H), 3.74 – 3.62 (m, 1H), 3.21 – 3.13 (m, 1H), 3.06 – 2.97 (m, 1H), 2.44 – 2.34 (m, 1H), 1.98 – 1.83 (m, 2H), 1.54 – 1.38 (m, 2H).
31		(2 <i>S</i> ,5 <i>R</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(3-(trifluoromethyl)phenyl)piperidine-2-carboxamide	(2 <i>S</i> ,5 <i>R</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 4) and 3-(trifluoromethyl)aniline	<i>M/Z</i> : 474, 476 [M+H] ⁺ , ESI ⁺ , RT = 2.37 (S4).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.04 (s, 1H), 8.16 (d, <i>J</i> = 3.1 Hz, 2H), 7.92 (dd, <i>J</i> = 28.2, 8.4 Hz, 2H), 7.59 – 7.47 (m, 2H), 7.40 (d, <i>J</i> = 7.8 Hz, 1H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.87 (ddd, <i>J</i> = 9.0, 2.9, 1.1 Hz, 1H), 4.53 (s, 2H), 3.76 – 3.68 (m, 1H), 3.24 – 3.19 (m, 2H), 3.08 – 3.00 (m, 1H), 2.44 – 2.39 (m, 2H), 1.99 – 1.87 (m, 2H), 1.54 – 1.43 (m, 2H).

39		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(2,2-difluoro-2 <i>H</i> -1,3-benzodioxol-5-yl)piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 2,2-difluoro-2 <i>H</i> -1,3-benzodioxol-5-amine hydrochloride	<i>M/Z</i> : 486, 488 [M+H] ⁺ , ESI ⁺ , RT = 2.32 (S4).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 7.94 (d, <i>J</i> = 8.1 Hz, 1H), 7.81 (d, <i>J</i> = 2.0 Hz, 1H), 7.50 (t, <i>J</i> = 8.9 Hz, 1H), 7.39 (dd, <i>J</i> = 8.8, 2.0 Hz, 1H), 7.33 (d, <i>J</i> = 8.8 Hz, 1H), 7.07 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.85 (ddd, <i>J</i> = 9.0, 2.8, 1.1 Hz, 1H), 4.51 (s, 2H), 3.73 – 3.64 (m, 1H), 3.17 (d, <i>J</i> = 7.9 Hz, 1H), 3.01 (dd, <i>J</i> = 11.9, 3.3 Hz, 1H), 2.43 – 2.35 (m, 1H), 1.97 – 1.84 (m, 2H), 1.51 – 1.40 (m, 2H).
40		2-(4-chloro-3-fluorophenoxy)- <i>N</i> -[(3 <i>S</i> ,6 <i>R</i>)-6-[5-(trifluoromethyl)-2,3-dihydro-1 <i>H</i> -isindole-2-carbonyl]piperidin-3-yl]acetamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 5-(trifluoromethyl)-2,3-dihydro-1 <i>H</i> -isindole	<i>M/Z</i> : 500, 502 [M+H] ⁺ , ESI ⁺ , RT = 2.33 (S4).	¹ H NMR (500 MHz, DMSO) δ 7.92 (dd, <i>J</i> = 8.0, 2.6 Hz, 1H), 7.78 – 7.72 (m, 1H), 7.69 – 7.63 (m, 1H), 7.58 (t, <i>J</i> = 8.7 Hz, 1H), 7.50 (t, <i>J</i> = 8.9 Hz, 1H), 7.07 (dd, <i>J</i> = 11.4, 2.6 Hz, 1H), 6.85 (dd, <i>J</i> = 8.9, 2.7 Hz, 1H), 5.13 (dd, <i>J</i> = 14.9, 5.2 Hz, 1H), 5.04 – 4.90 (m, 1H), 4.86 – 4.65 (m, 2H), 4.52 (s, 2H), 3.67 – 3.58 (m, 1H), 3.41 – 3.33 (m, 1H), 3.04 – 2.96 (m, 1H), 2.44 – 2.36 (m, 1H), 2.10 (s, 1H), 1.96 – 1.78 (m, 2H), 1.53 – 1.39 (m, 2H).
41		2-(4-chloro-3-fluorophenoxy)- <i>N</i> -[(3 <i>S</i> ,6 <i>R</i>)-6-[5-(trifluoromethoxy)-2,3-dihydro-1 <i>H</i> -isindole-2-carbonyl]piperidin-3-yl]acetamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 5-(trifluoromethoxy)-2,3-dihydro-1 <i>H</i> -isindole	<i>M/Z</i> : 516, 518 [M+H] ⁺ , ESI ⁺ , RT = 2.43 (S4).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.91 (d, <i>J</i> = 8.1 Hz, 1H), 7.53 – 7.43 (m, 2H), 7.39 (d, <i>J</i> = 8.6 Hz, 1H), 7.29 (d, <i>J</i> = 8.1 Hz, 1H), 7.07 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.85 (dd, <i>J</i> = 8.7, 2.4 Hz, 1H), 5.12 – 5.02 (m, 1H), 4.93 – 4.83 (m, 1H), 4.72 – 4.58 (m, 2H), 4.51 (s, 2H), 3.67 – 3.57 (m, 1H), 3.40 – 3.33 (m, 1H), 3.00 (dd, <i>J</i> = 9.6 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.17 – 2.05 (m, 1H), 1.96 – 1.88 (m, 1H), 1.87 – 1.78 (m, 1H), 1.54 – 1.38 (m, 2H).
42		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[1-methyl-5-(trifluoromethyl)-2,3-dihydro-1 <i>H</i> -isindole-2-carbonyl]piperidin-3-yl}acetamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 1-methyl-5-(trifluoromethyl)-2,3-dihydro-1 <i>H</i> -isindole	<i>M/Z</i> : 492, 494 [M+H] ⁺ , ESI ⁺ , RT = 3.04 (S6).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.14 (t, <i>J</i> = 6.0 Hz, 1H), 7.91 (d, <i>J</i> = 8.1 Hz, 1H), 7.50 (t, <i>J</i> = 8.9 Hz, 1H), 7.07 (dd, <i>J</i> = 11.4, 2.9 Hz, 1H), 6.89 – 6.82 (m, 1H), 6.70 (s, 1H), 4.50 (s, 2H), 4.28 –

