

TEAD INHIBITORS

Technical field

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The present invention relates to therapeutically active compounds useful in the inhibition of transcriptional enhancer associate domain (TEAD), and to pharmaceutical compositions containing such compounds. The compounds are useful in the treatment of diseases or disorders associated with increased TEAD activity or TEAD expression, such as various cancers and chronic pain.

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Background of the invention

TEA domain transcription factors (TEAD1-4) is a family of DNA binding transcription factors which regulate the expression of genes involved in cell proliferation, cell fate, cell differentiation, organ overgrowth and organ regeneration. YAP and TAZ are TEAD transcriptional co-activators which can shuttle between the cytoplasm and the nucleus. Altered actin dynamics and the Hippo signalling pathway promote YAP and TAZ phosphorylation, cytoplasmic retention and proteasomal degradation, consequently leading to low YAP and TAZ nuclear levels and TEAD transcriptional activity.

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The evolutionarily conserved Hippo signalling pathway is consisting of the large tumor suppressor 1/2 (LATS1/2), the serine/threonine kinases, sterile 20-like kinase 1/2 (MST1/2), and the adaptor proteins Salvador homolog 1 (SAV1) and MOB kinase activator 1A/B (MOB1A/B). The tumor suppressor neurofibromin 2 (NF2) (also known as Merlin) participates upstream of these kinases to inhibit YAP and TAZ activity by promoting the activation of the pathway. The Hippo pathway has been linked to many aspects of tumorigenesis, including cell proliferation, cell differentiation, cancer metastasis and cancer therapy resistance. Therefore, dysregulation in Hippo pathway signalling has been shown to drive oncogenesis across various cancer types. It has also been reported that YAP and TAZ are core mechanisms underlying the pathogenesis of chronic pain, such as chronic neuropathic pain and chronic musculoskeletal pain.

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Compounds with TEAD inhibition activity have been disclosed, for example, in WO 2020/081572, WO 2020/070181 and WO 2020051099. Anti-tumor effects of a TEAD inhibitor, K-975, *in vivo* on malignant pleural mesothelioma has been reported in Am J Cancer Res, 2020; 10(12): 4399-4415.

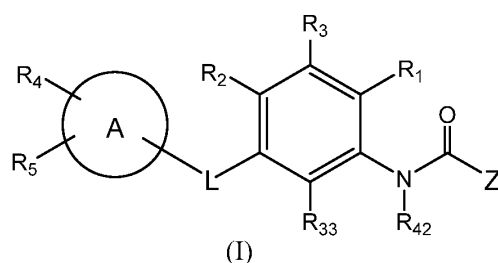
There is a need for compounds targeting diseases associated with dysregulation in the Hippo pathway components, for example compounds targeting the YAP-TEAD interaction. Such compounds would be useful for the treatment of diseases or conditions wherein inhibition of TEAD is desired, such as chronic pain including neuropathic pain and various cancers including cancers which are resistant to other treatments, such as chemotherapy, immunotherapy and targeted therapies.

Summary of the invention

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It has been found that compounds of formula (I) are potent inhibitors of YAP-TEAD interaction. The compounds are therefore useful for the treatment of conditions and diseases where inhibition of TEAD is desired. Such conditions and diseases include, but are not limited to, chronic pain, particularly chronic neuropathic pain and chronic musculoskeletal pain, and cancers, particularly cancers associated with dysregulation in the Hippo pathway components including YAP-TEAD. Particular cancers include, but are not restricted to, mesothelioma, squamous cell carcinomas, gynaecological cancers, bladder cancer, gastric cancer, liver cancer, lung cancer and colon cancer.

25 The present invention relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof



wherein

A is pyridyl, tetrahydropyranyl, a 4-10 membered carbocyclic ring;

L is -O-, -S-, -NH-, -C₁₋₇ alkyl-, -C₂₋₇ alkenyl-, -C₁₋₇ alkyl-O-, -O-C₁₋₇ alkyl- or -NH-C₁₋₇ alkyl-;

R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxyl, cyano, -C(O)NR₃₆R₃₇,
 5 or an optionally substituted 5-6 membered heterocyclic ring having 1-3 heteroatoms as ring atoms independently selected from O, S and N;

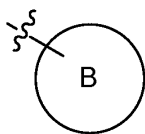
R₂ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy or halogen;

R₃ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, halogen C₁₋₇ alkyl or cyano, or
 R₁ and R₃ together with the carbon atoms to which they are attached form an optionally
 10 substituted 5-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

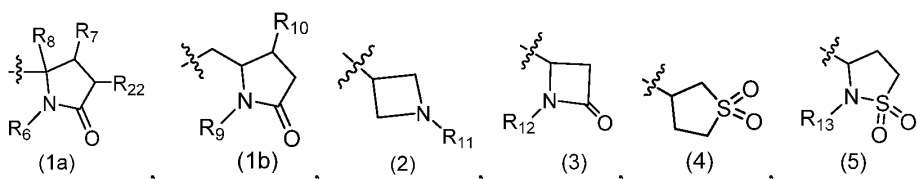
R₄ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, halogen C₁₋₇ alkyl,
 halogen C₁₋₇ alkoxy, cyano or C₁₋₇ alkylcarbonyl;

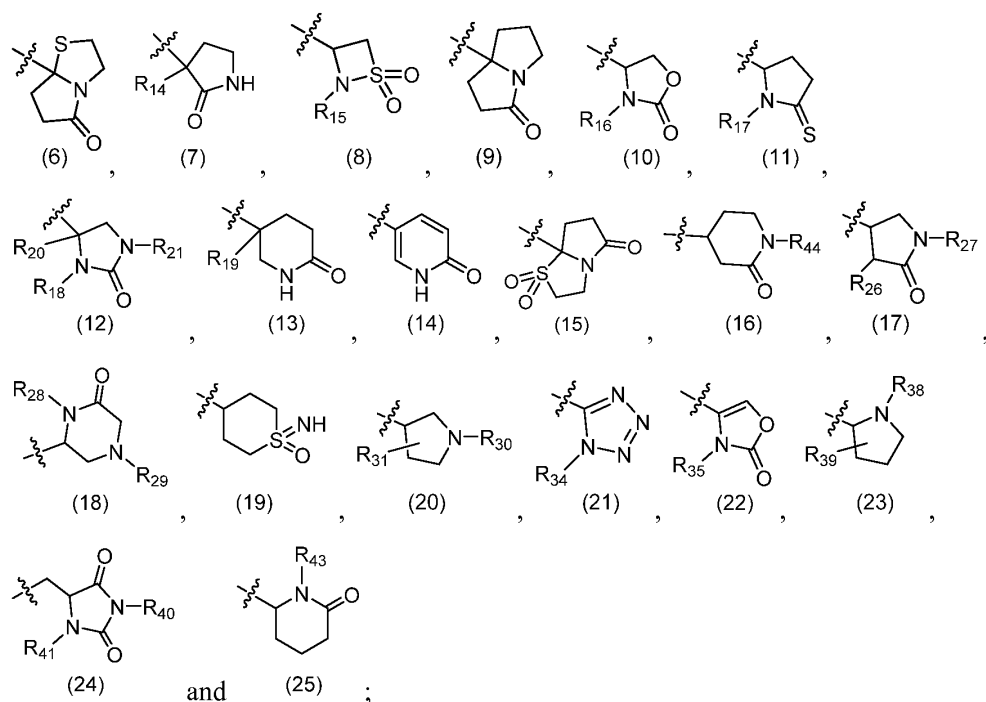
R₅ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, nitro, amino, hydroxyl, halogen
 15 C₁₋₇ alkyl, halogen C₁₋₇ alkoxy, or R₄ and R₅ together with the carbon atoms to which they are attached form an optionally substituted 5-6 membered ring having 1-3 heteroatoms as ring atoms independently selected from O, S and N;

Z is -CH(NHR₂₅)-(CH₂)₂-COOH or a group of formula



20 wherein B is any one of the following groups





5 provided that

when B is ring (2), then L is -O- or -O-C₁₋₇ alkyl-, and R₁ is C₁₋₇ alkoxy;

when B is ring (3), then L is -O-;

when B is ring (4), then L is -O- and R₁ is C₁₋₇ alkoxy;

10 when B is ring (20), (21), (23), (25) or (26), then L is -O- and R₁ is C₁₋₇ alkoxy;

when L is -C₁₋₇ alkyl-O-, then R₁ is C₁₋₇ alkoxy or R₁ and R₃ together with the carbon atoms to which they are attached form an optionally substituted 5-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

15 when A is a 4-, 5-, 7-, 8-, 9- or 10-membered carbocyclic ring, then R₁ is C₁₋₇ alkoxy;

R₆ and R₉ are, independently, hydrogen, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₇ alkyl, -C(O)-R_x, C₁₋₇ alkoxy C₁₋₇ alkyl, C₁₋₇ alkoxycarbonyl C₁₋₇ alkyl, -SO₂C₁₋₇ alkyl, -C₁₋₇ alkyl-C(O)-NR₂₃R₂₄ or an optionally substituted 4-6 membered ring
20 having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

R_X is C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₁₋₇ alkoxy C₁₋₇ alkyl, C₁₋₇ alkyl-NR₃₆R₃₇, or an optionally substituted 4-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

R₇, R₈, R₁₀, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂ and R₂₆ are,
 5 independently, hydrogen, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, hydroxyl, C₁₋₇ alkoxy or C₁₋₇ alkylcarbonyl;

R₁₁ is hydrogen, C₁₋₇ alkyl, halogen C₁₋₇ alkyl or C₁₋₇ alkylcarbonyl;

R₂₃, R₂₄, R₂₇, R₂₈, R₂₉, R₃₁, R₃₂, R₃₃, R₃₄, R₃₅, R₃₆, R₃₇, R₄₀, R₄₁, R₄₂, R₄₃, R₄₄, and R₄₅ are, independently, hydrogen, or C₁₋₇ alkyl;

10 R₂₅ is C₁₋₇ alkyl;

R₃₀ is C₁₋₇ alkyl, C₁₋₇ alkylcarbonyl or -SO₂C₁₋₇ alkyl;

R₃₈ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkylcarbonyl, C₁₋₇ alkoxy C₁₋₇ alkylcarbonyl or -C₁₋₇ alkyl-C(O)-NR₂₃R₂₄;

R₃₉ is hydrogen, C₁₋₇ alkyl or hydroxyl;

15 wherein optional substitution, in each occurrence, is 1-2 substituents independently selected from C₁₋₇ alkyl, halogen, halogen C₁₋₇ alkyl, C₁₋₇ alkoxy and oxo; with the proviso that compound of formula (I) is not

N-[2-Methyl-3-(phenoxy)methyl]phenyl]-5-oxo-2-pyrrolidinecarboxamide;

20 N-[5-[(3-Fluorophenoxy)methyl]-2-methoxyphenyl]-1-methyl-5-oxo-2-pyrrolidinecarboxamide;

N-[3-[(4-Chlorophenyl)methyl]phenyl]-5-oxo-2-pyrrolidinecarboxamide;

N-[3-[(Cyclohexyloxy)methyl]phenyl]-1-methyl-5-oxo-2-pyrrolidine-carboxamide;

25 N-[4-Methyl-3-[(4-methyl-2-pyridinyl)oxy]phenyl]-5-oxo-2-pyrrolidine-carboxamide;

N-[3-(Cyclopentylamino)phenyl]-1-methyl-5-oxo-2-pyrrolidinecarboxamide;

N-[3-[(3-Methylcyclohexyl)oxy]methyl]phenyl]-6-oxo-3-piperidine-carboxamide;

1-Ethyl-5-oxo-N-(3-phenoxyphenyl)-3-pyrrolidinecarboxamide;

30 N-[5-[(3-Fluorophenoxy)methyl]-2-methoxyphenyl]-2-pyrrolidinecarboxamide;

1-(1-Ethylpropyl)-N-[5-[(3-fluorophenoxy)methyl]-2-methoxyphenyl]-5-oxo-3-pyrrolidinecarboxamide;

N-[3-[(4-Chlorophenyl)methyl]phenyl]-1,6-dihydro-6-oxo-3-pyridine-carboxamide;

1,6-Dihydro-*N*-[4-methoxy-3-(phenylmethyl)phenyl]-6-oxo-3-pyridine-carboxamide;

5 1,6-Dihydro-6-oxo-*N*-[3-[2-(2-pyridinyl)ethenyl]phenyl]-3-pyridinecarboxamide;

N-[3-[(3-Fluorophenoxy)methyl]phenyl]-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxamide;

10 1-Methyl-*N*-[2-methyl-3-(phenoxyethyl)phenyl]-5-oxo-3-pyrrolidine-carboxamide;

N-[3-[(1,3-Benzodioxol-5-yl)oxy]methyl]phenyl]-1-(2-methylpropyl)-5-oxo-3-pyrrolidinecarboxamide;

1,6-Dihydro-*N*-[3-[[3-(methylcyclohexyl)oxy]methyl]phenyl]-6-oxo-3-pyridine-carboxamide;

15 *N*-[3-[(Cyclohexyloxy)methyl]phenyl]-1-ethyl-5-oxo-3-pyrrolidinecarboxamide;

1-Methyl-*N*-[3-[[3-(methylcyclohexyl)oxy]methyl]phenyl]-5-oxo-3-pyrrolidine-carboxamide;

2,3-Dihydro-3-methyl-*N*-[3-[[3-(methylcyclohexyl)oxy]methyl]phenyl]-2-oxo-1*H*-imidazole-4-carboxamide;

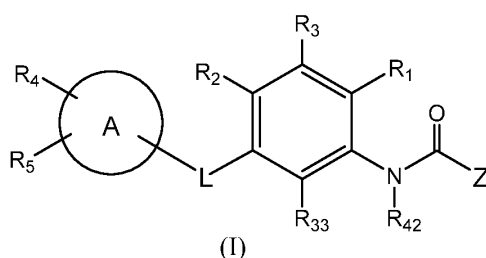
20 2,3-Dihydro-1,3-dimethyl-*N*-[3-[[3-(methylcyclohexyl)oxy]methyl]phenyl]-2-oxo-1*H*-imidazole-4-carboxamide;

1-Ethyl-*N*-[4-methoxy-3-(4-pyridinylmethoxy)phenyl]-5-oxo-3-pyrrolidine-carboxamide;

25 *N*-[4-Methoxy-3-(4-methoxyphenoxy)phenyl]-1-(2-methylpropyl)-5-oxo-3-pyrrolidinecarboxamide or

6-Oxo-*N*-(3-phenoxyphenyl)-2-piperazinecarboxamide.

According to one embodiment, the invention provides a method for the treatment of a disease or condition wherein inhibition of TEAD is desired comprising
30 administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof



wherein

A is pyridyl, tetrahydropyranyl, a 4-10 membered carbocyclic ring;

L is -O-, -S-, -NH-, -C₁₋₇ alkyl-, -C₂₋₇ alkenyl-, -C₁₋₇ alkyl-O-, -O-C₁₋₇ alkyl- or
 5 -NH-C₁₋₇ alkyl-;

R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxyl, cyano, -C(O)NR₃₆R₃₇,
 or an optionally substituted 5-6 membered heterocyclic ring having 1-3 heteroatoms as
 ring atoms independently selected from O, S and N;

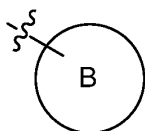
R₂ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy or halogen;

10 R₃ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, halogen C₁₋₇ alkyl or cyano, or
 R₁ and R₃ together with the carbon atoms to which they are attached form an optionally
 substituted 5-6 membered ring having 0-3 heteroatoms as ring atoms independently
 selected from O, S and N;

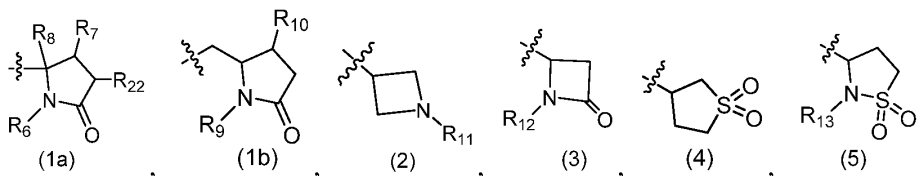
R₄ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, halogen C₁₋₇ alkyl,
 15 halogen C₁₋₇ alkoxy, cyano or C₁₋₇ alkylcarbonyl;

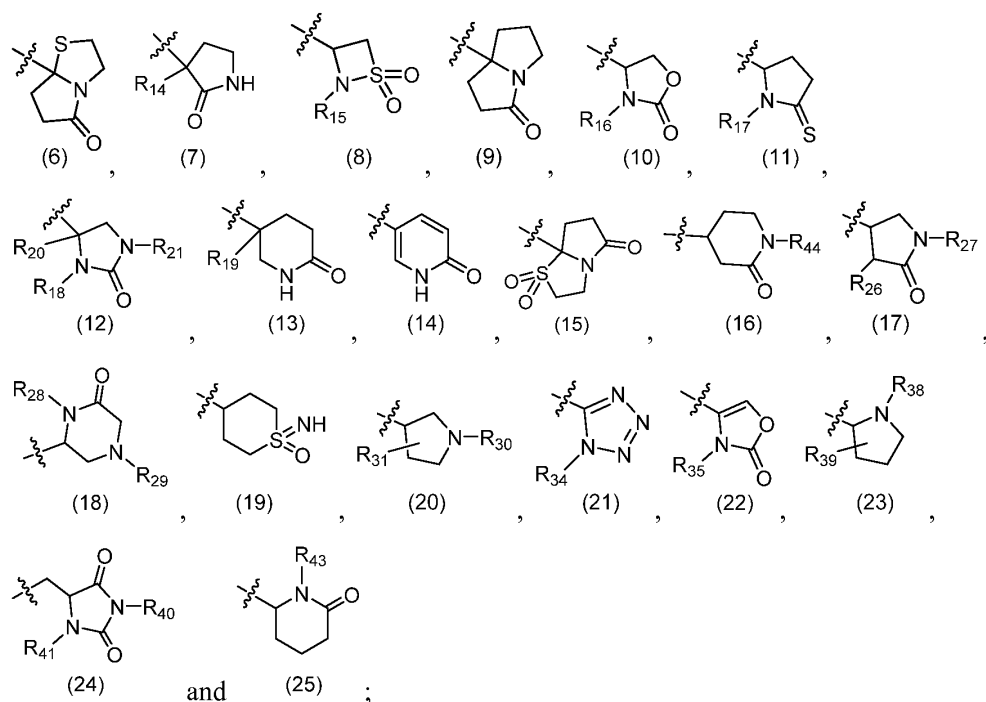
R₅ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, nitro, amino, hydroxyl, halogen
 C₁₋₇ alkyl, halogen C₁₋₇ alkoxy, or R₄ and R₅ together with the carbon atoms to which
 they are attached form an optionally substituted 5-6 membered ring having 1-3
 heteroatoms as ring atoms independently selected from O, S and N;

20 Z is -CH(NHR₂₅)-(CH₂)₂-COOH or a group of formula



wherein B is any one of the following groups





5 provided that

when B is ring (2), then L is -O- or -O-C₁₋₇ alkyl-, and R₁ is C₁₋₇ alkoxy;

when B is ring (3), then L is -O-;

when B is ring (4), then L is -O- and R₁ is C₁₋₇ alkoxy;

10 when B is ring (20), (21), (23), (25) or (26), then L is -O- and R₁ is C₁₋₇ alkoxy;

when L is -C₁₋₇ alkyl-O-, then R₁ is C₁₋₇ alkoxy or R₁ and R₃ together with the carbon atoms to which they are attached form an optionally substituted 5-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

15 when A is a 4-, 5-, 7-, 8-, 9- or 10-membered carbocyclic ring, then R₁ is C₁₋₇ alkoxy;

R₆ and R₉ are, independently, hydrogen, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₇ alkyl, -C(O)-R_x, C₁₋₇ alkoxy C₁₋₇ alkyl, C₁₋₇ alkoxycarbonyl C₁₋₇ alkyl, -SO₂C₁₋₇ alkyl, -C₁₋₇ alkyl-C(O)-NR₂₃R₂₄ or an optionally substituted 4-6 membered ring
20 having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

R_X is C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₁₋₇ alkoxy C₁₋₇ alkyl, C₁₋₇ alkyl-NR₃₆R₃₇, or an optionally substituted 4-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

R₇, R₈, R₁₀, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂ and R₂₆ are,
5 independently, hydrogen, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, hydroxyl, C₁₋₇ alkoxy or C₁₋₇ alkylcarbonyl;

R₁₁ is hydrogen, C₁₋₇ alkyl, halogen C₁₋₇ alkyl or C₁₋₇ alkylcarbonyl;

R₂₃, R₂₄, R₂₇, R₂₈, R₂₉, R₃₁, R₃₂, R₃₃, R₃₄, R₃₅, R₃₆, R₃₇, R₄₀, R₄₁, R₄₂, R₄₃, R₄₄, and R₄₅ are, independently, hydrogen, or C₁₋₇ alkyl;

10 R₂₅ is C₁₋₇ alkyl;

R₃₀ is C₁₋₇ alkyl, C₁₋₇ alkylcarbonyl or -SO₂C₁₋₇ alkyl;

R₃₈ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkylcarbonyl, C₁₋₇ alkoxy C₁₋₇ alkylcarbonyl or -C₁₋₇ alkyl-C(O)-NR₂₃R₂₄;

R₃₉ is hydrogen, C₁₋₇ alkyl or hydroxyl;

15 wherein optional substitution, in each occurrence, is 1-2 substituents independently selected from C₁₋₇ alkyl, halogen, halogen C₁₋₇ alkyl, C₁₋₇ alkoxy and oxo.

According to one embodiment, the disease or condition wherein inhibition of TEAD is desired is cancer, for example mesothelioma, squamous cell carcinoma, a
20 gynaecological cancer, bladder cancer, gastric cancer, liver cancer, lung cancer and colon cancer.

According to one embodiment, the disease or condition wherein inhibition of TEAD is desired is chronic pain, for example chronic neuropathic pain and chronic
25 musculoskeletal pain.

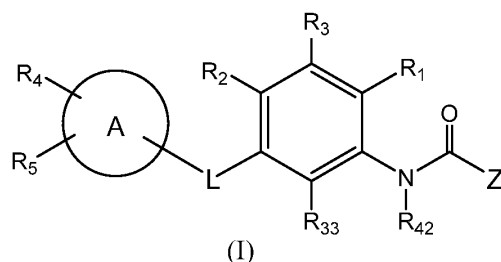
According to one embodiment, the invention provides a pharmaceutical composition comprising a compound of formula (I) together with a pharmaceutically acceptable carrier.

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Detailed description of the invention

The present application provides novel compounds of formula (I) or pharmaceutically acceptable salts thereof which are useful as TEAD inhibitors.

One of the embodiments of the present invention provides a compound of
 5 formula (I) or a pharmaceutically acceptable salt thereof



wherein

A is pyridyl, tetrahydropyranyl, a 4-10 membered carbocyclic ring;

L is -O-, -S-, -NH-, -C₁₋₇ alkyl-, -C₂₋₇ alkenyl-, -C₁₋₇ alkyl-O-, -O-C₁₋₇ alkyl- or
 10 -NH-C₁₋₇ alkyl-;

R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxyl, cyano, -C(O)NR₃₆R₃₇, or an optionally substituted 5-6 membered heterocyclic ring having 1-3 heteroatoms as ring atoms independently selected from O, S and N;

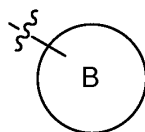
R₂ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy or halogen;

15 R₃ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, halogen C₁₋₇ alkyl or cyano, or R₁ and R₃ together with the carbon atoms to which they are attached form an optionally substituted 5-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

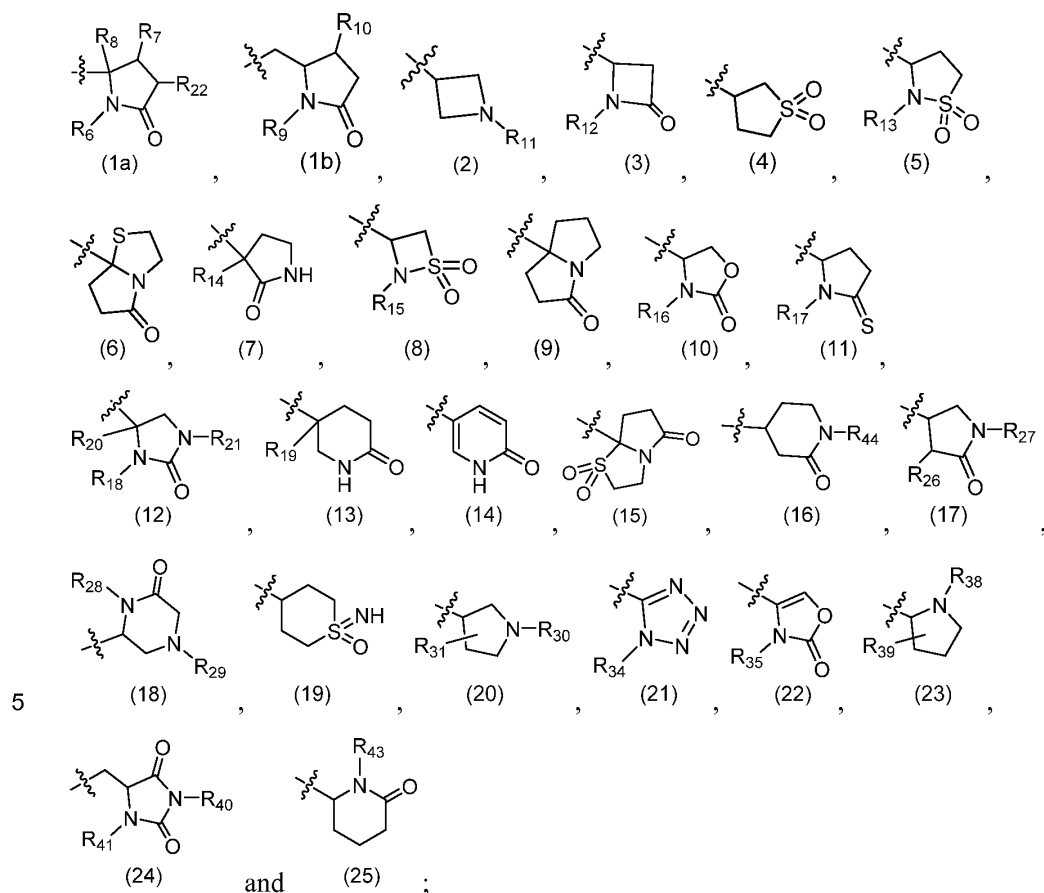
20 R₄ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, halogen C₁₋₇ alkyl, halogen C₁₋₇ alkoxy, cyano or C₁₋₇ alkylcarbonyl;

R₅ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, nitro, amino, hydroxyl, halogen C₁₋₇ alkyl, halogen C₁₋₇ alkoxy, or R₄ and R₅ together with the carbon atoms to which they are attached form an optionally substituted 5-6 membered ring having 1-3 heteroatoms as ring atoms independently selected from O, S and N;

25 Z is -CH(NHR₂₅)-(CH₂)₂-COOH or a group of formula



wherein B is any one of the following groups



provided that

when B is ring (2), then L is -O- or -O-C₁₋₇ alkyl-, and R₁ is C₁₋₇ alkoxy;

when B is ring (3), then L is -O-;

when B is ring (4), then L is -O- and R₁ is C₁₋₇ alkoxy;

when B is ring (20), (21), (23), (25) or (26), then L is -O- and R₁ is C₁₋₇ alkoxy;

when L is -C₁₋₇ alkyl-O-, then R₁ is C₁₋₇ alkoxy or R₁ and R₃ together with the carbon atoms to which they are attached form an optionally substituted 5-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

when A is a 4-, 5-, 7-, 8-, 9- or 10-membered carbocyclic ring, then R₁ is C₁₋₇ alkoxy;

R₆ and R₉ are, independently, hydrogen, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₇ alkyl, -C(O)-R_X, C₁₋₇ alkoxy C₁₋₇ alkyl, C₁₋₇ alkoxycarbonyl C₁₋₇ alkyl, -SO₂C₁₋₇ alkyl, -C₁₋₇ alkyl-C(O)-NR₂₃R₂₄ or an optionally substituted 4-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

- 5 R_X is C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₁₋₇ alkoxy C₁₋₇ alkyl, C₁₋₇ alkyl-NR₃₆R₃₇, or an optionally substituted 4-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

- R₇, R₈, R₁₀, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂ and R₂₆ are, independently, hydrogen, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, hydroxyl, C₁₋₇ alkoxy or C₁₋₇ alkylcarbonyl;

R₁₁ is hydrogen, C₁₋₇ alkyl, halogen C₁₋₇ alkyl or C₁₋₇ alkylcarbonyl;

R₂₃, R₂₄, R₂₇, R₂₈, R₂₉, R₃₁, R₃₂, R₃₃, R₃₄, R₃₅, R₃₆, R₃₇, R₄₀, R₄₁, R₄₂, R₄₃, R₄₄, and R₄₅ are, independently, hydrogen, or C₁₋₇ alkyl;

R₂₅ is C₁₋₇ alkyl;

- 15 R₃₀ is C₁₋₇ alkyl, C₁₋₇ alkylcarbonyl or -SO₂C₁₋₇ alkyl;

R₃₈ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkylcarbonyl, C₁₋₇ alkoxy C₁₋₇ alkylcarbonyl or -C₁₋₇ alkyl-C(O)-NR₂₃R₂₄;

R₃₉ is hydrogen, C₁₋₇ alkyl or hydroxyl;

wherein optional substitution, in each occurrence, is 1-2 substituents

- 20 independently selected from C₁₋₇ alkyl, halogen, halogen C₁₋₇ alkyl, C₁₋₇ alkoxy and oxo; with the proviso that compound of formula (I) is not

N-[2-Methyl-3-(phenoxy)methyl]phenyl]-5-oxo-2-pyrrolidinecarboxamide;

N-[5-[(3-Fluorophenoxy)methyl]-2-methoxyphenyl]-1-methyl-5-oxo-2-pyrrolidinecarboxamide;

- 25 N-[3-[(4-Chlorophenyl)methyl]phenyl]-5-oxo-2-pyrrolidinecarboxamide;

N-[3-[(Cyclohexyloxy)methyl]phenyl]-1-methyl-5-oxo-2-pyrrolidinecarboxamide;

N-[4-Methyl-3-[(4-methyl-2-pyridinyl)oxy]phenyl]-5-oxo-2-pyrrolidinecarboxamide;

- 30 N-[3-(Cyclopentylamino)phenyl]-1-methyl-5-oxo-2-pyrrolidinecarboxamide;

N-[3-[(3-Methylcyclohexyl)oxy]methyl]phenyl]-6-oxo-3-piperidinecarboxamide;

1-Ethyl-5-oxo-N-(3-phenoxyphenyl)-3-pyrrolidinecarboxamide;

- N*-[5-[(3-Fluorophenoxy)methyl]-2-methoxyphenyl]-2-pyrrolidinecarboxamide;
 1-(1-Ethylpropyl)-*N*-[5-[(3-fluorophenoxy)methyl]-2-methoxyphenyl]-5-oxo-3-pyrrolidinecarboxamide;
N-[3-[(4-Chlorophenyl)methyl]phenyl]-1,6-dihydro-6-oxo-3-pyridine-
 5 carboxamide;
 1,6-Dihydro-*N*-[4-methoxy-3-(phenylmethyl)phenyl]-6-oxo-3-pyridine-
 carboxamide;
 1,6-Dihydro-6-oxo-*N*-[3-[2-(2-pyridinyl)ethenyl]phenyl]-3-
 pyridinecarboxamide;
 10 *N*-[3-[(3-Fluorophenoxy)methyl]phenyl]-2,3-dihydro-2-oxo-1*H*-imidazole-4-
 carboxamide;
 1-Methyl-*N*-[2-methyl-3-(phenoxyethyl)phenyl]-5-oxo-3-pyrrolidine-
 carboxamide;
N-[3-[(1,3-Benzodioxol-5-yloxy)methyl]phenyl]-1-(2-methylpropyl)-5-oxo-3-
 15 pyrrolidinecarboxamide;
 1,6-Dihydro-*N*-[3-[(3-methylcyclohexyl)oxy]methyl]phenyl]-6-oxo-3-pyridine-
 carboxamide;
N-[3-[(Cyclohexyloxy)methyl]phenyl]-1-ethyl-5-oxo-3-pyrrolidinecarboxamide;
 1-Methyl-*N*-[3-[(3-methylcyclohexyl)oxy]methyl]phenyl]-5-oxo-3-pyrrolidine-
 20 carboxamide;
 2,3-Dihydro-3-methyl-*N*-[3-[(3-methylcyclohexyl)oxy]methyl]phenyl]-2-oxo-
 1*H*-imidazole-4-carboxamide;
 2,3-Dihydro-1,3-dimethyl-*N*-[3-[(3-methylcyclohexyl)oxy]methyl]phenyl]-2-
 oxo-1*H*-imidazole-4-carboxamide;
 25 1-Ethyl-*N*-[4-methoxy-3-(4-pyridinylmethoxy)phenyl]-5-oxo-3-pyrrolidine-
 carboxamide;
N-[4-Methoxy-3-(4-methoxyphenoxy)phenyl]-1-(2-methylpropyl)-5-oxo-3-
 pyrrolidinecarboxamide or
 6-Oxo-*N*-(3-phenoxyphenyl)-2-piperazinecarboxamide.

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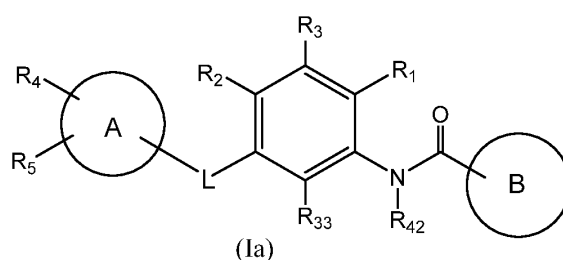
It is to be understood that the left bond of variants of linker L is attached to the ring A of formula (I) and the right bond to the phenyl group. The wavy line in variants of group B denotes the site of attachment to carboxamide group.

According to one embodiment, specifically provided is a compound according to formula (I) wherein A is phenyl, pyridyl or cyclohexyl. In a subgroup of the preceding embodiment, A is phenyl or cyclohexyl. In still another subgroup A is phenyl or
 5 pyridyl. In still another subgroup A is phenyl. In still another subgroup A is cyclohexyl. In still another subgroup A is pyridyl.

According to yet one embodiment, specifically provided are compounds according to any of the above embodiments wherein R₄₂ is hydrogen.

10

According to one embodiment, specifically provided are compounds according to formula (Ia) or a pharmaceutically acceptable salt thereof



wherein A, L, B, R₁, R₂, R₃, R₄, R₅, R₃₃ and R₄₂ are as defined above.

15

According to yet one embodiment, specifically provided are compounds according to any of the above embodiments wherein B is ring (1a), (3), (4), (6), (8), (9), (10), (11), (12), (13), (16), (17) or (18). In a subgroup of the preceding embodiment, B is ring (1a), (4), (10), (11), (12), (13), (16) or (17). In still another subgroup B is ring
 20 (1a), (10), (11) or (12). In still another subgroup B is ring (1a) or (12). In still another subgroup B is ring (1a). In still another subgroup B is ring (12).

In a subgroup of compounds wherein B is ring (1a) are compounds wherein R₇ and R₈ are hydrogen. In still another subgroup of the preceding embodiment are
 25 compounds wherein R₆ is hydrogen, C₁₋₇ alkyl or C₃₋₇ cycloalkyl. According to another subgroup are compounds wherein R₆ is -C(O)-R_x, wherein R_x is C₁₋₇ alkyl or an optionally substituted 4-6 membered ring having 1-3 heteroatoms as ring atoms independently selected from O, S and N. Particular examples of such rings are

pyrrolidine and azetidine rings optionally substituted by 1-2 substituents independently selected from C₁₋₇ alkyl and oxo.

In a subgroup of compounds wherein B is ring (12) are compounds wherein R₂₀
5 is hydrogen and R₁₈ is C₁₋₇ alkyl or C₃₋₇ cycloalkyl. In still another subgroup of the preceding embodiment are compounds wherein R₂₁ is hydrogen or C₁₋₇ alkyl.

According to yet one embodiment, specifically provided are compounds according to any of the above embodiments wherein L is -O-, -S-, -NH-, -C₁₋₇ alkyl-,
10 -C₂₋₇ alkenyl-, -C₁₋₇ alkyl-O-, or -O-C₁₋₇ alkyl-. In a subgroup of the preceding embodiment are compounds wherein L is -O-, -C₂₋₇ alkenyl-, -C₁₋₇ alkyl-O-, or -O-C₁₋₇ alkyl-. In a subgroup of the preceding embodiment are compounds wherein L is -O-, -C₂₋₇ alkenyl- or -O-C₁₋₇ alkyl-. In still another subgroup L is -O- or -C₂₋₇ alkenyl-. In still another subgroup L is -O-. A particular example of L being C₁₋₇ alkyl is -CH₂-
15 group. A particular example of L being -C₂₋₇ alkenyl- is -CH=CH- group. A particular example of L being -C₁₋₇ alkyl-O- is -CH₂-O- group. A particular example of L being -O-C₁₋₇ alkyl- is -O-CH₂- group.

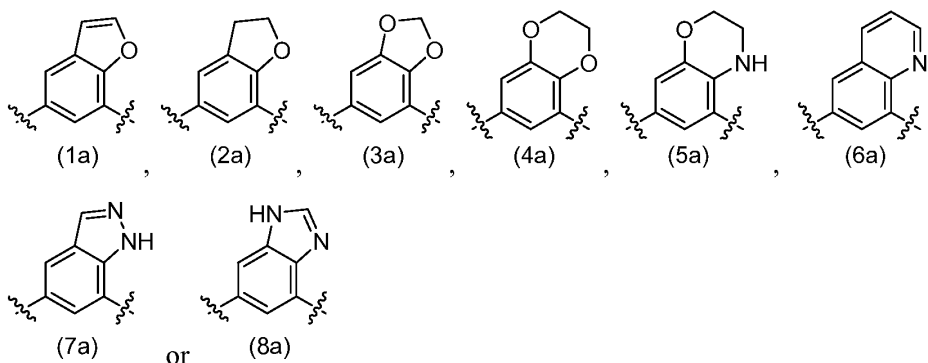
According to one embodiment, specifically provided are compounds according
20 to any of the above embodiments wherein R₁ is hydrogen, C₁₋₇ alkoxy or halogen. In a subgroup of the preceding embodiment are compounds wherein R₁ is C₁₋₇ alkoxy or halogen. In a subgroup of the preceding embodiment are compounds wherein R₁ is C₁₋₇ alkoxy, particularly a methoxy group. According to one embodiment, R₁ is an optionally substituted 5-6 membered heterocyclic ring having 1-3 heteroatoms as ring
25 atoms independently selected from O, S and N. Particular examples of such rings include oxadiazolyl and pyrazolyl rings optionally substituted by 1-2 C₁₋₇ alkyl or oxo substituents.

According to one embodiment, specifically provided are compounds according
30 to any of the above embodiments wherein R₂ is hydrogen, C₁₋₇ alkoxy or halogen. In a subgroup of the preceding embodiment are compounds wherein R₂ is hydrogen or halogen. In a subgroup of the preceding embodiment are compounds wherein R₂ is hydrogen.

According to one embodiment, specifically provided are compounds according to any of the above embodiments wherein R_3 is hydrogen, halogen or C_{1-7} alkoxy. In a subgroup are compounds wherein R_3 is hydrogen or C_{1-7} alkoxy. In a subgroup are
 5 compounds wherein R_3 is hydrogen.

According to one embodiment, specifically provided are compounds according to any of the above embodiments wherein R_1 and R_3 together with the carbon atoms to which they are attached form an optionally substituted 5-6 membered ring having 0-3
 10 heteroatoms as ring atoms independently selected from O, S and N. In a subgroup are compounds wherein R_1 and R_3 together with the carbon atoms to which they are attached form a 5-6 membered ring having 1-2 heteroatoms as ring atoms independently selected from O and N. In a subgroup are compounds wherein R_1 and R_3 together with the carbon atoms to which they are attached form a 5-6 membered ring having 1-2
 15 heteroatoms wherein the heteroatom is O. Particular examples of such rings are furanyl, dihydrofuranyl, tetrahydrofuranyl, dioxanyl, dioxolanyl, oxazinyl, pyridinyl, 2,3-dihydro-1,4-dioxinyl, 2,3-dihydro-1,4-oxazinyl rings optionally substituted by 1-2 substituents independently selected from C_{1-7} alkyl and oxo.

20 According to one embodiment, specifically provided are compounds according to any of the above embodiments wherein R_1 and R_3 together with the phenyl ring to which they are attached form an optionally substituted fused ring represented by any of the following groups:



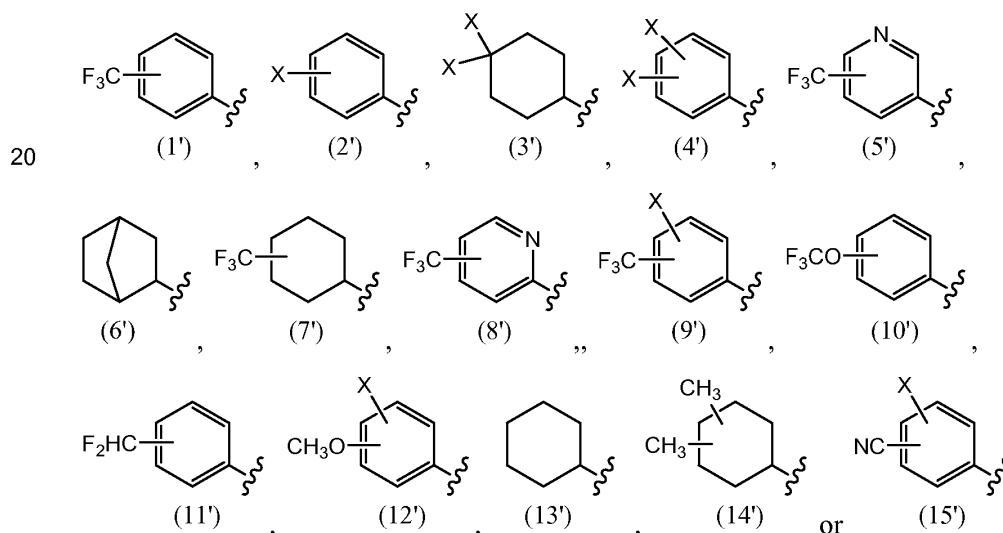
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wherein the left wavy line denotes the site of attachment to the L group and the right wavy line denotes the site of attachment to the carboxamide group. The optional

substitution may be 1-2 substituents independently selected from C₁₋₇ alkyl, halogen, halogen C₁₋₇ alkyl, C₁₋₇ alkoxy and oxo, in particular C₁₋₇ alkyl or oxo.

- According to one embodiment, specifically provided are compounds according
- 5 to any of the above embodiments wherein R₄ is hydrogen, halogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen C₁₋₇ alkyl or halogen C₁₋₇ alkoxy, and R₅ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, cyano, amino or halogen. In a subgroup are compounds wherein R₄ is halogen, C₁₋₇ alkyl, halogen C₁₋₇ alkyl or halogen C₁₋₇ alkoxy and R₅ is hydrogen, C₁₋₇ alkyl, cyano or halogen. In a subgroup are compounds wherein R₄ is halogen C₁₋₇ alkyl or
- 10 halogen C₁₋₇ alkoxy and R₅ is hydrogen or halogen. In a subgroup are compounds wherein R₄ is halogen C₁₋₇ alkyl or halogen C₁₋₇ alkoxy and R₅ is hydrogen. In another subgroup are compounds wherein both R₄ and R₅ are C₁₋₇ alkyl, for example methyl. In another subgroup are compounds wherein both R₄ and R₅ are halogen, for example fluoro. Particular examples of R₄ being halogen C₁₋₇ alkyl is -CF₃ and -CHF₂ groups. A
- 15 particular example of R₄ being halogen C₁₋₇ alkoxy is -OCF₃ group.