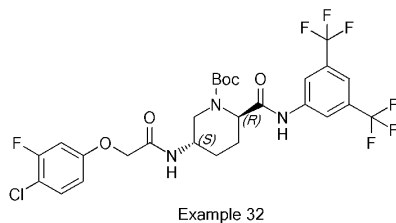
		hyl)-1 <i>H</i> -pyrazol-3-yl)methyl}piperidine-2-carboxamide	carboxylic acid (Intermediate 3) and 1-[1-methyl-5-(trifluoromethyl)-1 <i>H</i> -pyrazol-3-yl]methanamine hydrochloride		4.18 (m, 2H), 3.98 – 3.87 (m, 3H), 3.74 – 3.55 (m, 1H), 3.07 – 2.91 (m, 2H), 2.46 – 2.34 (m, 2H), 1.93 – 1.79 (m, 2H), 1.50 – 1.28 (m, 2H).
43		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[5-(trifluoromethyl)-1,2-oxazol-3-yl)methyl}piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 1-[5-(trifluoromethyl)-1,2-oxazol-3-yl]methanamine	<i>M/Z</i> : 479, 481 [M+H] ⁺ , ESI ⁺ , RT = 2.02 (S4).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.40 (t, <i>J</i> = 6.0 Hz, 1H), 7.92 (d, <i>J</i> = 8.1 Hz, 1H), 7.49 (t, <i>J</i> = 8.9 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.06 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.85 (ddd, <i>J</i> = 9.0, 2.8, 1.1 Hz, 1H), 4.50 (s, 2H), 4.45 – 4.34 (m, 2H), 3.69 – 3.60 (m, 1H), 3.06 – 2.94 (m, 2H), 2.56 – 2.52 (m, 1H), 2.38 – 2.32 (m, 1H), 1.91 – 1.80 (m, 2H), 1.46 – 1.31 (m, 2H).
44		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[4-(trifluoromethyl)pyridin-2-yl)methyl}piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 1-[4-(trifluoromethyl)pyridin-2-yl]methanamine hydrochloride	<i>M/Z</i> : 489, 491 [M+H] ⁺ , ESI ⁺ , RT = 1.94 (S4).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.80 (d, <i>J</i> = 5.1 Hz, 1H), 8.43 (t, <i>J</i> = 5.9 Hz, 1H), 7.94 (d, <i>J</i> = 8.1 Hz, 1H), 7.66 (d, <i>J</i> = 5.1 Hz, 1H), 7.60 (s, 1H), 7.51 (t, <i>J</i> = 8.9 Hz, 1H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.96 – 6.74 (m, 1H), 4.52 (s, 2H), 4.48 (d, <i>J</i> = 6.0 Hz, 2H), 3.75 – 3.62 (m, 1H), 3.12 – 3.05 (m, 1H), 3.00 (d, <i>J</i> = 12.5 Hz, 1H), 2.42 – 2.34 (m, 2H), 1.89 (dd, <i>J</i> = 25.1, 9.6 Hz, 2H), 1.55 – 1.35 (m, 2H).
45		2-(4-chloro-3-fluorophenoxy)- <i>N</i> -[(3 <i>S</i> ,6 <i>R</i>)-6-[4-(trifluoromethyl)-2,3-dihydro-1 <i>H</i> -indole-1-carbonyl]piperidin-3-yl]acetamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 4-(trifluoromethyl)-2,3-dihydro-1 <i>H</i> -indole	<i>M/Z</i> : 500, 502 [M+H] ⁺ , ESI ⁺ , RT = 2.41 (S4).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.36 (d, <i>J</i> = 6.7 Hz, 1H), 7.91 (d, <i>J</i> = 8.1 Hz, 1H), 7.50 (t, <i>J</i> = 8.9 Hz, 1H), 7.40 (t, <i>J</i> = 7.9 Hz, 1H), 7.32 (d, <i>J</i> = 7.8 Hz, 1H), 7.07 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.85 (dd, <i>J</i> = 9.0, 2.8 Hz, 1H), 4.52 (s, 2H), 4.42 (q, <i>J</i> = 9.1 Hz, 1H), 4.21 (q, <i>J</i> = 9.3 Hz, 1H), 3.71 – 3.59 (m, 1H), 3.43 (d, <i>J</i> = 8.0 Hz, 1H), 3.30 – 3.23 (m, 1H), 3.01 (dd, <i>J</i> = 12.5, 3.3 Hz, 1H), 2.55 (s, 1H),

					2.46 – 2.15 (m, 2H), 1.97 – 1.83 (m, 2H), 1.56 – 1.45 (m, 2H).
46		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-1-[(2,2-difluorocyclopropyl)piperidine-2-carboxamide]	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 1-(2,2-difluorocyclopropyl)-1 <i>H</i> -pyrazol-3-amine	<i>M/Z</i> : 472, 474 [M+H] ⁺ , ESI ⁺ , RT = 1.89 (S4).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.13 (s, 1H), 7.94 (d, <i>J</i> = 8.2 Hz, 1H), 7.77 (d, <i>J</i> = 2.4 Hz, 1H), 7.51 (t, <i>J</i> = 8.9 Hz, 1H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.86 (ddd, <i>J</i> = 9.0, 2.8, 1.1 Hz, 1H), 6.56 (d, <i>J</i> = 2.4 Hz, 1H), 4.52 (s, 2H), 4.48 – 4.38 (m, 1H), 3.73 – 3.59 (m, 1H), 3.24 – 3.16 (m, 1H), 3.02 – 2.93 (m, 1H), 2.42 – 2.23 (m, 4H), 1.93 – 1.83 (m, 2H), 1.50 – 1.38 (m, 2H).

Scheme for route 11



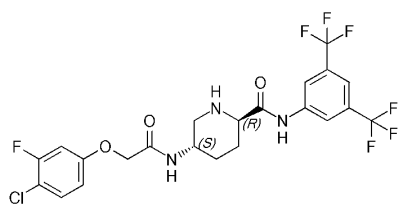
Example 32 (step 11.a): *tert*-butyl (2*R*,5*S*)-2-[[3,5-bis(trifluoromethyl)phenyl]carbamoyl]-5-[[2-(4-chloro-3-fluoro-phenoxy)acetyl]amino]piperidine-1-carboxylate



To a solution of (2*R*,5*S*)-1-[(*tert*-butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (200 mg, 0.441 mmol, Intermediate 3) in anhydrous DCM (4 mL) at 0 °C was added 3,5-bis(trifluoromethyl)aniline (101 mg, 0.441

mmol), pyridine (178 μ L, 2.20 mmol) and then POCl₃ (101 mg, 0.661 mmol), and the mixture was stirred at r.t. for 18 h. The reaction mixture was diluted with DCM (6 mL), cooled to 0 °C and then carefully added dropwise to a solution of satd aq NaHCO₃ solution (12 mL) at 0 °C. The resultant solution was allowed to warm to r.t. whilst stirring for 1 h. The organic layer was isolated using a phase separator cartridge and then concentrated *in vacuo* to afford the title compound (70% purity, 312 mg, 0.340 mmol, 77% yield) as an orange solid; *M/Z*: 488, 490 [M+H]⁺, RT = 1.13 (S2). The product was taken forward without further purification.

Example 33 (step 11.b): (2*R*,5*S*)-*N*-[3,5-bis(trifluoromethyl)phenyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxamide



Example 33

To a solution of *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 (70% purity, 312 mg, 0.340 mmol, example 32) in anhydrous 1,4-dioxane (2 mL) was added 4 M HCl in 1,4-dioxane (3.0 mL, 3.00 mmol) and the mixture was stirred at r.t. for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by prep. HPLC (Method 3) to afford the title compound (106 mg, 0.196 mmol, 58% yield) as a white powder; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.67 – 10.11 (m, 1H), 8.42 (s, 2H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.75 (s, 1H), 7.51 (t, *J* = 8.9 Hz, 1H), 7.08 (dd, *J* = 11.4, 2.8 Hz, 1H), 6.87 (ddd, *J* = 9.0, 2.8, 1.1 Hz, 1H), 4.53 (s, 2H), 3.82 – 3.64 (m, 1H), 3.25 – 3.19 (m, 1H), 3.09 – 3.00 (m, 1H), 2.45 – 2.38 (m, 1H), 2.03 – 1.85 (m, 2H), 1.57 – 1.41 (m, 2H); *M/Z*: 542, 544 [M+H]⁺, ESI⁺, RT = 2.61 (S4).

Example compounds in **Table 5** were synthesised according to general route 11 as exemplified by **Example 33** using the corresponding intermediates. The corresponding boc protected intermediates of the numbered examples are also examples of the invention.

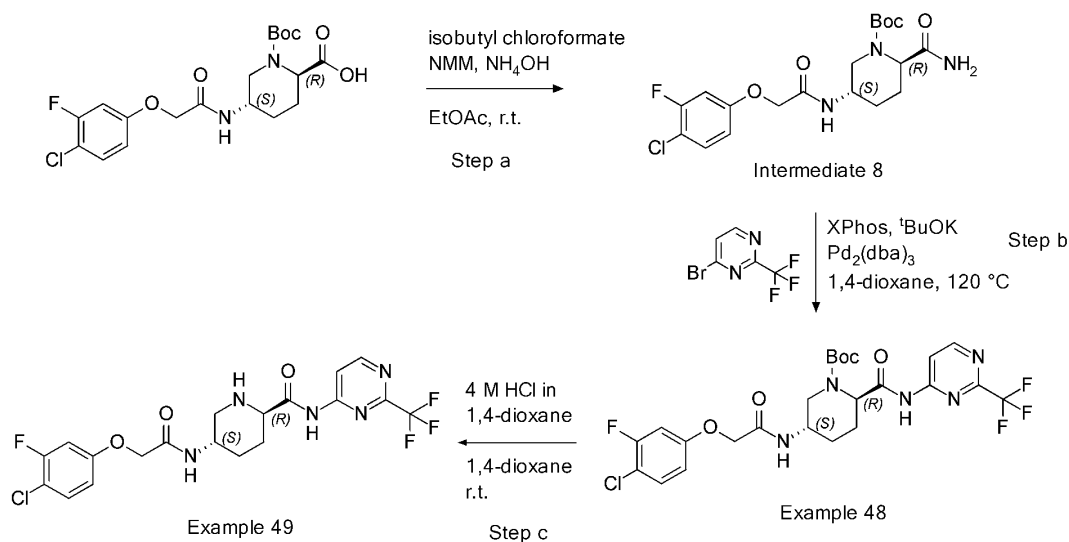
Table 5

Ex	Structure	Name	Intermediates	LCMS data	¹ H NMR
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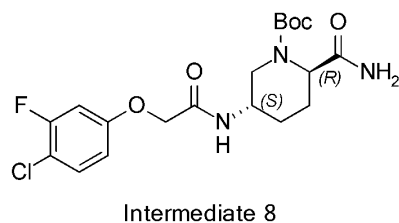
34		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[1-(trifluoromethyl)-1 <i>H</i> -pyrazol-3-yl]piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 1-(trifluoromethyl)pyrazol-3-amine	<i>M/Z</i> : 464, 466 [<i>M</i> + <i>H</i>] ⁺ , ESI ⁺ , RT = 3.11 (S6).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.64 (s, 1H), 8.37 (d, <i>J</i> = 2.9 Hz, 1H), 7.93 (d, <i>J</i> = 8.2 Hz, 1H), 7.51 (t, <i>J</i> = 8.9 Hz, 1H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.91 – 6.79 (m, 2H), 4.52 (s, 2H), 3.71 – 3.58 (m, 1H), 3.27 – 3.20 (m, 1H), 3.04 – 2.96 (m, 1H), 2.45 – 2.31 (m, 2H), 1.96 – 1.84 (m, 2H), 1.53 – 1.39 (m, 2H).
35		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[2-fluoro-5-(trifluoromethyl)phenyl]piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 2-fluoro-5-(trifluoromethyl)aniline	<i>M/Z</i> : 492, 494 [<i>M</i> + <i>H</i>] ⁺ , ESI ⁺ , RT = 3.66 (S6).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 9.72 (s, 1H), 8.45 (d, <i>J</i> = 7.6 Hz, 1H), 7.98 (d, <i>J</i> = 8.1 Hz, 1H), 7.59 – 7.45 (m, 3H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.93 – 6.82 (m, 1H), 4.53 (s, 2H), 3.80 – 3.61 (m, 1H), 3.33 – 3.32 (m, 1H), 3.02 (dd, <i>J</i> = 12.1, 3.1 Hz, 2H), 2.46 – 2.39 (m, 1H), 2.01 – 1.95 (m, 1H), 1.92 – 1.86 (m, 1H), 1.53 – 1.44 (m, 2H).
36		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[2-fluoro-3-(trifluoromethyl)phenyl]piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 2-fluoro-3-(trifluoromethyl)aniline	<i>M/Z</i> : 492, 494 [<i>M</i> + <i>H</i>] ⁺ , ESI ⁺ , RT = 2.31 (S4).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.73 (s, 1H), 8.22 (t, <i>J</i> = 7.2 Hz, 1H), 7.96 (d, <i>J</i> = 8.2 Hz, 1H), 7.58 – 7.46 (m, 2H), 7.39 (t, <i>J</i> = 8.1 Hz, 1H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.87 (ddd, <i>J</i> = 8.9, 2.8, 1.1 Hz, 1H), 4.53 (s, 2H), 3.80 – 3.60 (m, 1H), 3.30 – 3.27 (m, 1H), 3.07 – 2.97 (m, 1H), 2.46 – 2.39 (m, 1H), 2.03 – 1.83 (m, 2H), 1.56 – 1.43 (m, 2H).
37		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[6-(trifluoromethoxy)pyridin-2-yl]piperidine-2-carboxamide	(2 <i>R</i> ,5 <i>S</i>)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 6-(trifluoromethoxy)pyridin-2-amine	<i>M/Z</i> : 491, 493 [<i>M</i> + <i>H</i>] ⁺ , ESI ⁺ , RT = 2.34 (S4).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.07 (s, 1H), 8.10 (d, <i>J</i> = 8.0 Hz, 1H), 8.02 (t, <i>J</i> = 8.0 Hz, 1H), 7.95 (d, <i>J</i> = 8.2 Hz, 1H), 7.51 (t, <i>J</i> = 8.9 Hz, 1H), 7.08 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 7.00 (d, <i>J</i> = 7.9 Hz, 1H), 6.86 (dd, <i>J</i> = 8.9, 1.7 Hz, 1H), 4.52 (s, 2H), 3.72 – 3.62 (m, 1H), 3.27 – 3.23 (m,