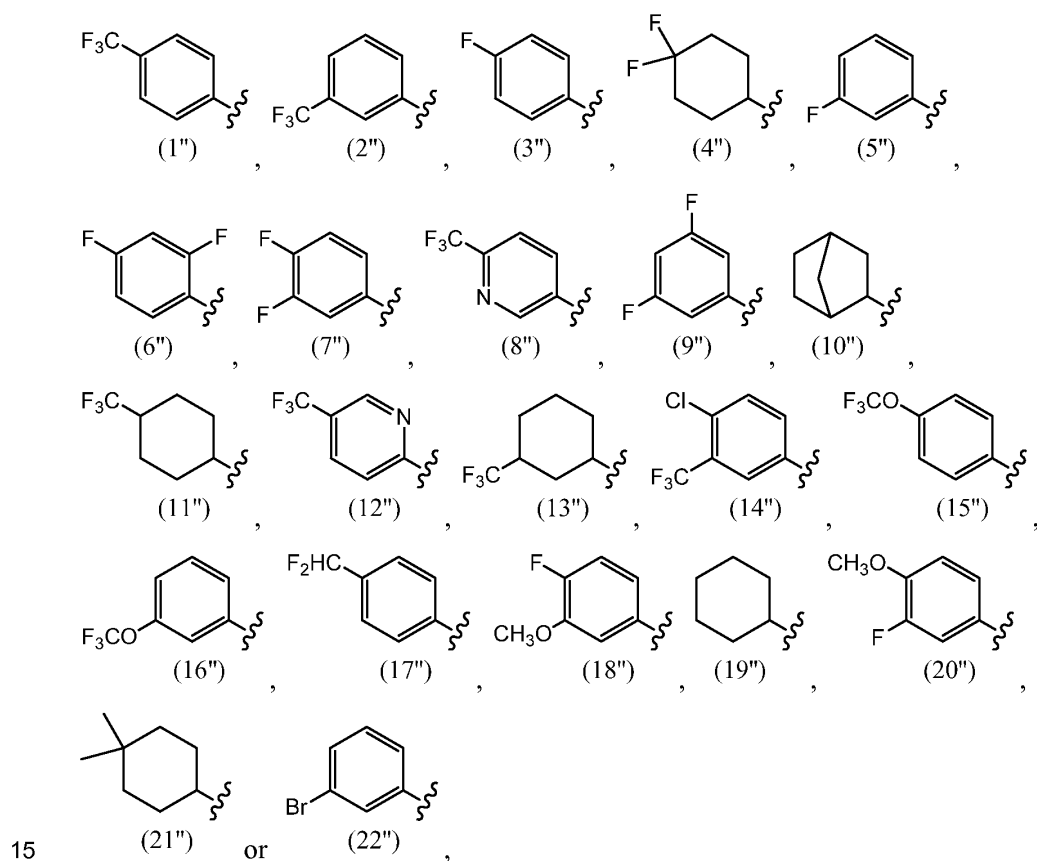
According to one embodiment, specifically provided are compounds according to any of the above embodiments wherein ring A together with R₄ and R₅ represent any of the following groups:



wherein X is halogen and the wavy line denotes the site of attachment to the L group.

- According to one embodiment, specifically provided is a compound according to any of the above embodiments wherein A together with R₄ and R₅ is group (1'), (2'), (3'), (4'), (7'), (8'), (10'), (11') or (13'). In a subgroup are provided a compound
- 5 according to any of the above embodiments wherein A together with R₄ and R₅ is group (1'), (4'), (7'), (8'), (10') or (11').

- According to one embodiment, specifically provided are compounds according to any of the above embodiments wherein ring A together with R₄ and R₅ are
- 10 represented by following groups:



wherein the wavy line denotes the site of attachment to the L group.

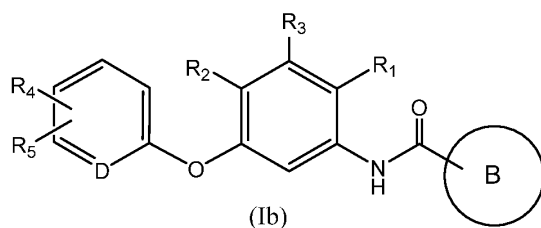
According to one embodiment, specifically provided is a compound according to any of the above embodiments wherein A together with R₄ and R₅ is group (1''), (2''),

(3''), (4''), (7''), (11''), (12''), (13''), (15''), (17''), (19'') or (21''). In a subgroup are provided a compound according to any of the above embodiments wherein A together with R₄ and R₅ is group (1''), (2''), (4''), (7''), (11''), (12''), (15'') or (21'').

5 According to one embodiment, specifically provided is a compound according to any of the above embodiments wherein A is phenyl or pyridyl, L is -O-, R₁ is C₁₋₇ alkoxy, R₂, R₃, R₅, R₃₃ and R₄₂ are hydrogen, Z is ring (1a) or (12) and R₄ is halogen C₁₋₇ alkyl.

10 According to one embodiment, specifically provided are compounds according to any of the above embodiments wherein Z can also be -CH(NHR₂₅)-(CH₂)₂-COOH.

According to one embodiment, specifically provided are compounds according to formula (Ib) or a pharmaceutically acceptable salt thereof



15

wherein

D is CH or N;

R₂ is H or halogen;

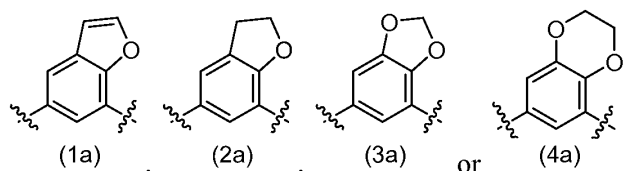
R₄ is H, halogen or cyano;

20

R₅ is halogen or halogen C₁₋₇ alkyl;

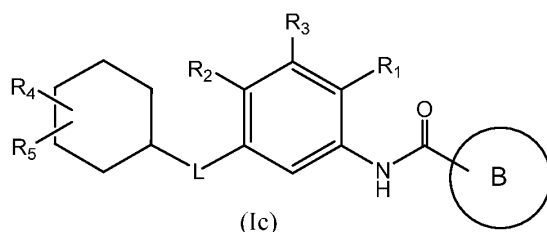
B is ring (1a), (10) or (12);

R₁ is -OCH₃ or halogen, or R₁ and R₃ together with the phenyl ring to which they are attached form a fused ring represented by any of the following groups:



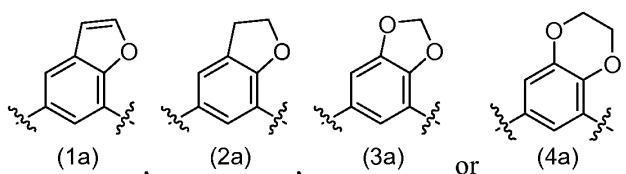
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According to one embodiment, specifically provided are compounds according to formula (Ic) or a pharmaceutically acceptable salt thereof



wherein

- 5 L is -O- or -CH=CH-;
 R₂ is H or halogen;
 R₄ is H, C₁₋₇ alkyl or halogen;
 R₅ is halogen, C₁₋₇ alkyl or halogen C₁₋₇ alkyl;
 B is ring (1a), (10) or (12);
 10 R₁ is -OCH₃ or halogen, or R₁ and R₃ together with the phenyl ring to which they are attached form a fused ring represented by any of the following groups:



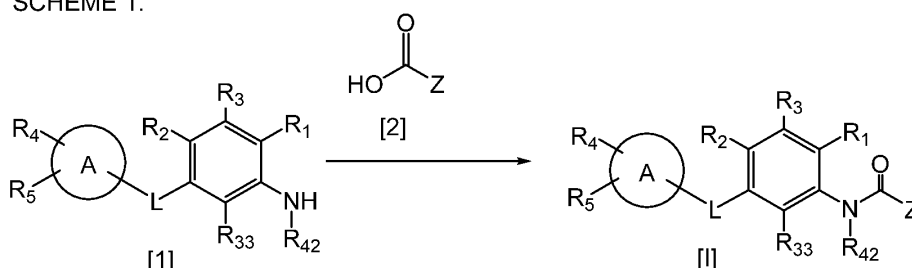
- 15 According to still one embodiment, the present invention provides a method for the treatment of a disease or condition wherein inhibition of TEAD is desired, such as cancer and chronic pain, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) as defined in any of the above embodiments.

- 20 The compounds of the invention can be prepared by a variety of synthetic routes analogously to the methods known in the literature using suitable starting materials. The compounds according to formula (I) can be prepared e.g. analogously or according to the following reaction Schemes. Some compounds included in the formula (I) can be obtained by converting the functional groups of the other compounds of formula (I)
 25 obtained in accordance with the following Schemes, by well known reaction steps such

as oxidation, reduction, hydrolysis, acylation, alkylation, amidation, amination, sulfonation and others. It should be noted that any appropriate leaving groups, e.g. N-protecting groups, such as a t-butoxycarbonyl (t-BOC) group or a phenylsulfonyl group, can be used in well known manner during the syntheses in order to improve the selectivity of the reaction steps.

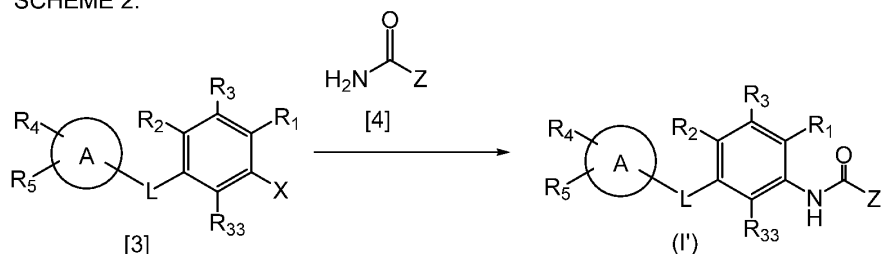
Compounds of formula (I) can be prepared, for example, according to Scheme 1, wherein A, L, Z, R₁, R₂, R₃, R₄, R₅, R₃₃ and R₄₂ are as defined above. In the method of Scheme 1, the aniline compound of formula [1] is coupled with a carboxylic acid derivative of formula [2] in a suitable solvent, such as anhydrous acetonitrile or DMF, in the presence of a suitable coupling reagent such as a combination of N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate and 1-methyl-1H-imidazole, or hexafluorophosphate azabenzotriazole tetramethyl uranium (HATU) and N,N-diisopropylethylamine (DIPEA) to produce a compound of formula (I).

SCHEME 1.



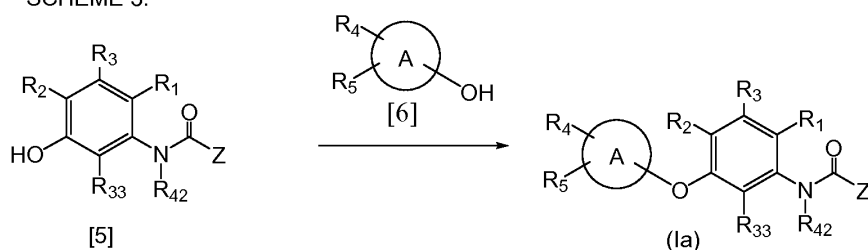
Alternatively, compounds of formula (I), wherein R₄₂ is H, can be prepared according to Scheme 2, wherein A, L, Z, R₁, R₂, R₃, R₄, R₅ and R₃₃ are as defined above and X is a halogen, for example bromo. In the method of Scheme 2, the compound of formula [3] is coupled with a carboxamide compound of formula [4] in a suitable solvent, such as toluene, in the presence a base, such as cesium carbonate, and a suitable catalyst system such as a combination Pd₂(dba) and 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos), or copper iodide and N1,N2-dimethylcyclohexane-1,2-diamine, to produce a compound of formula (I).

SCHEME 2.



Compounds of formula (I) wherein L is $-O-$ can also be prepared, for example, according to Scheme 3, wherein A , Z , R_1 , R_2 , R_3 , R_4 and R_5 are as defined above. In the method of Scheme 3, the compound of formula [3] is condensed with a compound of formula [4] in a suitable solvent, such as tetrahydrofuran, in the presence of Mitsunobu reagents, such as triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD), to produce a compound of formula (I).

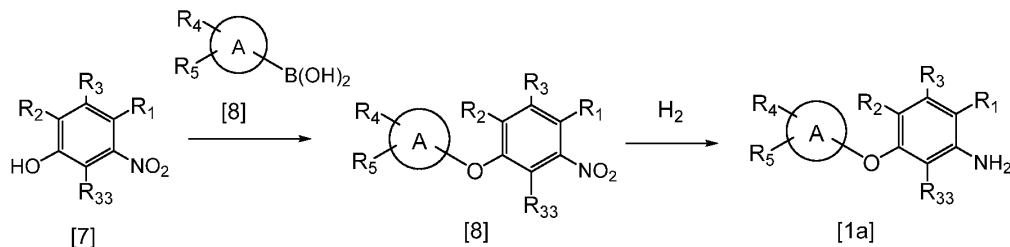
SCHEME 3.



Intermediate compounds can be prepared according to the methods disclosed in the literature or as disclosed in the present disclosure.

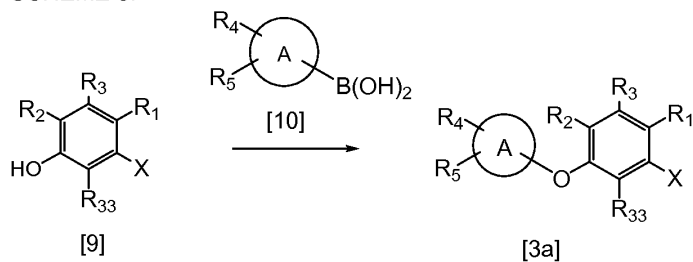
For example, intermediate compounds of formula [1a], wherein L is $-O-$, can be prepared according to Scheme 4, wherein A , R_1 , R_2 , R_3 , R_4 , R_5 and R_{33} are as defined above. In the method of Scheme 4, a compound of formula [7] is coupled with a compound of formula [8] in a suitable solvent such as dichloromethane, in the presence of a base such as pyridine and a catalyst such as diacetoxy copper to produce a compound of formula [8], which can be subsequently reduced, for example, by hydrogenation in the presence of suitable catalyst such as palladium-in-carbon to obtain the intermediate of formula [1a].

SCHEME 4.



- Intermediate compounds of formula [3a] wherein L is -O-, can be prepared, for example, according to Scheme 5, wherein A, R₁, R₂, R₃, R₄, R₅ and R₃₃ are as defined above and X is a halogen, for example bromo. In the method of Scheme 5, a compound of formula [9] is coupled with a compound of formula [10] in a suitable solvent such as dichloromethane, in the presence of a base such as pyridine and a catalyst such as diacetoxy copper to produce a compound of formula [3a],

SCHEME 5.

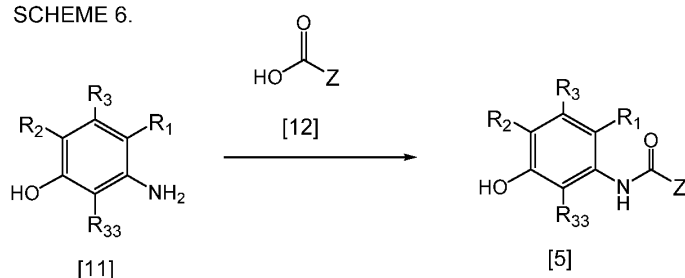


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- Intermediate compounds of formula [5] can be prepared, for example, according to Scheme 6, wherein Z, R₁, R₂ and R₃ are as defined above. In the method of Scheme 6, a compound of formula [11] is coupled with a compound of formula [12] in a suitable solvent such as DMF in the presence of a base such as *N,N*-diisopropylethylamine (DIPEA) and a coupling agent such as hexafluorophosphate azabenzotriazole tetramethyl uranium (HATU) to produce the intermediate of formula [5].

15

SCHEME 6.



Alternatively, the compounds of formula (I) can be prepared as disclosed in the specific Examples of the present disclosure.

5

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in art to which the subject matter herein belongs. As used herein, the following definitions are supplied in order to facilitate the understanding of the present invention.

10

The term “subject”, as employed herein, refers to humans and animals.

The term “halo” or “halogen”, as employed herein as such or as part of another group, refers to chlorine, bromine, fluorine or iodine. Preferred halogens are chlorine and fluorine.

15

The term “ C_{1-7} alkyl”, as employed herein as such or as part of another group, refers to a straight or branched chain saturated hydrocarbon group having 1, 2, 3, 4, 5, 6 or 7 carbon atom(s). Representative examples of C_{1-7} alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl and *n*-hexyl. One preferred embodiment of “ C_{1-7} alkyl” is C_{1-3} alkyl. The term “ C_{1-3} alkyl” refers to an embodiment of “ C_{1-7} alkyl” having 1, 2 or 3 carbon atoms. Examples of “ C_{1-3} alkyl” include, but are not limited to, methyl, ethyl, *n*-propyl and *iso*-propyl. One preferred “ C_{1-7} alkyl” is methyl group.

20

The term “ C_{2-7} alkenyl”, as employed herein as such or as part of another group, refers to an aliphatic hydrocarbon group having 2, 3, 4, 5, 6 or 7 carbon atoms and

25

containing one or several double bonds. Representative examples include, but are not limited to, ethenyl, propenyl and hexenyl. One preferred embodiment of “C₂₋₇ alkenyl” is C₂₋₄ alkenyl. The term “C₂₋₄ alkenyl” refers to an embodiment of “C₂₋₇ alkenyl” having 2, 3 or 4 carbon atoms. Representative examples include, but are not limited to, ethenyl, propenyl and butenyl. One preferred “C₂₋₇ alkenyl” is -CH=CH- group.

The term “C₃₋₇ cycloalkyl”, as employed herein as such or as part of another group, refers to a saturated cyclic hydrocarbon group containing 3, 4, 5, 6 or 7 carbon atoms. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. One preferred “C₃₋₇ cycloalkyl” is cyclopropyl group.

The term “hydroxy”, as employed herein as such or as part of another group, refers to an -OH group.

15

The term “cyano”, as employed herein as such or as part of another group, refers to a -CN group.

The term “carboxy”, as employed herein as such or as part of another group, refers to -COOH group.

20

The term “carbonyl”, as employed herein as such or as part of another group, refers to a carbon atom double-bonded to an oxygen atom (C=O).

The term “oxo”, as employed herein as such or as part of another group, refers to oxygen atom linked to another atom by a double bond (=O).

25

The term “C₁₋₇ alkoxy”, as employed herein as such or as part of another group, refers to C₁₋₇ alkyl, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of C₁₋₇ alkoxy include, but are not limited to methoxy, ethoxy, propoxy, butoxy, isobutoxy, *sec*-butoxy and *tert*-butoxy. One preferred embodiment of “C₁₋₇ alkoxy” is C₁₋₃ alkoxy. The term “C₁₋₃ alkoxy” refers to an embodiment of “C₁₋₇ alkoxy” having 1, 2 or 3 carbon atoms. Representative

30

examples of C₁₋₃ alkoxy include, but are not limited to methoxy, ethoxy, propoxy. One preferred "C₁₋₇ alkoxy" group is methoxy.

5 The term "hydroxy C₁₋₇ alkyl", as employed herein, refers to at least one hydroxy group, as defined herein, appended to the parent molecular moiety through a C₁₋₇ alkyl group, as defined herein. Representative examples of hydroxy C₁₋₇ alkyl include, but are not limited to, hydroxymethyl, 2,2-dihydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 1-hydroxypropyl, 1-methyl-1-hydroxyethyl and 1-methyl-1-hydroxypropyl.

10 The term "halogen C₁₋₇ alkyl", as employed herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through a C₁₋₇ alkyl group, as defined herein. Representative examples of halogen C₁₋₇ alkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-chloroethyl and 3-bromopropyl. Preferred "halogen C₁₋₇ alkyl" groups are trifluoromethyl and difluoromethyl.

15 The term "halogen C₁₋₇ alkoxy", as employed herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through a C₁₋₇ alkoxy group, as defined herein.

20 The term "C₁₋₇ alkoxy C₁₋₇ alkyl", as employed herein as such or as part of another group, refers to at least one C₁₋₇ alkoxy group, as defined herein, appended to the parent molecular moiety through a C₁₋₇ alkyl group, as defined herein.

25 The term "4-10 membered carbocyclic ring", as employed herein, refers to a saturated, partially saturated or aromatic ring with 4 to 10 ring atoms consisting of carbon atoms only. One embodiment of a "4-10 membered carbocyclic ring" is a "5-6 membered carbocyclic ring" which refers to a saturated, partially saturated or aromatic ring with 5 to 6 ring atoms consisting of carbon atoms only. Representative examples of a 4-10 membered carbocyclic ring include, but are not limited to, phenyl, cyclohexyl, 30 cyclohexenyl, cyclopentyl, cyclopentenyl and cyclobutyl rings.

The term "substituted" as used herein in connection with various residues refers to, if not otherwise defined, to halogen substituents, such as fluorine, chlorine, bromine,

iodine, or C₁₋₇ alkyl, C₃₋₇ cycloalkyl, hydroxy, amino, nitro, cyano, thiol C₁₋₇ alkyl, methylsulfonyl, C₁₋₇ alkoxy, halo C₁₋₇ alkyl, hydroxy C₁₋₇ alkyl or amino C₁₋₇ alkyl substituents. Preferred are halogen, C₁₋₇ alkyl, hydroxy, amino, halo C₁₋₇ alkyl, C₁₋₇ alkoxy and methylsulfonyl substituents. In one group of preferred substituents are 1-2
5 substituents selected from C₁₋₇ alkyl or halogen substituents, particularly C₁₋₃ alkyl or halogen substituents, particularly methyl, ethyl, chloro, fluoro or bromo substituents.

The "substituted" groups may contain 1 to 3, preferably 1 or 2, of the above mentioned substituents, if not otherwise defined.

10

Optically active enantiomers or diastereomers of compounds of formula (I) can be prepared e.g. by resolution of the racemic end product by known methods or by using suitable optically active starting materials. Similarly, racemic compounds of formula (I) can be prepared by using racemic starting materials. Resolution of racemic
15 compounds of formula (I) or a racemic starting material thereof can be carried out, for example, by converting the racemic compound into its diastereomeric salt mixture by reaction with an optically active acid and subsequent separation of the diastereomers by crystallization. Representative examples of said optically active acids include, but are not limited to, D-tartaric acid and dibenzoyl-D-tartaric acid. Alternatively, preparative
20 chiral chromatography may be used for resolution of the racemic mixture.

Pharmaceutically acceptable salts are well known in the field of pharmaceuticals. Non-limiting examples of suitable salts include metal salts, ammonium salts, salts with an organic base, salts with an inorganic acid, salts with organic acid, and salts with basic
25 or acidic amino acid. Non-limiting examples of metal salts include alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt, and magnesium salt. Non-limiting examples of salts with inorganic or organic acids include chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, methane sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates,
30 acetates, oxalates, fumarates, hemifumarates, and succinates. Pharmaceutically acceptable esters, when applicable, may be prepared by known methods using pharmaceutically acceptable acids that are conventional in the field of pharmaceuticals and that retain the pharmacological properties of the free form. Non-limiting examples

of these esters include esters of aliphatic or aromatic alcohols, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl esters. Phosphate esters and carbonate esters, are also within the scope of the invention.

5 The definition of formula (I) above is inclusive of all the possible isotopes and isomers, such as stereoisomers, of the compounds, including geometric isomers, for example *Z* and *E* isomers (*cis* and *trans* isomers), and optical isomers, e.g. diastereomers and enantiomers, and prodrug esters, e.g. phosphate esters and carbonate esters.

10

 It will be appreciated by those skilled in the art that the present compounds may contain at least one chiral center. Accordingly, the compounds may exist in optically active or racemic forms. It is to be understood that the formula (I) includes any racemic or optically active form, or mixtures thereof. In one embodiment, the compounds are the
15 pure (R)-isomers. In another embodiment, the compounds are the pure (S)-isomers. In another embodiment, the compounds are a mixture of the (R) and the (S) isomers. In another embodiment, the compounds are a racemic mixture comprising an equal amount of the (R) and the (S) isomers. The compounds may contain two chiral centers. In such case, according to one embodiment, the compounds are a mixture of diastereomers.
20 According to another embodiment, the compounds of the invention are a mixture of enantiomers. According to still another embodiment, the compounds are pure enantiomers. The individual isomers may be obtained using the corresponding isomeric forms of the starting material or they may be separated after the preparation of the end compound according to conventional separation methods. For the separation of optical
25 isomers, e.g. enantiomers or diastereomers, from the mixture thereof the conventional resolution methods, e.g. fractional crystallisation, may be used.

 The present compounds may also exist as tautomers or equilibrium mixtures thereof wherein a proton of a compound shifts from one atom to another. Examples of
30 tautomerism include, but are not limited to, amido-imido, keto-enol, phenol-keto, oxime-nitroso, nitro-aci, imine-enamine, annular tautomerism of heterocyclic rings such as pyrazole ring, and the like. Tautomeric forms are intended to be encompassed by compounds of formula (I), even though only one tautomeric form may be depicted.

- Examples of preferred compounds of one group of formula (I) include
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 1);
- 5 1-Acetyl-N-(5-(3-fluorophenoxy)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 2);
- 1-Acetyl-N-(5-((3-fluorophenoxy)methyl)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 3);
- N-(5-((3-Fluorophenoxy)methyl)-2,4-dimethoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 4);
- 10 1-(2-Fluoroethyl)-N-(5-((3-fluorophenoxy)methyl)-2-methoxyphenyl)azetidine-3-carboxamide (Compound 5);
- rac-(trans)-N-(5-((3-Fluorophenoxy)methyl)-2-methoxyphenyl)-3-methyl-5-oxopyrrolidine-2-carboxamide (Compound 6);
- 15 4-Oxo-N-(3-(3-(trifluoromethyl)phenoxy)phenyl)azetidine-2-carboxamide (Compound 7);
- N-(2-Methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)-4-oxoazetidine-2-carboxamide (Compound 8);
- N-(2-Methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)-2-(5-oxopyrrolidin-2-yl)acetamide (Compound 9);
- 20 N-(2-Methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 10);
- N-(2-Methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 11);
- 25 N-(2-Methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)tetrahydrothiophene-3-carboxamide 1,1-dioxide (Compound 12);
- N-(5-((3-Fluorophenoxy)methyl)-2-methoxyphenyl)-2-methylisothiazolidine-3-carboxamide 1,1-dioxide (Compound 13);
- N-(2-Methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)-2-methyl-5-oxopyrrolidine-2-carboxamide (Compound 14);
- 30 N-(5-(3-Fluorophenoxy)-2-methoxyphenyl)-2-methyl-5-oxopyrrolidine-2-carboxamide (Compound 15);

- 5-Oxo-N-(3-(3-(trifluoromethyl)phenoxy)phenyl) pyrrolidine-2-carboxamide (Compound 16);
- N-(5-((3-Fluorophenoxy)methyl)benzofuran-7-yl)-5-oxopyrrolidine-2-carboxamide (Compound 17);
- 5 N-(5-(3-Fluorophenoxy)-2-methoxyphenyl)-5-oxotetrahydropyrrolo[2,1-b]-thiazole-7a(5H)-carboxamide (Compound 18);
- N-(2-Methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)-5-oxotetrahydropyrrolo[2,1-b]thiazole-7a(5H)-carboxamide (Compound 19);
- 10 rac-(cis)-N-(5-((3-Fluorophenoxy)methyl)-2-methoxyphenyl)-3-methyl-5-oxopyrrolidine-2-carboxamide (Compound 20);
- (E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 21);
- (E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 22);
- 15 (E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide, enantiomer 1 (Compound 23);
- (E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide, enantiomer 1 (Compound 24);
- (R)-N-(5-(3-Fluorophenoxy)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 25);
- 20 N-(5-((3-Fluorophenoxy)methyl)-2-methoxyphenyl)-3-methyl-2-oxopyrrolidine-3-carboxamide (Compound 26);
- N-(6-((3-Fluorophenoxy)methyl)benzo[d][1,3]dioxol-4-yl)-5-oxopyrrolidine-2-carboxamide (Compound 27);
- 25 1-Methyl-5-oxo-N-(5-(3-(trifluoromethyl)phenoxy)benzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 28);
- 1-Acetyl-N-(2-methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 29);
- 1-Acetyl-N-(2-methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide, enantiomer 2 (Compound 30);
- 30 N-(5-((3-Fluorophenoxy)methyl)-2,3-dihydrobenzofuran-7-yl)-5-oxopyrrolidine-2-carboxamide (Compound 31);

- N-(5-((3-Fluorophenoxy)methyl)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide (Compound 32);
- 5-Oxo-N-(6-(3-(trifluoromethyl)phenoxy)benzo[d][1,3]dioxol-4-yl)pyrrolidine-2-carboxamide (Compound 33);
- 5 1-Methyl-5-oxo-N-(6-(3-(trifluoromethyl)phenoxy)benzo[d][1,3]dioxol-4-yl)-pyrrolidine-2-carboxamide (Compound 34);
- N-(3-Fluoro-5-((3-fluorophenoxy)methyl)-2-methoxyphenyl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide (Compound 35);
- N-(3-Fluoro-5-((3-fluorophenoxy)methyl)-2-methoxyphenyl)-5-oxopyrrolidine-10 2-carboxamide (Compound 36);
- 1-Ethyl-N-(2-methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 37);
- 1-(Cyclopropanecarbonyl)-N-(2-methoxy-5-(3-(trifluoromethyl)phenoxy)-phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 38);
- 15 1-Acetyl-N-(4-fluoro-2-methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 39);
- 1-Acetyl-N-(2-fluoro-5-(3-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 40);
- N-(2-Fluoro-5-(3-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-20 2-carboxamide (Compound 41);
- N-(5-(2,4-Difluorophenoxy)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 42);
- N-(5-(2,4-Difluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 43);
- 25 1-Acetyl-N-(5-(2,4-difluorophenoxy)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 44);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 45);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-30 carboxamide (Compound 46);
- 1-Acetyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-pyrrolidine-2-carboxamide (Compound 47);

N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 48);

N-(2-Methoxy-5-((3-(trifluoromethyl)phenoxy)methyl)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 49);

5 1-Acetyl-N-(2-methoxy-5-((3-(trifluoromethyl)phenoxy)methyl)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 50);

1-Acetyl-N-(2-methoxy-5-((3-(trifluoromethyl)benzyl)oxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 51);

10 N-(2-Methoxy-5-((3-(trifluoromethyl)benzyl)oxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 52);

N-(2-Methoxy-5-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 53);

N-(7-(3-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-isothiazolidine-3-carboxamide 1,1-dioxide (Compound 54);

15 5-Oxo-N-(7-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)pyrrolidine-2-carboxamide (Compound 55);

1-Acetyl-5-oxo-N-(7-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)pyrrolidine-2-carboxamide (Compound 56);

20 N-(7-((3-Fluorophenoxy)methyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-5-oxopyrrolidine-2-carboxamide (Compound 57);

N-(7-((3-Fluorophenoxy)methyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 58);

N-(5-(3,4-Difluorophenoxy)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 59);

25 N-(5-(3,4-Difluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 60);

N-(8-Methyl-7-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-5-oxopyrrolidine-2-carboxamide (Compound 61);

30 N-(2-Methoxy-5-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 62);

N-(2-Methoxy-5-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 63);

- (E)-N-(2-Methoxy-5-(2-(tetrahydro-2H-pyran-4-yl)vinyl)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 64);
- (E)-N-(2-Methoxy-5-(2-(tetrahydro-2H-pyran-4-yl)vinyl)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 65);
- 5 5-Oxo-N-(7-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)pyrrolidine-2-carboxamide (Compound 66);
- 1-Methyl-5-oxo-N-(7-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)pyrrolidine-2-carboxamide (Compound 67);
- 1-Ethyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 68);
- 10 (R)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 69);
- (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 70);
- 15 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-2-methyl-1,2-thiazetidine-3-carboxamide 1,1-dioxide (Compound 71);
- N-(2-Methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)-2-methyl-1,2-thiazetidine-3-carboxamide 1,1-dioxide (Compound 72);
- N-(4-Fluoro-5-((3-fluorophenoxy)methyl)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 73);
- 20 N-(2-Methoxy-5-((4-(trifluoromethyl)phenyl)amino)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 74);
- N-(2-Fluoro-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 75);
- 25 N-(2-Fluoro-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 76);
- 1-Acetyl-N-(5-(3,5-difluorophenoxy)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 77);
- N-(5-(3,5-Difluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 78);
- 30 N-(5-(2,5-Difluorophenoxy)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 79);

- 3-Oxo-N-(7-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)tetrahydro-1H-pyrrolizine-7a(5H)-carboxamide (Compound 80);
- 1-Isopropyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-pyrrolidine-2-carboxamide (Compound 81);
- 5 N-(5-(3,4-Difluorophenoxy)-2-methoxyphenyl)-1-isopropyl-5-oxopyrrolidine-2-carboxamide (Compound 82);
- N-(2-(1,3,4-Oxadiazol-2-yl)-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 83);
- N-(2-(1,3,4-Oxadiazol-2-yl)-5-(3-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 84);
- 10 N-(5-(3,4-Difluorophenoxy)-2-(1-methyl-1H-pyrazol-3-yl)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 85);
- N-(5-(3,4-Difluorophenoxy)-2-(1-methyl-1H-pyrazol-5-yl)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 86);
- 15 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxo-oxazolidine-4-carboxamide (Compound 87);
- N-(5-(3,4-Difluorophenoxy)-2-methoxyphenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 88);
- N-(5-((3,4-Difluorophenoxy)methyl)-2-methoxyphenyl)-3-methyl-2-oxo-oxazolidine-4-carboxamide (Compound 89);
- 20 N-(5-((3-Fluorophenoxy)methyl)-2-methoxyphenyl)-3-methyl-2-oxo-oxazolidine-4-carboxamide (Compound 90);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-thioxo-pyrrolidine-2-carboxamide (Compound 91);
- 25 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-thioxopyrrolidine-2-carboxamide (Compound 92);
- (R)-N-(5-(3,4-Difluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 93);
- (S)-N-(5-(3,4-Difluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 94);
- 30 N-(5-((3,4-Difluorophenoxy)methyl)-2-methoxyphenyl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide (Compound 95);

- N-(5-(Bicyclo[2.2.1]heptan-2-yloxy)-2-methoxyphenyl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide (Compound 96);
- (R)-N-(7-(3,4-Difluorophenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 97);
- 5 (S)-N-(7-(3,4-Difluorophenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 98);
- (R)-1-Methyl-5-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 99);
- (S)-N-(5-(3,4-Difluorophenoxy)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 100);
- 10 (R)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 101);
- (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 102);
- 15 (R)-N-(2-Methoxy-5-(((trans)-4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 103);
- N-(5-((4,4-Difluorocyclohexyl)oxy)-2-methoxyphenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 104);
- (S)-N-(2-Methoxy-5-(((trans)-4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 105);
- 20 1-Methyl-5-oxo-N-(3-oxo-7-(3-(trifluoromethyl)phenoxy)-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yl)pyrrolidine-2-carboxamide (Compound 106);
- (S)-1-Methyl-5-oxo-N-(5-(((cis)-4-(trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 107);
- 25 (R)-1-Methyl-5-oxo-N-(5-(((cis)-4-(trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 108);
- 1-Cyclopropyl-5-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 109);
- 1-Cyclopropyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 110);
- 30 1-Cyclopropyl-N-(5-(3,4-difluorophenoxy)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 111);

N-(2-Methoxy-5-((5-(trifluoromethoxy)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 112);

N-(7-(((4,4-Difluorocyclohexyl)oxy)methyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 113);

5 1-Cyclopropyl-5-oxo-N-(7-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)pyrrolidine-2-carboxamide (Compound 114);

N-(2-Methoxy-5-((5-(trifluoromethoxy)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 115);

10 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)tetrahydrothiophene-3-carboxamide 1,1-dioxide (Compound 116);

N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 117);

N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 118);

15 (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-6-oxopiperidine-3-carboxamide (Compound 119);

(R)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-6-oxopiperidine-3-carboxamide (Compound 120);

20 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-6-oxopiperidine-3-carboxamide (Compound 121);

N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (Compound 122);

N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3,4-dimethyl-2-oxoimidazolidine-4-carboxamide (Compound 123);

25 (R)-N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 124);

(S)-N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 125);

30 (R)-N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 126);

3-Ethyl-N-(2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-2-oxoimidazolidine-4-carboxamide (Compound 127);

- (R)-1-Cyclopropyl-N-(2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 128);
- (S)-1-Cyclopropyl-N-(2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 129);
- 5 (S)-N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 130);
- 3-Cyclopropyl-N-(2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-2-oxoimidazolidine-4-carboxamide (Compound 131);
- 1-(Cyclopropylmethyl)-N-(2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-phenyl)-5-oxopyrrolidine-2-carboxamide, enantiomer 1 (Compound 132);
- 10 1-(Cyclopropylmethyl)-N-(2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-phenyl)-5-oxopyrrolidine-2-carboxamide, enantiomer 2 (Compound 133);
- (R)-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1,2-dimethyl-5-oxopyrrolidine-2-carboxamide (Compound 134);
- 15 (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1,2-dimethyl-5-oxopyrrolidine-2-carboxamide (Compound 135);
- 1-(2-Amino-2-oxoethyl)-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 136);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-(1-methyl-1H-pyrazol-4-yl)-5-oxopyrrolidine-2-carboxamide (Compound 137);
- 20 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-1-(tetrahydrofuran-3-yl)pyrrolidine-2-carboxamide (Compound 138);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1,3-dimethyl-2-oxoimidazolidine-4-carboxamide (Compound 139);
- 25 (R)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 140);
- (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 141);
- 3-Acetyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-2-oxoimidazolidine-4-carboxamide (Compound 142);
- 30 (2S)-4-Methoxy-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 143);

N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-2-oxoimidazolidine-4-carboxamide (Compound 144);

N-(2-Methoxy-4-(4-(trifluoromethyl)phenoxy)phenyl)-1-(2-(methylamino)-2-oxoethyl)-5-oxopyrrolidine-2-carboxamide (Compound 145);

5 1-(2-(Dimethylamino)-2-oxoethyl)-N-(2-methoxy-4-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 146);

1-(Cyclopropylmethyl)-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide, enantiomer 1 (Compound 147);

10 1-(Cyclopropylmethyl)-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide, enantiomer 2 (Compound 148);

N-(5-(4-(Difluoromethyl)phenoxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 149);

(S)-1-Methyl-5-oxo-N-(5-(((trans)-4-(trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 150);

15 (R)-1-Methyl-5-oxo-N-(5-(((trans)-4-(trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 151);

N-(4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 152);

20 N-(4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 153);

(R)-N-(4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 154);

(R)-N-(4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 155);

25 (S)-N-(4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 156);

(S)-N-(4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 157);

30 N-(5-(2-Chloro-4-(trifluoromethyl)phenoxy)-4-fluoro-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 158);

3-Methyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)imidazolidine-4-carboxamide (Compound 159);

- 2-Oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)-piperidine-4-carboxamide (Compound 160);
- 6-Oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)piperidine-3-carboxamide (Compound 161);
- 5 (R)-1-Methyl-5-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 162);
- (S)-1-Methyl-5-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 163);
- 3-Cyclopropyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)imidazolidine-4-carboxamide (Compound 164);
- 10 (S)-1-Cyclopropyl-5-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 165);
- (R)-1-Cyclopropyl-5-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 166);
- 15 3-Ethyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)imidazolidine-4-carboxamide (Compound 167);
- (S)-3-Methyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)imidazolidine-4-carboxamide (Compound 168);
- (R)-3-Methyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)imidazolidine-4-carboxamide (Compound 169);
- 20 (R)-1-Ethyl-5-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 170);
- (S)-1-Ethyl-5-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 171);
- 25 (2R)-1-Methyl-N-(2-methyl-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)-5-oxopyrrolidine-2-carboxamide, enantiomer 1 (Compound 172);
- (2R)-1-Methyl-N-(2-methyl-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)-5-oxopyrrolidine-2-carboxamide, enantiomer 2 (Compound 173);
- 30 (S)-1-Methyl-5-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)chroman-8-yl)pyrrolidine-2-carboxamide (Compound 174);

- (R)-1-Methyl-5-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)chroman-8-yl)pyrrolidine-2-carboxamide (Compound 175);
- 3-Methyl-2-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)chroman-8-yl)-imidazolidine-4-carboxamide (Compound 176);
- 5 1-Methyl-5-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)chroman-8-yl)-pyrrolidine-2-carboxamide (Compound 177);
- 3-Methyl-2-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzo[d]-[1,3]dioxol-4-yl)imidazolidine-4-carboxamide (Compound 178);
- 1-Cyclopropyl-5-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzo[d]-[1,3]dioxol-4-yl)pyrrolidine-2-carboxamide (Compound 179);
- 10 (S)-3-Methyl-2-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzo[d][1,3]dioxol-4-yl)imidazolidine-4-carboxamide (Compound 180);
- (R)-3-Methyl-2-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzo[d][1,3]dioxol-4-yl)imidazolidine-4-carboxamide (Compound 181);
- 15 3-Methyl-2-oxo-N-(7-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzo-[b][1,4]dioxin-5-yl)imidazolidine-4-carboxamide (Compound 182);
- 3-Methyl-2-oxo-N-(7-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzo-[b][1,4]dioxin-5-yl)imidazolidine-4-carboxamide, enantiomer 1 (Compound 183);
- 3-Methyl-2-oxo-N-(7-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzo-[b][1,4]dioxin-5-yl)imidazolidine-4-carboxamide, enantiomer 2 (Compound 184);
- 20 1-Methyl-5-oxo-N-(5-(4-(trifluoromethyl)phenoxy)benzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 185);
- 3-Methyl-2-oxo-N-(6-(4-(trifluoromethyl)phenoxy)benzo[d][1,3]dioxol-4-yl)-imidazolidine-4-carboxamide (Compound 186);
- 25 2-Oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)-piperidine-4-carboxamide (Compound 187);
- 1-(2-(Methylamino)-2-oxoethyl)-5-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 188);
- 1-(2-Amino-2-oxoethyl)-5-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 189);
- 30 N-(5-((4,4-Difluorocyclohexyl)oxy)-2,3-dihydrobenzofuran-7-yl)-6-oxo-piperidine-3-carboxamide (Compound 190);

- N-(7-((4,4-Difluorocyclohexyl)oxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-6-oxopiperidine-3-carboxamide (Compound 191);
- 3-Methyl-2-oxo-N-(7-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]-dioxin-5-yl)imidazolidine-4-carboxamide (Compound 192);
- 5 3-Methyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-indazol-7-yl)-imidazolidine-4-carboxamide (Compound 193);
- 1-Methyl-N-(1-methyl-5-((5-(trifluoromethyl)pyridin-4-yl)oxy)-1H-indazol-7-yl)-5-oxopyrrolidine-2-carboxamide (Compound 194);
- (S)-N-(2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 195);
- 10 (R)-N-(2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 196);
- N-(2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 197);
- 15 (R)-N-(2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 198);
- (S)-N-(2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 199);
- N-(2-Methoxy-5-((4-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 200);
- 20 N-(2-Methoxy-5-((4-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 201);
- N-(5-((5-Fluoropyridin-2-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 202);
- 25 N-(5-((5-Chloropyridin-2-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 203);
- N-(5-(2-Fluoro-4-nitrophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 204);
- N-(5-(((4,4-Difluorocyclohexyl)oxy)methyl)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 205);
- 30 N-(5-((4,4-Difluorocyclohexyl)methoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 206);

- (2S)-N-(5-((4,4-Difluorocycloheptyl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 207);
- (R)-N-(2-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 208);
- 5 (R)-N-(2-Methoxy-5-(((cis)-4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 209);
- (S)-N-(2-Methoxy-5-(((cis)-4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 210);
- N-(5-((5-(Difluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 211);
- 10 N-(5-((5-(Difluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 212);
- N-(5-(4-(Difluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 213);
- 15 (S)-N-(5-(4-(Difluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 214);
- (R)-N-(5-(4-(Difluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 215);
- (S)-3-Methyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzofuran-7-yl)imidazolidine-4-carboxamide (Compound 216);
- 20 (R)-3-Methyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzofuran-7-yl)imidazolidine-4-carboxamide (Compound 217);
- (S)-3-Methyl-N-(1-methyl-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-benzodimidazol-4-yl)-2-oxoimidazolidine-4-carboxamide (Compound 218);
- 25 (R)-3-Methyl-N-(1-methyl-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-benzodimidazol-4-yl)-2-oxoimidazolidine-4-carboxamide (Compound 219);
- (S)-N-(4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 220);
- (R)-N-(4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 221);
- 30 N-(5-(3,4-Dichlorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 222);