					1H), 3.06 – 2.97 (m, 1H), 2.44 – 2.40 (m, 1H), 2.00 – 1.83 (m, 2H), 1.53 – 1.40 (m, 2H).
38		(2R,5S)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[4-(trifluoromethyl)pyridin-2-yl]piperidine-2-carboxamide	(2R,5S)-1-[(<i>tert</i> -butoxy)carbonyl]-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3) and 4-(trifluoromethyl)pyridin-2-amine	<i>M/Z</i> : 475, 477 [M+H] ⁺ , ESI ⁺ , RT = 2.11 (S4).	¹ H NMR (500 MHz, MeOD- <i>d</i> ₄) δ 8.43 (d, <i>J</i> = 5.2 Hz, 1H), 8.37 (s, 1H), 7.33 – 7.25 (m, 2H), 6.85 (dd, <i>J</i> = 11.0, 2.8 Hz, 1H), 6.74 (ddd, <i>J</i> = 8.9, 2.9, 1.2 Hz, 1H), 4.43 (s, 2H), 3.85 – 3.74 (m, 1H), 3.38 – 3.28 (m, 1H), 3.16 – 3.05 (m, 1H), 2.51 – 2.40 (m, 1H), 2.11 – 1.90 (m, 2H), 1.60 – 1.47 (m, 2H).

Scheme for route 12



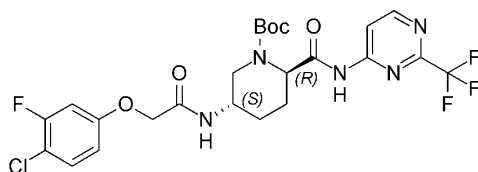
Intermediate 8 (step 12.a): *tert*-butyl (2R,5S)-2-carbamoyl-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-1-carboxylate



NMM (0.61 mL, 5.57 mmol) and isobutyl chloroformate (0.72 mL, 5.57 mmol) were added to a solution of (2R,5S)-1-[(*tert*-butoxy)carbonyl]-5-[2-(4-chloro-3-

fluorophenoxy)acetamido]piperidine-2-carboxylic acid (Intermediate 3, 2.00 g, 4.64 mmol) in anhydrous THF (32 mL). After 20 mins, NH₄OH (35%, 0.51 mL, 9.28 mmol) was added and the mixture was stirred at r.t. for 2 h. The reaction mixture was concentrated *in vacuo* and the resultant residue was dissolved in EtOAc (100 mL) and washed with H₂O (50 mL). The organic
 5 extracts were dried over MgSO₄ and concentrated *in vacuo* to afford the title compound (1.82 g, 4.02 mmol, 87% yield) as a white amorphous solid; ¹H NMR (500 MHz, CDCl₃) δ 7.32 (t, *J* = 8.6 Hz, 1H), 6.89 – 6.64 (m, 3H), 6.04 (s, 1H), 5.51 (s, 1H), 4.79 (s, 1H), 4.50 – 4.40 (m, 2H), 4.12 (s, 2H), 3.12 (d, *J* = 13.6 Hz, 1H), 2.21 – 2.15 (m, 1H), 1.95 – 1.88 (m, 1H), 1.71 – 1.63 (m, 2H), 1.44 (s, 9H); *M/Z*: 452, 454 [M+Na]⁺, ESI⁺, RT = 0.82 (S2).

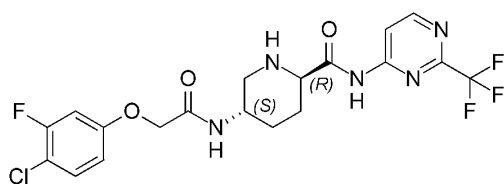
10 **Example 48 (step 12.b): *tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-
 {[2-(trifluoromethyl)pyrimidin-4-yl]carbamoyl}piperidine-1-carboxylate**



Example 48

To a solution of *tert*-butyl (2*R*,5*S*)-2-carbamoyl-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-1-carboxylate (Intermediate 8, 129 mg, 0.300 mmol) in
 15 anhydrous 1,4-dioxane (2 mL) was added 4-bromo-2-(trifluoromethyl)pyrimidine (68 mg, 0.300 mmol), Pd₂(dba)₃ (14 mg, 0.0150 mmol), ^tBuOK (47 mg, 0.420 mmol) and XPhos (14 mg, 0.0300 mmol). The reaction vial was degassed under N₂ before being heated at 120 °C under microwave irradiation for 2 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with H₂O (2 × 10 mL). The organic extracts were concentrated *in vacuo* and purified
 20 by FCC on silica gel (10 – 100% EtOAc in heptane) to afford the title compound (50% purity, 68 mg, 0.0590 mmol, 20% yield) as a yellow gum; *M/Z*: 476, 478 [M-Boc+H]⁺, ESI⁺, RT = 3.98 (S4).

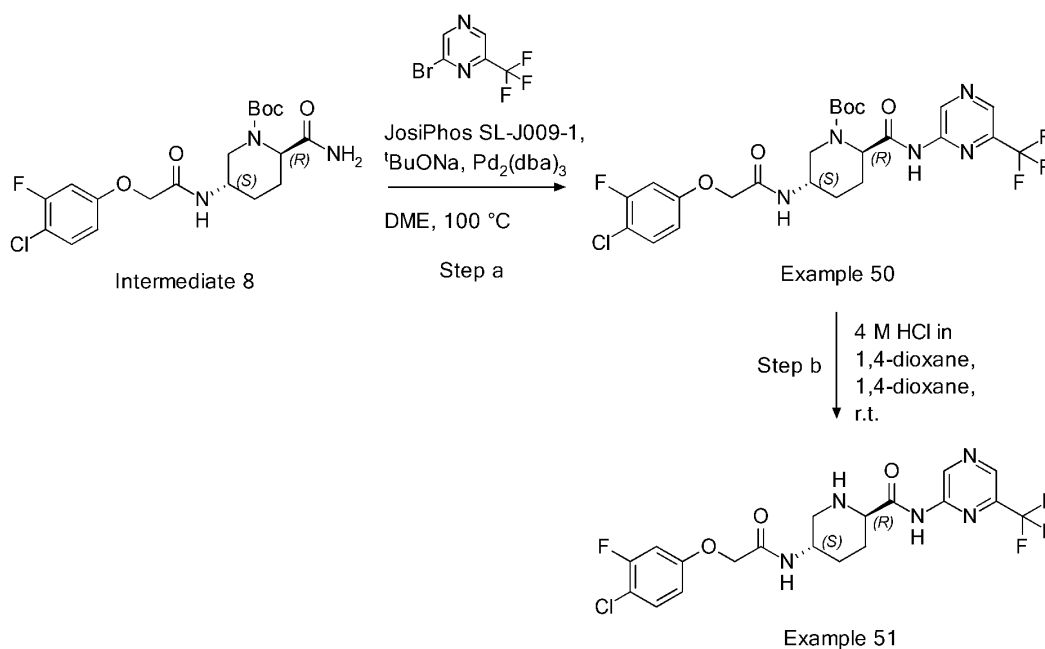
Example 49 (step 12.c): (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[2-(trifluoromethyl)pyrimidin-4-yl]piperidine-2-carboxamide



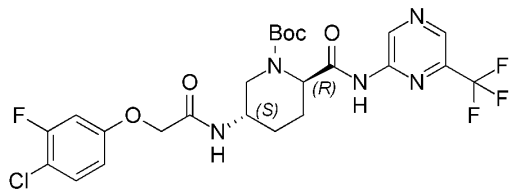
Example 49

To a solution of *tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[[2-(trifluoromethyl)pyrimidin-4-yl]carbamoyl]piperidine-1-carboxylate (Example 48, 50% purity, 68 mg, 0.0590 mmol) in anhydrous 1,4-dioxane (0.6 mL) was added 4 M HCl in 1,4-dioxane (1.2 mL, 5.00 mmol) and stirred at r.t. overnight. The reaction mixture was quenched with NaHCO₃ (15 mL) and washed with EtOAc (2 × 15 mL). The organic extracts were combined, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by prep. HPLC (Method 3) to afford the title compound (9.0 mg, 0.0189 mmol, 32% yield) as a white powder; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.88 (d, *J* = 5.8 Hz, 1H), 8.29 (d, *J* = 5.8 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.50 (t, *J* = 8.9 Hz, 1H), 7.07 (dd, *J* = 11.4, 2.9 Hz, 1H), 6.85 (ddd, *J* = 8.9, 1.8 Hz, 1H), 4.51 (s, 2H), 3.73 – 3.62 (m, 1H), 3.43 – 3.37 (m, 2H), 3.03 – 2.97 (m, 1H), 2.40 – 2.35 (m, 1H), 1.97 – 1.85 (m, 2H), 1.49 – 1.43 (m, 2H), 1.28 – 1.21 (m, 1H); *M/Z*: 476, 478 [M+H]⁺, ESI⁺, RT = 1.98 (S4).

Scheme for route 13



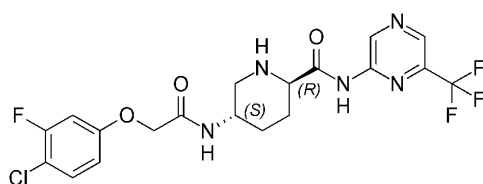
Example 50 (step 13.a): *tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[[6-(trifluoromethyl)pyrazin-2-yl]carbamoyl]piperidine-1-carboxylate



Example 50

Vial A was charged with Josiphos SL-J009-1 (12 mg, 0.0221 mmol) and Pd₂(dba)₃ (10 mg, 0.0110 mmol). Vial B was charged with *tert*-butyl (2*R*,5*S*)-2-carbamoyl-5-[2-(4-chloro-3-fluorophenoxy)acetamido]piperidine-1-carboxylate (Intermediate 8, 95 mg, 0.220 mmol), ^tBuONa (42 mg, 0.441 mmol) and 2-bromo-6-(trifluoromethyl)pyrazine (50 mg, 0.220 mmol). Both vials were sealed and purged with N₂. Degassed DME (4 mL) was added to vial A and the solution was stirred for 5 mins to form the active catalyst solution. This solution was then added to vial B and the mixture was stirred at 100 °C for 18h. The reaction mixture was allowed to cool to r.t., diluted with H₂O (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄ and concentrated *in vacuo* to afford the title compound (34% purity, 160 mg, 0.0945 mmol, 43% yield) as a brown oil; *M/Z*: 476, 478 [M-Boc+H]⁺, ESI⁺, RT = 1.05 (S2).

Example 51 (step 13.b): (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[6-(trifluoromethyl)pyrazin-2-yl]piperidine-2-carboxamide

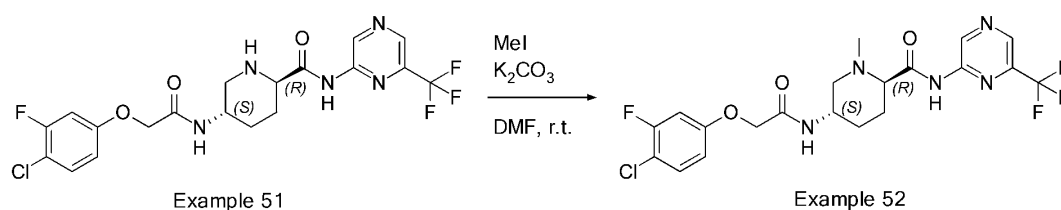


Example 51

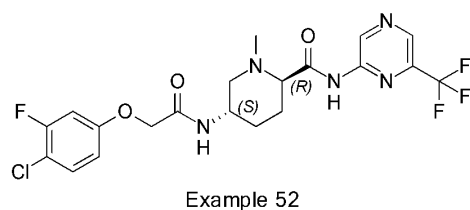
To a solution of *tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[[6-(trifluoromethyl)pyrazin-2-yl]carbamoyl]piperidine-1-carboxylate (Example 50, 34% purity, 160 mg, 0.0945 mmol) in anhydrous 1,4-dioxane (1 mL) was added 4 M HCl in 1,4-dioxane (2.0 mL, 8.00 mmol) and the mixture was stirred at r.t. for 24 h. The reaction mixture was quenched with NaHCO₃ (15 mL) and washed with EtOAc (2 × 15 mL). The combined organic extracts were dried over MgSO₄, concentrated *in vacuo*, and purified by prep. HPLC (Method