- N-(5-(3-Chloro-4-fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide (Compound 223);
- N-(5-(3,4-Difluorophenoxy)-2-(1,3,4-oxadiazol-2-yl)phenyl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide (Compound 224);
- 5 1-Methyl-5-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-1H-indazol-7-yl)-pyrrolidine-2-carboxamide (Compound 225);
- (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1,3-dimethyl-2-oxoimidazolidine-4-carboxamide (Compound 226);
- (R)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1,3-dimethyl-2-oxoimidazolidine-4-carboxamide (Compound 227);
- 10 4-Hydroxy-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-3-carboxamide (Compound 228);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-1-(5-oxopyrrolidine-2-carbonyl)pyrrolidine-2-carboxamide (Compound 229);
- 15 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-(1-methyl-5-oxopyrrolidine-2-carbonyl)-5-oxopyrrolidine-2-carboxamide (Compound 230);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-1-(4-oxoazetidine-2-carbonyl)pyrrolidine-2-carboxamide (Compound 231);
- N-(5-(3,4-difluorophenoxy)-2-methoxyphenyl)-5-oxo-1-(4-oxoazetidine-2-carbonyl)pyrrolidine-2-carboxamide (Compound 232);
- 20 1-Methyl-5-oxo-N-(7-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]-dioxin-5-yl)pyrrolidine-2-carboxamide (Compound 233);
- 1-Methyl-5-oxo-N-(7-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]-dioxin-5-yl)pyrrolidine-2-carboxamide, enantiomer 1 (Compound 234);
- 25 1-Methyl-5-oxo-N-(7-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]-dioxin-5-yl)pyrrolidine-2-carboxamide, enantiomer 2 (Compound 235);
- 1-Methyl-N-(8-methyl-7-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-5-oxopyrrolidine-2-carboxamide (Compound 236);
- 1-Methyl-5-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 237);
- 30 1-Methyl-5-oxo-N-(5-((3-(trifluoromethyl)benzyl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 238);

- N-(5-(3,4-Difluorophenoxy)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 239);
- N-(7-(3,4-Difluorophenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 240);
- 5 N-(7-(4-Fluorophenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 241);
- N-(5-((3,4-Difluorophenoxy)methyl)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 242);
- 10 N-(6-((3,4-Difluorophenoxy)methyl)-2,3-dihydrobenzofuran-4-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 243);
- 1-Methyl-N-(1-methyl-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-benzo[d]imidazol-4-yl)-5-oxopyrrolidine-2-carboxamide, enantiomer 1 (Compound 244);
- 1-Methyl-N-(1-methyl-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-benzo[d]imidazol-4-yl)-5-oxopyrrolidine-2-carboxamide, enantiomer 2 (Compound 245);
- 15 N-(5-(((3-Fluorophenyl)amino)methyl)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 246);
- N-(5-((4,4-Difluorocyclohexyl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 247);
- N-(5-((3,4-Difluorobenzyl)oxy)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 248);
- 20 N-(5-((3-Fluorophenoxy)methyl)benzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 249);
- N-(2-Fluoro-3-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 250);
- 25 N-(5-(3,4-difluorophenoxy)-2-fluoro-3-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 251);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxotetrahydropyrrolo-[2,1-b]thiazole-7a(5H)-carboxamide 1,1-dioxide (Compound 252);
- N-(3-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 253);
- 30 (E)-N-(5-(3-Fluorostyryl)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 254);

- N-(2-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide (Compound 255);
- N-(2-Methoxy-5-(3-(trifluoromethyl)benzyl)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 256);
- 5 N-(2-Methoxy-5-(4-(trifluoromethyl)benzyl)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 257);
- N-(2-Chloro-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 258);
- N-(4-Methoxy-3-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxo-
- 10 pyrrolidine-2-carboxamide (Compound 259);
- N-(5-(4-Fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 260);
- N-(3-Methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 261);
- 15 N-(5-((6-Fluoro-5-methylpyridin-3-yl)oxy)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 262);
- (R)-N-(5-((6-fluoro-5-methylpyridin-3-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 263);
- N-(2-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxo-
- 20 pyrrolidine-2-carboxamide (Compound 264);
- (R)-N-(2-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 265);
- N-(2-Methoxy-5-(((1R,3S)-3-(trifluoromethyl)cyclohexyl)oxy)phenyl)-5-oxo-pyrrolidine-2-carboxamide (Compound 266);
- 25 N-(2-Methoxy-5-(((1S,3S)-3-(trifluoromethyl)cyclohexyl)oxy)phenyl)-5-oxo-pyrrolidine-2-carboxamide (Compound 267);
- (R)-N-(2-Methoxy-5-(((1R,3S)-3-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 268);
- (R)-N-(2-Methoxy-5-(((1S,3S)-3-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-
- 30 methyl-5-oxopyrrolidine-2-carboxamide (Compound 269);
- N-(2-Fluoro-5-((4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide (Compound 270);

- (R)-N-(4-methoxy-3-(((1r,4R)-4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 271);
- (R)-N-(4-Methoxy-3-(((1s,4S)-4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 272);
- 5 N-(3-Methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 273);
- N-(3-(4-Chloro-3-(trifluoromethyl)phenoxy)-5-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 274);
- (R)-N-(3-((4,4-Difluorocyclohexyl)oxy)-5-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 275);
- 10 N-(2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 276);
- N-(3-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 277);
- 15 (R)-N-(3-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 278);
- N-(3-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 279);
- 1-Methyl-5-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)quinolin-8-yl)-pyrrolidine-2-carboxamide (Compound 280);
- 20 (R)-1-Methyl-5-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)quinolin-8-yl)pyrrolidine-2-carboxamide (Compound 281);
- (R)-N-(3-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 282);
- 25 (R)-N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 283);
- N-(3-(3,4-Difluorophenoxy)-5-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 284);
- (R)-N-(3-(3,4-Difluorophenoxy)-5-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 285);
- 30 N-(5-(Cyclohexyloxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 286);

- N-(5-(Cyclohex-2-en-1-yloxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 287);
- (S)-N-(5-((5-Chloropyridin-2-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 288);
- 5 1-Acetyl-N-(2-methoxy-5-(3-(trifluoromethyl)phenoxy)phenyl)azetidine-3-carboxamide (Compound 289);
- (R)-N-(2-Methoxy-5-(4-(trifluoromethoxy)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 290);
- N-(2-methoxy-5-(3-(trifluoromethoxy)phenoxy)phenyl)-1-methyl-5-oxo-
10 pyrrolidine-2-carboxamide (Compound 291);
- N-(5-(4-(Difluoromethyl)phenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 292);
- (R)-N-(5-(4-Fluoro-3-methoxyphenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 293);
- 15 N-(5-(Cyclohexylmethoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 294);
- N-(5-(3-Fluoro-4-methoxyphenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 295);
- N-(5-((4,4-Dimethylcyclohexyl)oxy)-2-methoxyphenyl)-1-methyl-5-oxo-
20 pyrrolidine-2-carboxamide (Compound 296);
- N-(5-((3,4-Difluorophenyl)thio)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 297);
- N-(5-((3,4-Difluorophenyl)thio)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 298);
- 25 N-(5-(3-Bromophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 299);
- N-(2-Methoxy-5-(4-(trifluoromethoxy)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 300);
- N-(5-(4-Isopropoxyphenoxy)-2-methoxyphenyl)-5-oxopyrrolidine-2-
30 carboxamide (Compound 301);
- N-(5-((3,3-Difluorocyclobutyl)methoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 302);

- N-(3-(4-Fluorophenoxy)-5-(trifluoromethyl)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 303);
- N-(5-(4-Chlorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 304);
- 5 N-(5-(4-Chloro-3-fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 305);
- N-(3-Cyano-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 306);
- (S)-N-(5-(4-Chlorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 307);
- 10 (R)-N-(5-(4-Chlorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 308);
- N-(5-(3-Chloro-4-cyanophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 309);
- 15 (S)-N-(5-(3-Chloro-4-cyanophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 310);
- (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-(methylsulfonyl)-pyrrolidine-2-carboxamide (Compound 311);
- (S)-N-(5-(4-Chloro-3-fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 312);
- 20 (S)-N-(5-(4-(Difluoromethyl)phenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 313);
- N-(2-Methoxy-5-((1-methyl-1H-indol-5-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 314);
- 25 N-(5-((2,3-Dihydrobenzofuran-5-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 315);
- N-(5-(3-Chlorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 316);
- N-(5-(4-Cyano-3-methylphenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 317);
- 30 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-(2-methoxyethyl)-5-oxopyrrolidine-2-carboxamide (Compound 318);

- (R)-N-(5-(4-(Difluoromethyl)phenoxy)-2-methoxyphenyl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide (Compound 319);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-6-oxo-piperidine-2-carboxamide (Compound 320);
- 5 N-(5-(3,4-Difluorophenoxy)-2-methoxyphenyl)-1-methyl-6-oxopiperidine-2-carboxamide (Compound 321);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-2-oxopiperidine-4-carboxamide (Compound 322);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-2-oxo-
- 10 piperidine-4-carboxamide (Compound 323);
- N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-2-oxopiperidine-4-carboxamide, enantiomer 1 (Compound 324);
- N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-2-oxopiperidine-4-carboxamide, enantiomer 2 (Compound 325);
- 15 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-(methylsulfonyl)-pyrrolidine-3-carboxamide (Compound 326);
- N-(2-methoxy-5-((4-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-2-oxopiperidine-4-carboxamide, enantiomer 1 (Compound 327);
- N-(2-Fluoro-5-(4-(trifluoromethoxy)phenoxy)phenyl)-1-methyl-5-oxo-
- 20 pyrrolidine-2-carboxamide (Compound 328);
- N-(2-Chloro-5-(4-(trifluoromethoxy)phenoxy)phenyl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide (Compound 329);
- N-(2-Carbamoyl-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 330);
- 25 N-(2-Methoxy-5-((4-(trifluoromethyl)-pyridin-2-yl)oxy)phenyl)-1-(2-methoxyacetyl)-5-oxopyrrolidine-2-carboxamide (Compound 331);
- (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-2-oxo-imidazolidine-4-carboxamide (Compound 332);
- (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-(2-methoxyacetyl)-
- 30 5-oxopyrrolidine-2-carboxamide (Compound 333);
- N-(5-((3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-1-(2-methoxyacetyl)-5-oxopyrrolidine-2-carboxamide (Compound 334);

- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-3-carboxamide (Compound 335);
- (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-(2-methoxyacetyl)-pyrrolidine-2-carboxamide (Compound 336);
- 5 (S)-1-(2-Amino-2-oxoethyl)-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)-phenyl)pyrrolidine-2-carboxamide (Compound 337);
- (S)-N-(5-(4-Chloro-3-fluorophenoxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 338);
- (S)-N-(5-((3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 339);
- 10 (S)-N-(5-(4-(Difluoromethyl)phenoxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 340);
- 2-(1,3-Dimethyl-2,5-dioxoimidazolidin-4-yl)-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)acetamide (Compound 341);
- 15 (S)-3-Acetyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-2-oxoimidazolidine-4-carboxamide (Compound 342);
- (S)-3-Acetyl-N-(5-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-1-methyl-2-oxoimidazolidine-4-carboxamide (Compound 343);
- N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-5-oxopyrrolidine-3-carboxamide (Compound 344);
- 20 (S)-N-(5-((3-Chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 345);
- (S)-N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1,3-dimethyl-2-oxoimidazolidine-4-carboxamide (Compound 346);
- 25 (R)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-(2-methoxyacetyl)-pyrrolidine-2-carboxamide (Compound 347);
- (S)-N-(5-(3-Chlorophenoxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 348);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-3-carboxamide (Compound 349);
- 30 N-(5-(2-Chloro-4-(trifluoromethyl)phenoxy)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 350);

- (S)-N-(3-Chloro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 351);
- N-(3-Chloro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 352);
- 5 (S)-N-(5-(4-(Fluoromethyl)phenoxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 353);
- Methyl 2-(2-((2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)carbonyl)-5-oxopyrrolidin-1-yl)acetate (Compound 354);
- (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-3-carboxamide (Compound 355);
- 10 (S)-N-(5-(4-Chlorophenoxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 356);
- (R)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-3-carboxamide (Compound 357);
- 15 (S)-1-Acetyl-N-(5-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)pyrrolidine-2-carboxamide (Compound 358);
- (S)-N-(5-((3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-1,3-dimethyl-2-oxoimidazolidine-4-carboxamide (Compound 359);
- (S)-1,3-Dimethyl-2-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzo[d]-[1,3]dioxol-4-yl)imidazolidine-4-carboxamide (Compound 360);
- 20 (S)-N-(2,4-Difluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 361);
- (S)-N-(3-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 362);
- 25 (S)-N-(2-Fluoro-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 363);
- (S)-1,3-Dimethyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)imidazolidine-4-carboxamide (Compound 364);
- (S)-N-(2-Fluoro-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 365);
- 30 N-(2-Bromo-5-(3-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 366);

- N*-(2-Cyano-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 367);
- N*-(2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 368);
- 5 *N*-(2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 369);
- (2*S*,4*R*)-4-Hydroxy-*N*-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)pyrrolidine-2-carboxamide (Compound 370);
- (*S*)-1-Acetyl-*N*-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 371);
- 10 *N*-(2-Hydroxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 372);
- (*S*)-*N*-(2-Hydroxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 373);
- 15 *N*-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-6-oxopiperazine-2-carboxamide (Compound 374);
- 4-Amino-5-((2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)amino)-5-oxopentanoic acid (Compound 375);
- 1-Methyl-6-oxo-*N*-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)piperazine-2-carboxamide (Compound 376);
- 20 (*R*)-*N*-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-1-(1*H*-pyrazol-4-yl)pyrrolidine-2-carboxamide (Compound 377);
- (*R*)-*N*-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-1-(1*H*-pyrazol-4-yl)pyrrolidine-2-carboxamide (Compound 378);
- 25 1-(3-Amino-3-oxopropyl)-*N*-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 379);
- (2*S*,4*S*)-4-Hydroxy-*N*-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 380);
- 1-Imino-*N*-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)hexahydro-1*λ*⁶-thiopyran-4-carboxamide 1-oxide (Compound 381);
- 30 *N*-(4-Fluoro-2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 382);

- 1,4-Dimethyl-6-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)piperazine-2-carboxamide (Compound 383);
- N-(5-(4-Amino-2-fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 384);
- 5 N-(5-(4-Chloro-2-fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 385);
- N-(5-(3-Acetylphenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 386);
- N-(5-(3-Acetylphenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-
10 carboxamide (Compound 387);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-2-oxo-2,3-dihydro-oxazole-4-carboxamide (Compound 388);
- N-(3-(3,4-Difluorophenoxy)-6-methoxy-2-methylphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 389);
- 15 N-(5-(3-Cyanophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 390);
- N-(2-Methoxy-5-(3-methoxy-4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 391);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1H-tetrazole-5-
20 carboxamide (Compound 392);
- (R)-N-(2-Methoxy-5-((4-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 393);
- (S)-N-(2-Methoxy-5-((4-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 394);
- 25 N-(2-Methoxy-5-(3-methoxy-4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 395);
- N-(5-(4-Cyano-3-(trifluoromethyl)phenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 396);
- N-(5-(3-Cyano-4-fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-
30 2-carboxamide (Compound 397);
- (S)-N-(5-(2-Fluoro-4-(trifluoromethyl)phenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 398);

- (N-(5-((5-Fluoro-6-(trifluoromethyl)pyridin-3-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 399);
- N-(5-((6-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 400);
- 5 (S)-N-(5-((6-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 401);
- (R)-N-(5-((6-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 402);
- (S)-N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 403);
- 10 (E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2-methoxyphenyl)-2-oxoimidazolidine-4-carboxamide (Compound 404);
- (R,E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 405);
- 15 (S,E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 406);
- (S,E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2,3-dihydrobenzofuran-7-yl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 407);
- (E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2-methoxyphenyl)-1,3-dimethyl-2-oxoimidazolidine-4-carboxamide (Compound 408);
- 20 ((S,E)-N-(6-(2-(4,4-Difluorocyclohexyl)vinyl)benzo[d][1,3]dioxol-4-yl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 409);
- N-(2-hydroxy-5-(3-methoxy-4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 410);
- 25 N-(5-(2-Hydroxy-4-(trifluoromethyl)phenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 411);
- 1-Acetyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)pyrrolidine-3-carboxamide (Compound 412);
- 1-Acetyl-N-(5-(3-fluorophenoxy)-2-methoxyphenyl)pyrrolidine-3-carboxamide (Compound 413);
- 30 1-Glycyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide, HCl (Compound 414);

(S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)pyrrolidine-2-carboxamide (Compound 415);

(S)-N-(5-((3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-pyrrolidine-2-carboxamide (Compound 416);

5 (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-N,1-dimethyl-5-oxopyrrolidine-2-carboxamide (Compound 417);

and tautomers and pharmaceutically acceptable salts thereof.

Compounds of the invention may be administered to a patient in therapeutically
10 effective amounts which range usually from about 0.5 to about 2000 mg, more typically
form about 1 to about 500 mg, for example from about 2 to about 100 mg, daily
depending on the age, sex, weight, ethnic group, condition of the patient, condition to be
treated, administration route and the active ingredient used. The compounds of the
invention can be formulated into dosage forms using the principles known in the art.

15 The compound can be given to a patient as such or in combination with suitable
pharmaceutical excipients in the form of tablets, granules, capsules, suppositories,
emulsions, suspensions or solutions. Choosing suitable ingredients for the composition
is a routine for those of ordinary skill in the art. Suitable carriers, solvents, gel forming
ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting
20 compounds and other ingredients normally used in this field of technology may also be
used. The compositions containing the active compound can be given enterally or
parenterally, the oral route being the preferred way. The contents of the active
compound in the composition is from about 0.5 to 100 %, typically from about 0.5 to
about 20 %, per weight of the total composition.

25

The compounds of the invention can be given to the subject as the sole active
ingredient or in combination with one of more other active ingredients for treatment of a
particular disease.

30 In the treatment of diseases and conditions wherein inhibition of TEAD is
desired, such as various cancers or chronic pain, a combination of therapeutic agents
and/or other treatments (e.g., radiation therapy) is often advantageous. The second (or

third) agent to be administered may have the same or different mechanism of action than the primary therapeutic agent.

Accordingly, a compound of the invention may be administered in combination
5 with other anti-cancer treatments useful in the treatment of cancers. For example, a compound of the invention can be packaged together with instructions that the compound is to be used in combination with other anti-cancer agents and treatments for the treatment of cancer. Similarly, a compound of the invention may be administered in combination with other pain reliever agents useful in the treatment of chronic pain. For
10 example, a compound of the invention can be packaged together with instructions that the compound is to be used in combination with other anti-cancer agents and treatments for the treatment of cancer, or with other pain reliever agents and treatments for the treatment of chronic pain. The present invention further comprises combinations of a compound of the invention and one or more additional agents in kit form, for example,
15 where they are packaged together or placed in separate packages to be sold together as a kit, or where they are packaged to be formulated together.

According to one embodiment of the invention, the therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof is
20 co-administered with one or more anti-cancer agents or pain reliever agents.

The optional other anti-cancer agents which can be administered in addition to a compound of formula (I) or a pharmaceutically acceptable salt thereof include, but are not limited to,

- 25 - chemotherapeutic agents (e.g. docetaxel and paclitaxel),
- tyrosine kinase inhibitors including EGFR inhibitors (e.g. gefitinib and osimertinib), VEGFR inhibitors (e.g. bevacizumab) and FGFR inhibitors (e.g. erdafitinib);
- immune checkpoint inhibitors (e.g. nivolumab and pembrolizumab),
- 30 - epigenetic modulators (e.g. BET inhibitors and HDAC inhibitors),
- mTOR inhibitors (e.g. everolimus);
- AKT inhibitors (e.g. AZ5363);
- radiopharmaceuticals (e.g. alpharadin);

- GnRH/LHRH analogues (such as leuprorelin);
- PI3K inhibitors (e.g. idelalisib); and
- CDK4/6 inhibitors (e.g. ribociclib)
- steroidogenesis inhibitors (e.g. CYP17A1 inhibitors such as abiraterone acetate and seviteronel); and
- a non-steroidal androgen receptor antagonist (e.g. enzalutamide, apalutamide and darolutamide).

According to still another embodiment, the present invention provides a pharmaceutical combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one additional active ingredient selected from the list consisting of

- chemotherapeutic agents (e.g. docetaxel and paclitaxel),
 - tyrosine kinase inhibitors including EGFR inhibitors (e.g. gefitinib and osimertinib), VEGFR inhibitors (e.g. bevacizumab) and FGFR inhibitors (e.g. erdafitinib);
 - immune checkpoint inhibitors (e.g. nivolumab and pembrolizumab),
 - epigenetic modulators (e.g. BET inhibitors and HDAC inhibitors),
 - mTOR inhibitors (e.g. everolimus);
 - AKT inhibitors (e.g. AZ5363);
 - radiopharmaceuticals (e.g. alpharadin);
 - GnRH/LHRH analogues (such as leuprorelin);
 - PI3K inhibitors (e.g. idelalisib); and
 - CDK4/6 inhibitors (e.g. ribociclib)
 - steroidogenesis inhibitors (e.g. CYP17A1 inhibitors such as abiraterone acetate and seviteronel); and
 - a non-steroidal androgen receptor antagonist (e.g. enzalutamide, apalutamide and darolutamide),
- for simultaneous, separate or sequential administration.

The above other therapeutic agents, when employed in combination with a compound of the invention can be used, for example, in those amounts indicated in the

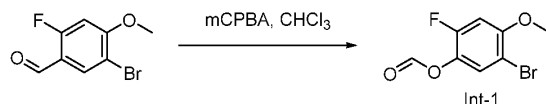
Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

The compounds of the invention can be prepared by a variety of synthetic routes analogously to the methods known in the literature using suitable starting materials. The present invention will be explained in more detail by the following experiments and examples. The experiments and examples are meant only for illustrating purposes and do not limit the scope of the invention defined in claims.

EXAMPLES:

Purification methods used:

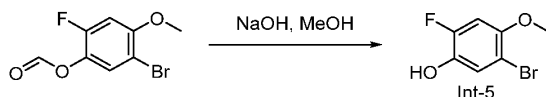
- A) Reverse phase HPLC (water/acetonitrile, 2-8 min 0-65 %, 30 mL/min, column: SunFire 100*19 mm).
- B) Reverse phase HPLC (water/methanol, 2-8 min 0-65 %, 30 mL/min, column: SunFire 100*19 mm).
- C) Reverse phase HPLC (water/acetonitrile/formic acid, 2-10 min 0-40 %, 30 mL/min, column: SunFire 100*19 mm).
- D) Reverse phase HPLC (water/acetonitrile/ammonia, 2-8 min 0-65 %, 30 mL/min, column: SunFire 100*19 mm).
- E) Reverse phase HPLC (water/methanol/ammonia, 2-10 min 40-50 %, 30 mL/min, column: SunFire 100*19 mm).
- F) Reverse phase HPLC (water/acetonitrile/trifluoroacetic acid, 2-10 min 0-50 %, 30 mL/min, column: SunFire 100*19 mm).
- G) Reverse phase HPLC (water/methanol/ trifluoroacetic acid, 2-10 min 10-50 %, 30 mL/min, column: SunFire 100*19 mm).
- H) Preparative chiral HPLC (methanol/isopropanol, 50-50, 12 mL/min, column: ChiralpakAD-H (250*20 mm).
- I) Preparative chiral HPLC (methanol/IPA/Hexane, 25-25-50, 0.6 mL/min, column: Chiralpak IC (250*4.6 mm).
- J) Preparative chiral HPLC (methanol/CO₂, 50-50, 2 mL/min, column: ChiralpakAD-H (250*4.6 mm).

Intermediate 1. 5-Bromo-2-fluoro-4-methoxyphenyl formate

To a solution of 5-bromo-2-fluoro-4-methoxybenzaldehyde (1.000 g, 1 eq., 4.291 mmol) in CHCl₃ (20 mL) was added 3-chlorobenzoperoxoic acid (1.851 g, 2.5 eq., 10.73 mmol) at 4 °C followed by stirring for 30 min. The mixture was diluted with water (50 ml) and the resulted mixture was extracted with ethyl acetate (3×10 mL). The organic layers were combined, washed with saturated solution of NaHCO₃ (2×10 mL) and brine (10 ml), dried over sodium sulfate, filtered and concentrated to give the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.57 (s, 1H), 7.69 (dd, 1H), 7.29 (dd, 1H), 3.86 (d, 3H).

The following intermediates were prepared according to the procedure described for Intermediate 1 from the starting materials indicated in the Table. Where LCMS/GCMS data was not informative, the data is not shown.

No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting material
Int-2		244 [M] ⁺	7-Bromobenzo[d][1,3]dioxole-5-carbaldehyde
Int-3		-	8-Bromo-2,3-dihydrobenzo[b]-[1,4]dioxine-6-carbaldehyde
Int-4		-	7-Bromo-2-methyl-2,3-dihydrobenzofuran-5-carbaldehyde

Intermediate 5. 5-Bromo-2-fluoro-4-methoxyphenol

Sodium hydroxide (1.606 g, 2.5 eq., 40.15 mmol) was added to a solution of 5-bromo-2-fluoro-4-methoxyphenyl formate (4.0 g, 1 eq., 16.06 mmol) in methanol (100 mL). The mixture was stirred at 25 °C for 12 h. Then the mixture was concentrated, diluted with 50 mL of water, acidified to pH 1 and extracted with ethyl acetate (3×30 mL). The combined organic phases were dried over Na₂SO₄ and concentrated. The crude product was purified twice by column chromatography using hexane-MTBE and chloroform-acetonitrile systems to give the title compound (1.4 g, 6.0 mmol, 37 %, 95 % purity). ¹H NMR (500 MHz, DMSO-*d*₆) δ: 9.66 (s, 1H), 7.12 (d, 1H), 7.04 (d, 1H), 3.73 (s, 3H).

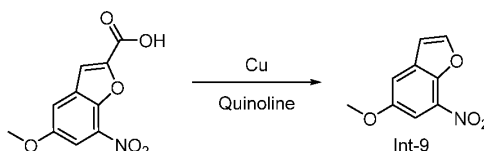
10

The following intermediates were prepared according to the procedure described for Intermediate 4 from the starting materials indicated in the Table. Where LCMS/GCMS data was not informative, the data is not shown.

No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting material
Int-6		-	7-Bromobenzo[d][1,3]dioxol-5-yl formate
Int-7		-	8-Bromo-2,3-dihydrobenzo[b]-[1,4]dioxin-6-yl formate
Int-8		-	7-Bromo-2-methyl-2,3-dihydrobenzofuran-5-yl formate

15

Intermediate 9. 5-Methoxy-7-nitrobenzofuran

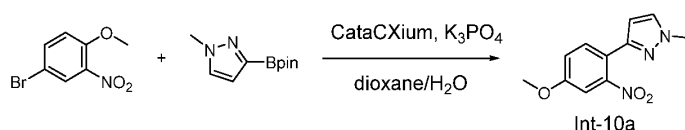


5-Methoxy-7-nitrobenzofuran-2-carboxylic acid (1 g, 1 eq., 4.22 mmol) and copper (201 mg, 0.75 eq., 3.16 mmol) were refluxed in quinoline (20 mL) for 30 min.

After cooling to RT the mixture was filtered and the filtrate was poured to 2 N hydrochloric acid and filtered. The obtained precipitate was concentrated three times with acetonitrile to give the title compound (710 mg, 3.5 mmol). ¹H NMR (500 MHz, DMSO-*d*₆) δ: 8.20 (s, 1H), 7.66 (d, 1H), 7.10 (s, 1H), 3.86 (s, 3H).

5

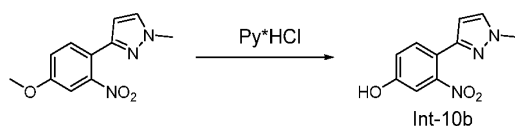
Intermediate 10a. 3-(4-Methoxy-2-nitrophenyl)-1-methyl-1H-pyrazole



1-Bromo-4-methoxy-2-nitrobenzene (0.272 g, 1.17 mmol), 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (244 mg, 1.17 mmol) and potassium phosphate (746 mg, 3.52 mmol) were mixed in dioxane (4 mL) and water (0.4 mL) under argon atmosphere and the mixture was heated to 100 °C. Then di(1-adamantyl)-*n*-butylphosphine (21.0 mg, 0.05 eq., 58.6 μmol) and (2'-amino-[1,1'-biphenyl]-2-yl)-((methylsulfonyl)oxy)palladium (21.7 mg, 0.05 eq., 58.6 μmol) were added and the mixture was stirred for 14 h at 100 °C. After cooling to RT the mixture was concentrated in vacuum. The residue was dissolved in ethyl acetate (5 mL), washed with brine (2×5 mL), dried over sodium sulfate, filtered and concentrated in vacuum to give crude title compound (0.2 g, 0.73 mmol) which was used in the next step without further purification. LCMS: *m/z* 234.2 [M+H]⁺.

20

Intermediate 10b. 4-(1-Methyl-1H-pyrazol-3-yl)-3-nitrophenol



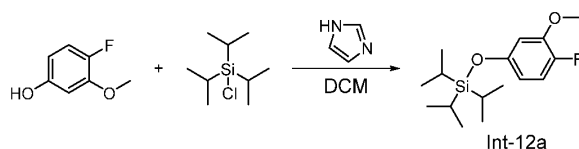
3-(4-Methoxy-2-nitrophenyl)-1-methyl-1H-pyrazole (1.2 g, 1 eq., 5.145 mmol) was mixed with pyridine HCl (2.973 g, 5 eq., 25.73 mmol) followed by stirring at 200 °C for 30 h. After cooling to RT the reaction mass was poured into water (10 mL) and extracted with ethyl acetate (3×20 mL). Combined organic phases were dried over sodium sulfate, filtered and concentrated to give the title compound (0.90 g, 3.7 mmol). ¹H NMR (400 MHz, DMSO-*d*₆) δ: 10.42 (s, 1H), 7.70 (d, 1H), 7.54 (d, 1H), 7.10 (d, 1H), 7.05 (dd, 1H), 6.33 (d, 1H), 3.81 (s, 3H).

25

The following intermediate was prepared according to the procedure described for Intermediate 10b from the starting material indicated in the Table.

No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting material
Int-11		LCMS: <i>m/z</i> 177.8 [M-H] ⁻ .	5-Methoxy-7-nitrobenzofuran

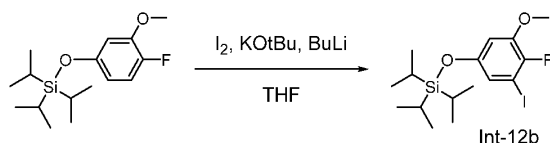
5 **Intermediate 12a.** (4-Fluoro-3-methoxyphenoxy)triisopropylsilane



To a stirred solution of 4-fluoro-3-methoxyphenol (6 g, 1 eq., 42.21 mmol) and imidazole (5.748 g, 2 eq., 84.43 mmol) in DCM (60 mL) at RT was added chlorotriisopropylsilane (8.546 g, 9.487 mL, 1.05 eq., 44.33 mmol). The mixture was stirred for 16 h and then poured into saturated aqueous NH₄Cl (40 mL), followed by extraction with DCM (3×50 mL). The combined extracts were washed with brine (30 mL), dried over Na₂SO₄, and concentrated in vacuum to give the title compound (10.00 g, 30 mmol). ¹H NMR (400 MHz, Chloroform-d) δ: 6.87 (dd, 1H), 6.48 (dd, 1H), 6.34 (dt, 1H), 3.82 (s, 3H), 1.23 (dh, 3H), 1.08 (d, 21H).

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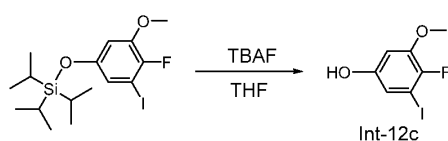
Intermediate 12b. (4-Fluoro-3-iodo-5-methoxyphenoxy)triisopropylsilane



(4-Fluoro-3-methoxyphenoxy)triisopropylsilane (6.544 g, 1 eq., 21.93 mmol) and potassium 2-methylpropan-2-olate (2.706 g, 1.1 eq., 24.12 mmol) were mixed in THF (60 mL) under argon atmosphere and cooled to -78 °C. Butyl lithium (1.545 g, 9.647 mL, 2.5 molar, 1.1 eq., 24.12 mmol) was added dropwise at -78 °C. Then the mixture was stirred for 1 h at the same temperature. The solution of iodine (6.678 g, 1.2 eq., 26.31 mmol) in THF (20 mL) was added dropwise at -78 °C. After stirring at RT

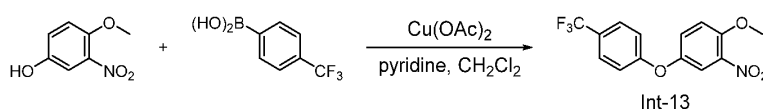
overnight, the mixture was cooled to -20 °C and aqueous solution of ammonium chloride (20 mL) was added dropwise. Then the solution was warmed to RT. EtOAc (70 mL) was added and the organic layer was washed with brine (2×30 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (hexane/MTBE) to give the title compound (2.0 g, 3.3 mmol). GCMS: m/z 424 [M]⁺.

Intermediate 12c. 4-Fluoro-3-iodo-5-methoxyphenol



(4-Fluoro-3-iodo-5-methoxyphenoxy)triisopropylsilane (2.3 g, 1 eq., 5.420 mmol) was dissolved in THF (10 mL) and tetrabutylammonium fluoride (3.543 g, 13.55 mL, 1 molar, 2.5 eq., 13.55 mmol) was added dropwise. The mixture was stirred at RT for 16 h and then concentrated in vacuum. The residue was dissolved in EtOAc (20 mL), washed with water (2×5 mL), dried under sodium sulfate and concentrated in vacuum. The obtained residue was purified by flash chromatography (hexane/MTBE) to give the title compound (0.575 g, 1.9 mmol). ¹H NMR (400 MHz, Chloroform-d) δ: 6.72 (t, 1H), 6.45 (dd, 1H), 4.86 (s, 1H), 3.82 (s, 3H).

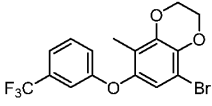
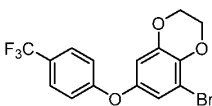
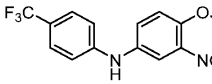
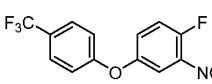
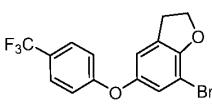
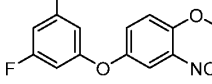
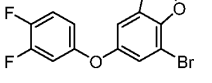
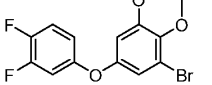
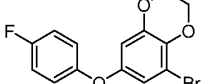
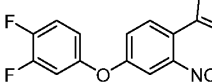
Intermediate 13. 1-Methoxy-2-nitro-4-(4-(trifluoromethyl)phenoxy)benzene

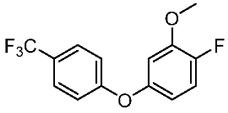
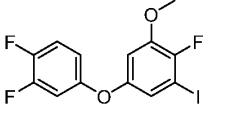
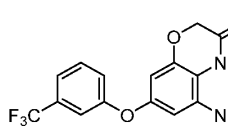
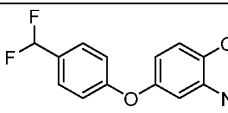
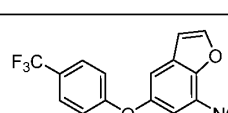
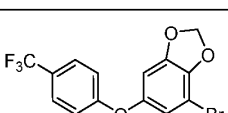
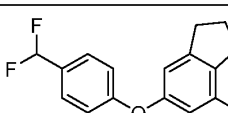
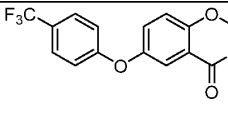
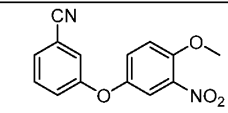
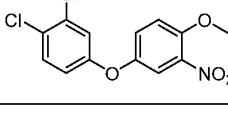


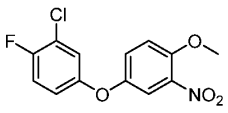
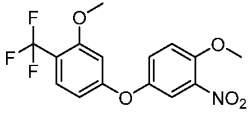
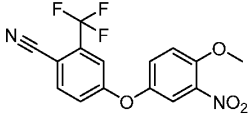
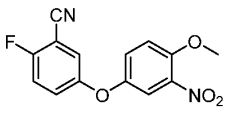
4-Methoxy-3-nitrophenol (1 g, 1 Eq., 6 mmol), (4-(trifluoromethyl)phenyl)-boronic acid (2 g, 2 eq., 0.01 mol), pyridine (0.9 g, 1 mL, 2 eq., 0.01 mol), diacetoxy-copper (1 g, 1.05 eq., 6 mmol) and powdered molecular sieves 4Å (1 g) were suspended in dichloromethane (10 mL). The air was bubbled through the resulting solution for 30 min and the mixture was stirred at RT overnight. The mixture was filtered. The filtrate was washed with water (2×30 mL), dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by method A to afford the title compound. LCMS: m/z 314.0 [M+H]⁺.

The following intermediates were prepared according to the procedure described for Intermediate 13 from the starting materials indicated in the Table. Where LCMS/GCMS data was not informative, the data is not shown.

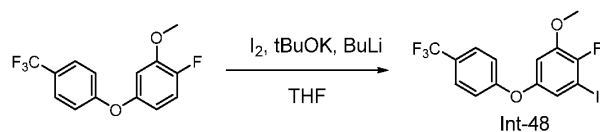
No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting material
Int-14		264.2 [M+H] ⁺	4-Methoxy-3-nitrophenol and (3-Fluorophenyl) boronic acid
Int-15		314.0 [M+H] ⁺	4-Methoxy-3-nitrophenol and (3-(Trifluoromethyl)phenyl)-boronic acid
Int-16		284.2 [M+H] ⁺	3-Nitrophenol and (3-(Trifluoromethyl)phenyl)boronic acid
Int-17		376.2 [M+H] ⁺	8-Bromo-2,3-dihydrobenzo[b]-[1,4]dioxin-6-ol and (3-(Trifluoromethyl)phenyl)boronic acid
Int-18		323.1 [M] ⁺	7-Nitrobenzofuran-5-ol and (3-(Trifluoromethyl)phenyl)boronic acid
Int-19		359.93 [M] ⁺	7-Bromobenzo[d][1,3]dioxol-5-ol and (3-(Trifluoromethyl)phenyl)-boronic acid
Int-20		320.0 [M+H] ⁺	2,4-Difluoro-5-nitrophenol and (3-(Trifluoromethyl)phenyl)-boronic acid
Int-21		301.0 [M] ⁺	4-Fluoro-3-nitrophenol and (3-(Trifluoromethyl)phenyl)boronic acid
Int-22		236.0 [M] ⁺	(4-Methoxyphenyl)boronic acid and 2,4-Difluorophenol
Int-23		282.0 [M+H] ⁺	4-Methoxy-3-nitrophenol and (3,4-Difluorophenyl)boronic acid

Int-24		390.2 [M+H] ⁺	8-Bromo-5-methyl-2,3-dihydrobenzo[b][1,4]dioxin-6-ol and (3-(Trifluoromethyl)phenyl)boronic acid
Int-25		376.2 [M+H] ⁺	8-Bromo-2,3-dihydrobenzo[b][1,4]dioxin-6-ol and (4-(Trifluoromethyl)phenyl)boronic acid
Int-26		313.2 [M+H] ⁺	4-Methoxy-3-nitroaniline and (4-(Trifluoromethyl)phenyl)boronic acid
Int-27		302.2 [M+H] ⁺	4-Fluoro-3-nitrophenol and (4-(Trifluoromethyl)phenyl)boronic acid
Int-28		358.0 [M] ⁺	7-Bromo-2,3-dihydrobenzofuran-5-ol and (4-(Trifluoromethyl)phenyl)boronic acid
Int-29		282.2 [M+H] ⁺	4-Methoxy-3-nitrophenol and (3,5-Difluorophenyl)boronic acid
Int-30		326.0 [M] ⁺	7-Bromo-2,3-dihydrobenzofuran-5-ol and (3,4-Difluorophenyl)boronic acid
Int-31		344.2 [M+H] ⁺	8-Bromo-2,3-dihydrobenzo[b][1,4]dioxin-6-ol and (3,4-Difluorophenyl)boronic acid
Int-32		326.0 [M+H] ⁺	8-Bromo-2,3-dihydrobenzo[b][1,4]dioxin-6-ol and (4-Fluorophenyl)boronic acid
Int-33		332.0 [M+H] ⁺	4-(1-Methyl-1H-pyrazol-3-yl)-3-nitrophenol and (3,4-Difluorophenyl)boronic acid

Int-34		-	4-Fluoro-3-methoxyphenol and (4-(Trifluoromethyl)phenyl)-boronic acid
Int-35		-	4-Fluoro-3-iodo-5-methoxyphenol and (3,4-Difluorophenyl)boronic acid
Int-36		355.0 [M+H] ⁺	7-Hydroxy-5-nitro-2H-benzo[b]-[1,4]oxazin-3(4H)-one and (3-(Trifluoromethyl)phenyl)boronic acid
Int-37		296.0 [M] ⁺	4-Methoxy-3-nitrophenol and (4-(Difluoromethyl)phenyl)boronic acid
Int-38		-	7-Nitrobenzofuran-5-ol and (4-(Trifluoromethyl)phenyl)boronic acid
Int-39		-	7-Bromobenzo[d][1,3]dioxol-5-ol and (4-(Trifluoromethyl)phenyl)-boronic acid
Int-40		-	7-Bromo-2,3-dihydrobenzofuran-5-ol and (4-(Difluoromethyl)-phenyl)boronic acid
Int-41		-	Methyl 5-hydroxy-2-methoxybenzoate and (4-(Trifluoromethyl)phenyl)boronic acid
Int-42		271.2 [M+H] ⁺	4-Methoxy-3-nitrophenol and 3-Cyanophenylboronic acid
Int-43		315.9 [M+H] ⁺	4-Methoxy-3-nitrophenol and 3,4-Dichlorophenylboronic acid

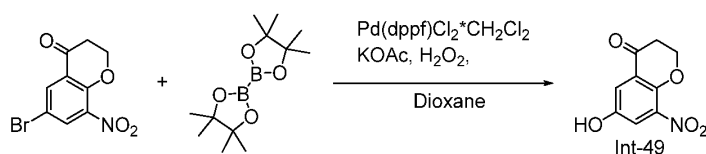
Int-44		297.9 [M+H] ⁺	4-Methoxy-3-nitrophenol and 3-Chloro-4-fluorophenylboronic acid
Int-45		344.3 [M+H] ⁺	4-Methoxy-3-nitrophenol and 3-Methoxy-4-(trifluoromethyl)-phenylboronic acid
Int-46		338.9 [M+H] ⁺	4-Methoxy-3-nitrophenol and (4-Cyano-3-(trifluoromethyl)-phenyl)boronic acid
Int-47		288.6 [M+H] ⁺	4-Methoxy-3-nitrophenol and 3-Cyano-4-fluorobenzene boronic acid

Intermediate 48. 2-Fluoro-1-iodo-3-methoxy-5-(4-(trifluoromethyl)phenoxy)-benzene



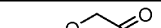
- 5 1-Fluoro-2-methoxy-4-(4-(trifluoromethyl)phenoxy)benzene (4.000 g, 1 eq., 13.97 mmol) and potassium 2-methylpropan-2-olate (1.725 g, 1.1 eq., 15.37 mmol) were mixed in THF (60 mL) and cooled to -78 °C under argon atmosphere. Butyl lithium (984.7 mg, 6.149 mL, 2.5 molar, 1.1 eq., 15.37 mmol) was added dropwise at -78 °C and the mixture was stirred for 2 h at the same temperature. A solution of iodine
- 10 (4.256 g, 1.2 eq., 16.77 mmol) in THF (20 mL) was added dropwise at -78 °C. After stirring at RT overnight, the mixture was cooled to -20 °C and aqueous solution of ammonium chloride (10 mL) was added dropwise. Then the solution was warmed to RT. EtOAc (100 mL) was added and the organic layer was washed with brine (2×25 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by
- 15 flash chromatography (hexane/MTBE) to give the title compound (0.900 g, 2.0 mmol, 14 %, 90 % purity).