3) to afford the title compound (26 mg, 0.0544 mmol, 58% yield) as a yellow powder; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.62 (s, 1H), 8.88 (s, 1H), 7.94 (d, $J = 8.2$ Hz, 1H), 7.50 (t, $J = 8.9$ Hz, 1H), 7.07 (dd, $J = 11.4, 2.8$ Hz, 1H), 6.86 (ddd, $J = 9.0, 2.8, 1.1$ Hz, 1H), 4.51 (s, 2H), 3.73 – 3.65 (m, 1H), 3.40 (dd, $J = 10.2, 2.9$ Hz, 1H), 3.01 (dd, $J = 12.3, 3.0$ Hz, 1H), 2.44 – 2.38 (m, 1H), 2.00 – 1.86 (m, 2H), 1.53 – 1.44 (m, 2H); M/Z : 476, 478 $[\text{M}+\text{H}]^+$, ESI^+ , $\text{RT} = 1.96$ (S4).

Scheme for route 14



Example 52: (2R,5S)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-1-methyl-N-[6-(trifluoromethyl)pyrazin-2-yl]piperidine-2-carboxamide

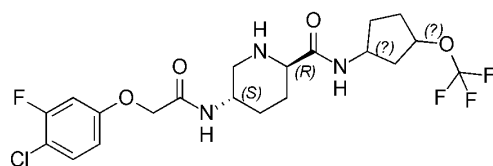


10

To a solution of (2R,5S)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[6-(trifluoromethyl)pyrazin-2-yl]piperidine-2-carboxamide (Example 51, 90% purity, 33 mg, 0.0624 mmol) and K_2CO_3 (17 mg, 0.125 mmol) in DMF (1 mL) was added MeI (3.5 μL , 0.0562 mmol) and the mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with H_2O (10 mL). The organic extracts were dried over MgSO_4 , concentrated *in vacuo*, and purified by prep. HPLC (Method 3) to afford the title compound (18 mg, 0.0357 mmol, 57% yield) as a white amorphous solid; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.01 (s, 1H), 9.63 (s, 1H), 8.88 (s, 1H), 8.03 (d, $J = 8.2$ Hz, 1H), 7.50 (t, $J = 8.9$ Hz, 1H), 7.08 (dd, $J = 11.4, 2.8$ Hz, 1H), 6.88 – 6.83 (m, 1H), 4.52 (s, 2H), 4.00 – 3.82 (m, 1H), 2.94 (dd, $J = 10.7, 3.6$ Hz, 1H), 2.80 (dd, $J = 10.8, 2.8$ Hz, 1H), 2.17 (s, 3H), 1.94 – 1.79 (m, 3H), 1.76 – 1.64 (m, 1H), 1.39 – 1.27 (m, 1H); M/Z : 490, 492 $[\text{M}+\text{H}]^+$, ESI^+ , $\text{RT} = 2.10$ (S4).

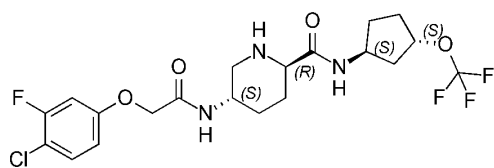
20

Scheme for route 15



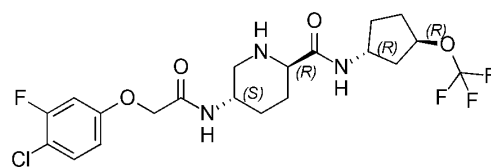
Example 47

Chiral
Separation
↓



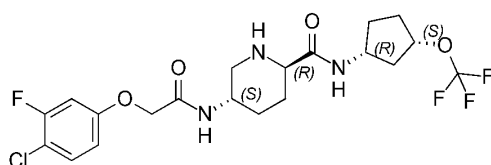
Example 53

stereochemistry of pentyl ring arbitrarily assigned
+

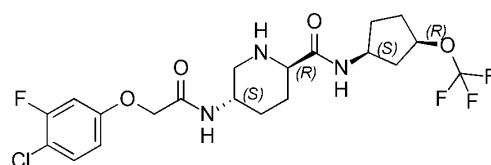


Example 54

stereochemistry of pentyl ring arbitrarily assigned
+



stereochemistry of pentyl ring arbitrarily assigned



stereochemistry of pentyl ring arbitrarily assigned

Example 53 and 54 : Chiral separation of (2R,5S)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide (Example 47)

(2R,5S)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide (148 mg, Example 47) was subjected to chiral purification using the following method:

Purification method = 90:10 heptane: EtOH + 0.2% DEA; Amylose-2, 21.2 × 250 mm, 5μm, at 18 ml/min. Sample diluent: MeOH, IPA.

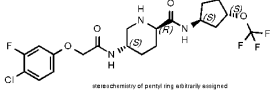
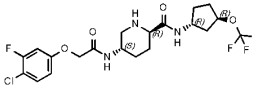
Followed by:

Purification method = 90:10 heptane: IPA; Chiralpak AD-H, 20 × 250mm, 5μm, at 18 ml/min. Sample diluent: MeOH, IPA.

This afforded (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(1*S*,3*S*)-3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide (Example 53, 4 mg) and (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(1*R*,3*R*)-3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide (Example 54, 18 mg), as well as two isomers (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(1*R*,3*S*)-3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide and (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(1*S*,3*R*)-3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide as white powders. The stereochemistry in the pentyl ring of each compound was arbitrarily assigned.

Example compounds in **Table 6** were chirally purified according to the general route 15 as exemplified by **Example 53** and **54**, using the corresponding intermediates and methods.