Intermediate 49. 6-Hydroxy-8-nitrochroman-4-one

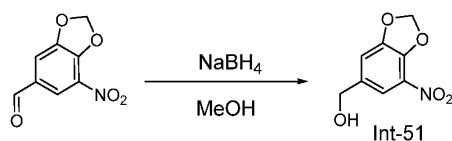


6-Bromo-8-nitrochroman-4-one (2.00 g, 1 eq., 7.35 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.24 g, 1.2 eq., 8.82 mmol) and potassium acetate (2.16 g, 3 eq., 22.1 mmol) were mixed in 1,4-dioxane (20 mL). Argon was bubbled into the solution at 25 °C for 1 h to remove any excess oxygen. PdCl₂(dppf)CH₂Cl₂ (180 mg, 0.03 eq., 221 μmol) was added to the mixture under argon atmosphere. The mixture was heated to 80 °C and stirred for 3 h until the reaction was completed. The mixture was cooled to 25 °C and then filtered. The precipitate was washed with dioxane (15 mL). The filtered solutions were combined, concentrated and then transferred to a reactor. Hydrogen peroxide (4.29 g, 4.29 mL, 35 w-%, 6 eq., 44.1 mmol) was added and the mixture was heated to 50 °C and stirred for 40 min until the reaction was completed. Water (10 mL) was added to the mixture, and the mixture was extracted with DCM (2×50 mL). The organic phase was collected, washed with 15 % brine (2×15 mL) and extracted with 15 % Na₂CO₃ (2×25 mL). The aqueous phase was collected and the pH value was adjusted to 4-5 with 3 M HCl. The aqueous phase was then extracted with ethyl acetate (2×50 mL). The organic phase was collected, dried over Na₂SO₄ and concentrated under reduced pressure to obtain the title compound (810 mg, 3.6 mmol). LCMS: *m/z* 208.0 [M+H]⁺

20 The following intermediate was prepared according to the procedure described for Intermediate 49 from the starting material indicated in the Table.

No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting material
Int-50		210.2 [M+H] ⁺ .	7-Bromo-5-nitro-2H-benzo[b]- [1,4]oxazin-3(4H)-one

Intermediate 51. (7-Nitrobenzo[d][1,3]dioxol-5-yl)methanol



- 7-Nitrobenzo[d][1,3]dioxole-5-carbaldehyde (1000 mg, 1 eq., 5.125 mmol) was dissolved in anhydrous methanol (40 mL). The mixture was cooled to 0 °C and sodium borohydride (232.6 mg, 1.2 eq., 6.150 mmol) was added portionwise during 10 min.
- 5 The mixture was stirred at RT for 18 h and then concentrated under reduced pressure. The resulting residue was treated with saturated ammonium chloride solution (30 mL), extracted with ethyl acetate (3×20 mL), dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give the title compound (0.693 g, 3.29 mmol, 64.1 %, 93.46 % purity). ¹H NMR (500 MHz, DMSO-d₆) δ: 7.50 (s, 1H), 7.21 (s, 1H),
- 10 6.28 (s, 2H), 5.41 (s, 1H), 4.45 (s, 2H).

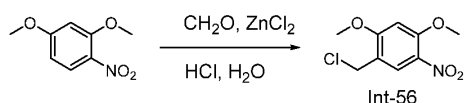
The following intermediates were prepared according to the procedure described for Intermediate 51 from the starting materials indicated in the table. Where LCMS/GCMS data was not informative, the data is not shown.

15

No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting material
Int-52		201.03 [M] ⁺	3-Fluoro-4-methoxy-5-nitrobenzaldehyde
Int-53		-	8-Nitro-2,3-dihydrobenzo[b]-[1,4]dioxine-6-carbaldehyde
Int-54		-	7-Bromo-2,3-dihydrobenzofuran-5-carbaldehyde
Int-55		212.0 [M+H] ⁺	6-Hydroxy-8-nitrochroman-4-one

Intermediate 56. 1-(Chloromethyl)-2,4-dimethoxy-5-nitrobenzene

70



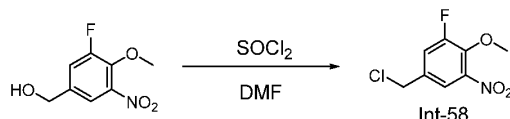
2,4-Dimethoxy-1-nitrobenzene (1 g, 1 eq., 5 mmol), formaldehyde (0.3 g, 2 eq., 0.01 mol, aq. 40 %) and zinc (II) chloride (0.07 g, 0.1 eq., 0.5 mmol) were dissolved in aqueous (37 %) hydrochloric acid (10 mL) followed by stirring at 100 °C for 12 h. After cooling to RT the reaction mixture was extracted with dichloromethane (2×50 mL), organic layers were combined, washed with water (2×100 mL), dried over sodium sulfate, filtered and concentrated in vacuum to give crude title compound (312 mg, 1.46 mmol, 30 %, 100 % purity), which was purified by method A. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.97 (s, 1H), 6.81 (d, 1H), 4.43 (d, 2H), 4.01 (d, 1H), 3.96 (dd, 6H).

10

The following intermediate was prepared according to the procedure described for Intermediate 56 from the starting material indicated in the table.

No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting material
Int-57		218.98 [M] ⁺	4-Fluoro-2-methoxy-1-nitrobenzene

Intermediate 58. 5-(Chloromethyl)-1-fluoro-2-methoxy-3-nitrobenzene



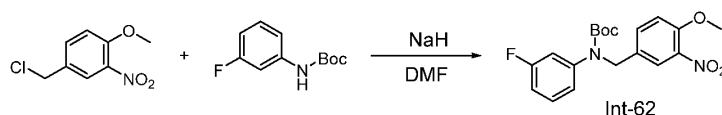
(3-Fluoro-4-methoxy-5-nitrophenyl)methanol (610 mg, 1 eq., 3.03 mmol) was dissolved in DCM (7 mL) and DMF (2.22 mg, 2.35 μL, 0.01 eq., 30.3 μmol) was added. The resulting solution was cooled to 0 °C and thionyl chloride (722 mg, 443 μL, 2 eq., 6.07 mmol) was added dropwise to the mixture at the same temperature and the solution was stirred at 0 °C for 10 min followed by warming to RT and stirring at this temperature overnight. The solution was then poured into 10 % aqueous sodium bicarbonate solution (10 mL) and stirred for 10 min. Then the aqueous layer was extracted with DCM (10 mL). Combined organic layers were dried over sodium sulfate, filtered and the solvent was evaporated under vacuum to give the title compound (602

mg, 2.4 mmol, 80 %, 88 % purity), which was used in the next step without further purification. LCMS: m/z 219.8 $[M+H]^+$.

- The following intermediates were prepared according to the procedure described for Intermediate 58 from the starting materials indicated in the table. Where LCMS/GCMS data was not informative, the data is not shown.

No.	Structure	LCMS/ GCMS m/z	Starting material
Int-59		215.8 $[M+H]^+$	(7-Nitrobenzo[d][1,3]dioxol-5-yl)methanol
Int-60		230.2 $[M+H]^+$	(8-Nitro-2,3-dihydrobenzo[b]-[1,4]dioxin-6-yl)methanol
Int-61		-	(7-Bromo-2,3-dihydrobenzofuran-5-yl)methanol

- Intermediate 62.** tert-Butyl (3-fluorophenyl)(4-methoxy-3-nitrobenzyl)-
10 carbamate



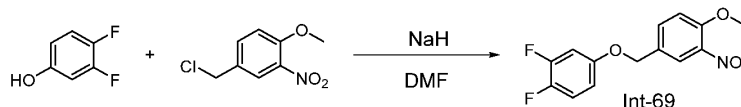
- To a solution of tert-butyl (3-fluorophenyl)carbamate (1.048 g, 1 eq., 4.960 mmol) in DMF (20 mL) at 0 °C sodium hydride (238.1 mg, 60 %, 1.2 eq., 5.952 mmol) was added and the mixture was stirred at RT for 30 min. 4-(Chloromethyl)-1-methoxy-2-nitrobenzene (1.000 g, 1 eq., 4.960 mmol) was added in a single portion and the mixture was stirred at RT for 18 h. The resulting mixture was filtered, and the filtrate was diluted with water (50 mL) and ethyl acetate (50 mL). Layers were separated, the organic phase was washed with brine (4×30 mL), dried over sodium sulfate, filtered and the solvent was removed under reduced pressure, to afford the title compound, which
20 was used in the next step without further purification.

The following intermediates were prepared according to the procedure described for Intermediate 62 from the starting materials indicated in the table.

No.	Structure	LCMS/ GCMS m/z	Starting materials
Int-63		293.2 [M+H] ⁺	6-(Chloromethyl)-4-nitrobenzo[d][1,3]dioxole and 3-fluorophenol
Int-64		328.2 [M+H] ⁺	4-(Chloromethyl)-1-methoxy-2-nitrobenzene and 3-(Trifluoromethyl)phenol
Int-65		328.2 [M+H] ⁺	4-Methoxy-3-nitrophenol and 1-(Bromomethyl)-3-(trifluoromethyl)benzene
Int-66		307.2 [M+H] ⁺	7-(Chloromethyl)-5-nitro-2,3-dihydrobenzo[b][1,4]dioxine and 3-Fluorophenol
Int-67		315.0 [M+H] ⁺	4-Methoxy-3-nitrophenol and 5-Fluoro-2-(trifluoromethyl)pyridine
Int-68		378.0 [M+H] ⁺	8-Bromo-2,3-dihydrobenzo[b][1,4]dioxin-6-ol and 2-Fluoro-5-(trifluoromethyl)pyridine

5

Intermediate 69. 4-((3,4-Difluorophenoxy)methyl)-1-methoxy-2-nitrobenzene



3,4-Difluorophenol (2.00 g, 1 eq., 15.4 mmol) was dissolved in DMF (20 mL), sodium hydride (676 mg, 60 %, 1.1 eq., 16.9 mmol) was added at RT and the mixture was stirred at this temperature for 30 min. 4-(Chloromethyl)-1-methoxy-2-nitrobenzene (3.41 g, 1.1 eq., 16.9 mmol) was added and the mixture was heated at 100 °C for 16 h.

10

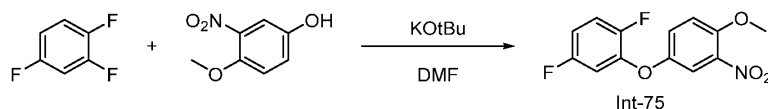
The solution was cooled to RT and concentrated. The residue was taken up in ethyl acetate (60 mL). The resulting solution was washed with brine (3×50 mL), dried over sodium sulfate, filtered and evaporated to give the title compound (4.5 g, 14 mmol, 94 %, 95 % purity). The crude product was used in the next step without further purification.

The following intermediates were prepared according to the procedure described for Intermediate 69 from the starting materials indicated in the table. Where LCMS/GCMS data was not informative, the data is not shown.

10

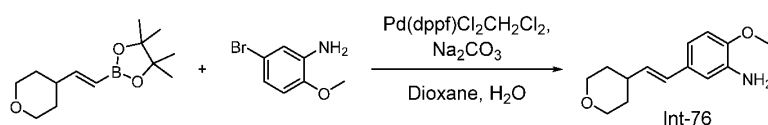
No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting materials
Int-70		-	7-(Chloromethyl)-5-nitro-2,3-dihydrobenzo[b][1,4]dioxine and 4,4-Difluorocyclohexan-1-ol
Int-71		281.0 [M+H] ⁺	4-Methoxy-3-nitrophenol and 5-Chloro-2-fluoropyridine
Int-72		279.0 [M+H] ⁺	5-Hydroxy-2-methoxy-benzenaminium chloride and 1,2-Difluoro-4-nitrobenzene
Int-73		-	4,4-Difluorocyclohexan-1-ol and 4-(Chloromethyl)-1-methoxy-2-nitrobenzene
Int-74		325.0 [M+H] ⁺	7-Nitrobenzofuran-5-ol and 2-Fluoro-5-(trifluoromethyl)pyridine

Intermediate 75. 4-(2,5-Difluorophenoxy)-1-methoxy-2-nitrobenzene



1,2,4-Trifluorobenzene (2.4 g, 1 eq., 18 mmol), 4-methoxy-3-nitrophenol (3.1 g, 1 eq., 18 mmol) and potassium 2-methylpropan-2-olate (2.2 g, 1.1 eq., 20 mmol) were dissolved in DMF (50 mL) and the resulting mixture was stirred at 80 °C for 10 h. Then EtOAc (50 mL) was added and the organic layer was washed with brine (5×30 mL),
 5 dried and evaporated under reduced pressure to afford title compound, which was used in the next step without further purification. GCMS: m/z 281 $[M]^+$

Intermediate 76. (E)-2-Methoxy-5-(2-(tetrahydro-2H-pyran-4-yl)vinyl)aniline

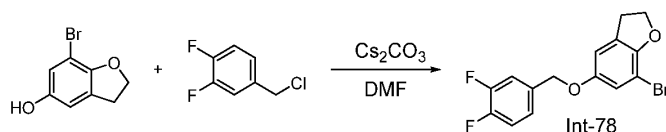


10 5-Bromo-2-methoxyaniline (730 mg, 1 eq., 3.61 mmol), (E)-4,4,5,5-tetramethyl-2-(2-(tetrahydro-2H-pyran-4-yl)vinyl)-1,3,2-dioxaborolane (1.29 g, 1.5 eq., 5.42 mmol), sodium carbonate (383 mg, 1 eq., 3.61 mmol) and $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ adduct (295 mg, 0.1 eq., 361 μmol) were suspended in degassed 1,4-dioxane (12 mL) and water (2.4 mL). The mixture was heated under argon at 90 °C overnight. After cooling to RT the
 15 solvent was evaporated in vacuum, the residue was dissolved in ethyl acetate (30 mL), washed with brine (20 mL), dried over sodium sulfate, filtered, concentrated in vacuum and the residue was purified by method A to give the title compound (205 mg, 839 μmol , 23.2 %, 95.5 % purity). LCMS: m/z 234.2 $[M+H]^+$.

20 The following intermediates were prepared according to the procedure described for Intermediate 76 from the starting materials indicated in the table.

No.	Structure	LCMS/ GCMS m/z	Starting materials
Int-77		268.0 $[M+H]^+$	5-Bromo-2-methoxyaniline and (E)-2-(2-(4,4-difluorocyclohexyl)-vinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Intermediate 78. 7-Bromo-5-((3,4-difluorobenzyl)oxy)-2,3-dihydrobenzofuran



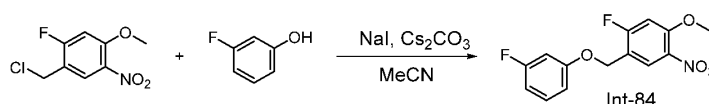
7-Bromo-2,3-dihydrobenzofuran-5-ol (0.500 g, 1 eq., 2.33 mmol) was dissolved in N,N-Dimethylformamide (5 mL) and cesium carbonate (1.52 g, 2 eq., 4.65 mmol) was added. The mixture was stirred at RT for 10 min and 4-(chloromethyl)-1,2-difluorobenzene (378 mg, 1 eq., 2.33 mmol) was added. The mixture was stirred at RT for 12 h. The resulting solution was concentrated under reduced pressure. The residue was taken up in ethyl acetate (20 mL). The obtained solution was washed with brine (20 mL), water (20 mL), dried over sodium sulfate, filtered and evaporated to afford the title compound. The crude product was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ: 7.22 – 7.02 (m, 3H), 6.85 (s, 1H), 6.75 (s, 1H), 4.90 (s, 2H), 4.61 (t, 2H), 3.26 (t, 2H).

The following intermediates were prepared according to the procedure described for Intermediate 78 from the starting materials indicated in the table. Where LCMS/GCMS data was not informative, the data is not shown.

No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting materials
Int-79		308.2 [M] ⁺	1-(Chloromethyl)-2,4-dimethoxy-5-nitrobenzene and 3-Fluorophenol
Int-80		322.0 [M] ⁺	7-Bromo-5-(chloromethyl)-2,3-dihydrobenzofuran and 3-Fluorophenol
Int-81		295.04 [M] ⁺	5-(Chloromethyl)-1-fluoro-2-methoxy-3-nitrobenzene and 3-Fluorophenol
Int-82		371.6 [M-H] ⁻	7-Bromo-2,3-dihydrobenzofuran-5-ol and 1-(Chloromethyl)-3-(trifluoromethyl)benzene

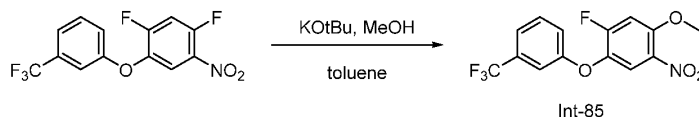
Int-83		-	7-Bromo-5-(chloromethyl)-2,3-dihydrobenzofuran and 3,4-Difluorophenol
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Intermediate 84. 1-Fluoro-2-((3-fluorophenoxy)methyl)-5-methoxy-4-nitrobenzene

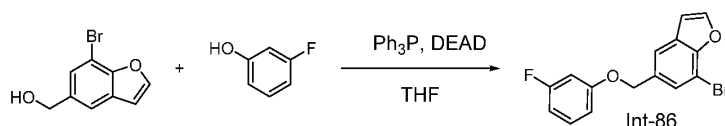


- 5 1-(Chloromethyl)-2-fluoro-4-methoxy-5-nitrobenzene (0.306 g, 1 eq., 1.39 mmol) was dissolved in acetonitrile (3 mL), cesium carbonate (908 mg, 2 eq., 2.79 mmol) and sodium iodide (209 mg, 1 eq., 1.39 mmol) were added. The mixture was stirred for 10 min and 3-fluorophenol (141 mg, 114 μ L, 0.9 eq., 1.25 mmol) was added. The mixture was stirred at RT for 10 h. The resulting solution was filtered and
- 10 concentrated to give the title compound (0.362 g, 0.61 mmol, 44 %, 50 % purity), which was used in the next step without further purification. LCMS: m/z 297.2 $[M+H]^+$

Intermediate 85. 1-Fluoro-5-methoxy-4-nitro-2-(3-(trifluoromethyl)phenoxy)benzene



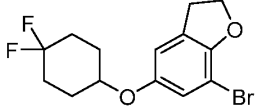
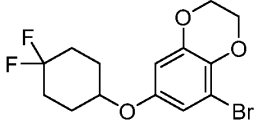
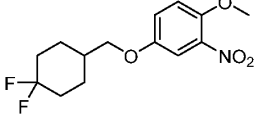
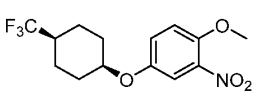
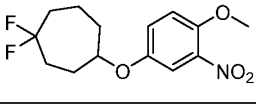
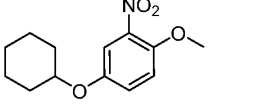
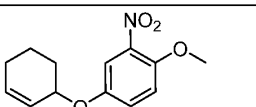
- 15 1,5-Difluoro-2-nitro-4-(3-(trifluoromethyl)phenoxy)benzene (150 mg, 1 eq., 470 μ mol) was dissolved in toluene (2 mL). The solution was cooled to 0 $^{\circ}$ C, then methanol (15.1 mg, 19.0 μ L, 1 eq., 470 μ mol) was added at 0 $^{\circ}$ C. To the obtained solution potassium tert-butoxide (52.7 mg, 1 eq., 470 μ mol) was added at 0 $^{\circ}$ C. The mixture was
- 20 stirred at 0 $^{\circ}$ C for 10 minutes, then temperature was raised to RT followed by stirring for 12 h. The reaction mixture was quenched with water (15 mL) followed by stirring for 15 minutes. Toluene (10 mL) was added to the mixture. The layers were separated, and the aqueous layer was extracted with toluene (2 $\times$ 10 mL). Combined organic layers were washed with water (20 mL), brine (20 mL) and dried over sodium sulfate. The
- 25 solvent was evaporated under reduced pressure to afford the title compound which was used in next step without further purification. GCMS: m/z 331.0 $[M]^+$.

Intermediate 86. 7-Bromo-5-((3-fluorophenoxy)methyl)benzofuran

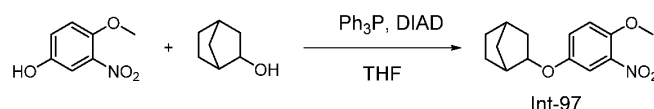
A solution of (7-bromobenzofuran-5-yl)methanol (3.110 g, 1 eq., 13.70 mmol) and triphenylphosphine (4.311 g, 1.2 eq., 16.44 mmol) in THF (100 mL) was cooled to 0 °C under inert atmosphere. Diethyl (E)-diazene-1,2-dicarboxylate (2.863 g, 2.58 mL, 1.2 eq., 16.44 mmol) was slowly added and the mixture was stirred for 30 min followed by addition of 3-fluorophenol (1.612 g, 1.302 mL, 1.05 eq., 14.38 mmol). The ice-bath was removed and the mixture was stirred at RT for 17 h. The THF was evaporated, and the mixture was dissolved in MTBE (10 mL), washed with NaOH (3 mL, 10 %) and water (3 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash-chromatography (MTBE/hexane, flow rate 30 mL/min) to give the title compound (1.42 g, 4.2 mmol, 31 %, 95 % purity). ¹H NMR (400 MHz, DMSO-*d*₆) δ: 8.03 (s, 1H), 7.72 (s, 1H), 7.59 (s, 1H), 7.33 – 7.23 (m, 1H), 7.03 (d, 1H), 6.83 (d, 2H), 6.75 – 6.65 (m, 1H), 5.17 (s, 2H).

The following intermediates were prepared according to the procedure described for Intermediate 86 from the starting materials indicated in the table. Where LCMS/GCMS data was not informative, the data is not shown.

No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting materials
Int-87		320.0 [M+H] ⁺	4-Methoxy-3-nitrophenol and (trans)-4-(Trifluoromethyl)cyclohexan-1-ol
Int-88		-	7-Bromo-2,3-dihydrobenzofuran-5-ol and (cis)-4-(Trifluoromethyl)cyclohexan-1-ol
Int-89		364 [M] ⁺	7-Bromo-2,3-dihydrobenzofuran-5-ol and (trans)-4-(Trifluoro-

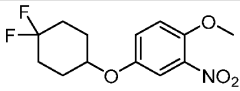
			methyl) cyclohexan-1-ol
Int-90		333.8 [M+H] ⁺	7-Bromo-2,3-dihydrobenzofuran-5-ol and 4,4-Difluorocyclohexan-1-ol
Int-91		348 [M] ⁺	8-Bromo-2,3-dihydrobenzo[b][1,4]dioxin-6-ol and 4,4-Difluorocyclohexan-1-ol
Int-92		302.0 [M+H] ⁺	(4,4-Difluorocyclohexyl)methanol and 4-Methoxy-3-nitrophenol
Int-93		-	(trans)-4-(Trifluoromethyl)cyclohexan-1-ol and 4-Methoxy-3-nitrophenol
Int-94		-	4-Methoxy-3-nitrophenol and 4,4-Difluorocycloheptan-1-ol
Int-95		252.1 [M+H] ⁺	4-Methoxy-3-nitrophenol and Cyclohexanol
Int-96		250.1 [M+H] ⁺	4-Methoxy-3-nitrophenol and Cyclohex-2-en-1-ol

Intermediate 97. 2-(4-Methoxy-3-nitrophenoxy)bicyclo[2.2.1]heptane



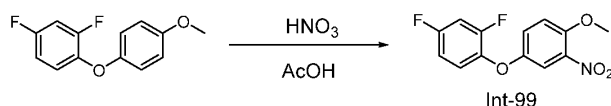
- 4-Methoxy-3-nitrophenol (5.00 g, 1 eq., 29.6 mmol), triphenylphosphine (15.5 g, 2 eq., 59.1 mmol) and bicyclo[2.2.1]heptan-2-ol (3.32 g, 1 eq., 29.6 mmol) were dissolved in THF (50 mL). The mixture was cooled to 4 °C and diisopropyl diazene-1,2-dicarboxylate (12.0 g, 11.5 mL, 2 eq., 59.1 mmol) was added. The mixture was stirred at RT for 16 h, then concentrated and purified by flash-chromatography (MTBE/hexane, flow rate 30 mL/min) to afford the title compound.

The following intermediate was prepared according to the procedure described for Intermediate 97 from the starting materials indicated in the table. Where LCMS/GCMS data was not informative, the data is not shown.

No.	Structure	LCMS/ GCMS m/z	Starting materials
Int-98		-	4-Methoxy-3-nitrophenol and 4,4-Difluorocyclohexan-1-ol

5

Intermediate 99. 4-(2,4-Difluorophenoxy)-1-methoxy-2-nitrobenzene

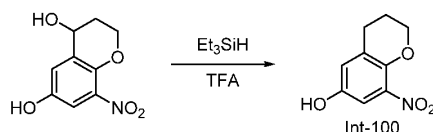


2,4-Difluoro-1-(4-methoxyphenoxy)benzene (0.180 g, 1 eq., 762 μmol) was dissolved in acetic acid (1 mL) and the solution was cooled to 0 °C. Then nitric acid (144 mg, 102 μL , 3 eq., 2.29 mmol) was added to the mixture dropwise and the resulting solution was stirred at RT for 10 h. Then the mixture was poured into ice-cooled saturated sodium carbonate solution (5 mL) and EtOAc (5 mL) was added. The organic layer was separated, dried over sodium sulfate and concentrated in vacuum to afford the title compound, which was used in the next step without further purification.

GCMS: m/z 281 $[\text{M}]^+$

15

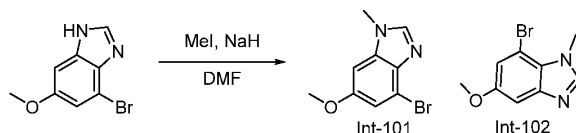
Intermediate 100. 8-Nitrochroman-6-ol



8-Nitrochromane-4,6-diol (135 mg, 1 eq., 639 μmol) was dissolved in TFA (2 mL) and triethylsilane (372 mg, 0.511 mL, 5.00 eq., 3.20 mmol) was added. The mixture was stirred at 23 °C for 16 h, then concentrated, mixed with hexane (10 mL) and filtered. Obtained precipitate was dried under reduced pressure to give the title compound (100 mg, 0.49 mmol). The crude product was used in the next step without further purification. LCMS: m/z 196.0 $[\text{M}+\text{H}]^+$

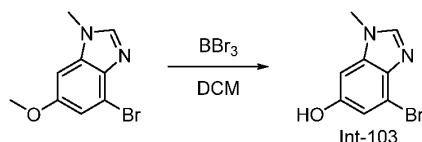
20

Intermediate 101 and 102. 4-Bromo-6-methoxy-1-methyl-1H-benzo[d]-imidazole and 7-Bromo-5-methoxy-1-methyl-1H-benzo[d]imidazole



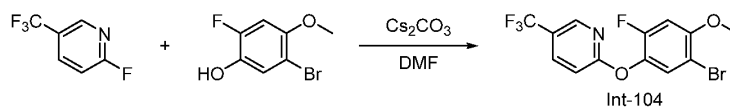
- 5 7-Bromo-5-methoxy-1H-benzo[d]imidazole (0.3 g, 1 eq., 1.32 mmol) was dissolved in DMF (5 mL). The mixture was cooled to 5 °C and sodium hydride (58.1 mg, 60 w-%, 1.1 eq., 1.45 mmol) was added in portions. The mixture was stirred at 5 °C for 30 min and methyl iodide (206 mg, 90.9 µL, 1.1 eq., 1.45 mmol) was added dropwise at the same temperature. The resulting mixture was heated to 20 °C and stirred
- 10 for 12 h, poured into ice-cooled water (10 mL) and extracted with EtOAc (2x20 mL). The combined organic layers were washed with brine (4x5 mL), dried and concentrated to give a mixture of crude products, which were separated by HPLC (Method A) to give two regioisomers 7-bromo-5-methoxy-1-methyl-1H-benzo[d]imidazole (0.0467 g, 194 µmol) and 4-bromo-6-methoxy-1-methyl-1H-benzo[d]imidazole (0.0868 g, 360
- 15 µmol). LCMS: m/z 243.0 $[M+H]^+$.

Intermediate 103. 4-Bromo-1-methyl-1H-benzo[d]imidazol-6-ol



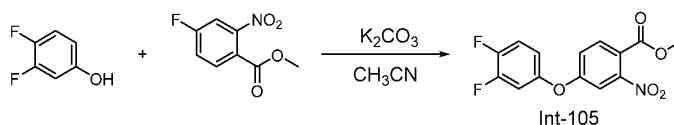
- 20 4-Bromo-6-methoxy-1-methyl-1H-benzo[d]imidazole (80 mg, 1 eq., 0.33 mmol) was dissolved in DCM (2 mL) and tribromoborane (0.83 g, 0.32 mL, 10 eq., 3.3 mmol) was added to the mixture dropwise at 4 °C. The resulting mixture was stirred at 28 °C for 18 h and the MeOH (5 mL) was added to the mixture at 4 °C dropwise. The mixture was concentrated under reduced pressure and the residue was poured into saturated aqueous sodium carbonate solution (10 mL) and extracted with ethyl acetate
- 25 (3x50 mL). The combined organic layer was dried over sodium sulfate and concentrated to give crude 4-bromo-1-methyl-1H-benzo[d]imidazol-6-ol (80 mg, 0.26 mmol) which was used in the next step without further purification. LCMS: m/z 227.0 $[M+H]^+$

Intermediate 104. 2-(5-Bromo-2-fluoro-4-methoxyphenoxy)-5-(trifluoromethyl)pyridine



The mixture of 5-bromo-2-fluoro-4-methoxyphenol (4.75 g, 1 eq., 21.49 mmol), 2-fluoro-5-(trifluoromethyl)pyridine (3.548 g, 1 eq., 21.49 mmol) and cesium carbonate (14 g, 2 eq., 42.98 mmol) in DMF (100 mL) was stirred at 60 °C for 18 h. Water (100 mL) was added to the residue and the resulted mixture was extracted with ethyl acetate (100×20 mL). Organic layers were combined, washed with brine (4×100 mL), dried over sodium sulfate, filtered and evaporated to give crude title compound (6.35 g, 14.8 mmol) which was used in the next step without further purification. ¹H NMR (400 MHz, Chloroform-d) δ: 8.38 (s, 1H), 7.91 (dd, 1H), 7.42 (d, 1H), 7.07 (d, 1H), 6.78 (d, 1H), 3.88 (s, 3H).

Intermediate 105. Methyl 4-(3,4-difluorophenoxy)-2-nitrobenzoate



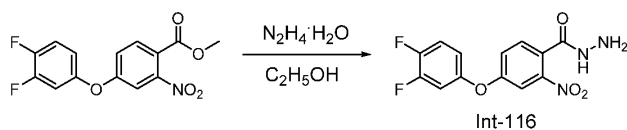
Methyl 4-fluoro-2-nitrobenzoate (5.0 g, 1 eq., 25.11 mmol), 3,4-difluorophenol (3.593 g, 1.1 eq., 27.62 mmol) and potassium carbonate (6.940 g, 2 eq., 50.22 mmol) were mixed in acetonitrile (100 mL) followed by heating at reflux temperature for 14 h. After cooling to RT, the mixture was concentrated under reduced pressure, extracted with EtOAc (100 mL) and washed with water (20 mL), K₂CO₃ solution (20 mL, 15 % in water) and brine (20 mL). The organic phase was dried over Na₂SO₄ and concentrated in vacuum to give the title compound (6.68 g, 19 mmol, 77 %, 90 % purity). ¹H NMR (500 MHz, DMSO-d₆) δ: 7.89 (d, 1H), 7.63 (d, 1H), 7.59 – 7.50 (m, 1H), 7.47 (dq, 1H), 7.33 (dd, 1H), 7.12 – 7.03 (m, 1H), 3.81 (s, 3H).

The following intermediates were prepared according to the procedure described for Intermediate 105 from the starting materials indicated in the table. Where LCMS/GCMS data was not informative, the data is not shown.

No.	Structure	LCMS/ GCMS m/z	Starting materials
Int-106		341.1 [M] ⁺	Methyl 4-fluoro-2-nitrobenzoate and 4-(Trifluoromethyl)phenol
Int-107		341.1 [M] ⁺	Methyl 4-fluoro-2-nitrobenzoate and 3-(Trifluoromethyl)phenol
Int-108		294.2 [M+H] ⁺	1-(4-Fluoro-2-nitrophenyl)ethan-1-one and 3,4-Difluorophenol
Int-109		331.0 [M+H] ⁺	2-Fluoro-5-(trifluoromethoxy)-pyridine and 4-Methoxy-3-nitrophenol
Int-110		299.0 [M-H] ⁻	4-Methoxy-3-nitrophenol and 2-Fluoro-5-(trifluoromethyl)-pyridine
Int-111		-	2-Chloro-5-(trifluoromethyl)-pyridine and 7-Bromo-2,3-dihydrobenzofuran-5-ol
Int-112		341.0 [M] ⁺	8-Nitrochroman-6-ol and 2-Fluoro-5-(trifluoromethyl)-pyridine
Int-113		265.0 [M] ⁺	4-Methoxy-3-nitrophenol and 2,5-Difluoropyridine
Int-114		297.0 [M+H] ⁺	4-Methoxy-3-nitrophenol and 5-(Difluoromethyl)-2-fluoropyridine
Int-115		371.8 [M+H] ⁺	4-Bromo-1-methyl-1H-benzo[d]-imidazol-6-ol and 2-Fluoro-5-(trifluoromethyl)pyridine

Intermediate 116. 4-(3,4-Difluorophenoxy)-2-nitrobenzohydrazide

83



To a solution of the methyl 4-(3,4-difluorophenoxy)-2-nitrobenzoate (2.000 g, 1 eq., 6.468 mmol) in ethanol (20 mL) was added hydrazine hydrate (2.266 g, 7 eq., 45.28 mmol). The mixture was heated under reflux overnight. Then the solvent was

5 evaporated under reduced pressure, and water (20 mL) was added to the residue. The obtained solid was filtered, washed with water, hexane and dried in vacuum to give the title compound (1.900 g, 5.5 mmol, 85 %, 90 % purity). ¹H NMR (500 MHz, DMSO-d₆) δ: 9.77 (s, 1H), 7.59 (d, 1H), 7.59 – 7.49 (m, 2H), 7.47 – 7.42 (m, 1H), 7.33 (dd, 1H), 7.07 – 6.99 (m, 1H), 4.32 (s, 1H).

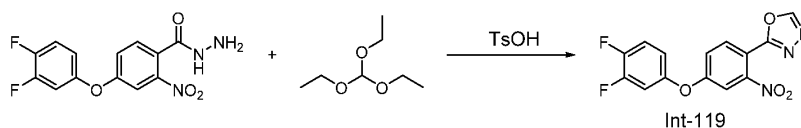
10

The following intermediates were prepared according to the procedure described for Intermediate 116 from the starting materials indicated in the table.

No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting materials
Int-117		342.2 [M+H] ⁺	Methyl 2-nitro-4-(4-(trifluoromethyl)phenoxy)benzoate and Hydrazine hydrate
Int-118		342.4 [M+H] ⁺	Methyl 2-nitro-4-(3-(trifluoromethyl)phenoxy)benzoate and Hydrazine hydrate

15

Intermediate 119. 2-(4-(3,4-Difluorophenoxy)-2-nitrophenyl)-1,3,4-oxadiazole



4-(3,4-Difluorophenoxy)-2-nitrobenzohydrazide (1.000 g, 1 eq., 3.234 mmol), 4-methylbenzenesulfonic acid (111.4 mg, 0.2 eq., 646.8 μmol) and triethoxymethane (20

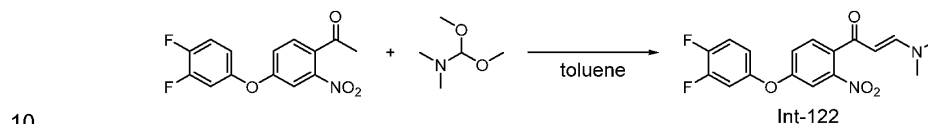
20 mL) were heated at reflux temperature for 14 h. The mixture was then concentrated in

vacuum to give the title compound (1.00 g, 2.2 mmol, 69 %, 71 % purity) LCMS: m/z 320.0 $[M+H]^+$.

The following intermediates were prepared according to the procedure described
5 for Intermediate 119 from the starting materials indicated in the table.

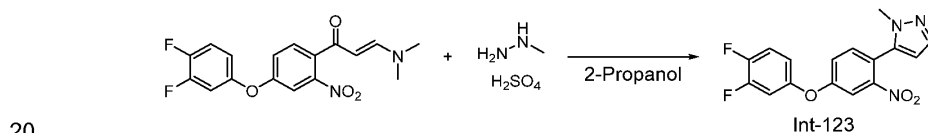
No.	Structure	LCMS/ GCMS m/z	Starting materials
Int-120		352.0 $[M+H]^+$	2-Nitro-4-(4-(trifluoromethyl)-phenoxy)benzohydrazide and Triethoxymethane
Int-121		352.2 $[M+H]^+$	2-Nitro-4-(3-(trifluoromethyl)-phenoxy)benzohydrazide and Triethoxymethane

Intermediate 122. (E)-1-(4-(3,4-Difluorophenoxy)-2-nitrophenyl)-3-(dimethyl-amino)prop-2-en-1-one



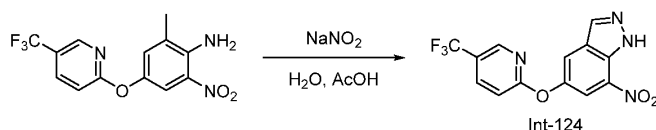
A solution of 1-(4-(3,4-difluorophenoxy)-2-nitrophenyl)ethan-1-one (0.300 g, 1
eq., 1.02 mmol), DMF-DMA (244 mg, 272 μ L, 2 Eq, 2.05 mmol) and toluene (3 mL)
was stirred and heated at reflux temperature for 16 h followed by cooling to RT. The
resulting solid was filtered, washed with toluene, hexane and dried in vacuum to afford
15 the title compound (0.246 g, 706 μ mol, 69.0 %) as a yellow solid. LCMS: m/z 349.2
 $[M+H]^+$.

Intermediate 123. 5-(4-(3,4-Difluorophenoxy)-2-nitrophenyl)-1-methyl-1H-pyrazole



(E)-1-(4-(3,4-Difluorophenoxy)-2-nitrophenyl)-3-(dimethylamino)prop-2-en-1-one (0.246 g, 1 eq., 706 μmol) and methylhydrazine sulfate (112 mg, 1.1 eq., 777 μmol) were mixed in 2-propanol (4 mL) and heated at reflux temperature for 18 h. The mixture was cooled to RT, concentrated in vacuum and purified by method C to give the title compound (0.109 g, 329 μmol , 46.6 %, 100 % purity). LCMS: m/z 332.0 $[\text{M}+\text{H}]^+$.

Intermediate 124. 7-Nitro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-indazole

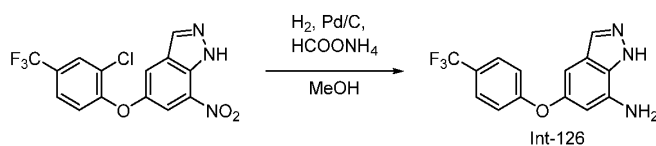


To a stirred solution of 2-methyl-6-nitro-4-((5-(trifluoromethyl)pyridin-2-yl)-oxy)aniline (1.524 g, 1 eq., 4.865 mmol) in acetic acid (70.5 mL), a solution of sodium nitrite (369.2 mg, 1.1 eq., 5.352 mmol) in water (2.4 mL) was added and the mixture was stirred for 1 h. After completion of the reaction, acetic acid was distilled off and the obtained residue was mixed with ice water (200 mL) and extracted with MTBE (3 $\times$ 30 mL). The combined organic phase was washed with water (2 $\times$ 10 mL), dried under sodium sulfate and concentrated under reduced pressure to yield the title compound (1.5 g, 3.9 mmol, 80 %, 84 % purity). LCMS: m/z 325.0 $[\text{M}+\text{H}]^+$.

The following intermediate was prepared according to the procedure described for Intermediate 124 from the starting material indicated in the table.

No.	Structure	LCMS/ GCMS m/z	Starting materials
Int-125		358.0 $[\text{M}+\text{H}]^+$	4-(2-Chloro-4-(trifluoromethyl)phenoxy)-2-methyl-6-nitroaniline

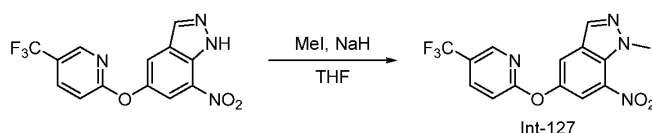
Intermediate 126. 5-(4-(Trifluoromethyl)phenoxy)-1H-indazol-7-amine



5-(2-Chloro-4-(trifluoromethyl)phenoxy)-7-nitro-1H-indazole (0.093 g, 1 eq., 0.26 mmol) was dissolved in methanol (15 mL). Formic acid, ammonia salt (0.33 g, 20 eq., 5.2 mmol) and palladium (0.22 g, 10 w-%, 0.8 eq., 0.21 mmol) were added. The resulting mixture was stirred at 65 °C for 16 h, cooled to RT and filtered. The filtrate was concentrated under reduced pressure and treated with EtOAc (10 mL). The precipitate was filtered and dried under reduced pressure to give the title compound (0.044 g, 0.15 mmol, 58 %, 100 % purity) which was used in the next step without further purification. ¹H NMR (500 MHz, DMSO-*d*₆) δ: 7.87 (s, 1H), 7.65 (d, 2H), 7.06 (d, 2H), 6.62 (s, 1H), 6.18 (s, 1H), 5.69 (s, 2H).

10

Intermediate 127. 1-Methyl-7-nitro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-indazole

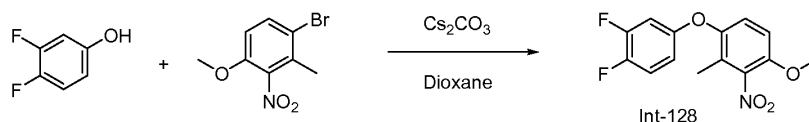


To a solution of 7-nitro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-indazole (0.1 g, 1 eq., 308 μmol) in THF (4 mL) cooled to 0 °C sodium hydride (14.8 mg, 60 w-%, 1.2 eq., 370 μmol) was added. After stirring for 1 h at 23 °C, methyl iodide (46.0 mg, 20.3 μL, 1.05 eq., 324 μmol) was added dropwise at 0 °C. The mixture was stirred for 16 h at 23 °C. Water (1 mL) was added and the resulting mixture was concentrated under reduced pressure. The crude material was dissolved in EtOAc (10 mL), washed with water and brine, dried over MgSO₄ and the solvent removed under reduced pressure to give the title compound (0.129 g, 310 μmol, 100 %, 81.2 % purity), which was used in the next step without further purification. LCMS: *m/z* 339.2 [M+H]⁺.

20

Intermediate 128. 1-(3,4-Difluorophenoxy)-4-methoxy-2-methyl-3-nitrobenzene

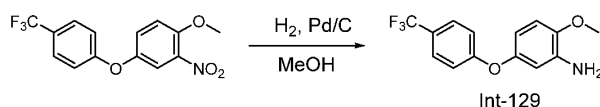
25



A mixture of 1-Bromo-4-methoxy-2-methyl-3-nitrobenzene (0.384 g, 1.5 mmol), 3,4-difluorophenol (0.13 g, 1.0 mmol), Cs₂CO₃ (0.652 g, 2.0 mmol), CuI (0.057

g, 0.3 mmol) and N,N-dimethylglycine (0.031 g, 0.3 mmol) in dioxane (5 ml) was heated at 130 °C for 24 hours. The mixture was evaporated and the residue was purified by normal phase chromatography to yield 0.175 g of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 2.07 (3 H, s), 3.87 (3 H, s), 6.71 - 6.79 (1 H, m), 7.12 - 7.19 (1 H, m), 7.19 - 7.27 (2 H, m), 7.38 - 7.49 (1 H, m).

Intermediate 129. 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline

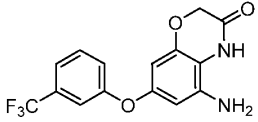
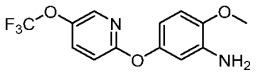
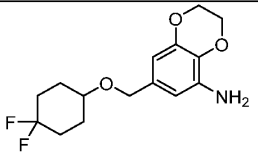
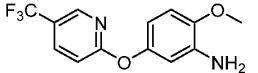
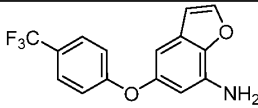
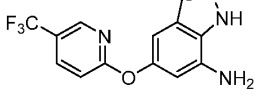
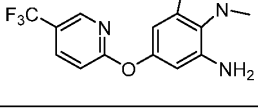
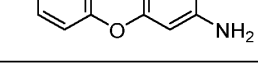
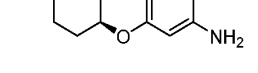
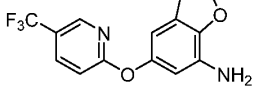


1-Methoxy-2-nitro-4-(4-(trifluoromethyl)phenoxy)benzene (558 mg, 1 eq., 1.78 mmol) was dissolved in methanol (20 mL) and treated with Pd/C (37.9 mg, 0.2 eq., 356 μmol). The resulting mixture was hydrogenated at 1 atm pressure at RT overnight. The catalyst was filtered off and the solvent was evaporated under reduced pressure to afford the crude title product which was used in the next step without further purification. LCMS: *m/z* 284.2 [M+H]⁺.