Table 6

Ex	Structure	Name	Intermediate and Method	LCMS data	¹ H NMR
53		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1 <i>S</i> ,3 <i>S</i>)-3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide (stereochemistry of pentyl ring arbitrarily assigned)	(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide (Example 47)	<i>M/Z</i> : 482, 484 [M+H] ⁺ , ESI ⁺ , RT = 2.19 (S4).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.90 (d, <i>J</i> = 8.1 Hz, 1H), 7.72 (d, <i>J</i> = 7.6 Hz, 1H), 7.49 (t, <i>J</i> = 8.9 Hz, 1H), 7.06 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.84 (ddd, <i>J</i> = 9.0, 2.8, 1.1 Hz, 1H), 4.86 – 4.78 (m, 1H), 4.49 (s, 2H), 4.05 (p, <i>J</i> = 7.2 Hz, 1H), 2.94 (d, <i>J</i> = 10.9 Hz, 2H), 2.32 (dd, <i>J</i> = 14.0, 7.6 Hz, 2H), 1.96 – 1.78 (m, 5H), 1.71 – 1.63 (m, 1H), 1.58 (dq, <i>J</i> = 11.6, 7.7 Hz, 1H), 1.45 – 1.27 (m, 2H).
54		(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1 <i>R</i> ,3 <i>R</i>)-3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide (stereochemistry of pentyl ring arbitrarily assigned)	(2 <i>R</i> ,5 <i>S</i>)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[3-(trifluoromethoxy)cyclopentyl]piperidine-2-carboxamide (Example 47)	<i>M/Z</i> : 482, 484 [M+H] ⁺ , ESI ⁺ , RT = 2.18 (S4).	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.90 (d, <i>J</i> = 8.1 Hz, 1H), 7.73 (t, <i>J</i> = 8.4 Hz, 1H), 7.49 (t, <i>J</i> = 8.9 Hz, 1H), 7.06 (dd, <i>J</i> = 11.4, 2.8 Hz, 1H), 6.84 (ddd, <i>J</i> = 9.0, 2.8, 1.1 Hz, 1H), 4.82 (d, <i>J</i> = 4.1 Hz, 1H), 4.49 (s, 2H), 4.04 (q, <i>J</i> = 7.3 Hz, 1H), 2.94 (d, <i>J</i> = 10.9 Hz, 2H), 2.32 (dd, <i>J</i> = 13.4, 8.2 Hz, 2H), 1.96 – 1.77 (m,

					5H), 1.71 – 1.62 (m, 1H), 1.62 – 1.53 (m, 1H), 1.44 – 1.26 (m, 2H).
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II Assays

HEK-ATF4 High Content Imaging assay

5 Example compounds were tested in the HEK-ATF4 High Content Imaging assay to assess their pharmacological potency to prevent Tunicamycin induced ISR. Wild-type HEK293 cells were plated in 384-well imaging assay plates at a density of 12,000 cells per well in growth medium (containing DMEM/F12, 10% FBS, 2 mM L-Glutamine, 100 U/mL Penicillin – 100 µg/mL Streptomycin) and incubated at 37°C, 5% CO₂. 24 h later, the medium was changed to 50 µL

10 assay medium per well (DMEM/F12, 0.3% FBS, 2mM L-Glutamine, 100 U/mL Penicillin – 100 µg/mL Streptomycin). Example compounds were serially diluted in DMSO, spotted into intermediate plates and prediluted with assay medium containing 3.3 µM Tunicamycin to give an 11-fold excess of final assay concentration. In addition to the example compound testing area, the plates also contained multiples of control wells for assay normalization purposes, wells

15 containing Tunicamycin but no example compounds (High control), as well as wells containing neither example compound nor Tunicamycin (Low control). The assay was started by transferring 5 µL from the intermediate plate into the assay plates, followed by incubation for 6 h at 37 °C, 5% CO₂. Subsequently, cells were fixed (4% PFA in PBS, 20 min at r.t.) and submitted to indirect ATF4 immunofluorescence staining (primary antibody rabbit anti ATF4,

20 clone D4B8, Cell Signaling Technologies; secondary antibody Alexa Fluor 488 goat anti-rabbit IgG (H+L), Thermofisher Scientific). Nuclei were stained using Hoechst dye (Thermofisher Scientific), and plates were imaged on an Opera Phenix High Content imaging platform equipped with 405 nm and 488 nm excitation. Finally, images were analyzed using script based algorithms. The main readout *HEK-ATF4* monitored the ATF4 signal ratio between nucleus

25 and cytoplasm. Tunicamycin induced an increase in the overall ATF4 ratio signal, which was prevented by ISR modulating example compounds. In addition, HEK-CellCount readout was derived from counting the number of stained nuclei corresponding to healthy cells. This readout served as an internal toxicity control. The example compounds herein did not produce significant reduction in CellCount.

30

HEK ATF4 Activity of the tested example compounds is provided in **Table 6** as follows:

+++ = IC₅₀ 1-500 nM; ++ = IC₅₀ >500-2000 nM; + = IC₅₀ >2000-15000 nM.

Table 6

Example number	HEK-ATF4 Activity
2	+
4	+++
5	+
6	+
8	+++
9	+
10	+
11	+++
12	+++
13	+++
14	+
15	+
16	+
17	+
18	+++
19	+

20	+
21	+++
22	+++
23	++
24	+++
25	++
26	+
27	++
28	+
29	+
30	++
31	+++
33	++
34	++
35	++
36	+++
37	+++
38	++
39	+++
40	+++
41	+++
42	+++
43	++
44	+
45	+
46	+
47	++
49	+++
51	+++
52	+++
53	+++
54	++

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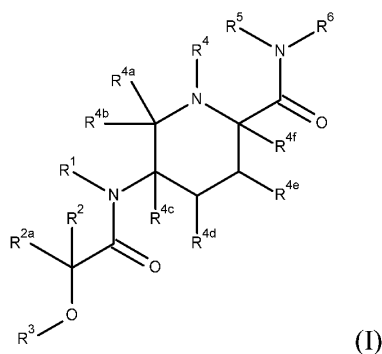
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Patent Claims

1. A compound of formula (I)



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

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

R² is H, F or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more halogen, which are the same or different;

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

R³ is phenyl or 6 membered aromatic heterocyclyl, wherein R³ is optionally substituted with one or more R⁷, which are the same or different;

R⁷ is halogen, CN, C(O)OR⁸, OR⁸, C(O)R⁸, C(O)N(R^{8a}R^{8b}), S(O)₂N(R^{8a}R^{8b}), S(O)N(R^{8a}R^{8b}), S(O)₂R⁸, S(O)R⁸, N(R⁸)S(O)₂N(R^{8a}R^{8b}), SR⁸, N(R^{8a}R^{8b}), NO₂, OC(O)R⁸, N(R⁸)C(O)R^{8a}, N(R⁸)S(O)₂R^{8a}, N(R⁸)S(O)R^{8a}, N(R⁸)C(O)OR^{8a}, N(R⁸)C(O)N(R^{8a}R^{8b}), OC(O)N(R^{8a}R^{8b}), C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are optionally substituted with one or more R⁹, 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;

5 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 $OC(O)N(R^{10}R^{10a})$;

10 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.