The following intermediates were prepared according to the procedure described for Intermediate 129 from the starting material indicated in the table.

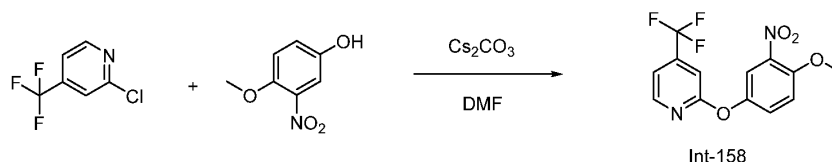
No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting materials
Int-130		234.2 [M+H] ⁺	4-(3-Fluorophenoxy)-1-methoxy-2-nitrobenzene
Int-131		279.2 [M+H] ⁺	1-((3-Fluorophenoxy)methyl)-2,4-dimethoxy-5-nitrobenzene
Int-132		284.2 [M+H] ⁺	1-Methoxy-2-nitro-4-(3-(trifluoromethyl)phenoxy)benzene
Int-133		254.2 [M+H] ⁺	1-Nitro-3-(3-(trifluoromethyl)phenoxy)benzene

Int-134		347.2 [M+H] ⁺	tert-Butyl (3-fluorophenyl)(4-methoxy-3-nitrobenzyl)-carbamate
Int-135		294.0 [M+H] ⁺	7-Nitro-5-(3-(trifluoromethyl)-phenoxy)benzofuran
Int-136		266.0 [M+H] ⁺	1-Fluoro-5-((3-fluorophenoxy)methyl)-2-methoxy-3-nitrobenzene
Int-137		302.0 [M+H] ⁺	1-Fluoro-5-methoxy-4-nitro-2-(3-(trifluoromethyl)phenoxy)-benzene
Int-138		272.0 [M+H] ⁺	1-Fluoro-2-nitro-4-(3-(tri-fluoromethyl)phenoxy)benzene
Int-139		252.0 [M+H] ⁺	4-(2,4-Difluorophenoxy)-1-methoxy-2-nitrobenzene
Int-140		251.0 [M+H] ⁺	4-(3,4-Difluorophenoxy)-1-methoxy-2-nitrobenzene
Int-141		286.0 [M+H] ⁺	5-(4-Methoxy-3-nitro-phenoxy)-2-(trifluoromethyl)-pyridine
Int-142		266.2 [M+H] ⁺	1-Fluoro-2-((3-fluoro-phenoxy)methyl)-5-methoxy-4-nitrobenzene
Int-143		271.07 [M] ⁺	1-Fluoro-2-nitro-4-(4-(tri-fluoromethyl)phenoxy)benzene
Int-144		252.2 [M+H] ⁺	4-(2,5-Difluorophenoxy)-1-methoxy-2-nitrobenzene
Int-145		290.2 [M+H] ⁺	2-(4-(3,4-Difluorophenoxy)-2-nitrophenyl)-1,3,4-oxadiazole
Int-146		290.2 [M+H] ⁺	1-Methoxy-2-nitro-4-(((trans)-4-(trifluoromethyl)cyclohexyl)-

			oxy) benzene
Int-147		325.0 [M+H] ⁺	5-Nitro-7-(3-(trifluoromethyl)-phenoxy)-2H-benzo[b][1,4]-oxazin-3(4H)-one
Int-148		301.0 [M+H] ⁺	2-(4-Methoxy-3-nitro-phenoxy)-5-(trifluoromethoxy)pyridine
Int-149		300.2 [M+H] ⁺	7-(((4,4-Difluorocyclohexyl)-oxy)methyl)-5-nitro-2,3-dihydrobenzo[b][1,4]dioxine
Int-150		285.0 [M+H] ⁺	2-(4-Methoxy-3-nitro-phenoxy)-5-(trifluoromethyl)-pyridine
Int-151		294.2 [M+H] ⁺	7-Nitro-5-(4-(trifluoromethyl)-phenoxy)benzofuran
Int-152		295.0 [M+H] ⁺	7-Nitro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-indazole
Int-153		309.0 [M+H] ⁺	1-Methyl-7-nitro-5-((5-(trifluoromethyl)pyridin-2-yl)-oxy)-1H-indazole
Int-154		235.2 [M+H] ⁺	5-Fluoro-2-(4-methoxy-3-nitrophenoxy)pyridine
Int-155		290.2 [M+H] ⁺	1-Methoxy-2-nitro-4-(((cis)-4-(trifluoromethyl)cyclohexyl)-oxy)benzene
Int-156		295.0 [M+H] ⁺	2-((7-Nitrobenzofuran-5-yl)-oxy)-5-(trifluoromethyl)-pyridine

Int-157		272.2 [M+H] ⁺	1,1-Difluoro-4-(4-methoxy-3-nitrophenoxy)cycloheptane
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Intermediate 158. 2-(4-Methoxy-3-nitrophenoxy)-4-(trifluoromethyl)pyridine



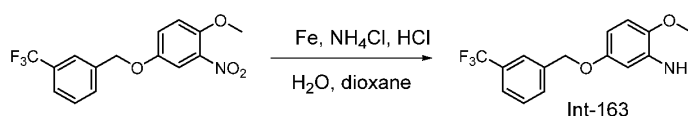
A mixture of 2-chloro-4-(trifluoromethyl)pyridine (2.72 g, 15.0 mmol), 4-methoxy-3-nitrophenol (2.80 g, 15.8 mmol) and Cs₂CO₃ (5.68 g, 17.3 mmol) in DMF (20 ml) was heated at 100 °C for 7 h. Water was added (50 ml) and the mixture was extracted with EtOAc (3 x 50 ml). The organic layers were combined and evaporated to yield 4.71 g of the crude title compound which was used in the next reaction without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.96 (3 H, s), 7.44 (1 H, d), 7.50 - 7.59 (3 H, m), 7.84 (1 H, d), 8.41 (1 H, d). LCMS: *m/z* 315.4 [M+H]⁺

The following intermediates were prepared according to the procedure described for Intermediate 158 from the starting material indicated in the table.

No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting materials
Int-159		332.0 [M+H] ⁺	4-Methoxy-3-nitrophenol and 2,4-Difluoro-1-(trifluoromethyl)-benzene
Int-160		332.0 [M+H] ⁺	4-Methoxy-3-nitrophenol and 3,4-difluorobenzotrifluoride (DMSO solvent, 120 °C for 4 h)
Int-161		333.2 [M+H] ⁺	4-Methoxy-3-nitrophenol and 3,5-Difluoro-2-(trifluoromethyl)-pyridine
Int-162		332.9 [M+H] ⁺	4-Methoxy-3-nitrophenol and 2,6-Difluoro-3-trifluoromethyl-

			pyridine
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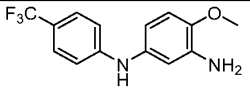
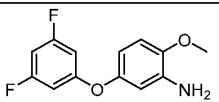
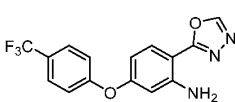
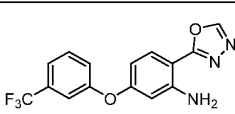
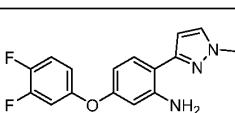
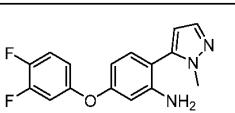
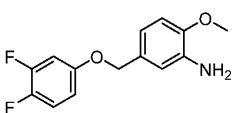
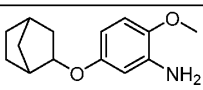
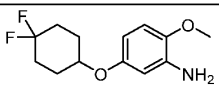
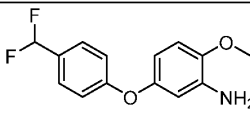
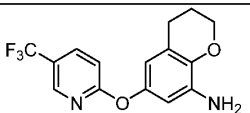
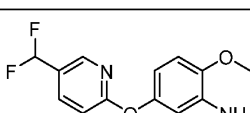
Intermediate 163. 2-Methoxy-5-((3-(trifluoromethyl)benzyl)oxy)aniline hydrochloride



- 5 1-Methoxy-2-nitro-4-((3-(trifluoromethyl)benzyl)oxy)benzene (8.70 g, 1 eq., 26.6 mmol), water (7.43 g, 7.4 mL, 15.5 eq., 412 mmol), ammonia hydrochloride (142 mg, 0.1 eq., 2.66 mmol) and hydrogen chloride (266 mg, 226 μ L, 36.5 % aqueous, 0.1 eq., 2.66 mmol) were mixed in 1,4-dioxane (200 mL) followed by addition of iron (7.42 g, 5 eq., 133 mmol). The mixture was stirred at 110 °C for 5 h and at RT for 16 h. The
- 10 mixture was filtered through thin layer of silica, concentrated and the residue was added to dioxane saturated with hydrochloric acid (30 mL). The solution was evaporated under reduced pressure. The obtained residue was washed with ethyl acetate and dried to give the title compound. LCMS: m/z 334.2 $[M+H]^+$.

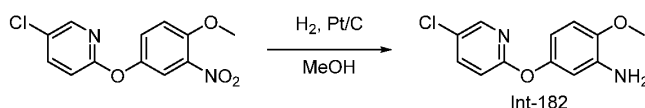
- 15 The following intermediates were prepared according to the procedure described for Intermediate 163 from the starting material indicated in the table.

No.	Structure	LCMS/ GCMS m/z	Starting materials
Int-164		262.0 $[M+H]^+$	6-((3-Fluorophenoxy)methyl)-4-nitrobenzo[d][1,3]dioxole
Int-165		298.2 $[M+H]^+$	1-Methoxy-2-nitro-4-((3-(tri-fluoromethyl)phenoxy)methyl)-benzene
Int-166		276.0 $[M+H]^+$	7-((3-Fluorophenoxy)methyl)-5-nitro-2,3-dihydrobenzo[b][1,4]-dioxine

Int-167		283.2 [M+H] ⁺	4-Methoxy-3-nitro-N-(4-(trifluoromethyl)phenyl)aniline
Int-168		252.2 [M+H] ⁺	4-(3,5-Difluorophenoxy)-1-methoxy-2-nitrobenzene
Int-169		322.0 [M+H] ⁺	2-(2-Nitro-4-(4-(trifluoromethyl)phenoxy)phenyl)-1,3,4-oxadiazole
Int-170		322.2 [M+H] ⁺	2-(2-Nitro-4-(3-(trifluoromethyl)phenoxy)phenyl)-1,3,4-oxadiazole
Int-171		302.0 [M+H] ⁺	3-(4-(3,4-Difluorophenoxy)-2-nitrophenyl)-1-methyl-1H-pyrazole
Int-172		302.2 [M+H] ⁺	5-(4-(3,4-Difluorophenoxy)-2-nitrophenyl)-1-methyl-1H-pyrazole
Int-173		302.2 [M+H] ⁺	4-((3,4-Difluorophenoxy)-methyl)-1-methoxy-2-nitrobenzene
Int-174		334.0[M+H] ⁺	2-(4-Methoxy-3-nitrophenoxy)-bicyclo[2.2.1]heptane
Int-175		258.2 [M+H] ⁺	4-((4,4-Difluorocyclohexyl)-oxy)-1-methoxy-2-nitrobenzene
Int-176		266.2 [M+H] ⁺	4-(4-(Difluoromethyl)phenoxy)-1-methoxy-2-nitrobenzene
Int-177		311.2 [M+H] ⁺	2-((8-Nitrochroman-6-yl)oxy)-5-(trifluoromethyl)pyridine
Int-178		267.0 [M+H] ⁺	5-(Difluoromethyl)-2-(4-methoxy-3-nitrophenoxy)-pyridine

Int-179		285.0 [M+H] ⁺	2-(4-Methoxy-3-nitrophenoxy)-4-(trifluoromethyl)pyridine
Int-180		272.0 [M+H] ⁺	4-(((4,4-Difluorocyclohexyl)oxy)methyl)-1-methoxy-2-nitrobenzene
Int-181		272.2 [M+H] ⁺	4-(((4,4-Difluorocyclohexyl)methoxy)-1-methoxy-2-nitrobenzene

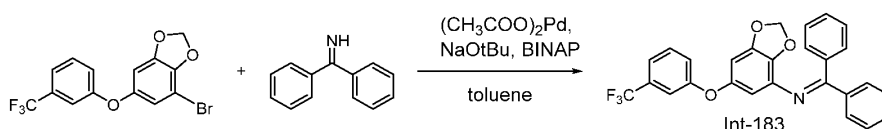
Intermediate 182. 5-((5-Chloropyridin-2-yl)oxy)-2-methoxyaniline



5-Chloro-2-(4-methoxy-3-nitrophenoxy)pyridine (197 mg, 1 eq., 702 μ mol) was dissolved in methanol (5 mL) and platinum (20.5 mg, 0.15 eq., 105 μ mol) was added. The mixture was degassed and stirred in atmosphere of hydrogen for 12 h, then filtered and the solvent was evaporated to give the title compound (175 mg, 0.66 mmol, 94 %, 95 % purity) which was used in next step without further purification. LCMS: m/z 251.0 [M+H]⁺.

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Intermediate 183. 1,1-Diphenyl-N-(6-(3-(trifluoromethyl)phenoxy)benzo[d][1,3]dioxol-4-yl) methanimine



4-Bromo-6-(3-(trifluoromethyl)phenoxy)benzo[d][1,3]dioxole (1.20 g, 1 eq., 3.32 mmol), diphenylmethanimine (663 mg, 1.1 eq., 3.66 mmol), sodium 2-methylpropan-2-olate (335 mg, 1.05 eq., 3.49 mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (207 mg, 0.1 eq., 332 μ mol) were dissolved in toluene (20 mL). The solution was bubbled with argon for 1 min, then diacetoxypalladium (37.3 mg, 0.05 eq., 166 μ mol) was added and the mixture was stirred at 110 °C for 12 h in argon atmosphere. The mixture was filtered and the solid was washed with ethyl acetate (2×20 mL). Then ethyl acetate solution was washed with brine (2×50 mL). The organic phase was dried

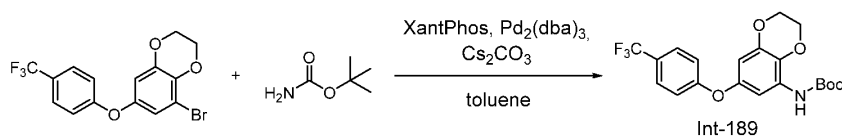
20

over sodium sulfate and filtered. Solvent was evaporated under reduced pressure to give title compound which was used in the next step without further purification. LCMS: m/z 462.0 $[M+H]^+$.

- 5 The following intermediates were prepared according to the procedure described for Intermediate 183 from the starting material indicated in the table.

No.	Structure	LCMS/ GCMS m/z	Starting materials
Int-184		422.2 $[M+H]^+$	7-Bromo-5-((3-fluorophenoxymethyl)benzofuran and Diphenylmethanimine
Int-185		425.2 $[M+H]^+$	7-Bromo-5-((3-fluorophenoxymethyl)-2,3-dihydrobenzofuran and Diphenylmethanimine
Int-186		463.0 $[M+H]^+$	2-((7-Bromobenzo[d][1,3]dioxol-5-yl)oxy)-5-(trifluoromethyl)pyridine and Diphenylmethanimine
Int-187		462.2 $[M+H]^+$	4-Bromo-6-(4-(trifluoromethyl)phenoxy)benzo[d][1,3]dioxole and Diphenylmethanimine
Int-188		475.2 $[M+H]^+$	2-((7-Bromo-2-methyl-2,3-dihydrobenzofuran-5-yl)oxy)-5-(trifluoromethyl)pyridine and Diphenylmethanimine

- 10 **Intermediate 189.** tert-Butyl (7-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)carbamate



To a mixture of 5-bromo-7-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b]-[1,4]dioxine (1.410 g, 1 eq., 3.759 mmol), tert-butyl carbamate (660.5 mg, 1.5 eq., 5.638 mmol) and cesium carbonate (3.674 g, 3 eq., 11.28 mmol) in toluene (40 mL) under argon XantPhos (326.2 mg, 0.15 eq., 563.8 μ mol) and tris(dibenzylideneacetone)-dipalladium (172.1 mg, 0.05 eq., 187.9 μ mol) were added and the mixture was heated at 110 °C for 18 h. After cooling to RT the mixture was filtered and concentrated. The residue was diluted with ethyl acetate (10 mL) and washed with brine (2 $\times$ 50 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was recrystallized from acetonitrile to give the title compound. LCMS: *m/z* 412.2 [M+H]⁺.

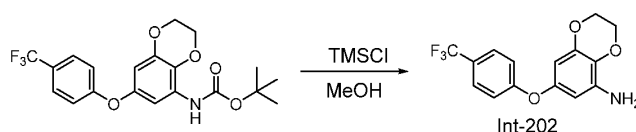
The following intermediates were prepared according to the procedure described for Intermediate 189 from the starting materials indicated in the table. Where LCMS/GCMS data was not informative, the data is not shown.

No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting materials
Int-190		380.0 [M+H] ⁺	5-Bromo-7-(3,4-difluorophenoxy)-2,3-dihydrobenzo[b]-[1,4]dioxine and tert-Butyl carbamate
Int-191		364.2 [M+H] ⁺	7-Bromo-5-(3,4-difluorophenoxy)-2,3-dihydrobenzofuran and tert-Butyl carbamate
Int-192		402.0 [M+H] ⁺	7-Bromo-5-(((cis)-4-(trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran and tert-Butyl carbamate

Int-193		396.0 [M+H] ⁺	7-Bromo-5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran and tert-Butyl carbamate
Int-194		303.0 [M+H] ⁺	2-(5-Bromo-2-fluoro-4-methoxyphenoxy)-5-(trifluoromethyl)pyridine and tert-Butyl carbamate
Int-195		-	7-Bromo-5-(((trans)-4-(trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran and tert-Butyl carbamate
Int-196		336.0 [M+H] ⁺	1-Bromo-5-(2-chloro-4-(trifluoromethyl)phenoxy)-4-fluoro-2-methoxybenzene and tert-Butyl carbamate
Int-197		-	2-((7-Bromo-2,3-dihydrobenzofuran-5-yl)oxy)-5-(trifluoromethyl)pyridine and tert-Butyl carbamate
Int-198		411.0 [M+H] ⁺	2-((8-Bromo-2,3-dihydrobenzob[b][1,4]dioxin-6-yl)oxy)-5-(trifluoromethyl)pyridine and tert-Butyl carbamate
Int-199		268.8 [M-H] ⁻	7-Bromo-5-((4,4-difluorocyclohexyl)oxy)-2,3-dihydrobenzofuran and tert-Butyl carbamate
Int-200		387.2 [M+H] ⁺	5-Bromo-7-((4,4-difluorocyclohexyl)oxy)-2,3-dihydrobenzob[b][1,4]dioxine and tert-Butyl carbamate

Int-201		278.0 [M+H] ⁺	7-Bromo-5-(4-(difluoromethyl)-phenoxy)-2,3-dihydrobenzofuran and tert-Butyl carbamate
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Intermediate 202. 7-(4-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine hydrochloride



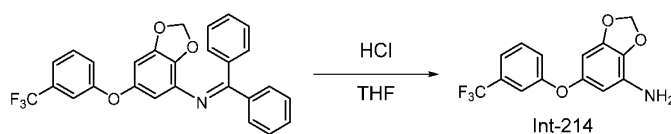
- 5 Chlorotrimethylsilane (1.320 g, 1.54 mL, 5 eq., 12.15 mmol) was added to methanol (25 mL) at 0 °C dropwise. The mixture was stirred for 30 min and tert-butyl (7-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)carbamate (1 g, 1 eq., 2.431 mmol) was added and this solution was stirred at RT for 48 h. The mixture was concentrated in vacuum to give crude title compound (808 mg, 2.11 mmol, 86.9 %, 10 90.93 % purity). LCMS: m/z 312.2 [M+H]⁺.

The following intermediates were prepared according to the procedure described for Intermediate 202 from the starting material indicated in the table.

No.	Structure	LCMS/ GCMS m/z	Starting materials
Int-203		280.0 [M+H] ⁺	tert-Butyl (7-(3,4-difluorophenoxy)-2,3-dihydrobenzo[b]-[1,4]dioxin-5-yl)carbamate
Int-204		264.2 [M+H] ⁺	tert-Butyl (5-(3,4-difluorophenoxy)-2,3-dihydrobenzofuran-7-yl)carbamate
Int-205		302.2 [M+H] ⁺	tert-Butyl (5-(((cis)-4-(trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran-7-yl)carbamate

Int-206		296.0 [M+H] ⁺	tert-Butyl (5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)carbamate
Int-207		303.0 [M+H] ⁺	tert-Butyl (4-fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)carbamate
Int-208		302.0 [M+H] ⁺	tert-Butyl (5-(((trans)-4-(trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran-7-yl)-carbamate
Int-209		313.0 [M+H] ⁺	tert-Butyl (7-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)carbamate
Int-210		270.2 [M+H] ⁺	tert-Butyl (5-((4,4-difluorocyclohexyl)oxy)-2,3-dihydrobenzofuran-7-yl)carbamate
Int-211		286.2 [M+H] ⁺	tert-Butyl (7-((4,4-difluorocyclohexyl)oxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)carbamate
Int-212		278.2 [M+H] ⁺	tert-Butyl (5-(4-(difluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)carbamate
Int-213		297.0 [M+H] ⁺	tert-Butyl (5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)-carbamate

Intermediate 214. 6-(3-(Trifluoromethyl)phenoxy)benzo[d][1,3]dioxol-4-amine

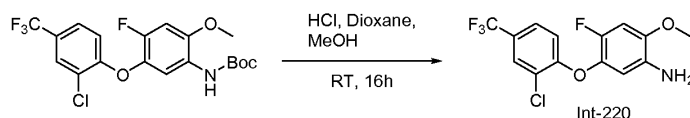


1,1-Diphenyl-N-(6-(3-(trifluoromethyl)phenoxy)benzo[d][1,3]dioxol-4-yl)-methanimine (0.800 g, 1 eq., 1.73 mmol) was dissolved in THF (10 mL) and HCl solution (253 mg, 6.93 mL, 1 molar, 4 eq., 6.93 mmol) was added at RT. A mixture was stirred at RT for 10 min and then evaporated in vacuum to give the title compound (640 mg, 1.1 mmol, 62 %, 50 % purity) which was used in the next step without further purification. LCMS: m/z 298.0 $[M+H]^+$.

The following intermediates were prepared according to the procedure described for Intermediate 214 from the starting material indicated in the table.

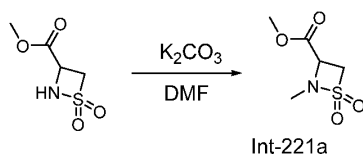
No.	Structure	LCMS/ GCMS m/z	Starting materials
Int-215		258.2 $[M+H]^+$	N-(5-((3-Fluorophenoxy)-methyl)benzofuran-7-yl)-1,1-diphenylmethanimine
Int-216		260.2 $[M+H]^+$	N-(5-((3-Fluorophenoxy)-methyl)-2,3-dihydrobenzofuran-7-yl)-1,1-diphenylmethanimine
Int-217		299.1 $[M+H]^+$	1,1-Diphenyl-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-benzo[d][1,3]dioxol-4-yl)-methanimine
Int-218		298.0 $[M+H]^+$	1,1-Diphenyl-N-(6-(4-(trifluoromethyl)phenoxy)benzo[d][1,3]dioxol-4-yl)methanimine
Int-219		311.1 $[M+H]^+$	N-(2-Methyl-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)-1,1-diphenylmethanimine

Intermediate 220. 5-(2-Chloro-4-(trifluoromethyl)phenoxy)-4-fluoro-2-methoxyaniline hydrochloride



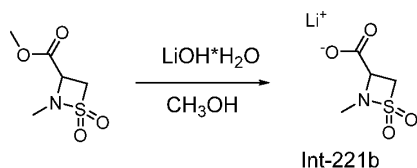
- 5 tert-Butyl (5-(2-chloro-4-(trifluoromethyl)phenoxy)-4-fluoro-2-methoxyphenyl)carbamate (0.185 g, 1 eq., 425 μ mol) was dissolved in methanol (5 mL) and the solution of HCl (155 mg, 104 μ L, 10 w-%, 1 eq., 425 μ mol) in dioxane was added dropwise at 25 °C. The mixture was stirred at 25 °C for 56 h and then concentrated under reduced pressure to give the title compound (0.150 g, 0.32 mmol, 76 %, 80 %
- 10 purity) which was used in the next step without further purification. ^1H NMR (500 MHz, DMSO- d_6) δ : 8.00 (s, 1H), 7.66 (d, 1H), 7.21 (d, 1H), 6.97 (m, 2H), 3.85 (s, 3H). LCMS: m/z 336.0 $[\text{M}+\text{H}]^+$.

Intermediate 221a. Methyl N-methylalaninate 1,1-dioxide



- 15 Methyl alaninate 1,1-dioxide (350 mg, 1 eq., 2.12 mmol) and potassium carbonate (879 mg, 3 eq., 6.36 mmol) were mixed in anhydrous DMF (5 mL) followed by adding iodomethane (1.50 g, 660 μ L, 5 eq., 10.6 mmol) in a single portion. The mixture was stirred at 27 °C for 18 h. The mixture was concentrated in vacuum, the
- 20 residue was treated with water (5 mL) and the obtained suspension was extracted with ethyl acetate (2 $\times$ 20 mL). Combined organic phases were washed with brine (2 $\times$ 15 mL), dried over sodium sulfate, filtered and concentrated in vacuum to give the title compound (116 mg, 0.39 mmol, 18 %, 60 % purity) which was used in the next step without further purification. ^1H NMR (500 MHz, DMSO- d_6) δ : 4.56 – 4.46 (m, 1H),
- 25 4.38 (m, 1H), 3.95 (m, 1H), 3.71 (s, 3H), 2.67 (s, 3H).

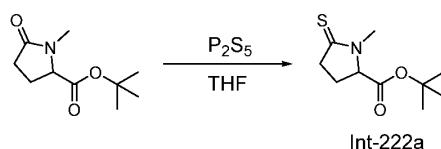
Intermediate 221b. Lithium N-methylalaninate 1,1-dioxide



Methyl N-methylalaninate 1,1-dioxide (100 mg, 1 eq., 558 μ mol) and lithium hydroxide hydrate (23.4 mg, 1 eq., 558 μ mol) were dissolved in methanol (2 mL) and stirred at RT for 16 h. The mixture was concentrated and the residue was concentrated three times with acetonitrile to give the title compound (77 mg, 0.43 mmol, 77 %, 95 %

5 purity) which was used in the next step without further purification. ^1H NMR (400 MHz, DMSO- d_6) δ : 4.10 – 3.96 (m, 2H), 3.13 (t, 1H), 2.61 (s, 3H).

Intermediate 222a. tert-Butyl 1-methyl-5-thioxopyrrolidine-2-carboxylate



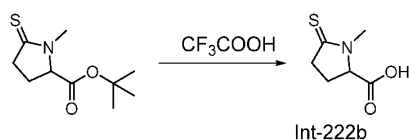
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To a solution of tert-butyl 1-methyl-5-oxopyrrolidine-2-carboxylate (470 mg, 1 eq., 2.36 mmol) in THF (3 mL) phosphorus (V) sulfide (262 mg, 0.5 eq., 1.18 mmol) was added. The mixture was refluxed with stirring for 24 h. The solution was cooled and filtered. Chloroform (20 mL) was added, and the organic phase was washed with

15 saturated sodium hydrocarbonate, (20 mL). The aqueous phase was extracted with chloroform (20 mL). The combined organic phases were dried and concentrated under vacuum to give the title compound (500 mg, 1.8 mmol, 76 %, 77 % purity) which was used in next step without further purification. GCMS: m/z 216.1 $[\text{M}]^+$.

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Intermediate 222b. 1-Methyl-5-thioxopyrrolidine-2-carboxylic acid

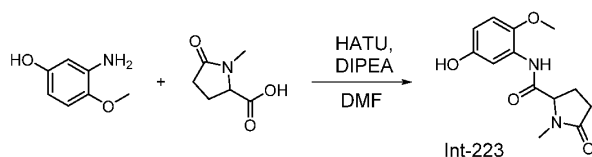


tert-Butyl 1-methyl-5-thioxopyrrolidine-2-carboxylate (500 mg, 1 eq., 2.32 mmol) was dissolved in trifluoroacetic acid (2.65 g, 1.79 mL, 10 eq., 23.2 mmol) and the solution was stirred at RT for 12 h. Then the solvent was evaporated and the residue

25 was dissolved in toluene (5 mL) and concentrated to remove excess of TFA to give the

title compound (370 mg, 1.2 mmol, 50 %, 50 % purity) which was used in the next step without further purification.

Intermediate 223. N-(5-Hydroxy-2-methoxyphenyl)-1-methyl-5-oxo-
5 pyrrolidine-2-carboxamide



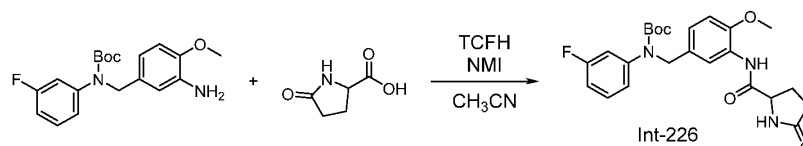
1-Methyl-5-oxopyrrolidine-2-carboxylic acid (0.5 g, 1.2 eq., 3.49 mmol) was dissolved in N,N-dimethylformamide (5 mL) and HATU (1.33 g, 1.2 eq., 3.49 mmol) was added. The solution was stirred for 5 min at RT. To this solution, 3-amino-4-methoxyphenol hydrochloride (511 mg, 1 eq., 2.91 mmol) was added, followed by the addition of DIPEA (1.05 g, 1.42 mL, 2.8 eq., 8.15 mmol). The mixture was then stirred at RT for 2 h. The solvent was removed in vacuum. The crude material was dissolved in ethyl acetate (10 mL), washed with brine (50 mL) and water (50 mL), dried and the solvent was evaporated. The residue was purified using method B to give the title compound (0.0667 g). ¹H NMR (400 MHz, DMSO-d₆) δ: 9.34 (s, 1H), 8.96 (s, 1H), 7.54 (s, 1H), 6.85 (d, 1H), 6.45 (d, 1H), 4.42 (d, 1H), 3.32 (s, 2H), 2.66 (s, 3H), 2.37 – 2.11 (m, 3H), 1.87 (s, 1H). LCMS: m/z 265.2 [M+H]⁺.

The following intermediate was prepared according to the procedure described for Intermediate 223 from the starting material indicated in the table.

No.	Structure	LCMS/ GCMS <i>m/z</i>	Starting materials
Int-224		479.5 [M-H] ⁻	2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-(tert-Butoxycarbonyl)-pyrrolidine-3-carboxylic acid
Int-225		586.192 (M+H) ⁺	2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-(((Benzyloxy)carbonyl)-

			glycyl)-5-oxopyrrolidine-2-carboxylic acid
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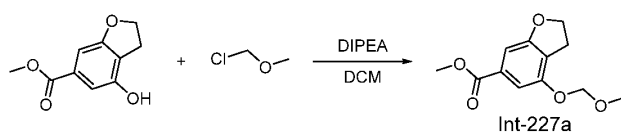
Intermediate 226. tert-Butyl (3-fluorophenyl)(4-methoxy-3-(5-oxopyrrolidine-2-carboxamido)benzyl)carbamate



5 To a mixture of tert-butyl (3-amino-4-methoxybenzyl)(3-fluorophenyl)carbamate (200 mg, 1 eq., 577 μ mol), 5-oxopyrrolidine-2-carboxylic acid (74.5 mg, 1 eq., 577 μ mol) and 1-methyl-1H-imidazole (237 mg, 5 eq., 2.89 mmol) in acetonitrile (4 mL) was added N-(chloro(dimethylamino)methylene)-N-methylmethanaminium hexafluorophosphate(V) (243 mg, 1.5 eq., 866 μ mol). The
10 mixture was stirred at RT for 18 h and then concentrated in vacuum. Water (20 mL) was added to the residue and the resulted mixture was extracted with ethyl acetate (2 $\times$ 20 mL). Organic layers were combined, washed with brine (20 mL), dried over sodium sulfate, filtered and evaporated to give the title compound (0.3 g) which was used in the next step without further purification. LCMS: m/z 358.0 [M+H]⁺.

15

Intermediate 227a. Methyl 4-(methoxymethoxy)-2,3-dihydrobenzofuran-6-carboxylate

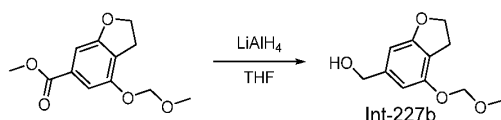


To the solution of methyl 4-hydroxy-2,3-dihydrobenzofuran-6-carboxylate (2 g, 1 eq., 10.30 mmol) and N-ethyl-N-isopropylpropan-2-amine (3.994 g, 5.38 mL, 3 eq., 30.90 mmol) in DCM (80 mL) chloro(methoxy)methane (1.309 g, 1.24 mL, 95 w-%, 1.5 eq., 15.45 mmol) was added at 0 °C followed by stirring the mixture at 20 °C for 18 h. The mixture was washed with brine (3 $\times$ 10 mL), dried over sodium sulfate, filtered and evaporated to afford the title compound (2.3 g, 8.834 mmol, 85.78 %, 90.75 %
25 purity) which was used in the next step without further purification. ¹H NMR (500

MHz, Chloroform-d) δ : 7.29 (s, 1H), 7.13 (s, 1H), 5.23 (s, 2H), 4.63 (t, 2H), 3.87 (s, 3H), 3.49 (s, 3H), 3.20 (t, 2H).

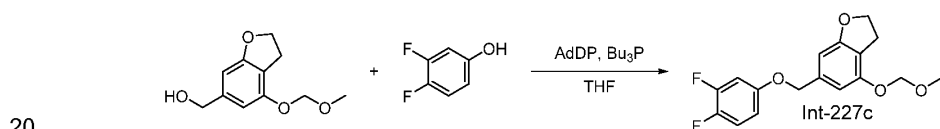
Intermediate 227b. (4-(Methoxymethoxy)-2,3-dihydrobenzofuran-6-yl)-

5 methanol



The solution of LiAlH₄ (127 mg, 2 eq., 3.36 mmol) in THF (5 mL) was cooled to 0 °C and the solution of methyl 4-(methoxymethoxy)-2,3-dihydrobenzofuran-6-carboxylate (400 mg, 1 eq., 1.68 mmol) in THF (5 mL) was added dropwise. The cooling bath was removed and the mixture was stirred at 20 °C for 18 h. The mixture was cooled to 0 °C and water (130 μ L) and 30 % solution of K₂CO₃ (4 $\times$ 130 μ L) were added dropwise. The mixture was filtered and the residue was washed by THF (5 mL). The organic layer was separated and concentrated to afford the crude title compound (340 mg, 1.48 mmol, 88.0 %, 91.31 % purity) as yellow oil, which was used in the next step without further purification. ¹H NMR (400 MHz, Chloroform-d) δ : 6.59 (s, 1H), 6.48 (s, 1H), 5.17 (s, 2H), 4.66 – 4.48 (m, 4H), 3.47 (s, 3H), 3.14 (t, 2H).

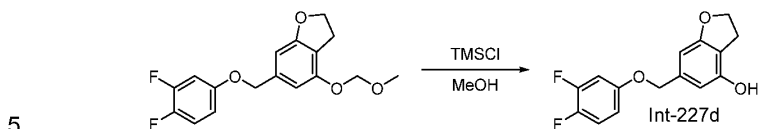
Intermediate 227c. 5-((3,4-Difluorophenoxy)methyl)-4-(methoxymethoxy)-2,3-dihydrobenzofuran



To the mixture of (7-(methoxymethoxy)-2,3-dihydrobenzofuran-5-yl)methanol (200 mg, 1 eq., 951 μ mol) and 3,4-difluorophenol (124 mg, 1 eq., 951 μ mol) in THF (40 mL) at 0 °C under Ar atmosphere were added tributylphosphane (385 mg, 0.48 mL, 2 eq., 1.90 mmol) and then (E)-diazene-1,2-diylbis(piperidin-1-ylmethanone) (480 mg, 2 eq., 1.90 mmol). The mixture was stirred at 20 °C for 18 h. The solvent of the mixture was evaporated under reduced pressure. The residue was purified by reverse phase HPLC (water-acetonitrile) to afford the title compound (178 mg, 552 μ mol, 58.1 %). ¹H

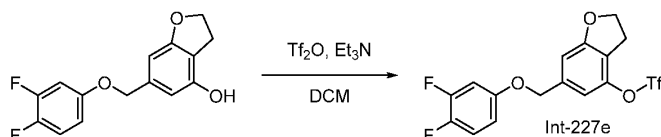
NMR (500 MHz, Chloroform-*d*) δ : 7.04 (q, 1H), 6.83 – 6.71 (m, 1H), 6.64 (s, 2H), 6.54 (s, 1H), 5.19 (s, 2H), 4.92 (s, 2H), 4.60 (t, 2H), 3.49 (s, 3H), 3.17 (t, 2H).

Intermediate 227d. 5-((3,4-Difluorophenoxy)methyl)-2,3-dihydrobenzofuran-4-ol

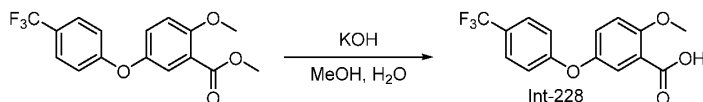


Chlorotrimethylsilane (146 mg, 170 μ L, 2 eq., 1.34 mmol) was added to MeOH (4 mL) at 0 °C dropwise. The mixture was stirred for 30 min and 5-((3,4-difluorophenoxy)methyl)-4-(methoxymethoxy)-2,3-dihydrobenzofuran (216 mg, 1 eq., 670 μ mol) in MeOH (1 mL) was added followed by stirring at 20 °C for 18 h. The mixture
10 was concentrated under reduced pressure to give crude title compound (178 mg, 623 μ mol, 92.9 %, 97.37 % purity) as a beige solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ : 9.50 (s, 1H), 7.34 – 7.27 (m, 1H), 7.14 – 7.01 (m, 1H), 6.83 – 6.73 (m, 1H), 6.34 (s, 1H), 6.28 (s, 1H), 4.92 (s, 2H), 4.47 (t, 2H), 2.99 (t, 2H).

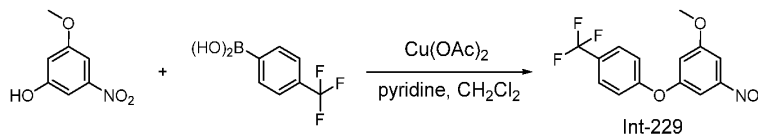
Intermediate 227e. 6-((3,4-Difluorophenoxy)methyl)-2,3-dihydrobenzofuran-4-yl trifluoromethanesulfonate
15



To a solution of 5-((3,4-difluorophenoxy)methyl)-2,3-dihydrobenzofuran-4-ol (178 mg, 1 eq., 640 μ mol) and triethylamine (84.2 mg, 116 μ L, 1.3 eq., 832 μ mol) in DCM (5 mL) trifluoromethanesulfonic anhydride (199 mg, 118 μ L, 1.1 eq., 704 μ mol) was added dropwise at 0 °C followed by stirring the mixture at 20 °C for 18 h. DCM (10 mL) was added to mixture and the solution was washed with NaHSO₄ solution (2 $\times$ 5 mL), dried over sodium sulfate, filtered and evaporated to give the title compound (238 mg, 0.52 mmol, 82 %, 90 % purity) as a brown oil, which was used in the next step without further purification. ¹H NMR (500 MHz, Chloroform-*d*) δ : 7.06 (q, 1H), 6.84 (s, 1H), 6.80 (s, 1H), 6.79 – 6.72 (m, 1H), 6.66 – 6.60 (m, 1H), 4.96 (s, 2H), 4.68 (t, 2H), 3.34 (t, 2H).
20
25

Intermediate 228. 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)benzoic acid

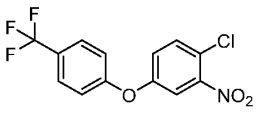
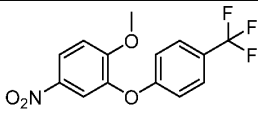
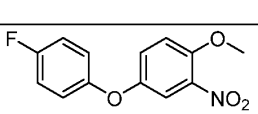
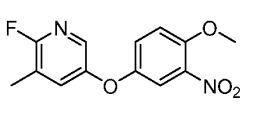
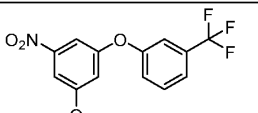
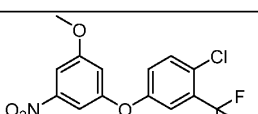
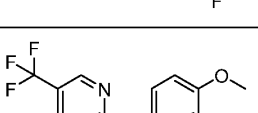
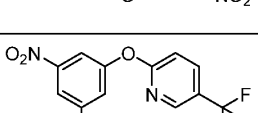
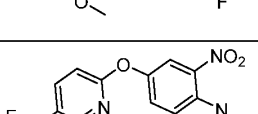
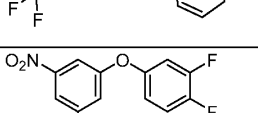
Solution of potassium hydroxide (51.6 mg, 1.5 eq., 919 μ mol) in water (0.6 mL) was added to a solution of methyl 2-methoxy-5-(4-(trifluoromethyl)phenoxy)-
 5 benzoate (0.200 g, 1 eq., 613 μ mol) in methanol (5 mL). The mixture was stirred for 16 h at 25 °C and then concentrated under reduced pressure. The residue was dissolved in water (5 mL) and washed with EtOAc (2×2 mL). The aqueous mixture was acidified with NaHSO₄ (5 mL, 15 % in water). The resulting mixture was extracted with EtOAc (2×8 mL). The combined organic layers were dried under sodium sulfate and
 10 concentrated under reduced pressure to give the title compound (0.08 g, 0.26 mmol, 42 %). LCMS: m/z 311.0 [M-H]⁻.

Intermediate 229. 1-Methoxy-3-nitro-5-(4-(trifluoromethyl)phenoxy)benzene

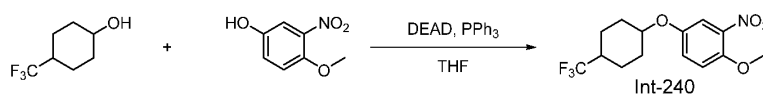
15 3-Methoxy-5-nitrophenol (0.5 g, 1 eq., 2.96 mmol), 4-trifluorophenylboronic acid (0.7 g, 1.5 eq., 4.43 mmol), pyridine (1.2 g, 1.2 mL, 5 eq., 14.8 mmol), diacetoxy-copper (0.54 g, 1 eq., 2.96 mmol) and powdered molecular sieves 4 Å (1 g) were suspended in DCM (15 mL). The air was bubbled through the resulting solution for 30 min and the mixture was stirred at RT overnight. The mixture was filtered, the filtrate
 20 was washed with water (2×30 mL), dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by method A to afford the title compound. LCMS: m/z 314.2 [M+H]⁺.

The following intermediates were prepared according to the procedure described
 25 for Intermediate 229 from the starting material indicated in the table.

No.	Structure	LCMS/ GCMS m/z	Starting materials
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Int-230		317.1 [M] ⁺	4-(Trifluoromethyl)phenylboronic acid and 4-Chloro-3-nitrophenol
Int-231		312.0 [M+H] ⁺	4-(Trifluoromethyl)phenylboronic acid and (2-Methoxy-5-nitrophenol
Int-232		264.0 [M+H] ⁺	4-Methoxy-3-nitrophenol and 4-Fluorobenzeneboronic acid
Int-233		279.1 [M+H] ⁺	4-Methoxy-3-nitrophenol and (6-Fluoro-5-methylpyridin-3-yl)-boronic acid
Int-234		314.2 [M+H] ⁺	3-Bromo-5-nitro anisole and 3-(Trifluoromethyl)phenol
Int-235		346.3 [M+H] ⁺	3-Bromo-5-nitro anisole and 4-Chloro-3-(trifluoromethyl)-phenol
Int-236		315.1 [M+H] ⁺	4-Methoxy-3-nitrophenol and 2-Chloro-5-(trifluoromethyl)-pyridine
Int-237		316.1 [M+H] ⁺	3-Methoxy-5-nitrophenol and 2-Chloro-5-(trifluoromethyl)-pyridine
Int-238		337.1 [M+H] ⁺	8-Nitroquinolin-6-ol and 2-Chloro-5-(trifluoromethyl)-pyridine
Int-239		283.1 [M+H] ⁺	3,4-Difluorophenylboronic acid and 3-Methoxy-5-nitrophenol

Intermediate 240. 1-Methoxy-2-nitro-4-((4-(trifluoromethyl)cyclohexyl)oxy)-benzene



To a mixture of 4-methoxy-3-nitrophenol (0.25 g, 1.47 mmol), 4-trifluoromethyl-1-hydroxycyclohexane (0.20 ml, 1.47 mmol) and triphenylphosphine (465 mg, 1.77 mmol) in anhydrous THF (10 mL) under nitrogen was added DEAD (0.28 ml, 1.77 mmol) dropwise at RT and the mixture was left stirring for 24 h. The mixture was diluted with Et₂O (30 ml) and washed with NaOH (2×10 ml), water (10 ml) and brine (10 ml). The organic phase was dried over sodium sulfate, filtered and concentrated. The crude residue was purified further with the purification method A to give 0.1 g of the title compound. LCMS: m/z 320.28 [M+H]⁺

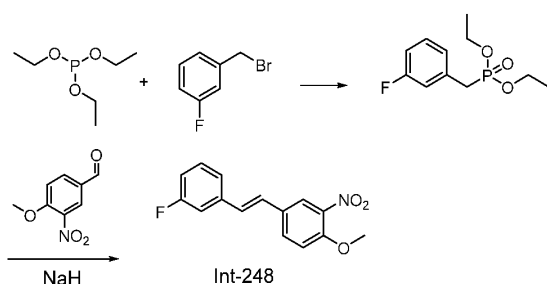
10

The following intermediates were prepared according to the procedure described for Intermediate 240 from the starting material indicated in the table.

No.	Structure	LCMS/ GCMS m/z	Starting materials
Int-241		320.1 [M+H] ⁺	3-Methoxy-5-nitrophenol and 4-Trifluoromethyl-1-hydroxycyclohexane
Int-242		320.1 [M+H] ⁺	4-Methoxy-3-nitrophenol and 4-Trifluoromethyl-1-hydroxycyclohexane
Int-243		320.2 [M+H] ⁺	4-Methoxy-3-nitrophenol and 3-(Trifluoromethyl)cyclohexanol, mixture of cis/trans isomers
Int-244		320.2 [M+H] ⁺	4-Fluoro-3-nitrophenol and 4-Trifluoromethyl-1-hydroxycyclohexane
Int-245		320.3 [M+H] ⁺	2-Methoxy-5-nitrophenol and 4-Trifluoromethyl-1-hydroxycyclohexane

Int-246		320.3 [M+H] ⁺	2-Methoxy-5-nitrophenol and 4-Trifluoromethyl-1-hydroxy-cyclohexane
Int-247		288.1 [M+H] ⁺	3-Methoxy-5-nitrophenol and 1,1-Difluoro-4-hydroxycyclohexane

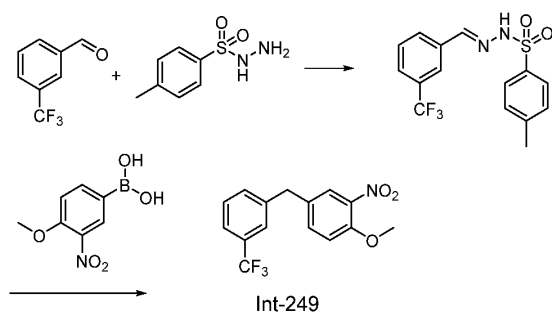
Intermediate 248. (E)-4-(3-Fluorostyryl)-1-methoxy-2-nitrobenzene



- Triethyl phosphine (5.6 ml, 32.6 mmol) was added to 3-fluorobenzyl bromide (2.0 ml, 16.3 mmol) at RT under N₂. The resulting mixture was heated at 150 °C for 2 h. The mixture was cooled and purified by flash chromatography to yield diethyl (3-fluorobenzyl)phosphonate. To the mixture of diethyl (3-fluorobenzyl)phosphonate (0.82 g, 3.3 mmol) in dry THF (10 ml) at 0 – 5 °C was added NaH (0.27 g, 11.0 mmol). After 30 min 4-methoxy-3-nitro benzaldehyde (0.5 g, 2.8 mmol) in dry THF (10 ml) was added dropwise to the mixture followed by stirred at RT for 3 h. The mixture was cooled, quenched with ice water (20 ml), made acidic with 2 M HCl and then extracted with ethyl acetate (2 x 10 ml). The combined organic layers were washed with water, dried, evaporated and then purified by flash chromatography to yield the title compound.
- LCMS *m/z* 274.2 [M+H]⁺. ¹H NMR (Chloroform-d, 400 MHz) δ: 8.0-8.0 (m, 1H), 7.6-7.7 (m, 1H), 7.2-7.4 (m, 4H), 6.9-7.1 (m, 3H), 3.99 (s, 3H).

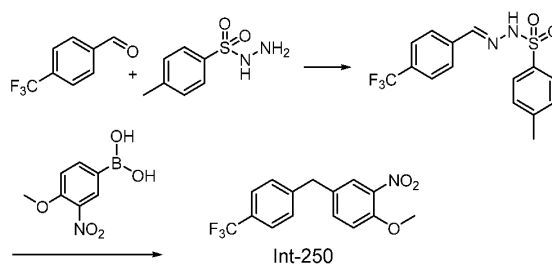
Intermediate 249. 1-Methoxy-2-nitro-4-(3-(trifluoromethyl)benzyl)benzene

110



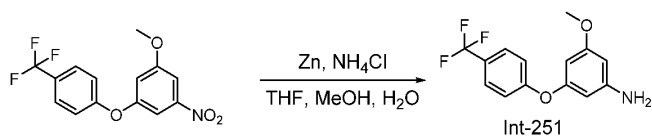
A mixture of 3-(trifluoromethyl)benzaldehyde (0.20 ml, 1.4 mmol) and toluene sulfonylhydrazide (0.27 g, 1.4 mmol) in 1,4-dioxane (10 ml) was heated at 60 °C for 90 min. To the obtained crude product of (E)-4-methyl-N'-(3-(trifluoromethyl)benzylidene)benzenesulfonylhydrazide (0.4 g, 1.168 mmol) was added K₂CO₃ (0.24 g, 1.8 mmol) and 4-methoxy-3-nitrophenylboronic acid (0.23 g, 1.2 mmol). The mixture was heated under nitrogen atmosphere at 110 °C for 4 h followed by cooling to RT. The mixture was quenched with 2 M NaHCO₃ (5 ml) and then extracted with ethyl acetate (2 x 10 ml). The combined organic layers were washed with water, dried, evaporated and purified by flash chromatography to yield the title compound. LCMS *m/z* 312.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ: 3.89 - 4.00 (m, 3 H), 4.02 (s, 2 H), 7.03 (d, 1 H), 7.27 - 7.35 (m, 3 H), 7.49 - 7.62 (m, 2 H), 7.65 - 7.70 (m, 1 H).

Intermediate 250. 1-Methoxy-2-nitro-4-(4-(trifluoromethyl)benzyl)benzene



1-Methoxy-2-nitro-4-(4-(trifluoromethyl)benzyl)benzene was prepared using the procedure described for Intermediate 234 using 4-(trifluoromethyl)benzaldehyde as starting material. LCMS *m/z* 312.3 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ: 3.90 - 4.04 (m, 5 H), 6.99 - 7.26 (m, 1 H), 7.32 - 7.34 (m, 1 H), 7.39 - 7.63 (m, 4 H), 7.69 (d, 1 H).

Intermediate 251. 1-Methoxy-2-nitro-4-(4-(trifluoromethyl)benzyl)benzene



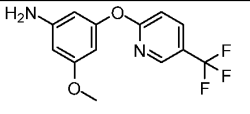
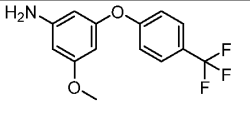
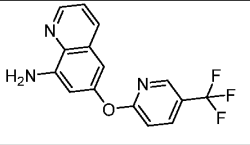
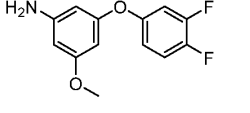
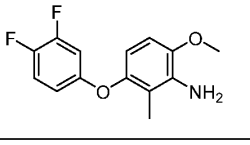
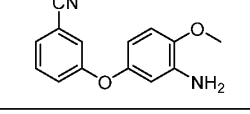
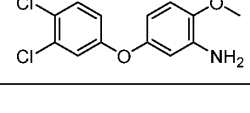
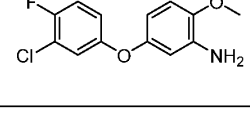
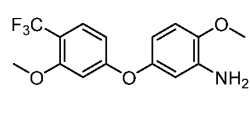
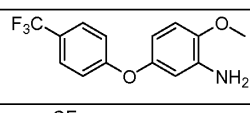
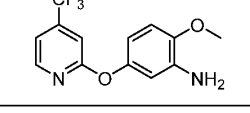
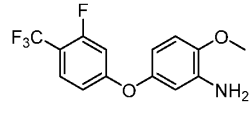
A mixture of 1-methoxy-3-nitro-5-(4-(trifluoromethyl)phenoxy)benzene (0.1 g, 1 eq., 0.32 mmol), zinc (0.21 g, 10 eq., 3.2 mmol), ammonium chloride (0.17 g, 10 eq., 3.2 mmol) in THF (5 ml), MeOH (2.5 ml) and water (2.5 ml) was stirred at RT for 4 h.

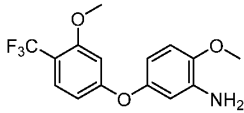
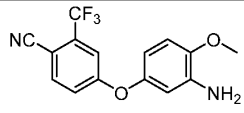
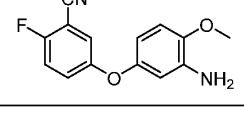
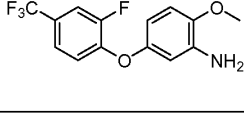
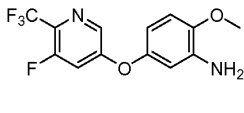
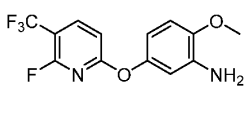
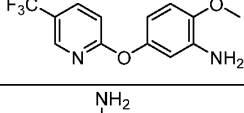
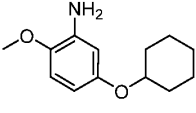
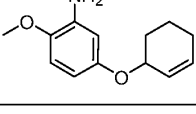
- 5 The mixture was filtered through celite. The filtrate was washed with water (2×30 mL), dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography to afford the title compound. LCMS m/z 284.1 $[M]^+$

- 10 The following intermediates were prepared according to the procedure described for Intermediate 251 from the starting material indicated in the table.

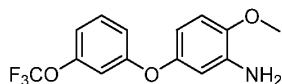
No.	Structure	LCMS/ GCMS m/z	Starting materials
Int-252		244.2 $[M+H]^+$	(E)-4-(3-fluorostyryl)-1-methoxy-2-nitrobenzene
Int-253		290.6 $[M+H]^+$	1-Methoxy-2-nitro-4-((4-(trifluoromethyl)cyclohexyl)oxy)-benzene
Int-254		282.2 $[M+H]^+$	1-Methoxy-2-nitro-4-(3-(trifluoromethyl)benzyl)benzene
Int-255		286.1 $[M]^+$	1-Chloro-2-nitro-4-(4-(trifluoromethyl)phenoxy)benzene
Int-256		284.1 $[M+H]^+$	1-Methoxy-4-nitro-2-(4-(trifluoromethyl)phenoxy)benzene
Int-257		234.1 $[M+H]^+$	4-(4-Fluorophenoxy)-1-methoxy-2-nitrobenzene

Int-258		284.1 [M+H] ⁺	1-Methoxy-3-nitro-5-(4-(tri-fluoromethyl)phenoxy)benzene
Int-259		249.3 [M+H] ⁺	2-Fluoro-5-(4-methoxy-3-nitro-phenoxy)-3-methylpyridine
Int-260		291.1 [M+H] ⁺	1-Methoxy-3-nitro-5-((4-(tri-fluoromethyl)cyclohexyl)oxy)-benzene
Int-261		291.1 [M+H] ⁺	1-Methoxy-2-nitro-4-((4-(tri-fluoromethyl)cyclohexyl)oxy)-benzene
Int-262		291.2 [M+H] ⁺	1-Methoxy-2-nitro-4-((3-(tri-fluoromethyl)cyclohexyl)oxy)-benzene
Int-263		278.1 [M+H] ⁺	1-Fluoro-2-nitro-4-((4-(trifluoro-methyl)cyclohexyl)oxy)benzene
Int-264		290.1 [M+H] ⁺	1-Methoxy-4-nitro-2-(((1r,4r)-4-(trifluoromethyl)cyclohexyl)oxy)benzene
Int-265		290.1 [M+H] ⁺	1-Methoxy-4-nitro-2-(((1s,4s)-4-(trifluoromethyl)cyclohexyl)oxy)benzene
Int-266		284.3 [M+H] ⁺	1-Methoxy-3-nitro-5-(3-(tri-fluoromethyl)phenoxy)benzene
Int-267		318.2 [M+H] ⁺	1-Chloro-4-(3-methoxy-5-nitro-phenoxy)-2-(trifluoromethyl)-benzene
Int-268		259.1 [M+H] ⁺	1-((4,4-Difluorocyclohexyl)-oxy)-3-methoxy-5-nitrobenzene

Int-269		286.1 [M+H] ⁺	2-(3-Methoxy-5-nitrophenoxy)-5-(trifluoromethyl)pyridine
Int-270		284.1 [M+H] ⁺	1-Methoxy-3-nitro-5-(4-(trifluoromethyl)phenoxy)benzene
Int-271		306.0 [M+H] ⁺	8-Nitro-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)quinolone
Int-272		254.0 [M+H] ⁺	1,2-Difluoro-4-(3-methoxy-5-nitrophenoxy)benzene
Int-273		265.6 [M+H] ⁺	1-(3,4-Difluorophenoxy)-4-methoxy-2-methyl-3-nitrobenzene
Int-274		241.5 [M+H] ⁺	3-(4-Methoxy-3-nitrophenoxy)benzonitrile
Int-275		285.1 [M+H] ⁺	1,2-Dichloro-4-(4-methoxy-3-nitrophenoxy)benzene
Int-276		267.1 [M+H] ⁺	2-Chloro-1-fluoro-4-(4-methoxy-3-nitrophenoxy)benzene
Int-277		314.5 [M+H] ⁺	2-Methoxy-4-(4-methoxy-3-nitrophenoxy)-1-(trifluoromethyl)benzene
Int-278		284.4 [M+H] ⁺	1-Methoxy-2-nitro-4-(4-(trifluoromethyl)phenoxy)benzene
Int-279		285.5 [M+H] ⁺	2-(4-Methoxy-3-nitrophenoxy)-4-(trifluoromethyl)pyridine
Int-280		302.5 [M+H] ⁺	2-Fluoro-4-(4-methoxy-3-nitrophenoxy)-1-(trifluoromethyl)benzene

Int-281		314.5 [M+H] ⁺	2-Methoxy-4-(4-methoxy-3-nitrophenoxy)-1-(trifluoromethyl)benzene
Int-282		309.5 [M+H] ⁺	4-(4-Methoxy-3-nitrophenoxy)-2-(trifluoromethyl)benzonitrile
Int-283		259.5 [M+H] ⁺	2-Fluoro-5-(4-methoxy-3-nitrophenoxy)benzonitrile
Int-284		302.4 [M+H] ⁺	2-Fluoro-1-(4-methoxy-3-nitrophenoxy)-4-(trifluoromethyl)benzene
Int-285		303.3 [M+H] ⁺	3-Fluoro-5-(4-methoxy-3-nitrophenoxy)-2-(trifluoromethyl)pyridine
Int-286		303.3 [M+H] ⁺	2-Fluoro-6-(4-methoxy-3-nitrophenoxy)-3-(trifluoromethyl)pyridine
Int-287		285.4 [M+H] ⁺	2-(4-Methoxy-3-nitrophenoxy)-5-(trifluoromethyl)pyridine
Int-288		222.2 [M+H] ⁺	4-(Cyclohexyloxy)-1-methoxy-2-nitrobenzene
Int-289		220.2 [M+H] ⁺	4-(Cyclohex-2-en-1-yloxy)-1-methoxy-2-nitrobenzene

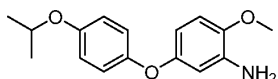
Intermediate 290. 2-Methoxy-5-(3-(trifluoromethoxy)phenoxy)aniline



- A mixture of 1-methoxy-2-nitro-4-(3-(trifluoromethoxy)phenoxy)benzene (0.050 g, 0.152 mmol), zinc powder (0.050 g, 0.759 mmol), NH₄Cl (0.041 g, 0.759 mmol), ethanol (1.5 ml) and water (0.5 ml) was stirred at 50 °C until the reaction was completed. The mixture was filtered through a pad of Celite. Celite layer was further

washed with ethanol and the filtrate was evaporated to afford 0.040 g of the title compound. LCMS: m/z 299.8 $[M+H]^+$.

Intermediate 291. 5-(4-Isopropoxyphenoxy)-2-methoxyaniline

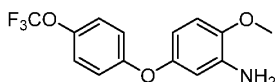


5

The compound was prepared according to the procedure of Intermediate 257 starting from 4-(4-isopropoxyphenoxy)-1-methoxy-2-nitrobenzene (0.22 g, 0.725 mmol) using 4 eq. of zinc powder and 4 eq. of NH_4Cl . Raw product was purified by reverse phase flash chromatography to afford the title compound. Yield: 0.044 g.

10 LCMS: m/z 273.9 $[M+H]^+$.

Intermediate 292. 2-Methoxy-5-(4-(trifluoromethoxy)phenoxy)aniline

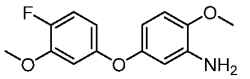
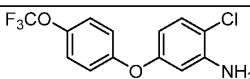


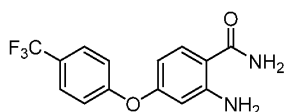
15 A mixture of 1-methoxy-2-nitro-4-(4-(trifluoromethoxy)phenoxy)benzene (0.12 g, 0.364 mol), iron powder (0.061 g, 1.093 mmol), anhydrous $CaCl_2$ (0.040 g, 0.364 mmol), ethanol (1.0 ml) and water (0.25 ml) was stirred at 60 °C until the reaction was completed. The mixture was filtered through a pad of Celite. Celite layer was washed with EtOAc. The filtrate was washed with water (2x), dried and evaporated to afford 0.090 g of the title compound. LCMS: m/z 299.7 $[M]^+$

20

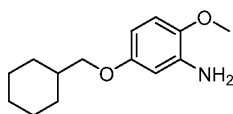
The following intermediates were prepared according to the procedure described for Intermediate 292 from the starting material indicated in the table.

No.	Structure	LCMS m/z	Starting materials
Int-293		287.9 $[M]^+$	1-Fluoro-2-nitro-4-(4-(trifluoromethoxy)phenoxy)benzene
Int-294		265.6 $[M]^+$	4-(4-(Difluoromethyl)phenoxy)-1-methoxy-2-nitrobenzene

Int-295		263.6 [M] ⁺	1-Fluoro-2-methoxy-4-(4-methoxy-3-nitrophenoxy)-benzene
Int-296		304.5 [M+H] ⁺	1-Chloro-2-nitro-4-(4-(trifluoromethoxy)phenoxy)benzene

Intermediate 297. 2-Amino-4-(4-(trifluoromethyl)phenoxy)benzamide

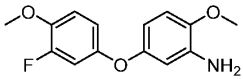
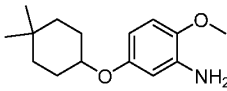
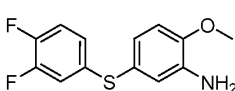
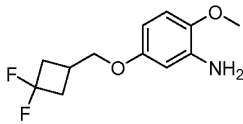
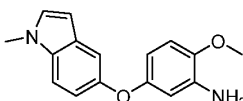
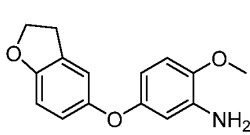
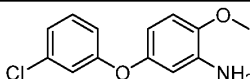
- The compound was prepared according to the procedure of Intermediate 292
- 5 starting from 2-nitro-4-(4-(trifluoromethyl)phenoxy)benzonitrile (0.36 g, 1.168 mmol). Raw product was purified by flash chromatography to afford the title compound. Yield: 0.21g. LCMS: *m/z* 296.8 [M]⁺.

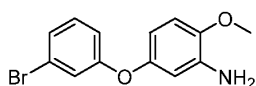
Intermediate 298. 5-(Cyclohexylmethoxy)-2-methoxyaniline

- 10 A mixture of 4-(cyclohexylmethoxy)-1-methoxy-2-nitrobenzene (0.26 g, 0.98 mol), zinc powder (0.32 g, 4.90 mmol, 5.0 eq.), NH₄Cl (0.262 g, 4.90 mmol, 5.0 eq.), THF (3.0 ml), methanol (0.75 ml) and water (0.75 ml) was stirred at RT until the reaction was completed. The mixture was filtered through a pad of Celite. Celite layer
- 15 was washed with EtOAc. The filtrate was washed with water (2x), dried and evaporated. Crude was purified by flash chromatography to afford 0.15 g of the title compound. LCMS: *m/z* 235.4 [M]⁺

- The following intermediates were prepared according to the procedure described
- 20 for Intermediate 298 from the starting material indicated in the table.

No.	Structure	Purification; LCMS <i>m/z</i>	Starting materials
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Int-299		Crude; 263.6 [M] ⁺	2-Fluoro-1-methoxy-4-(4-methoxy-3-nitrophenoxy)-benzene
Int-300		Crude; 249.4 [M] ⁺	4-((4,4-Dimethylcyclohexyl)-oxy)-1-methoxy-2-nitrobenzene
Int-301		Flash chromatography ; 267.7 [M] ⁺	(3,4-Difluorophenyl)(4-methoxy-3-nitrophenyl)sulfane
Int-302		Crude; 244.6 [M+H] ⁺	4-((3,3-Difluorocyclobutyl)-methoxy)-1-methoxy-2-nitrobenzene
Int-303		Flash chromatography ; 269.5 [M+H] ⁺	5-(4-Methoxy-3-nitrophenoxy)-1-methyl-1H-indole
Int-304		Flash chromatography ; 258.5 [M+H] ⁺	5-(4-Methoxy-3-nitrophenoxy)-2,3-dihydrobenzofuran
Int-305		Crude; 251.1 [M+H] ⁺	4-(3-Chlorophenoxy)-1-methoxy-2-nitrobenzene

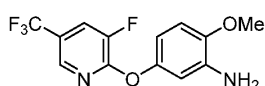
Intermediate 306. 5-(3-Bromophenoxy)-2-methoxyaniline

- The compound was prepared using the procedure as described for Intermediate 298 starting from 4-(3-bromophenoxy)-1-methoxy-2-nitrobenzene (0.46 g, 1.419 mmol) using 7.5 eq. of zinc powder and 7.5 eq. of NH₄Cl. Yield: 0.34 g. LCMS: *m/z* 294.2 [M]⁺.

The following intermediates were prepared according to the procedure described for Intermediate 306 from the starting material indicated in the table.

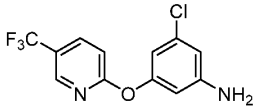
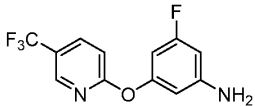
No.	Structure	Purification; LCMS m/z	Starting materials
Int-307		Flash chromatography; 332.2 [M] ⁺	1-Bromo-2-nitro-4-(3-(trifluoromethyl)phenoxy)benzene
Int-308		Crude; 272.4 [M+H] ⁺	1-(4-Fluorophenoxy)-3-nitro-5-(trifluoromethyl)benzene
Int-309		Crude; 251.2 [M+H] ⁺	4-(4-Chlorophenoxy)-1-methoxy-2-nitrobenzene
Int-310		Crude; 269.2 [M+H] ⁺	1-Chloro-2-fluoro-4-(4-methoxy-3-nitrophenoxy)-benzene
Int-311		Crude; 248.6 [M+H] ⁺	4-(4-(Fluoromethyl)phenoxy)-1-methoxy-2-nitrobenzene

5 **Intermediate 312.** 5-((3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyaniline

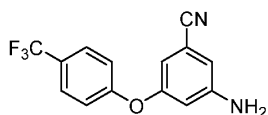


The compound was prepared according to the procedure of Intermediate 298 starting from 3-fluoro-2-(4-methoxy-3-nitrophenoxy)-5-(trifluoromethyl)pyridine (0.50 g, 1.505 mmol) using 10 eq. of zinc powder and 10 eq. of NH₄Cl. Yield: 0.43 g. LCMS: *m/z* 303.5 [M+H]⁺.

The following intermediates were prepared according to the procedure described for Intermediate 312 from the starting material indicated in the table.

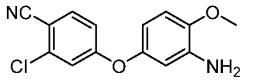
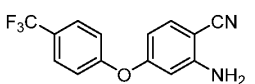
No.	Structure	Purification; LCMS m/z	Starting materials
Int-313		Crude; 289.5 [M+H] ⁺	2-(3-Chloro-5-nitrophenoxy)- 5-(trifluoromethyl)pyridine
Int-314		Flash chromatography ; 273.6 [M+H] ⁺	2-(3-Fluoro-5-nitrophenoxy)-5- (trifluoromethyl)pyridine

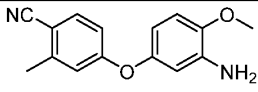
Intermediate 315. 3-Amino-5-(4-(trifluoromethyl)phenoxy)benzonitrile



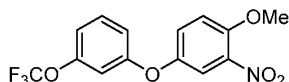
- To a mixture of 3-nitro-5-(4-(trifluoromethyl)phenoxy)benzonitrile (0.22 g, 0.714 mmol) in 1,4-dioxane (3.5 ml) was added tin(II) chloride dihydrate (0.805 g, 3.57 mmol) dissolved in 37 % aqueous HCl (1.0 ml). The mixture was stirred at RT until the reaction was completed. The mixture was made basic with 6 M NaOH solution. DCM was added and the mixture was filtered through a short plug of Celite. Celite was washed with DCM. Filtrate was dried and solvent evaporated to afford the title compound. Yield: 0.14 g. LCMS: m/z 279.3 [M+H]⁺.

The following intermediates were prepared according to the procedure described for Intermediate 315 from the starting material indicated in the table.

No.	Structure	Purification; LCMS m/z	Starting materials
Int-316		Crude; 276.2 [M+H] ⁺	2-Chloro-4-(4-methoxy-3-nitrophenoxy)benzonitrile
Int-317		Flash chromatography ; 279.2 [M+H] ⁺	2-Nitro-4-(4-(trifluoromethyl)- phenoxy)benzonitrile

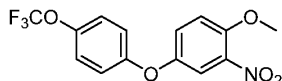
Int-318		Crude; 255.5 [M+H] ⁺	4-(4-Methoxy-3-nitro- phenoxy)-2-methylbenzonitrile
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Intermediate 319. 1-Methoxy-2-nitro-4-(3-(trifluoromethoxy)phenoxy)benzene



To a mixture of 4-methoxy-3-nitrophenol (0.169 g, 1.00 mmol), 3-(trifluoro-
5 methoxy)phenylboronic acid (0.448 g, 2.18 mmol), anhydrous Cu(OAc)₂ (0.182 g, 1.00
mmol) and powdered 4 Å molecular sieves (0.25 g) in dry DCM (7.5 ml) was added
DIPEA (0.871 ml, 5.00 mmol). The mixture was stirred at RT until maximal conversion
was obtained (48 h). The mixture was filtered through a plug of Celite and the Celite
layer was washed with EtOAc. Filtrate was washed with 5 % aqueous NH₄OH solution,
10 dried and evaporated. Crude was purified by reverse phase flash chromatography to
afford 0.050 g of the title compound. LCMS: *m/z* 330.2 [M+H]⁺.

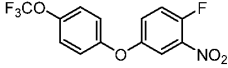
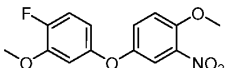
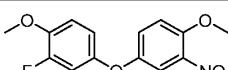
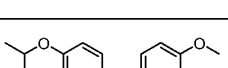
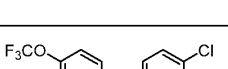
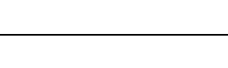
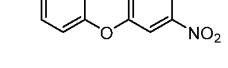
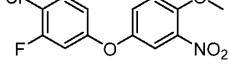
Intermediate 320. 1-Methoxy-2-nitro-4-(4-(trifluoromethoxy)phenoxy)benzene

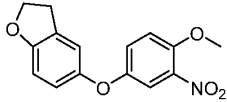
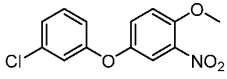


To a mixture of 4-methoxy-3-nitrophenol (0.338 g, 2.00 mmol), 4-(trifluoro-
15 methoxy)phenylboronic acid (0.618 g, 3.00 mmol), anhydrous Cu(OAc)₂ (0.363 g, 2.00
mmol) and powdered 4 Å molecular sieves (0.25 g) in dry DCM (15 ml) was added
pyridine (0.809 ml, 10.0 mmol). The mixture was stirred at RT until maximal
conversion was obtained (24-48 h). The mixture was filtered through a plug of Celite
20 and the Celite layer was washed with DCM. Filtrate was washed with 5 % aqueous
NH₄OH solution, dried and evaporated. Crude was purified by flash chromatography to
afford 0.33 g of the title compound. LCMS: *m/z* 330.2 [M+H]⁺.

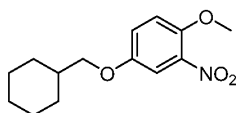
The following intermediates were prepared according to the procedure described
25 for Intermediate 320 from the starting material indicated in the table.

No.	Structure	LCMS <i>m/z</i> / ¹ H NMR (400 MHz,	Starting materials
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		CDCl₃	
Int-321		δ : 7.63-7.69 (m, 1H), 7.23-7.32 (m, 4H), 7.01-7.08 (m, 2H)	4-Fluoro-3-nitrophenol and 4-(Trifluoromethoxy)- phenylboronic acid (2.2 eq.)
Int-322		294.0 [M+H] ⁺	4-Methoxy-3-nitrophenol and 4-Fluoro-3-methoxy- phenylboronic acid (2.2 eq.)
Int-323		294.1 [M+H] ⁺	4-Methoxy-3-nitrophenol and 3-Fluoro-4-methoxy- phenylboronic acid (1.8 eq.)
Int-324		δ : 7.55 (d, 1H), 7.19- 7.29 (m, 3H), 7.07- 7.14 (m, 2H), 6.92 (ddd, 1H), 3.97 (s, 3H)	4-Methoxy-3-nitrophenol and 3-Bromophenylboronic acid (2.2 eq.)
Int-325		304.1 [M+H] ⁺	4-Methoxy-3-nitrophenol and (4-Isopropoxyphenyl)- boronic acid (1.5 eq.)
Int-326		δ : 7.51 (d, 1H), 7.47 (d, 1H), 7.24-7.30 (m, 2H), 7.16 (dd, 1H), 7.05-7.11 (m, 2H)	4-Chloro-3-nitrophenol and (4-(Trifluoromethoxy)- phenyl)boronic acid (1.5 eq)
Int-327		δ : 7.70 (d, 1H), 7.47- 7.57 (m, 2H), 7.47 (d, 1H), 7.30-7.33 (m, 1H), 7.21-7.25 (m, 1H), 7.09 (dd, 1H)	4-Bromo-3-nitrophenol and (3-(Trifluoromethyl)- phenyl)boronic acid (2.2 eq)
Int-328		279.9 [M] ⁺	4-Methoxy-3-nitrophenol and (4-Chlorophenyl)- boronic acid (1.5 eq.)
Int-329		δ : 7.55 (d, 1H), 7.35 (t, 1H), 7.25 (dd, 1H), 7.11 (d, 1H), 6.79 (dd, 1H), 6.72 (ddd, 1H), 3.97 (s, 3H)	4-Methoxy-3-nitrophenol and (4-Chloro-3-fluoro- phenyl)boronic acid (1.5 eq.)
Int-330		299.1 [M+H] ⁺	4-Methoxy-3-nitrophenol and (1-Methyl-1H-indol-5-

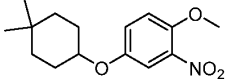
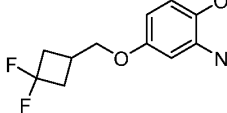
			yl)-boronic acid (1.5 eq.)
Int-331		287.8 [M] ⁺	4-Methoxy-3-nitrophenol and (2,3-Dihydrobenzofuran-5-yl)boronic acid (1.5 eq.)
Int-332		279.9 [M] ⁺	4-Methoxy-3-nitrophenol and (3-Chlorophenyl)-boronic acid

Intermediate 333. 4-(Cyclohexylmethoxy)-1-methoxy-2-nitrobenzene



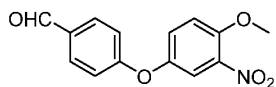
To a cooled (0-5 °C) mixture of cyclohexylmethanol (0.285 g, 2.50 mmol), 4-methoxy-3-nitrophenol (0.423 g, 2.50 mmol) and triphenylphosphine (0.984 g, 3.75 mmol) in dry THF (17 ml) was added diisopropyl azodicarboxylate (0.738 ml, 3.75 mmol). The mixture was stirred over night at RT. THF was evaporated and the residue was dissolved in DCM. Organic phase was washed with water and brine, dried and evaporated. Crude product was purified by flash chromatography to afford 0.26 g of the title compound. LCMS: m/z 266.2 [M+H]⁺

The following intermediates were prepared according to the procedure described for Intermediate 333 from the starting material indicated in the table.

No.	Structure	LCMS m/z	Starting materials
Int-334		280.0 [M+H] ⁺	4-Fluoro-3-nitrophenol and 4,4-Dimethylcyclohexan-1-ol
Int-335		273.8 [M] ⁺	4-Methoxy-3-nitrophenol and (3,3-Difluorocyclobutyl)-methanol

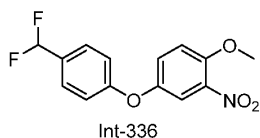
Intermediate 336. 4-(4-(Difluoromethyl)phenoxy)-1-methoxy-2-nitrobenzene

a) 4-(4-Methoxy-3-nitrophenoxy)benzaldehyde



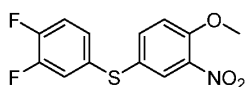
A mixture of 4-fluorobenzaldehyde (0.215 ml, 2.00 mmol), 4-methoxy-3-nitrophenol (0.338 g, 2.00 mmol) and potassium carbonate (0.553 g, 4.00 mmol) in dry DMA (4.0 ml) was stirred at 120 °C until the reaction was completed. Water was added to the cooled mixture and the mixture was extracted with EtOAc. Organic phase was washed with water, dried and evaporated to afford 0.49 g of the title compound. LCMS: m/z 274.1 $[M+H]^+$.

b) 4-(4-(Difluoromethyl)phenoxy)-1-methoxy-2-nitrobenzene



10

4-(4-Methoxy-3-nitrophenoxy)benzaldehyde (0.49 g, 1.793 mmol) was dissolved in dry DCM (5.5 ml) and cooled to 0-5 °C. Diethylaminosulfur trifluoride (0.521 ml, 3.95 mmol) was added in small portions and the mixture was stirred at RT for 24 h. The mixture was diluted with DCM and saturated NaHCO_3 solution was added in small portions. Phases were separated and aqueous phase was extracted with DCM. Combined organic phases were washed with water and brine, dried and evaporated. Crude was purified by flash chromatography to afford 0.37 g of the title compound. LCMS: m/z 296.0 $[M+H]^+$.

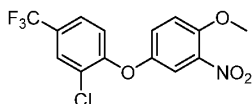
20 **Intermediate 337.** (3,4-Difluorophenyl)(4-methoxy-3-nitrophenyl)sulfane

To a mixture of 3,4-difluorothiophenol (0.155 ml, 1.40 mmol), 4-methoxy-3-nitrophenylboronic acid (0.197 g, 1.00 mmol), copper(II) sulfate (8.0 mg, 0.05 mmol) and 1,10-phenanthroline (9.0 mg, 0.05 mmol) in ethanol (1.0 ml) (bubbled with oxygen before use) was added 40 % aqueous tetrabutylammoniumhydroxide (1.0 ml, 3.82 mmol). The mixture was stirred over night at RT. Then mixture was diluted with EtOAc and filtered through a pad of Celite. Celite layer was further washed with EtOAc. Filtrate was evaporated and crude was purified by flash chromatography to afford 0.17 g

of the title compound. ^1H NMR (400 MHz, CDCl_3): δ 7.88 (d, 1H), 7.56 (dd, 1H), 7.00-7.16 (m, 4H), 3.98 (s, 3H).

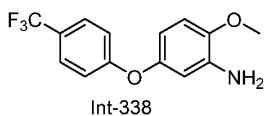
Intermediate 338. 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline

5 a) 2-Chloro-1-(4-methoxy-3-nitrophenoxy)-4-(trifluoromethyl)benzene



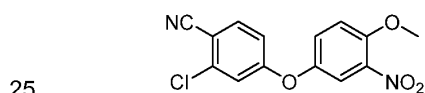
A mixture of 2-chloro-1-fluoro-4-(trifluoromethyl)benzene (0.397 g, 2.00 mmol), 4-methoxy-3-nitrophenol (0.372 g, 2.20 mmol) and potassium carbonate (0.608 g, 4.40 mmol) in dry DMF (4.0 ml) was stirred at 120 °C until the reaction was
10 completed. Water was added to the cooled mixture followed by stirring at RT for 1 h. The formed precipitate was filtered, washed with water and dried under reduced pressure to afford 0.62 g of the title compound. LCMS: m/z 348.1 $[\text{M}+\text{H}]^+$.

b) 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline



15 To a mixture of 2-chloro-1-(4-methoxy-3-nitrophenoxy)-4-(trifluoromethyl)benzene (0.66 g, 1.898 mmol) and ammonium formate (1.197 g, 18.98 mmol) in dry methanol (35 ml) was added 10 wt-% palladium on carbon (0.253 g, 0.237 mmol). The mixture was vigorously stirred at RT until the reaction was completed. The mixture was filtered through a plug of Celite and the Celite layer was washed with methanol. Filtrate
20 was evaporated and the residue was dissolved in EtOAc. Organic phase was washed with water, dried and evaporated to afford 0.52 g of the title compound. LCMS: m/z 284.5 $[\text{M}+\text{H}]^+$.

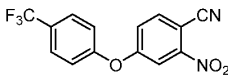
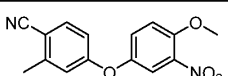
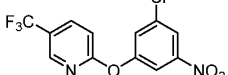
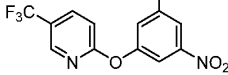
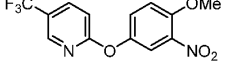
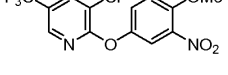
Intermediate 339. 2-Chloro-4-(4-methoxy-3-nitrophenoxy)benzonitrile

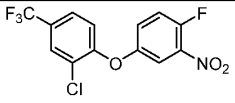
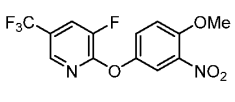


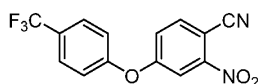
A mixture of 4-methoxy-3-nitrophenol (0.677 g, 4.00 mmol, 1.0 eq.), 2-chloro-4-fluorobenzonitrile (0.622 g, 4.00 mmol, 1.0 eq.) and potassium carbonate (1.216 g, 8.80 mmol, 2.2 eq.) in dry DMF (5.5 ml) was stirred at 100-120 °C until reaction was

- completed. Cooled mixture was treated with water and the formed precipitate was filtered and dried to afford the title compound. Yield: 1.06 g. LCMS: m/z 304.5 $[M+H]^+$. If the product did not precipitate from water, it was extracted with EtOAc. Organic phase was washed with water, dried and evaporated to afford the title compound which was used as such or purified by flash chromatography.

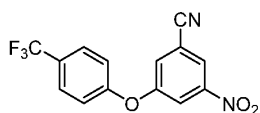
The following intermediates were prepared according to the procedure described for Intermediate 339 from the starting material indicated in the table.

No.	Structure	Purification/ LCMS m/z	Starting materials (eq.), base (eq.)
Int-340		Flash chromatography; 309.0 $[M+H]^+$	4-(Trifluoromethyl)phenol (1.1) and 4-Fluoro-2-nitrobenzonitrile (1.0); K_2CO_3 (2.2)
Int-341		Precipitation; 285.0 $[M+H]^+$	4-Methoxy-3-nitrophenol (1.0) and 4-Fluoro-2-methylbenzonitrile (1.0); K_2CO_3 (2.2)
Int-342		Precipitation; 319.2 $[M+H]^+$	3-Chloro-5-nitrophenol (1.1) and 2-Chloro-5-(trifluoromethyl)pyridine (1.0); K_2CO_3 (1.5)
Int-343		Crude; 303.2 $[M+H]^+$	3-Fluoro-5-nitrophenol (1.0) and 2-Chloro-5-(trifluoromethyl)pyridine (1.0); K_2CO_3 (1.5)
Int-344		Precipitation;	4-Methoxy-3-nitrophenol (1.1) and 2-Chloro-5-(trifluoromethyl)pyridine (1.0); K_2CO_3 (1.5)
Int-345		Precipitation; 315.3 $[M+H]^+$	4-Methoxy-3-nitrophenol (1.1) and 2,3-Dichloro-5-(trifluoromethyl)pyridine (1.0); K_2CO_3 (1.5)

Int-346		Crude; 306.5 [M+H] ⁺	4-Fluoro-3-nitrophenol (1.1) and 2-Chloro-1-fluoro-4-(trifluoro- methyl)benzene (1.0); K ₂ CO ₃ (1.5)
Int-347		Flash chromatography ; 333.0 [M+H] ⁺	4-Methoxy-3-nitrophenol (1.0) and 2,3-Difluoro-5-(trifluoro- methyl)pyridine (1.0); Cs ₂ CO ₃ (1.25)

Intermediate 348. 2-Nitro-4-(4-(trifluoromethyl)phenoxy)benzonitrile

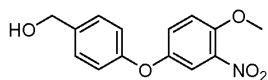
A mixture of 4-(trifluoromethyl)phenol (0.40 g, 2.467 mmol), 4-fluoro-2-nitro-
 5 benzonitrile (0.40 g, 2.408 mmol) and potassium carbonate (0.666 g, 4.82 mmol) in dry
 DMA (5.0 ml) was stirred at 100 °C until the reaction was completed. Cooled mixture
 was diluted with water and extracted with EtOAc. Organic phase was dried and
 evaporated. Crude was purified by flash chromatography to afford the title compound.
 Yield: 0.40 g. ¹H NMR (400 MHz, CDCl₃) δ: 7.89 (d, 1H), 7.87 (d, 1H), 7.74-7.79 (m,
 10 2H), 7.36 (dd, 1H), 7.20-7.25 (m, 2H).

Intermediate 349. 3-Nitro-5-(4-(trifluoromethyl)phenoxy)benzonitrile

A mixture of 4-(trifluoromethyl)phenol (0.324 g, 2.00 mmol), 3,5-dinitrobenzo-
 15 nitrile (0.463 g, 2.40 mmol) and potassium phosphate (0.849 g, 4.00 mmol) in dry DMA
 (3.0 ml) was stirred at 100 °C until the reaction was completed. Cooled mixture was
 diluted with water and extracted with EtOAc. Organic phase was dried and evaporated.
 Crude was purified by flash chromatography to afford the title compound. Yield: 0.42 g.
 LCMS: *m/z* 309.2 [M+H]⁺.