15 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- 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

20 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;

25 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

30 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;

R¹², R^{12a} are independently selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl and A², wherein C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are optionally substituted with one or more R¹⁵, which are the same or different;

5

R¹³ is halogen, OR¹⁴, CN or A²;

R¹⁴ is H or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more halogen, which are the same or different;

10

R¹⁵ is halogen, CN, OR¹⁴, OA² or A²;

A¹ is 3 to 7 membered heterocyclyl or 7 to 12 membered heterobicyclyl, wherein A¹ is optionally substituted with one or more R¹⁶, which are the same or different;

15

A² is phenyl, naphthyl, C₃₋₇ cycloalkyl, C₄₋₁₂ bicycloalkyl, 3 to 7 membered heterocyclyl or 7 to 12 membered heterobicyclyl, wherein A² is optionally substituted with one or more R^{16a}, which are the same or different;

20

R¹⁶, R^{16a} are independently selected from the group consisting of R¹⁷, OH, OR¹⁷, halogen and CN;

R¹⁷ is cyclopropyl, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein R¹⁷ is optionally substituted with one or more R¹⁸, which are the same or different;

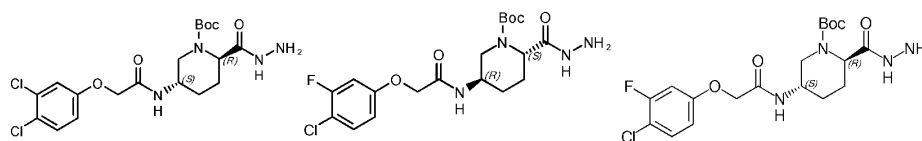
25

R¹⁸ is halogen, CN or OR¹⁹;

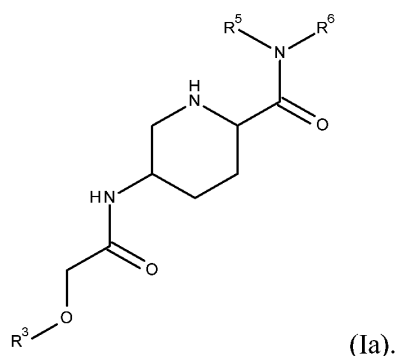
R¹⁹ is H or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more halogen, which are the same or different;

30

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 $CH_2CH_2OCH_3$;
5 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
10 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,
15 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.
20
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)



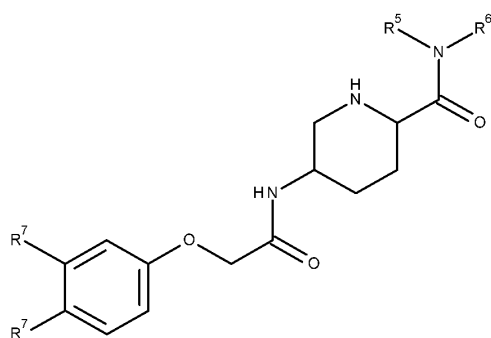
7. The compound of any one of claims 1 to 6 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^3 is phenyl or pyridyl, preferably phenyl, wherein R^3 is optionally substituted with one or more R^7 , which are the same or different.

5

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.

- 10 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 , $\text{CH}=\text{O}$, CH_2OH or CH_3 ; preferably R^7 is CF_3 , F or Cl, more preferably F or Cl.

- 15 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)



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

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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.

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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_{1-6} alkyl

or C₁₋₆ alkenyl, wherein C₁₋₆ alkyl and C₁₋₆ alkenyl are substituted with one or more R¹³, 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 R⁶ is R¹¹ and R¹¹ is C₁₋₆ alkyl, preferably ethyl or n-propyl, wherein C₁₋₆ alkyl is substituted with one R¹³.
14. The compound of any one of claims 1 to 13 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R⁶ is R¹¹ and R¹¹ is ethyl or n-propyl, each substituted with one R¹³, wherein R¹³ is OR¹⁴, preferably OCF₃.
15. The compound of any one of claims 1 to 12 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R⁶ is R¹¹ and R¹¹ is C₁₋₆ alkyl, preferably n-propyl or n-pentyl, wherein C₁₋₆ alkyl is substituted with three F; more preferably R¹¹ 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 R⁶ is R¹¹ and R¹¹ is C₁₋₆ alkyl, preferably methyl, wherein C₁₋₆ alkyl is substituted with one R¹³, wherein R¹³ is A², 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 R⁶ is R¹¹ and R¹¹ is A², 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 A² 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 CH₃, CHF₂, CF₃, CH₂CF₃, OCHF₂, OCH₂CF₃, OCF₃, OCH₃, 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 R⁵ and R⁶ are joined to form together with the nitrogen atom to which they are attached a ring A¹.

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21. The compound of claim 20, wherein A¹ is azetidine, piperidine, oxazepane, indoline, isoindoline, tetrahydroisoquinoline azabicyclo[3.1.0]hexane or azaspiro[3.3]heptane and wherein A¹ is optionally substituted with one or more R¹⁶, which are the same or different.

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22. The compound of claim 20 or 21 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A¹ is unsubstituted or substituted with one R¹⁶.

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23. The compound of any one of claims 20 to 22 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R¹⁶ is CF₃, OCF₃ or OCH₂CH₂OCF₃.

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24. The compound of any one of claims 1 to 23 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R¹, R², R^{2a}, R³, R⁴, R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f}, R⁵, R⁶ in formula (I) are selected to give

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

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

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(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;
5 (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;
10 (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;
15 (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;
20 (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;
25 (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;
30 (2*R*,5*S*)-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;
5 (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-
10 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;
15 (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-
20 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;
25 (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-
30 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*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-[[2-(trifluoromethoxy)ethoxy]carbamoyl}piperidine-1-carboxylate;

- tert*-butyl (2*S*,5*R*)-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;
- 5 *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;
- 10 *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;
- 15 *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;
- 20 *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;
- 25 *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;
- 30 *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;

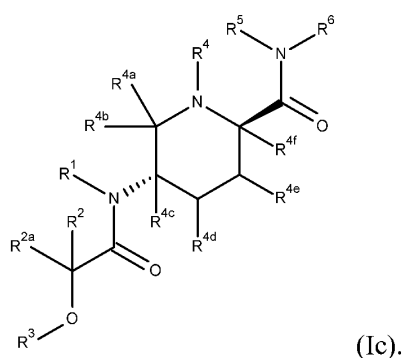
- tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2- {[5-methyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl]carbamoyl} piperidine-1-carboxylate;
- tert*-butyl (2*R*,5*S*)-5-[2-(4-chloro-3-fluorophenoxy)acetamido]-2- {[1*s*,3*s*]-3-(trifluoromethoxy)cyclobutyl]carbamoyl} piperidine-1-carboxylate;
- 5 *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;
- 10 *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;
- 15 *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
- 20 *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;
- 25 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;
- 30 (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;
5 (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;
10 *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;
15 (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;
20 *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;
25 *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;
30 *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.

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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)



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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. 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 for use in a method of treating or preventing of one or more diseases or disorders associated with integrated stress response.
29. 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 for use in a method of treating or preventing of one or more diseases or disorders selected from the group consisting of leukodystrophies, intellectual

5 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.