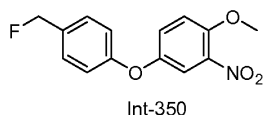
20

Intermediate 350. 4-(4-(Fluoromethyl)phenoxy)-1-methoxy-2-nitrobenzene
 a) (4-(4-Methoxy-3-nitrophenoxy)phenyl)methanol



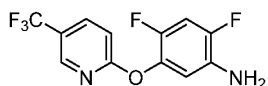
To a mixture of 4-(4-methoxy-3-nitrophenoxy)benzaldehyde (0.98 g, 3.59 mmol) in MeOH (15 ml) was added NaBH₄ (0.204 g, 5.38 mmol) in small portions and stirred at RT until the reaction was completed. Solvent was evaporated and the residue was treated with water and EtOAc. Phases were separated and the aqueous phase was extracted with EtOAc. Combined organic phases were washed with water and brine, dried and evaporated to afford the title compound. Yield 0.97 g. LCMS: *m/z* 258.3 [M-H₂O+H]⁺.

b) 4-(4-(Fluoromethyl)phenoxy)-1-methoxy-2-nitrobenzene



To a cooled (-78 °C) solution of (4-(4-methoxy-3-nitrophenoxy)phenyl)methanol (0.48 g, 1.744 mmol) in dry DCM (5.0 ml) was added diethylaminosulfur trifluoride (DAST) (0.25 ml, 1.892 mmol). Cooling bath was removed and the mixture was allowed to warm to RT and stirred until the reaction was completed. The mixture was diluted with DCM (15 ml) and cooled to 0-5 °C. Saturated NaHCO₃ solution (5 ml) was added to adjust pH to 7-8. Phases were separated and aqueous phase was extracted with DCM. Combined organic phases were washed with water and brine, dried and evaporated. Crude product was purified by flash chromatography to afford the title compound. Yield: 0.26 g. ¹H NMR (400 MHz, CDCl₃) δ: 7.53 (d, 1H), 7.36-7.41 (m, 2H), 7.25 (dd, 1H), 7.08 (d, 1H), 6.98-7.03 (m, 2H), 5.35 (d, 2H), 3.96 (s, 3H).

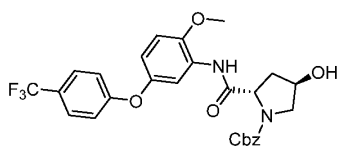
Intermediate 351. 2,4-Difluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)aniline



A mixture of 5-amino-2,4-difluorophenol (0.218 g, 1.50 mmol) and potassium *tert*-butoxide (0.185 g, 1.65 mmol) in dry DMSO (3.0 ml) was stirred at RT for 1 h. 2-Chloro-5-(trifluoromethyl)pyridine (0.272 g, 1.50 mmol) and K₂CO₃ (0.104 g, 0.75 mmol) were added and stirring was continued at 120 °C until the reaction was completed. Cooled mixture was diluted with water and extracted with EtOAc. Organic phase was washed with 1 M NaOH and water, dried and evaporated. Crude product was

purified by filtration through a short plug of silica gel eluting with EtOAc-heptane (4:1). Filtrate was evaporated and the residue dried under vacuum to afford the title compound. Yield: 0.25 g. LCMS: m/z 291.5 $[M+H]^+$.

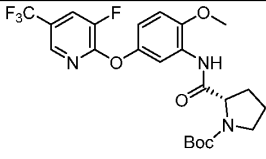
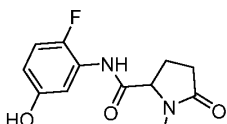
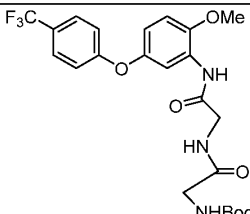
- 5 **Intermediate 352.** Benzyl (2*S*,4*R*)-4-hydroxy-2-((2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)carbamoyl)pyrrolidine-1-carboxylate



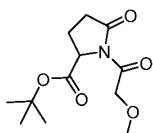
- To a mixture of 2-methoxy-5-(4-(trifluoromethyl)phenoxy)aniline (0.085 g, 0.30 mmol), (2*S*,4*R*)-1-((benzyloxy)-carbonyl)-4-hydroxypyrrolidine-2-carboxylic acid
 10 (0.080 g, 0.30 mmol) in EtOAc (0.40 ml) and pyridine (0.20 ml) was added 1-propane-phosphonic acid cyclic anhydride, 50 wt-% in EtOAc (0.30 ml, 0.509 mmol). The mixture was stirred at RT overnight. The reaction was quenched with 0.5 % HCl-solution and diluted with water and EtOAc. Phases were separated and organic phase was washed with 0.5 % HCl-solution, water and brine, dried and evaporated to afford
 15 the title compound. Yield: 0.111 g. LC-MS: m/z 531.3 $[M+H]^+$. Crude product was used as such or purified by reverse phase flash chromatography to afford the pure compound.

- The following intermediates were prepared according to the procedure described
 20 for Intermediate 352 from the starting material indicated in the table.

No.	Structure	Purification/ LCMS m/z	Starting materials
Int-353		Crude; 481.4 $[M+H]^+$	2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (<i>S</i>)-1-(<i>tert</i> -butoxycarbonyl)-5-oxopyrrolidine-2-carboxylic acid

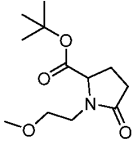
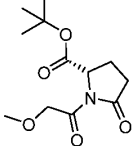
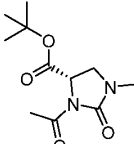
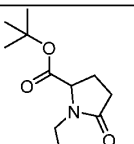
Int-354		Crude; 500.4 [M+H] ⁺	5-((3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyaniline and (<i>tert</i> -Butoxycarbonyl)- <i>L</i> -proline
Int-355		Reverse phase flash chromatography; 253.3 [M+H] ⁺	3-Amino-4-fluorophenol and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid
Int-356		Crude; 498.4 [M+H] ⁺	2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (<i>tert</i> -Butoxycarbonyl)glycylglycine

Intermediate 357. *tert*-Butyl 1-(2-methoxyacetyl)-5-oxopyrrolidine-2-carboxylate

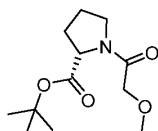


- 5 To a cooled (0-5 °C) mixture of *tert*-butyl 5-oxopyrrolidine-2-carboxylate (0.37 g, 2.00 mmol) in dry THF (5.0 ml) was added 60 wt-% NaH in oil (0.10 g, 2.50 mmol) followed by stirring at 0-5 °C for 30 min. 2-Methoxyacetyl chloride (0.26 g, 2.40 mmol) dissolved in dry THF (2.5 ml) was added and stirring continued at RT overnight. Solvent was evaporated and the residue treated with DCM and water. Phases were
- 10 separated and the organic phase was washed with water and brine. Organic phase was dried and evaporated to afford the title compound. Yield: 0.51 g. LCMS: *m/z* 258.0 [M+H]⁺. Crude product was used as such or purified by reverse phase flash chromatography to afford the pure compound.

- 15 The following intermediates were prepared according to the procedure described for Intermediate 357 from the starting material indicated in the table.

No.	Structure	Purification/ LCMS m/z	Starting materials (eq.), base (eq.)
Int-358		Reverse phase flash chromatography; 244.2 [M+H] ⁺	<i>tert</i> -Butyl 5-oxopyrrolidine-2-carboxylate (1.0) and 1-Iodo-2-methoxyethane (1.38); NaH (1.75)
Int-359		Crude; 257.1 [M] ⁺	<i>tert</i> -Butyl (<i>S</i>)-5-oxopyrrolidine-2-carboxylate (1.0) and 2-Methoxyacetyl chloride (1.25); NaH (1.35)
Int-360		Crude; 243.3 [M+H] ⁺	<i>tert</i> -Butyl (<i>S</i>)-1-methyl-2-oxoimidazolidine-4-carboxylate (1.0) and Acetyl chloride (2.0); NaH (1.75)
Int-361		Reverse phase flash chromatography; 258.2 [M+H] ⁺	<i>tert</i> -butyl 1-(2-Methoxy-2-oxoethyl)-5-oxopyrrolidine-2-carboxylate (1.0) and Methyl 2-bromoacetate (2.5); NaH (2.0)

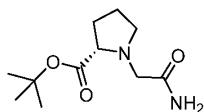
Intermediate 362. *tert*-Butyl (2-methoxyacetyl)-*L*-prolinate



To a cooled (0-5 °C) solution of *tert*-butyl *L*-prolinate (0.342 g, 2.00 mmol) and triethylamine (0.558 ml, 4.00 mmol) in dry DCM (10 ml) was added 2-methoxyacetyl chloride (0.239 g, 2.20 mmol). The mixture was stirred overnight at RT. The mixture was filtered and the filtrate was washed with saturated NH₄Cl solution, saturated NaHCO₃ solution, and brine, dried and evaporated to afford the title compound. Yield: 0.34 g. LCMS: m/z 244.2 [M+H]⁺.

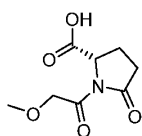
10

Intermediate 363. *tert*-Butyl (2-methoxyacetyl)-*L*-prolinate



A mixture of *tert*-butyl *L*-prolinate (0.342 g, 2.00 mmol), 2-bromoacetamide (0.331 g, 2.40 mmol) and potassium hydrogencarbonate (0.30 g, 3.00 mmol) in dry acetonitrile (10 ml) was stirred at 80 °C until the reaction was completed. Cooled mixture was filtered and the filtrate evaporated. Residue was treated with water and
 5 DCM. Phases were separated and the aqueous phase was extracted with DCM. Combined organic phases were dried and evaporated to afford the title compound. Yield: 0.34 g. LCMS: *m/z* 229.4 [M+H]⁺.

Intermediate 364. (*S*)-1-(2-Methoxyacetyl)-5-oxopyrrolidine-2-carboxylic acid

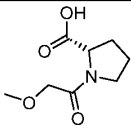
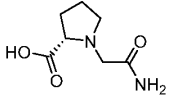
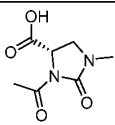
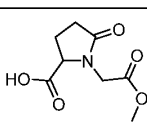


10

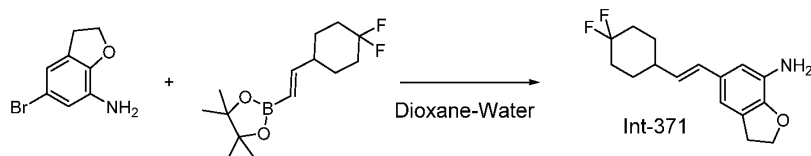
To a mixture of *tert*-butyl (*S*)-1-(2-methoxyacetyl)-5-oxopyrrolidine-2-carboxylate (0.77 g, 2.99 mmol) in dry DCM (15 ml) was added trifluoroacetic acid (2.50 ml, 32.4 mmol, 10.8 eq) followed by stirring overnight at RT. Solvent was evaporated and the residue was treated with toluene and evaporated again. This
 15 procedure was repeated and residue was dried under vacuum to afford the title compound. The crude product was either: (a) used in the next step as such or (b) extracted with DCM after basification with saturated Na₂CO₃ solution followed by drying and evaporating the organic phase. LCMS: *m/z* 201.9 [M+H]⁺

20 The following intermediates were prepared according to the procedure described for Intermediate 364 from the starting material indicated in the table.

No.	Structure	Purification / LCMS <i>m/z</i>	Starting materials (eq.); TFA (eq.)
Int-365		A / 202.0 [M+H] ⁺	<i>tert</i> -Butyl 1-(2-methoxyacetyl)-5-oxopyrrolidine-2-carboxylate; TFA (10.5)
Int-366		A / 188.0 [M+H] ⁺	<i>tert</i> -Butyl 1-(2-methoxyethyl)-5-oxopyrrolidine-2-carboxylate; TFA (12.5)

Int-367		A / 187.9 [M+H] ⁺	<i>tert</i> -Butyl (2-methoxyacetyl)- <i>L</i> -prolinate; TFA (11.2)
Int-368		A / 173.0 [M+H] ⁺	<i>tert</i> -Butyl (2-amino-2-oxoethyl)- <i>L</i> -prolinate; TFA (10.5)
Int-369		A / 187.0 [M+H] ⁺	<i>tert</i> -Butyl (<i>S</i>)-3-acetyl-1-methyl-2-oxoimidazolidine-4-carboxylate; TFA (10.3)
Int-370		A / 202.1 [M+H] ⁺	<i>tert</i> -Butyl 1-(2-methoxy-2-oxoethyl)-5-oxopyrrolidine-2-carboxylate; TFA (10.4)

Intermediate 371 . (E)-5-(2-(4,4-Difluorocyclohexyl)vinyl)-2,3-dihydrobenzofuran-7-amine



- 5 A mixture of 5-bromo-2,3-dihydrobenzofuran-7-amine (0.158 g, 0.738 mmol), 2-[(E)-2-(4,4-difluorocyclohexyl)ethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.243 g, 1.15 mmol), K₃PO₄ (0.313 g, 2.0 mmol) and SPhos Pd G2 (0.040 g, 0.075 mmol) in dioxane (1 ml) and water (1 ml) was heated under nitrogen atmosphere at 85 °C for 8 h. The mixture was extracted with ethyl acetate (2 x 4 ml). The combined
- 10 organic layers were evaporated and then purified by normal phase chromatography to yield 0.144 g of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.34 - 1.46 (2 H, m), 1.76 - 1.95 (4 H, m), 1.97 - 2.09 (2 H, m), 2.20 - 2.29 (1 H, m), 3.08 (2 H, t), 4.47 (2 H, t), 4.57 (2 H, s), 5.88 - 5.95 (1 H, m), 6.21 (1 H, d), 6.50 (1 H, d), 6.53 (1 H, br s). LCMS: m/z 280.7 [M+H]⁺

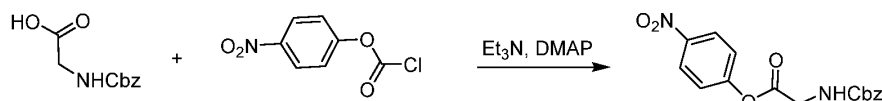
15

The following intermediate was prepared according to the procedure described for Intermediate 371 from the starting material indicated in the table.

No.	Structure	LCMS/ GCMS m/z	Starting materials
Int-372		282.5 [M+H] ⁺	6-Bromo-1,3-dioxaindan-4-amine and 2-[(E)-2-(4,4-difluorocyclohexyl)ethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

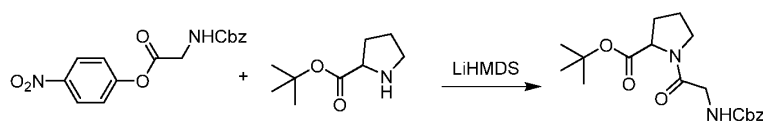
Intermediate 373. 1-(((Benzyloxy)carbonyl)glycyl)-5-oxopyrrolidine-2-carboxylic acid

a) 4-Nitrophenyl ((benzyloxy)carbonyl)glycinate



Triethylamine (290 mg, 2.87 mmol, 1.2 eq.) was added to a suspension of the N-carbobenzyloxyglycine (1 eq.) in anhydrous CH₂Cl₂ (12 mL). The stirred mixture was cooled to 0 °C and 4-nitrophenyl chloroformate (578 mg, 2.87 mmol, 1.2 eq.) was added. After 10 min, DMAP (29.2 mg, 0.239 mmol, 0.1 eq.) was added and the mixture was stirred at 0 °C for 1 h. The mixture was further diluted with CH₂Cl₂ (20 mL) and washed with saturated NaHCO₃ solution (10 mL), 0.1 M HCl solution (10 mL), brine (10 mL), and then dried (Na₂SO₄), filtered and evaporated in vacuum to give the crude product. The crude residue was purified further with reversed phase chromatography to obtain the title compound. LCMS: m/z 331.068 (M+H)⁺.

b) tert-Butyl 1-(((benzyloxy)carbonyl)glycyl)-5-oxopyrrolidine-2-carboxylate

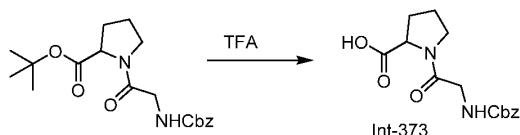


LiHMDS (896 μ L, 0.896 mmol, 1.06 eq.) was added dropwise to a solution of 5-oxo-2-pyrrolidinecarboxylic acid tert-butyl ester (157 mg, 0.845 mmol, 1 eq.) in anhydrous THF (3 ml) at -78 °C under nitrogen. The mixture stirred at RT for 15 min followed by the addition of a solution of 4-nitrophenyl ((benzyloxy)carbonyl)glycinate in anhydrous THF (4 ml) at -78 °C. The mixture was stirred for 1 h at this temperature. The mixture was diluted with ethyl acetate (20 ml) and washed with NH₄Cl (10 ml),

brine (10 ml) and then dried (Na_2SO_4), filtered and solvent evaporated in vacuum to give the crude product. The crude residue was purified further with reverse phase chromatography to obtain the title compound. LCMS: m/z 377.155 ($\text{M}+\text{H}$) $^+$.

c) 1-(((Benzyloxy)carbonyl)glycyl)-5-oxopyrrolidine-2-carboxylic acid

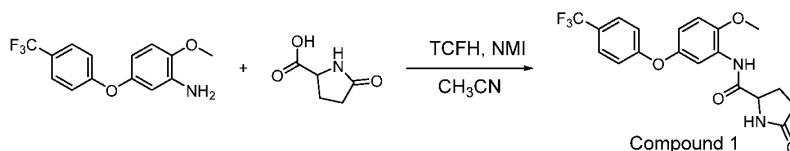
5 (intermediate 373)



Trifluoroacetic acid was added dropwise to a solution of tert-butyl 1-(((benzyloxy)carbonyl)glycyl)-5-oxopyrrolidine-2-carboxylate (285 mg, 0.76 mmol, 1 eq.) in anhydrous DCM under nitrogen at 0 °C. The mixture was stirred at 0 °C for 2 h.

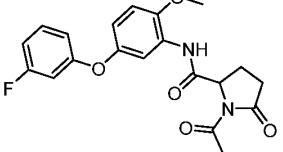
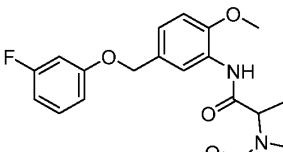
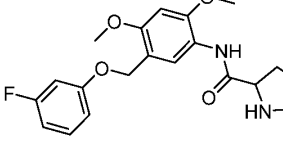
10 DCM and trifluoroacetic acid residue were removed in vacuum to give the crude product. The crude residue was purified further with reverse phase chromatography to obtain the title compound. LCMS: m/z 321.031 ($\text{M}+\text{H}$) $^+$.

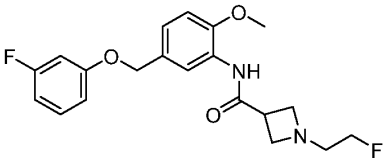
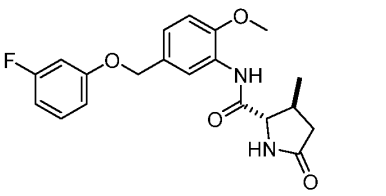
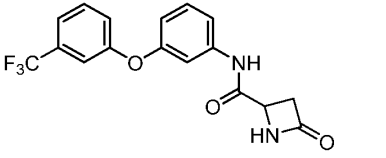
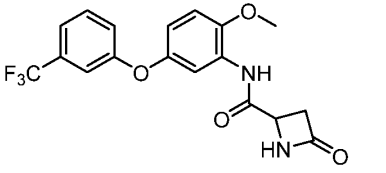
Example 1. N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-
15 pyrrolidine-2-carboxamide (Compound 1)

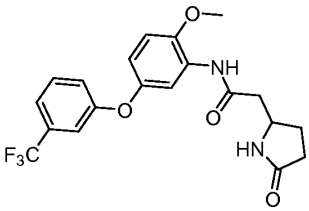
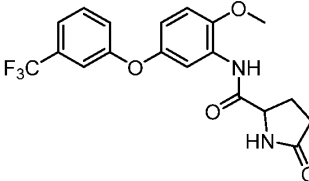
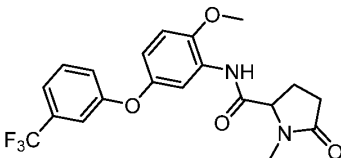
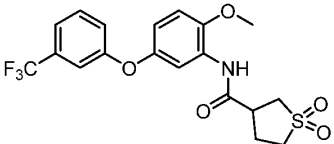


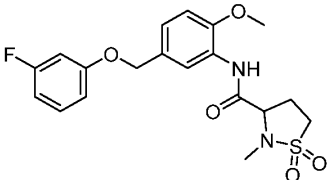
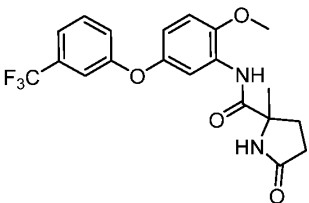
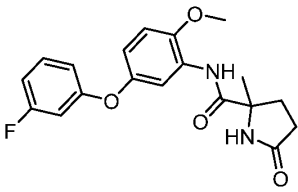
To a solution of 2-methoxy-5-(4-(trifluoromethyl)phenoxy)aniline (215 mg, 1 eq., 759 μmol) in anhydrous acetonitrile (5 mL) were added 5-oxopyrrolidine-2-carboxylic acid (98.0 mg, 1 eq., 759 μmol) and 1-methyl-1H-imidazole (312 mg, 5 eq., 3.80 mmol). The mixture was stirred at RT for 10 min and N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (319 mg, 1.5 eq., 1.14 mmol) was added in a single portion. The resulting solution was stirred at RT overnight and the mixture was directly purified by method A to afford the title compound (0.194 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 9.35 (s, 1H), 7.91 (d, 2H), 7.71 (d, 2H), 7.14 (d, 1H), 7.08 (d, 2H),
20 6.91 (dd, 1H), 4.38 (dd, 1H), 3.88 (s, 3H), 2.38 – 2.27 (m, 1H), 2.26 – 2.07 (m, 2H),
25 2.02 – 1.90 (m, 1H). LCMS: m/z 395.0 [$\text{M}+\text{H}$] $^+$.

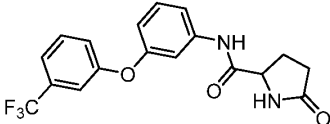
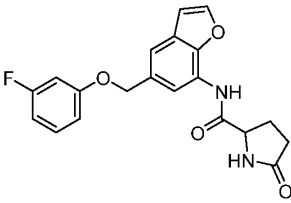
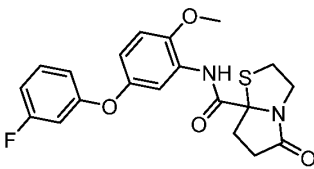
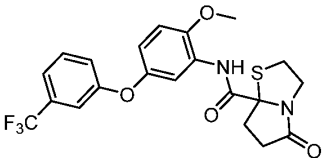
The following compounds were prepared according to the procedure described for Compound 1. The compound code, structure, starting materials, purification method and characterization data are indicated in the table.

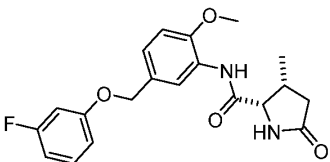
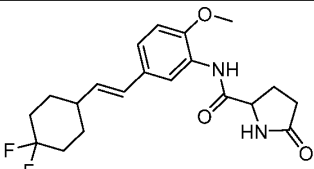
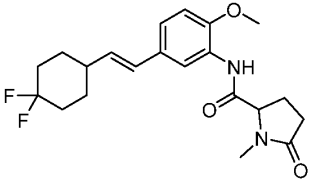
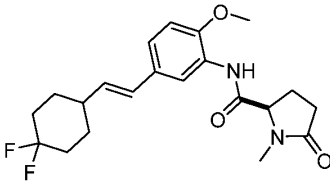
No.	Structure and starting material	Purification method and characterization data
2	 Starting materials: 5-(3-Fluorophenoxy)-2-methoxyaniline and 1-Acetyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.73 (s, 1H), 7.84 (d, 1H), 7.41-7.29 (m, 1H), 7.10 (d, 1H), 6.94-6.80 (m, 2H), 6.80-6.69 (m, 2H), 5.07 (d, 1H), 2.65-2.51 (m, 2H), 2.37 (s, 3H), 2.34-2.19 (m, 1H), 1.97-1.83 (m, 1H). LCMS: m/z 387.2 [M+H]⁺
3	 Starting materials: 5-((3-Fluorophenoxy)methyl)-2-methoxyaniline and 1-Acetyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.62 (s, 1H), 8.09 (d, 1H), 7.36-7.25 (m, 1H), 7.18 (d, 1H), 7.11-6.99 (m, 1H), 6.91-6.79 (m, 2H), 6.79-6.68 (m, 1H), 5.05 (dd, 1H), 4.99 (s, 2H), 3.86 (s, 3H), 2.71-2.53 (m, 2H), 2.34-2.23 (m, 1H), 1.99-1.84 (m, 1H). LCMS: m/z 401.4 [M+H]⁺
4	 Starting materials: 5-((3-Fluorophenoxy)methyl)-2,4-dimethoxyaniline and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.11 (s, 1H), 7.90 (s, 1H), 7.83 (s, 1H), 7.37-7.22 (m, 1H), 6.89-6.71 (m, 4H), 4.96 (s, 2H), 4.34-4.19 (m, 1H), 3.87 (d, 6H), 2.31-2.04 (m, 3H), 2.01-1.90 (m, 1H). LCMS: m/z 389.2 [M+H]⁺

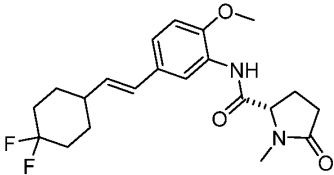
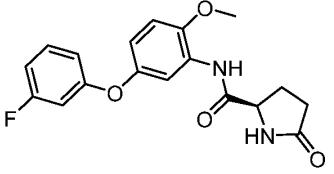
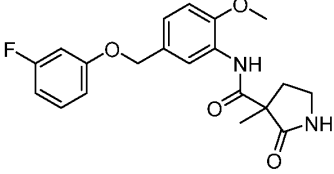
5	 Starting materials: 5-((3-Fluorophenoxy)methyl)-2-methoxyaniline HCl and Lithium 1-(2-fluoroethyl)-azetidine-3-carboxylate	Purification method B. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.26 (s, 1H), 8.11 (s, 1H), 7.35-7.26 (m, 1H), 7.16 (d, 1H), 7.04 (d, 1H), 6.94-6.81 (m, 2H), 6.79-6.71 (m, 1H), 5.01 (s, 2H), 4.45 (t, 1H), 4.33 (t, 1H), 3.83 (s, 3H), 3.56-3.41 (m, 3H), 3.28-3.21 (m, 2H), 2.70 (t, 1H), 2.62 (t, 1H). LCMS: m/z 377.2 [M+H]⁺
6	 Starting materials: 5-((3-Fluorophenoxy)methyl)-2-methoxyaniline HCl and rac-(trans)-3-Methyl-5-oxo-pyrrolidine-2-carboxylic acid	Purification method B. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.28 (d, 1H), 8.09 – 8.00 (m, 1H), 7.86 (d, 1H), 7.34-7.25 (m, 1H), 7.19 (d, 1H), 7.07 (d, 1H), 6.91-6.80 (m, 2H), 6.80-6.69 (m, 1H), 5.02 (s, 2H), 4.36 (d, 1H), 3.85 (s, 3H), 2.24-1.84 (m, 1H), 1.07 (dd, 3H). LCMS: m/z 373.2 [M+H]⁺
7	 Starting materials: 3-(3-(Trifluoromethyl)phenoxy)aniline and 4-Oxoazetidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.31 (s, 1H), 8.23 (s, 1H), 7.68-7.61 (m, 1H), 7.51 (d, 1H), 7.47-7.30 (m, 5H), 6.82 (d, 1H), 4.12 (d, 1H), 3.16 (dd, 1H), 2.91-2.78 (m, 1H). LCMS: m/z 351.2 [M+H]⁺
8	 Starting materials: 2-Methoxy-5-(3-(trifluoromethyl)phenoxy)aniline and 4-Oxoazetidine-2-carboxylic acid	Purification method A. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ: 9.48 (s, 1H), 8.25 (s, 1H), 7.89 (s, 1H), 7.61-7.55 (m, 1H), 7.42 (d, 1H), 7.25-7.18 (m, 2H), 7.11 (d, 1H), 6.88 (dd, 1H), 4.37-4.31 (m, 1H), 3.86 (s, 3H), 3.15 (dd, 1H), 2.83 (d, 1H). LCMS:

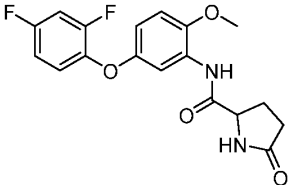
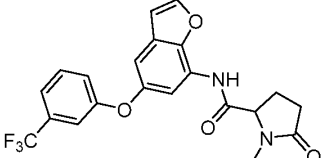
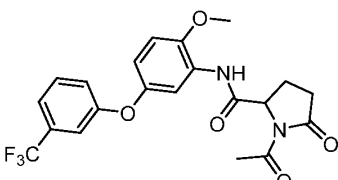
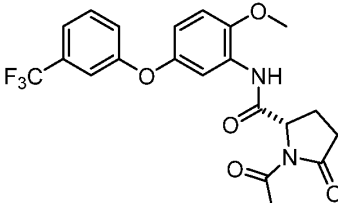
		m/z 281.0 [M+H] ⁺
9	 Starting materials: 2-Methoxy-5-(3-(trifluoromethyl)phenoxy)aniline and 2-(5-Oxopyrrolidin-2-yl)acetic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.32 (s, 1H), 7.88 (s, 1H), 7.63-7.53 (m, 2H), 7.42 (d, 1H), 7.25-7.18 (m, 2H), 7.09 (d, 1H), 6.85 (dd, 1H), 3.88 (d, 1H), 3.86 (s, 3H), 2.69-2.57 (m, 2H), 2.22-2.02 (m, 3H), 1.74-1.60 (m, 1H). LCMS: m/z 409.2 [M+H]⁺
10	 Starting materials: 2-Methoxy-5-(3-(trifluoromethyl)phenoxy)aniline and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.34 (s, 1H), 7.95-7.87 (m, 2H), 7.58 (dd, 1H), 7.43 (d, 1H), 7.26-7.19 (m, 2H), 7.12 (d, 1H), 6.88 (dd, 1H), 4.38 (dd, 1H), 3.87 (s, 3H), 2.39-2.27 (m, 1H), 2.27-2.03 (m, 2H), 2.02-1.88 (m, 1H). LCMS: m/z 395.0 [M+H]⁺
11	 Starting materials: 2-Methoxy-5-(3-(trifluoromethyl)phenoxy)aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.63 (s, 1H), 7.85 (d, 1H), 7.63-7.55 (m, 1H), 7.43 (d, 1H), 7.25-7.19 (m, 2H), 7.13 (d, 1H), 6.90 (dd, 1H), 4.52-4.41 (m, 1H), 3.88 (s, 3H), 2.64 (s, 3H), 2.33-2.15 (m, 3H), 1.93-1.85 (m, 1H). LCMS: m/z 409.2 [M+H]⁺
12	 Starting materials: 2-Methoxy-5-(3-(trifluoromethyl)phenoxy)aniline and Tetrahydrothiophene-3-carboxylic acid 1,1-dioxide	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.61 (s, 1H), 7.85 (d, 1H), 7.63-7.54 (m, 1H), 7.43 (d, 1H), 7.21 (s, 2H), 7.12 (d, 1H), 6.89 (dd, 3.0 Hz, 1H), 3.69-3.59 (m, 1H), 3.40-3.33 (m, 1H), 3.29-3.20 (m, 1H), 3.17-3.01 (m, 2H),

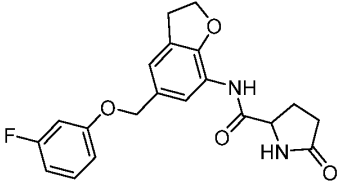
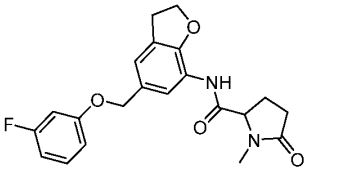
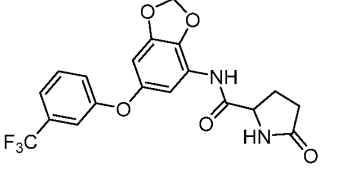
		2.45-2.37 (m, 1H), 2.21-2.07 (m, 1H). LCMS: m/z 430.0 [M+H] ⁺
13	 Starting materials: 5-((3-Fluorophenoxy)methyl)-2-methoxyaniline HCl and 2-Methylisothiazolidine-3-carboxylic acid 1,1-dioxide	Purification method A. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.36 (s, 1H), 8.11 (s, 1H), 7.37-7.26 (m, 1H), 7.22 (d, 1H), 7.08 (d, 1H), 6.93-6.80 (m, 2H), 6.80-6.72 (m, 1H), 5.03 (s, 2H), 4.02 (t, 1H), 3.86 (s, 3H), 3.41-3.33 (m, 1H), 3.29-3.20 (m, 1H), 2.64 (s, 3H), 2.63-2.58 (m, 1H), 2.32-2.20 (m, 1H). LCMS: m/z 409.2 [M+H] ⁺
14	 Starting materials: 2-Methoxy-5-(3-(trifluoromethyl)phenoxy)aniline and 2-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ: 8.85 (s, 1H), 8.36 (s, 1H), 7.90 (d, 1H), 7.62-7.54 (m, 1H), 7.43 (d, 1H), 7.25-7.18 (m, 2H), 7.13 (d, 1H), 6.88 (dd, 1H), 3.86 (s, 3H), 2.31-2.26 (m, 1H), 2.22 (t, 2H), 2.00-1.89 (m, 1H), 1.40 (s, 3H). LCMS: m/z 409.2 [M+H] ⁺
15	 Starting materials: 5-(3-Fluorophenoxy)-2-methoxyaniline and 2-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ: 8.83 (s, 1H), 8.36 (s, 1H), 7.89 (d, 1H), 7.40-7.33 (m, 1H), 7.11 (d, 1H), 6.94-6.88 (m, 1H), 6.85 (dd, 1H), 6.80-6.70 (m, 2H), 3.86 (s, 3H), 2.32-2.25 (m, 1H), 2.25-2.20 (m, 2H), 2.00-1.91 (m, 1H), 1.40 (s, 3H). LCMS: m/z 359.2 [M+H] ⁺

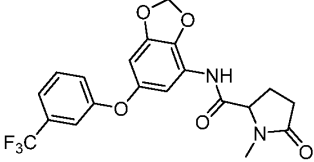
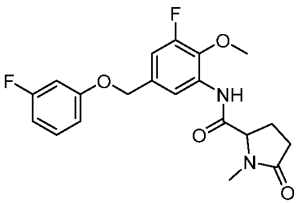
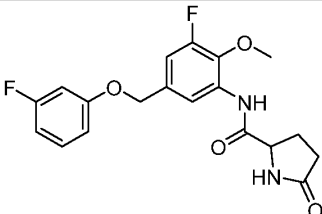
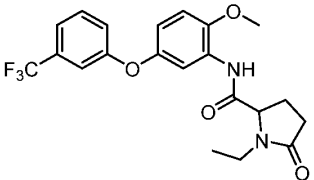
16	 Starting materials: 3-(3-(Trifluoromethyl)phenoxy)aniline and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.15 (s, 1H), 7.84 (s, 1H), 7.68 – 7.59 (m, 1H), 7.51 (d, 1H), 7.45-7.28 (m, 5H), 6.81 (d, 1H), 4.15 (dd, 1H), 2.36-2.27 (m, 1H), 2.22-2.04 (m, 2H), 2.03-1.90 (m, 1H). LCMS: m/z 364.2 [M+H]⁺
17	 Starting materials: 5-((3-Fluorophenoxy)methyl)benzofuran-7-amine and 5-Oxopyrrolidine-2-carboxylic acid	Purification method C. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.20 (s, 1H), 8.07 (s, 1H), 7.90 (d, 2H), 7.53 (s, 1H), 7.35-7.27 (m, 1H), 7.04-7.00 (m, 1H), 6.95-6.85 (m, 2H), 6.82-6.73 (m, 1H), 5.18 (d, 2H), 4.41 (dd, 1H), 2.38 (q, 1H), 2.29-2.12 (m, 2H), 2.11-1.99 (m, 1H). LCMS: m/z 369.0 [M+H]⁺
18	 Starting materials: 5-(3-Fluorophenoxy)-2-methoxyaniline and 5-Oxotetrahydropyrrolo[2,1-b]thiazole-7a(5H)-carboxylic acid	Purification method A. ¹H NMR (400 MHz, Methanol-<i>d</i>₄) δ: 7.83 (d, 1H), 7.36-7.26 (m, 1H), 7.09 (d, 1H), 6.87 (dd, 1H), 6.84-6.72 (m, 2H), 6.71-6.60 (m, 1H), 4.59 (s, 1H), 4.47-4.38 (m, 1H), 3.94 (s, 3H), 3.26-3.19 (m, 3H), 2.89-2.70 (m, 2H), 2.67-2.52 (m, 2H). LCMS: m/z 403.2 [M+H]⁺
19	 Starting materials: 2-Methoxy-5-(3-(trifluoromethyl)phenoxy)aniline and 5-Oxotetrahydropyrrolo[2,1-b]thiazole-7a(5H)-carboxylic acid	Purification method B. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.19 (s, 1H), 7.70 (d, 1H), 7.63-7.55 (m, 1H), 7.44 (d, 1H), 7.23 (d, 2H), 7.15 (d, 1H), 6.94 (dd, 1H), 4.38-4.23 (m, 1H), 3.87 (s, 3H), 3.18-3.00 (m,

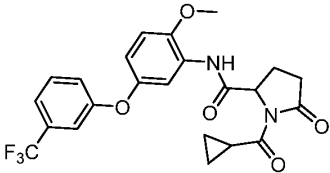
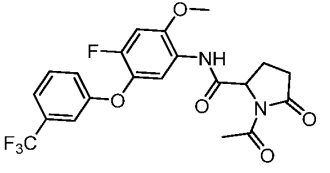
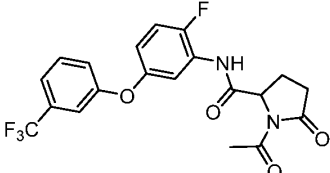
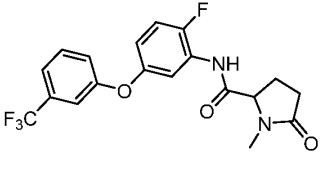
	5-Oxotetrahydropyrrolo[2,1-b]-thiazole-7a(5H)-carboxylic acid	3H), 2.75-2.56 (m, 3H), 2.47-2.38 (m, 1H). LCMS: m/z 453.0 [M+H] ⁺
20	 Starting materials: 5-((3-Fluorophenoxy)methyl)-2-methoxyaniline HCl and rac-(cis)-3-methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method B. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.32 (s, 1H), 8.04 (d, 1H), 7.81 (s, 1H), 7.37-7.26 (m, 1H), 7.19 (dd, 1H), 7.07 (d, 1H), 6.92-6.80 (m, 2H), 6.80-6.69 (m, 1H), 5.02 (s, 2H), 4.36 (d, 1H), 3.85 (s, 3H), 2.70-2.62 (m, 1H), 2.20 (dd, 1H), 1.91 (dd, 1H), 0.99 (d, 3H). LCMS: m/z 373.2 [M+H]⁺
21	 Starting materials: (E)-5-(2-(4,4-Difluorocyclohexyl)vinyl)-2-methoxyaniline and 5-Oxopyrrolidine-2-carboxylic acid	Purification method B. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.19 (s, 1H), 8.05 (s, 1H), 7.94 (s, 1H), 7.12 (d, 1H), 7.00 (d, 1H), 6.35 (d, 1H), 6.05 (dd, 1H), 4.35 (d, 1H), 3.83 (s, 3H), 2.35-1.79 (m, 11H), 1.43 (q, 2H). LCMS: m/z 379.2 [M+H]⁺
22	 Starting materials: (E)-5-(2-(4,4-difluorocyclohexyl)vinyl)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.47 (s, 1H), 8.01 (s, 1H), 7.13 (d, 1H), 7.00 (d, 1H), 6.35 (d, 1H), 6.06 (dd, 1H), 4.48-4.39 (m, 1H), 3.83 (s, 3H), 2.67 (s, 3H), 2.39-2.15 (m, 4H), 2.09-1.97 (m, 2H), 1.97-1.74 (m, 5H), 1.43 (q, 2H). LCMS: m/z 393.2 [M+H]⁺
23		Purification method A followed by method H. Retention time = 17.42 min; ee 98 %. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.49 (s, 1H), 8.02 (d,

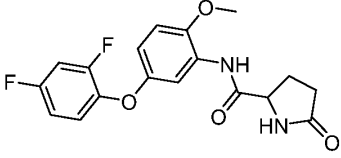
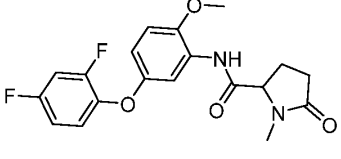
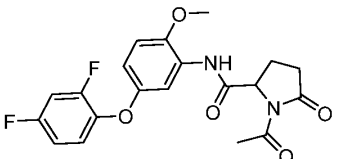
	Starting materials: rac-(E)-N-(5-(2-(4,4-difluorocyclohexyl)vinyl)-2-methoxyphenyl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide	1H), 7.13 (dd, 1H), 7.00 (d, 1H), 6.34 (d, 1H), 6.06 (dd, 1H), 4.51-4.35 (m, 1H), 3.83 (s, 3H), 2.67 (s, 3H), 2.28-2.20 (m, 4H), 2.14-1.75 (m, 7H), 1.50-1.32 (m, 2H). LCMS: m/z 393.2 [M+H] ⁺
24	 Starting materials: rac-(E)-N-(5-(2-(4,4-difluorocyclohexyl)vinyl)-2-methoxyphenyl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide	Purification method A followed by method H. Retention time = 20.55 min; ee 100 %. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.49 (s, 1H), 8.02 (d, 1H), 7.13 (dd, 1H), 7.00 (d, 1H), 6.34 (d, 1H), 6.06 (dd, 1H), 4.51-4.36 (m, 1H), 3.83 (s, 3H), 2.67 (s, 3H), 2.34-2.17 (m, 4H), 2.11-1.98 (m, 2H), 1.98-1.76 (m, 5H), 1.51-1.32 (m, 2H). LCMS: m/z 393.2 [M+H] ⁺
25	 Starting materials: 5-(3-Fluorophenoxy)-2-methoxyaniline and (R)-5-Oxopyrrolidine-2-carboxylic acid	Purification method B. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.33 (s, 1H), 7.91 (s, 1H), 7.87 (d, 1H), 7.44-7.34 (m, 1H), 7.10 (d, 1H), 6.93-6.88 (m, 1H), 6.85 (dd, 1H), 6.80-6.72 (m, 2H), 4.38 (dd, 1H), 3.86 (s, 3H), 2.35-2.25 (m, 1H), 2.24-2.03 (m, 2H), 2.03-1.82 (m, 1H). LCMS: m/z 354.2 [M+H] ⁺
26	 Starting materials: 5-((3-Fluorophenoxy)methyl)-2-methoxyaniline HCl and 3-Methyl-2-oxopyrrolidine-	Purification method B. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 10.11 (s, 1H), 8.35 (s, 1H), 8.19 (s, 1H), 7.37-7.24 (m, 1H), 7.14 (d, 1H), 7.05 (d, 1H), 6.95-6.80 (m, 2H), 6.80-6.71 (m, 1H), 5.02 (s, 2H), 3.29-3.12 (m, 2H), 2.58-2.52 (m, 1H), 2.05-1.89

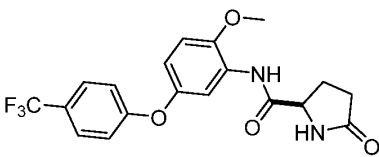
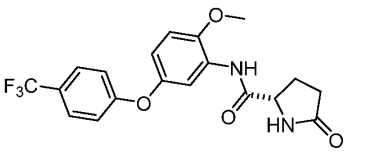
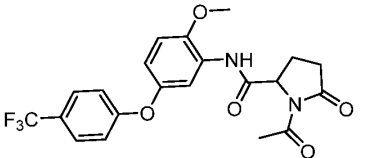
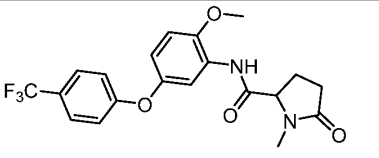
	3-carboxylic acid	(m, 1H), 1.41 (s, 3H). LCMS: m/z 373.0 [M+H] ⁺
27	 Starting materials: 6-((3-Fluorophenoxy)methyl) benzo[d][1,3]-dioxol-4-amine and 5-Oxopyrrolidine-2-carboxylic acid	Purification method B. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.84 (s, 1H), 7.88 (s, 1H), 7.36 (d, 1H), 7.35-7.25 (m, 1H), 6.91-6.80 (m, 3H), 6.80-6.73 (m, 1H), 6.07 (d, 2H), 4.99 (s, 2H), 4.28 (dd, 1H), 2.38-2.27 (m, 1H), 2.27-2.05 (m, 2H), 2.05-1.89 (m, 1H). LCMS: m/z 374.2 [M+H]⁺
28	 Starting materials: 5-(3-(Trifluoromethyl)phenoxy)benzofuran-7-amine and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method C. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.61 (s, 1H), 8.14 (d, 1H), 7.70 (d, 1H), 7.63-7.57 (m, 1H), 7.46 (d, 1H), 7.31-7.24 (m, 2H), 7.19 (d, 1H), 7.01 (d, 1H), 4.51-4.43 (m, 1H), 2.68 (s, 3H), 2.34-2.22 (m, 3H), 2.00-1.92 (m, 1H). LCMS: m/z 419.0 [M+H]⁺
29	 Starting materials: 2-Methoxy-5-(3-(trifluoromethyl)phenoxy)aniline and 1-Acetyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.74 (s, 1H), 7.85 (d, 1H), 7.61-7.53 (m, 1H), 7.42 (d, 1H), 7.20 (d, 2H), 7.12 (d, 1H), 6.88 (dd, 1H), 5.07 (d, 1H), 3.89 (s, 3H), 3.37-3.32 (m, 1H), 2.47-2.40 (m, 1H), 2.37 (s, 3H), 2.35-2.22 (m, 1H), 1.99-1.87 (m, 1H). LCMS: m/z 437.0 [M+H]⁺
30		Purification method A followed by method I. Retention time 23.52 min; ee 100 %. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.74 (s, 1H), 7.85 (d, 1H), 7.61-7.53 (m, 1H), 7.42 (d, 1H),

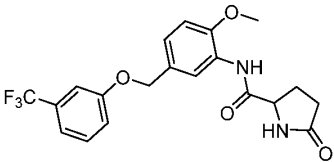
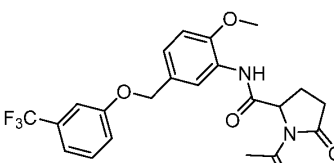
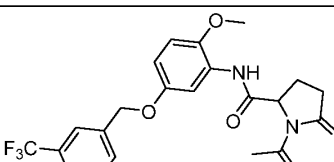
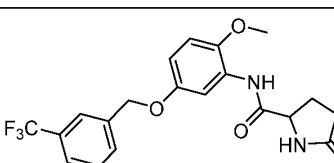
	Starting materials: 2-Methoxy-5-(3-(trifluoromethyl)phenoxy)aniline and 1-Acetyl-5-oxopyrrolidine-2-carboxylic acid	7.20 (d, 2H), 7.12 (d, 1H), 6.88 (dd, 1H), 5.07 (d, 1H), 3.89 (s, 3H), 3.37-3.32 (m, 1H), 2.47-2.40 (m, 1H), 2.37 (s, 3H), 2.35-2.22 (m, 1H), 1.99-1.87 (m, 1H). LCMS: m/z 437.0 [M+H] ⁺
31	 Starting materials: 5-((3-Fluorophenoxy)methyl)-2,3-dihydrobenzofuran-7-amine and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.49 (s, 1H), 7.88 (s, 1H), 7.75 (s, 1H), 7.36-7.25 (m, 1H), 7.11 (s, 1H), 6.91-6.80 (m, 2H), 6.80-6.69 (m, 1H), 4.98 (s, 2H), 4.61 (t, 2H), 4.32 (dd, 1H), 3.23 (t, 2H), 2.35-2.25 (m, 1H), 2.25-2.06 (m, 2H), 2.06-1.89 (m, 1H). LCMS: m/z 371.2 [M+H]⁺
32	 Starting materials: 5-((3-Fluorophenoxy)methyl)-2,3-dihydrobenzofuran-7-amine and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.77 (s, 1H), 7.73 (s, 1H), 7.32-7.24 (m, 1H), 7.10 (s, 1H), 6.89-6.79 (m, 2H), 6.74 (dd, 1H), 4.96 (s, 2H), 4.60 (t, 2H), 4.39-4.31 (m, 1H), 3.22 (t, 2H), 2.64 (s, 3H), 2.31-2.17 (m, 3H), 1.94-1.84 (m, 1H). LCMS: m/z 385.2 [M+H]⁺
33	 Starting materials: 6-(3-(Trifluoromethyl)phenoxy) benzo[d][1,3]-dioxol-4-amine and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.95 (s, 1H), 7.83 (s, 1H), 7.64-7.54 (m, 1H), 7.45 (d, 1H), 7.25 (d, 2H), 7.13 (d, 1H), 6.68 (d, 1H), 6.12 (s, 2H), 4.29 (dd, 1H), 2.35-2.25 (m, 1H), 2.22-2.06 (m, 2H), 2.00-1.86 (m, 1H). LCMS: m/z 409.2 [M+H]⁺

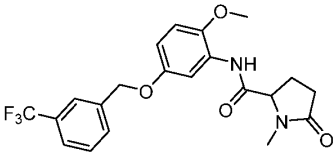
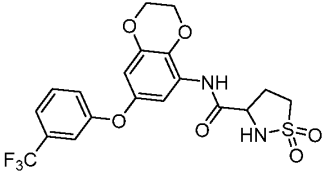
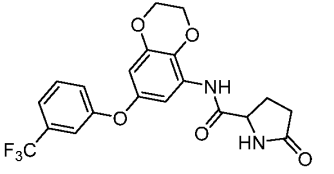
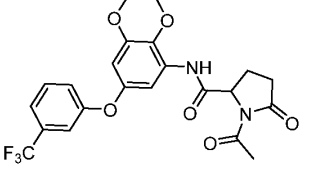
34	 Starting materials: 6-(3-(Trifluoromethyl)phenoxy) benzo[d][1,3]-dioxol-4-amine and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.19 (s, 1H), 7.63-7.54 (m, 1H), 7.44 (d, 1H), 7.24 (d, 2H), 7.15 (d, 1H), 6.73-6.66 (m, 1H), 6.13 (d, 2H), 4.34 (dd, 1H), 2.69-2.60 (m, 3H), 2.31-2.14 (m, 3H), 1.94-1.83 (m, 1H). LCMS: m/z 423.0 [M+H]⁺
35	 Starting materials: 3-Fluoro-5-((3-fluorophenoxy)methyl)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.80 (s, 1H), 7.88 (s, 1H), 7.35-7.26 (m, 1H), 7.15 (dd, 1H), 6.90-6.86 (m, 1H), 6.85-6.80 (m, 1H), 6.80-6.74 (m, 1H), 5.03 (s, 2H), 4.48-4.43 (m, 1H), 3.85 (s, 3H), 2.66 (s, 3H), 2.32-2.17 (m, 3H), 1.95-1.89 (m, 1H). LCMS: m/z 391.2 [M+H]⁺
36	 Starting materials: 3-Fluoro-5-((3-fluorophenoxy)methyl)-2-methoxyaniline and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.52 (s, 1H), 7.91 (s, 2H), 7.36-7.25 (m, 1H), 7.13 (dd, 1H), 6.89-6.85 (m, 1H), 6.83 (dd, 1H), 6.79-6.72 (m, 1H), 5.04 (s, 2H), 4.39 (dd, 1H), 3.84 (s, 3H), 2.38-2.30 (m, 1H), 2.25-2.16 (m, 1H), 2.16-2.06 (m, 1H), 2.03-1.94 (m, 1H). LCMS: m/z 377.1 [M+H]⁺
37	 Starting materials: 2-Methoxy-5-(3-(trifluoromethyl)phenoxy)aniline and	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.66 (s, 1H), 7.85 (d, 1H), 7.63-7.55 (m, 1H), 7.43 (d, 1H), 7.24-7.18 (m, 2H), 7.13 (d, 1H), 6.90 (dd, 1H), 4.63-4.56 (m, 1H), 3.88 (s, 3H), 3.53-3.43

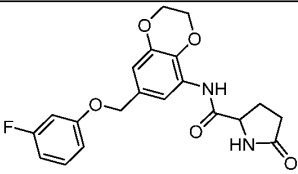
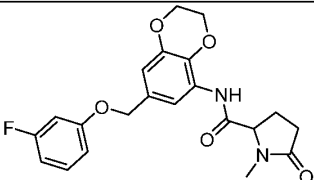
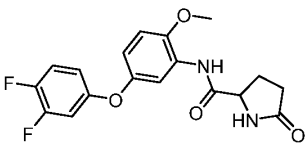
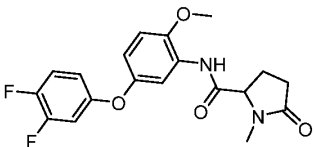
	1-Ethyl-5-oxopyrrolidine-2-carboxylic acid	(m, 1H), 2.88-2.77 (m, 1H), 2.33-2.15 (m, 3H), 1.96-1.87 (m, 1H), 1.00 (t, 3H). LCMS: m/z 423.0 [M+H] ⁺
38	 Starting materials: 2-Methoxy-5-(3-(trifluoromethyl)phenoxy)aniline and 1-(Cyclopropanecarbonyl)-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.70 (s, 1H), 7.85 (d, 1H), 7.61-7.54 (m, 1H), 7.42 (d, 1H), 7.23-7.15 (m, 2H), 7.12 (d, 1H), 6.87 (dd, 1H), 5.06 (dd, 1H), 3.88 (s, 3H), 3.18-3.07 (m, 1H), 2.70-2.54 (m, 2H), 2.36-2.24 (m, 1H), 1.98-1.86 (m, 1H), 0.99-0.76 (m, 4H). LCMS: m/z 463.0 [M+H]⁺
39	 Starting materials: 4-Fluoro-2-methoxy-5-(3-(trifluoromethyl)phenoxy)aniline and 1-Acetyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.77 (s, 1H), 7.93 (d, 1H), 7.62-7.54 (m, 1H), 7.44 (d, 1H), 7.28-7.15 (m, 4H), 5.03 (d, 1H), 3.92 (s, 3H), 2.65-2.57 (m, 2H), 2.37 (s, 3H), 2.31-2.22 (m, 1H), 1.99-1.88 (m, 1H). LCMS: m/z 455.1 [M+H]⁺
40	 Starting materials: 2-Fluoro-5-(3-(trifluoromethyl)phenoxy)aniline and 1-Acetyl-5-oxopyrrolidine-2-carboxylic acid	Purification method C. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.29 (s, 1H), 7.80 (dd, 1H), 7.64-7.56 (m, 1H), 7.48 (d, 1H), 7.41-7.22 (m, 3H), 6.96-6.87 (m, 1H), 4.98 (dd, 1H), 2.68-2.52 (m, 2H), 2.38 (s, 3H), 2.35-2.25 (m, 1H), 2.01-1.93 (m, 1H). LCMS: m/z 383.2 [M+H]⁺
41		Purification method A. ¹H NMR (400 MHz, Methanol-<i>d</i>₄) δ: 7.81 (dd, 1H), 7.59-7.52 (m, 1H), 7.41 (d, 1H), 7.30-7.19 (m, 3H), 6.93-6.84

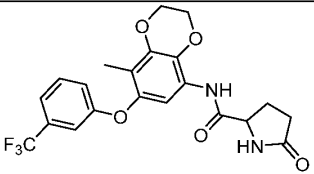
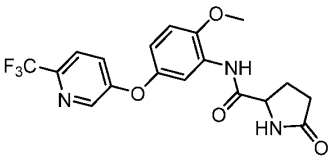
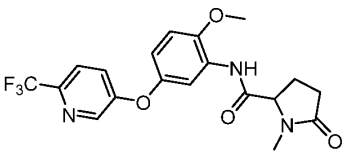
	Starting materials: 2-Fluoro-5-(3-(trifluoromethyl)phenoxy)aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	(m, 1H), 4.42 (dd, 1H), 2.83 (s, 3H), 2.57-2.32 (m, 3H), 2.13-2.05 (m, 1H). LCMS: m/z 397.0 [M+H] ⁺
42	 Starting materials: 5-(2,4-Difluorophenoxy)-2-methoxyaniline and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ: 9.27 (s, 1H), 7.89 (s, 1H), 7.81 (d, 1H), 7.47-7.39 (m, 1H), 7.19-7.12 (m, 1H), 7.09-7.05 (m, 1H), 7.03 (d, 1H), 6.71 (dd, 1H), 4.35 (dd, 1H), 3.82 (s, 3H), 2.33-2.25 (m, 1H), 2.20-2.13 (m, 1H), 2.12-2.05 (m, 1H), 1.95-1.89 (m, 1H). LCMS: m/z 363.2 [M+H] ⁺
43	 Starting materials: 5-(2,4-Difluorophenoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.57 (s, 1H), 7.80 (d, 1H), 7.50-7.42 (m, 1H), 7.21-7.11 (m, 1H), 7.07 (dd, 2H), 6.74 (dd, 1H), 4.50-4.40 (m, 1H), 3.84 (s, 3H), 2.64 (s, 3H), 2.29-2.11 (m, 3H), 1.92-1.83 (m, 1H). LCMS: m/z 377.2 [M+H] ⁺
44	 Starting materials: 5-(2,4-Difluorophenoxy)-2-methoxyaniline and 1-Acetyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.67 (s, 1H), 7.81 (d, 1H), 7.50-7.39 (m, 1H), 7.17-7.10 (m, 1H), 7.10-7.02 (m, 2H), 6.72 (dd, 1H), 5.06 (dd, 1H), 3.85 (s, 3H), 2.66-2.54 (m, 2H), 2.38 (s, 3H), 2.33-2.20 (m, 1H), 1.97-1.85 (m, 1H). LCMS: m/z 405.0 [M+H] ⁺

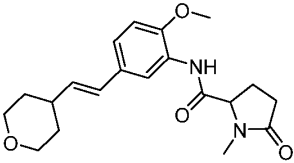
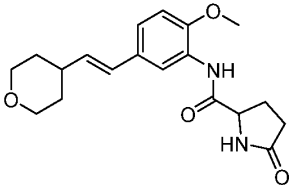
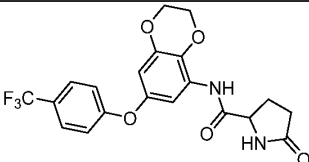
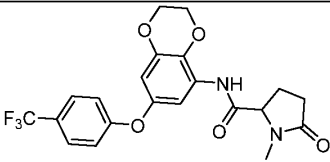
45	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A followed by method I. Retention time 4.29 min; ee 100 %. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.35 (s, 1H), 7.91 (d, 2H), 7.71 (d, 2H), 7.14 (d, 1H), 7.08 (d, 2H), 6.91 (dd, 1H), 4.38 (dd, 1H), 3.88 (s, 3H), 2.38-2.27 (m, 1H), 2.26-2.07 (m, 2H), 2.02-1.90 (m, 1H). LCMS: <i>m/z</i> 395.2 [M+H] ⁺ .
46	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A followed by method I. Retention time 7.87 min; ee 99 %. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.35 (s, 1H), 7.91 (d, 2H), 7.71 (d, 2H), 7.14 (d, 1H), 7.08 (d, 2H), 6.91 (dd, 1H), 4.38 (dd, 1H), 3.88 (s, 3H), 2.38-2.27 (m, 1H), 2.26-2.07 (m, 2H), 2.02-1.90 (m, 1H). LCMS: <i>m/z</i> 395.0 [M+H] ⁺ .
47	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-Acetyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ: 9.73 (s, 1H), 7.85 (d, 1H), 7.68 (d, 2H), 7.12 (d, 1H), 7.04 (d, 2H), 6.88 (dd, 1H), 5.05 (dd, 1H), 2.64-2.53 (m, 2H), 2.35 (s, 3H), 2.33-2.20 (m, 1H), 1.95-1.86 (m, 1H). LCMS: <i>m/z</i> 437.0 [M+H] ⁺
48	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-Methyl-5-oxopyrrolidine-2-	Purification method B. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.64 (s, 1H), 7.87 (d, 1H), 7.71 (d, 2H), 7.14 (d, 1H), 7.08 (d, 2H), 6.92 (dd, 1H), 4.47 (d, 1H), 3.89 (s, 3H), 2.64 (s, 3H), 2.31-2.16 (m, 3H), 1.94-

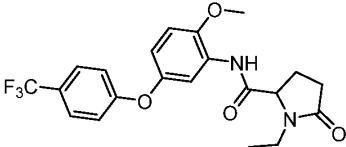
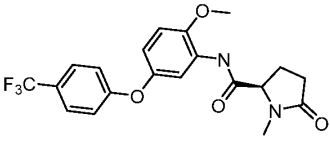
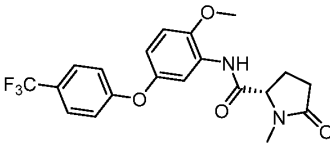
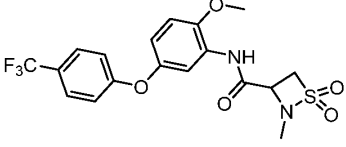
	carboxylic acid	1.80 (m, 1H). GCMS m/z 409.13 [M] ⁺
49	 Starting materials: 2-Methoxy-5-((3-(trifluoromethyl)phenoxy)methyl)-aniline HCl and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.23 (s, 1H), 8.12 (s, 1H), 7.94 (s, 1H), 7.57-7.47 (m, 1H), 7.32-7.24 (m, 3H), 7.21 (d, 1H), 7.08 (d, 1H), 5.10 (s, 2H), 4.36 (d, 1H), 3.85 (s, 3H), 2.34-1.96 (m, 4H). LCMS: m/z 409.2 [M+H]⁺
50	 Starting materials: 2-Methoxy-5-((3-(trifluoromethyl)phenoxy)methyl)-aniline HCl and 1-Acetyl-5-oxo-pyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.60 (s, 1H), 8.10 (d, 1H), 7.52-7.45 (m, 1H), 7.31-7.24 (m, 3H), 7.18 (dd, 1H), 7.05 (d, 1H), 5.06 (s, 2H), 5.04 (dd, 1H), 3.85 (s, 3H), 2.64-2.50 (m, 2H), 2.38 (s, 3H), 2.32-2.23 (m, 1H), 1.95-1.89 (m, 1H). LCMS: m/z 452.1 [M+H]⁺
51	 Starting materials: 2-Methoxy-5-((3-(trifluoromethyl)benzyl)oxy)aniline HCl and 1-Acetyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.58 (s, 1H), 7.86-7.56 (m, 5H), 6.98 (d, 1H), 6.74 (dd, 1H), 5.12 (s, 2H), 5.10-5.03 (m, 1H), 3.81 (s, 3H), 2.72-2.56 (m, 1H), 2.40 (s, 3H), 2.36-2.18 (m, 1H), 1.98-1.86 (m, 1H). LCMS: m/z 451.0 [M+H]⁺
52	 Starting materials: 2-Methoxy-5-((3-(trifluoromethyl)benzyl)oxy)aniline	Purification method A. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ: 9.17 (s, 1H), 7.93 (s, 1H), 7.87-7.57 (m, 5H), 6.96 (d, 1H), 6.73 (dd, 1H), 5.12 (s, 2H), 4.35 (dd, 1H), 3.78 (s, 3H), 2.37-2.26 (m, 1H), 2.24-2.02 (m,

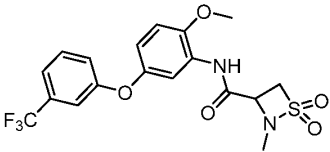
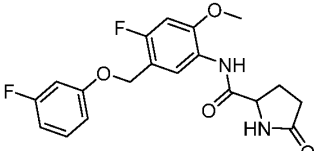
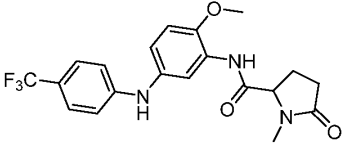
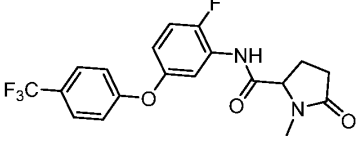
	HCl and 5-Oxopyrrolidine-2-carboxylic acid	2H), 2.01-1.86 (m, 1H). LCMS: m/z 409.2 [M+H] ⁺
53	 Starting materials: 2-Methoxy-5-((3-(trifluoromethyl)benzyl)oxy)aniline HCl and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.49 (s, 1H), 7.84-7.60 (m, 5H), 6.99 (d, 1H), 6.77 (d, 1H), 5.14 (s, 2H), 4.49-4.43 (m, 1H), 3.80 (s, 3H), 2.66 (s, 3H), 2.28-2.16 (m, 3H), 1.93-1.88 (m, 1H). LCMS: m/z 423.0 [M+H]⁺
54	 Starting materials: 7-(3-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine HCl and Isothiazolidine-3-carboxylic acid 1,1-dioxide	Purification method D. ¹H NMR (600 MHz, Acetonitrile-<i>d</i>₃) δ: 9.03 (s, 1H), 7.65 (d, 1H), 7.57-7.51 (m, 1H), 7.42 (d, 1H), 7.27 (d, 1H), 7.23 (dd, 1H), 6.45 (d, 1H), 4.39-4.30 (m, 4H), 4.25 (dd, 1H), 3.30-3.21 (m, 1H), 3.08-2.99 (m, 1H), 2.91-2.80 (m, 1H), 2.46-2.37 (m, 1H). LCMS: m/z 458.9 [M+H]⁺
55	 Starting materials: 7-(3-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine HCl and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.38 (s, 1H), 7.89 (s, 1H), 7.63-7.55 (m, 1H), 7.47-7.38 (m, 2H), 7.27-7.16 (m, 2H), 6.48 (d, 1H), 4.39-4.25 (m, 5H), 2.35-2.26 (m, 1H), 2.23-2.07 (m, 2H), 2.01-1.89 (m, 1H). LCMS: m/z 423.2 [M+H]⁺
56	 Starting materials: 7-(3-(Trifluoro-	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.79 (s, 1H), 7.64-7.55 (m, 1H), 7.50-7.38 (m, 2H), 7.28-7.14 (m, 2H), 6.47 (d, 1H), 5.06 (dd, 1H), 4.41-4.27 (m,

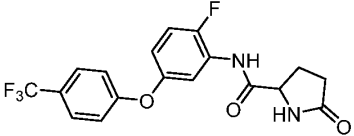
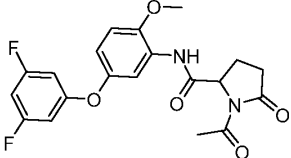
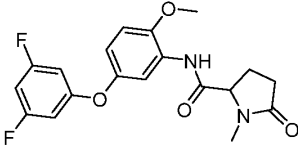
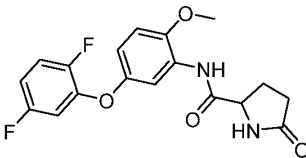
	methyl)phenoxy)-2,3-dihydrobenzo- [b][1,4]dioxin-5-amine HCl and 1- Acetyl-5-oxopyrrolidine-2- carboxylic acid	4H), 2.64-2.52 (m, 2H), 2.37 (s, 3H), 2.32-2.20 (m, 1H), 1.95 – 1.86 (m, 1H). LCMS: m/z 465.0 [M+H] ⁺
57	 Starting materials: 7-((3-Fluoro- phenoxy)methyl)-2,3-dihydrobenzo- [b][1,4]dioxin-5-amine and 5-Oxo- pyrrolidine-2-carboxylic acid	Purification method B. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.26 (s, 1H), 7.93 (s, 1H), 7.64 (s, 1H), 7.35-7.27 (m, 1H), 6.91-6.80 (m, 2H), 6.80-6.73 (m, 2H), 4.97 (s, 2H), 4.41- 4.21 (m, 5H), 2.38-2.27 (m, 1H), 2.27- 2.04 (m, 2H), 2.01-1.90 (m, 1H). LCMS: m/z 388.0 [M+H]⁺
58	 Starting materials: 7-((3-Fluoro- phenoxy)methyl)-2,3-dihydrobenzo- [b][1,4]dioxin-5-amine and 1- Methyl-5-oxopyrrolidine-2- carboxylic acid	Purification method B. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.57 (s, 1H), 7.61 (s, 1H), 7.34-7.25 (m, 1H), 6.88-6.81 (m, 2H), 6.81-6.67 (m, 2H), 4.97 (s, 2H), 4.43 (s, 1H), 4.30 (dd, 4H), 2.66 (s, 3H), 2.36-2.17 (m, 3H), 1.95-1.84 (m, 1H). LCMS: m/z 401.0 [M+H]⁺
59	 Starting materials: 5-(3,4-Difluoro- phenoxy)-2-methoxyaniline and 5- Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.32 (s, 1H), 7.95-7.83 (m, 2H), 7.47- 7.36 (m, 1H), 7.09 (d, 2H), 6.83 (dd, 1H), 6.76 (d, 1H), 4.38 (dd, 1H), 3.86 (s, 3H), 2.39-2.05 (m, 3H), 2.01-1.92 (m, 1H). LCMS: m/z 363.2 [M+H]⁺
60		Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.58 (s, 1H), 7.81 (d, 1H), 7.45-7.36 (m, 1H), 7.11-7.03 (m, 2H), 6.82 (dd,

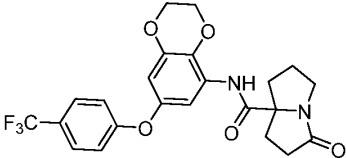
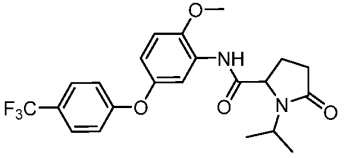
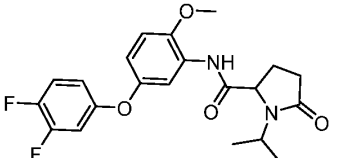
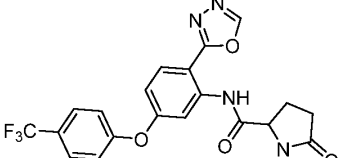
	Starting materials: 5-(3,4-Difluorophenoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H, 6.79-6.65 (m, 1H), 4.45 (dd, 1H), 3.85 (s, 3H), 2.62 (s, 3H), 2.29-2.12 (m, 3H), 1.92-1.81 (m, 1H). LCMS: m/z 377.2 [M+H] ⁺
61	 Starting materials: 8-Methyl-7-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine hydrochloride and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.32 (s, 1H), 7.87 (s, 1H), 7.62-7.51 (m, 2H), 7.45-7.35 (m, 2H), 7.16 (d, 1H), 7.13-7.06 (m, 1H), 4.40-4.28 (m, 5H), 2.34-2.26 (m, 1H), 2.23-2.02 (m, 2H), 1.93 (s, 3H), 1.92-1.87 (m, 1H). LCMS: m/z 437.0 [M+H]⁺
62	 Starting materials: 2-Methoxy-5-((6-(trifluoromethyl)pyridin-3-yl)oxy)-aniline and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.40 (s, 1H), 8.51 (d, 1H), 7.97-7.89 (m, 2H), 7.87 (d, 1H), 7.46 (dd, 1H), 7.16 (d, 1H), 6.98 (dd, 1H), 4.39 (dd, 1H), 3.89 (s, 3H), 2.38-2.26 (m, 1H), 2.26-2.05 (m, 2H), 2.05-1.87 (m, 1H). LCMS: m/z 396.2 [M+H]⁺
63	 Starting materials: 2-Methoxy-5-((6-(trifluoromethyl)pyridin-3-yl)oxy)-aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.68 (s, 1H), 8.50 (d, 1H), 7.92 (d, 1H), 7.87 (d, 1H), 7.46 (dd, 1H), 7.16 (d, 1H), 6.99 (dd, 1H), 4.53-4.39 (m, 1H), 3.89 (s, 3H), 2.36-2.14 (m, 3H), 1.97-1.83 (m, 1H). LCMS: m/z 410.2 [M+H]⁺

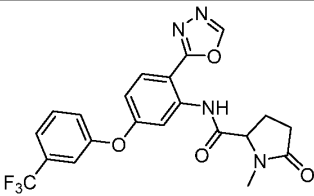
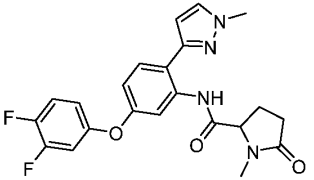
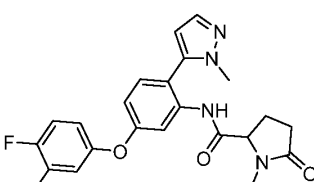
64	 Starting materials: (E)-2-Methoxy-5-(2-(tetrahydro-2H-pyran-4-yl)-vinyl)aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.47 (s, 1H), 8.02 (d, 1H), 7.12 (dd, 1H), 7.00 (d, 1H), 6.31 (d, 1H), 6.04 (dd, 1H), 4.47-4.42 (m, 1H), 3.90-3.85 (m, 2H), 3.83 (s, 3H), 2.67 (s, 3H), 2.37-2.21 (m, 3H), 1.97-1.87 (m, 1H), 1.64 (d, 2H), 1.49-1.34 (m, 2H). LCMS: m/z 359.2 [M+H]⁺
65	 Starting materials: (E)-2-Methoxy-5-(2-(tetrahydro-2H-pyran-4-yl)-vinyl)aniline and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.19 (s, 1H), 8.06 (d, 1H), 7.94 (s, 1H), 7.11 (dd, 1H), 6.99 (d, 1H), 6.31 (d, 1H), 6.03 (dd, 1H), 3.91-3.84 (m, 2H), 3.83 (s, 3H), 2.40-2.30 (m, 2H), 2.30-2.04 (m, 2H), 2.04-1.93 (m, 1H), 1.64 (d, 2H), 1.49-1.32 (m, 2H). LCMS: m/z 345.2 [M+H]⁺
66	 Starting materials: 7-(4-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine HCl and 5-Oxopyrrolidine-2-carboxylic acid	Purification method B. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.38 (s, 1H), 7.89 (s, 1H), 7.71 (d, 2H), 7.44 (d, 1H), 7.09 (d, 2H), 6.51 (d, 1H), 4.39-4.30 (m, 5H), 2.25-1.85 (m, 4H). LCMS: m/z 423.1 [M+H]⁺
67	 Starting materials: 7-(4-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine HCl and 1-	Purification method B. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.70 (s, 1H), 7.71 (d, 2H), 7.42 (s, 1H), 7.09 (d, 2H), 6.52 (d, 1H), 4.48-4.43 (m, 1H), 4.37-4.29 (m, 4H), 2.63 (s, 3H), 2.28-2.15 (m, 3H), 1.93-1.82

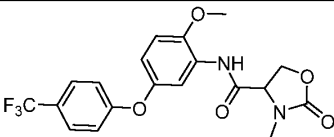
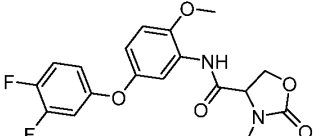
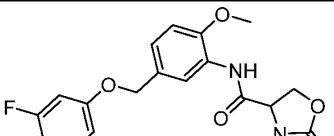
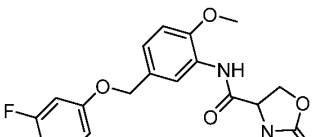
	Methyl-5-oxopyrrolidine-2-carboxylic acid	(m, 1H). LCMS: m/z 437.2 [M+H] ⁺
68	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-Ethyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.67 (s, 1H), 7.86 (d, 1H), 7.71 (d, 2H), 7.14 (d, 1H), 7.08 (d, 2H), 6.92 (dd, 1H), 4.67-4.58 (m, 1H), 3.89 (s, 3H), 3.53-3.44 (m, 1H), 2.86-2.76 (m, 1H), 2.35-2.13 (m, 3H), 1.98-1.84 (m, 1H), 1.00 (t, 3H). LCMS: m/z 423.1 [M+H]⁺
69	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.66 (s, 1H), 7.87 (d, 1H), 7.71 (d, 2H), 7.14 (d, 1H), 7.07 (d, 2H), 6.92 (dd, 1H), 4.52-4.43 (m, 1H), 3.88 (s, 3H), 2.64 (s, 3H), 2.30-2.13 (m, 3H), 1.93-1.82 (m, 1H). LCMS: m/z 409.2 [M+H]⁺
70	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.65 (s, 1H), 7.87 (d, 1H), 7.70 (d, 2H), 7.14 (d, 1H), 7.08 (d, 2H), 6.92 (dd, 1H), 4.51-4.41 (m, 1H), 3.89 (s, 3H), 2.64 (s, 3H), 2.31-2.15 (m, 3H), 1.95-1.82 (m, 1H). LCMS: m/z 409.2 [M+H]⁺
71	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.68 (s, 1H), 7.91 (d, 1H), 7.71 (d, 2H), 7.17 (d, 1H), 7.09 (d, 2H), 6.95 (dd, 1H), 4.51 (dd, 1H), 4.37 (dd, 1H),

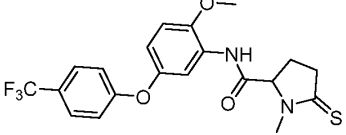
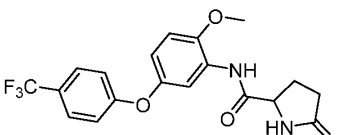
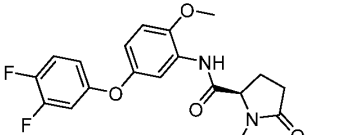
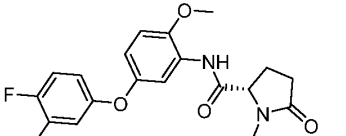
	Lithium N-methylalaninate 1,1-dioxide	4.07 (dd, 1H), 2.70 (s, 3H). LCMS: m/z 431.2 [M+H] ⁺
72	 Starting materials: 2-Methoxy-5-(3-(trifluoromethyl)phenoxy)aniline and Lithium N-methylalaninate 1,1-dioxide	Purification method C. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.68 (s, 1H), 7.91 (d, 1H), 7.71 (d, 2H), 7.17 (d, 1H), 7.09 (d, 2H), 6.95 (dd, 1H), 4.51 (dd, 1H), 4.37 (dd, 1H), 4.07 (dd, 1H), 2.70 (s, 3H). LCMS: m/z 431.0 [M+H]⁺
73	 Starting materials: 4-Fluoro-5-((3-fluorophenoxy)methyl)-2-methoxyaniline and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.16 (s, 1H), 7.87 (s, 1H), 7.72 (d, 1H), 7.01-6.91 (m, 2H), 6.56-6.46 (m, 2H), 4.28 (dd, 1H), 3.81 (s, 3H), 3.76 (s, 2H), 2.31-2.04 (m, 3H), 2.00-1.88 (m, 1H). LCMS: m/z 375.0 [M-H]⁻
74	 Starting materials: 4-Methoxy-N1-(4-(trifluoromethyl)phenyl)benzene-1,3-diamine and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.52 (s, 1H), 8.48 (s, 1H), 7.90 (d, 1H), 7.46 (d, 2H), 7.02 (dd, 3H), 6.94 (dd, 1H), 4.51-4.41 (m, 1H), 3.84 (s, 3H), 2.65 (s, 3H), 2.34-2.15 (m, 3H), 1.98-1.82 (m, 1H). LCMS: m/z 408.2 [M+H]⁺
75	 Starting materials: 2-Fluoro-5-(4-(trifluoromethyl)phenoxy)aniline and 1-Methyl-5-oxopyrrolidine-2-	Purification method A. ¹H NMR (400 MHz, Chloroform-<i>d</i>) δ: 8.12 (dd, 1H), 7.72 (s, 1H), 7.59 (d, 2H), 7.19-7.12 (m, 1H), 7.05 (d, 2H), 6.82 (dd, 1H), 4.14 (dd, 1H), 2.95 (s, 3H), 2.64-2.40 (m, 3H), 2.22-2.13 (m, 1H). LCMS: m/z 397.2 [M+H]⁺

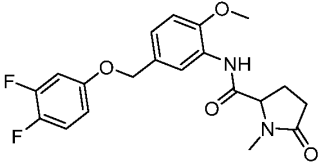
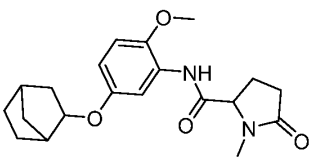
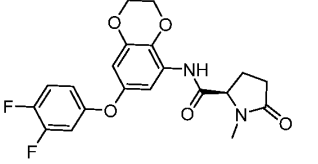
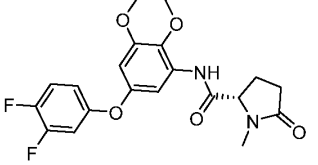
	carboxylic acid	
76	 Starting materials: 2-Fluoro-5-(4-(trifluoromethyl)phenoxy)aniline and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, Chloroform-<i>d</i>) δ: 8.12 (dd, 1H), 7.72 (s, 1H), 7.59 (dd, 2H), 7.20-7.12 (m, 1H), 7.05 (d, 2H), 6.82 (dd, 1H), 4.14 (dd, 1H), 2.65-2.39 (m, 3H), 2.22-2.12 (m, 1H). LCMS: m/z 383.2 [M+H]⁺
77	 Starting materials: 5-(3,5-Difluorophenoxy)-2-methoxyaniline HCl and 1-Acetyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.76 (s, 1H), 7.85 (d, 1H), 7.12 (d, 1H), 6.98-6.85 (m, 2H), 6.67-6.58 (m, 2H), 5.07 (d, 1H), 3.89 (s, 3H), 2.61-2.55 (m, 1H), 2.38 (s, 3H), 2.34-1.82 (m, 3H). LCMS: m/z 405.2 [M+H]⁺
78	 Starting materials: 5-(3,5-Difluorophenoxy)-2-methoxyaniline HCl and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.67 (s, 1H), 7.86 (d, 1H), 7.13 (d, 1H), 6.98-6.88 (m, 2H), 6.64 (dd, 2H), 4.47 (d, 1H), 3.88 (s, 3H), 2.64 (s, 3H), 2.32-2.17 (m, 3H), 1.93-1.79 (m, 1H). LCMS: m/z 377.0 [M+H]⁺
79	 Starting materials: 5-(2,5-Difluorophenoxy)-2-methoxyaniline and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.32 (s, 1H), 7.97-7.82 (m, 2H), 7.53-7.35 (m, 1H), 7.09 (d, 1H), 7.06-6.97 (m, 1H), 6.96-6.88 (m, 1H), 6.83 (dd, 1H), 4.38 (dd, 1H), 3.86 (s, 3H), 2.35-2.25 (m, 1H), 2.25-2.03 (m, 2H), 2.02-1.87 (m, 1H). LCMS: m/z 363.0 [M+H]⁺

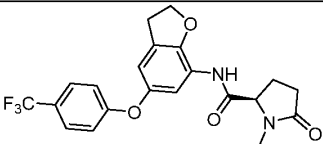
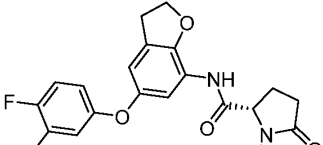
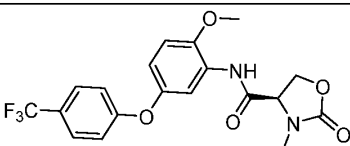
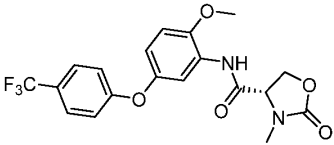
80	 Starting materials: 7-(4-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine HCl and Lithium 3-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 8.90 (s, 1H), 7.70 (d, 2H), 7.32 (d, 1H), 7.08 (d, 2H), 6.53 (d, 1H), 4.35-4.24 (m, 4H), 3.60-3.50 (m, 1H), 3.10-3.01 (m, 1H), 2.71-2.63 (m, 1H), 2.35-2.24 (m, 3H), 2.21-2.14 (m, 1H), 1.97-1.87 (m, 1H), 1.86-1.77 (m, 1H), 1.73-1.65 (m, 1H). LCMS: m/z 463.2 [M+H]⁺
81	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-Isopropyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, Acetonitrile-<i>d</i>₃) δ: 8.51 (s, 1H), 8.06 (d, 1H), 7.68 (d, 2H), 7.09 (dd, 3H), 6.88 (dd, 1H), 4.38 (dd, 1H), 4.22-4.12 (m, 1H), 2.58-2.44 (m, 1H), 2.36-2.20 (m, 3H), 1.22 (d, 3H), 1.10 (d, 3H). LCMS: m/z 437.2 [M+H]⁺
82	 Starting materials: 5-(3,4-Difluorophenoxy)-2-methoxyaniline and 1-Isopropyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, Acetonitrile-<i>d</i>₃) δ: 8.49 (s, 1H), 8.02 (dd, 1H), 7.31-7.18 (m, 1H), 7.04 (dd, 1H), 6.99-6.88 (m, 1H), 6.85-6.73 (m, 2H), 4.42-4.34 (m, 1H), 4.24-4.10 (m, 1H), 3.92 (d, 3H), 2.54-2.43 (m, 1H), 2.40-2.24 (m, 1H), 1.25-1.18 (m, 3H), 1.13-1.04 (m, 3H). LCMS: m/z 405.2 [M+H]⁺
83	 Starting materials: 2-(1,3,4-Oxadi-	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.91 (s, 1H), 9.42 (s, 1H), 8.07 (s, 1H), 8.01 (d, 1H), 7.83 (d, 2H), 7.34 (d, 2H), 7.07 (dd, 1H), 4.29 (dd, 1H),

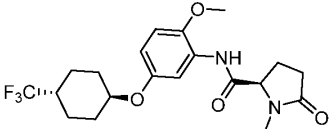
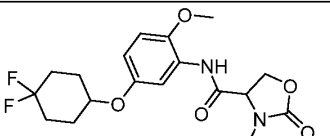
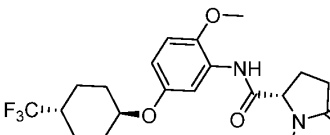
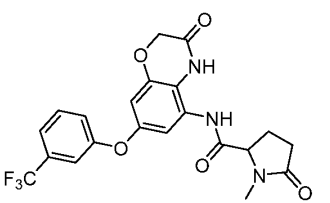
	azol-2-yl)-5-(4-(trifluoromethyl)-phenoxy)aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	2.72 (s, 3H), 2.45-2.20 (m, 3H), 2.07-1.95 (m, 1H). LCMS: m/z 447.0 [M+H] ⁺
84	 Starting materials: 2-(1,3,4-Oxadiazol-2-yl)-5-(3-(trifluoromethyl)-phenoxy)aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.91 (s, 1H), 9.41 (s, 1H), 8.08-7.97 (m, 2H), 7.76-7.67 (m, 1H), 7.63 (d, 1H), 7.54 (s, 1H), 7.48 (d, 1H), 7.01 (dd, 1H), 4.28 (d, 1H), 2.72 (s, 3H), 2.39-2.21 (m, 3H), 2.05-1.94 (m, 1H). LCMS: m/z 447.0 [M+H]⁺
85	 Starting materials: 5-(3,4-Difluorophenoxy)-2-(1-methyl-1H-pyrazol-3-yl)aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method C. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 11.79 (s, 1H), 8.34 (d, 1H), 7.90-7.79 (m, 2H), 7.55-7.44 (m, 1H), 7.35-7.25 (m, 1H), 6.98-6.90 (m, 1H), 6.87-6.77 (m, 2H), 4.20 (dd, 1H), 3.94 (s, 3H), 2.79 (s, 3H), 2.44-2.24 (m, 3H), 2.02-1.89 (m, 1H). LCMS: m/z 427.0 [M+H]⁺
86	 Starting materials: 5-(3,4-Difluorophenoxy)-2-(1-methyl-1H-pyrazol-5-yl)aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method C. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.61 (s, 1H), 7.55-7.46 (m, 1H), 7.44 (d, 1H), 7.37 (d, 1H), 7.35-7.31 (m, 1H), 7.28 (d, 1H), 7.01-6.92 (m, 2H), 6.21 (d, 1H), 4.10-4.03 (m, 1H), 3.63 (s, 3H), 2.17-2.09 (m, 3H), 1.75-1.66 (m, 1H). LCMS: m/z 427.0 [M+H]⁺

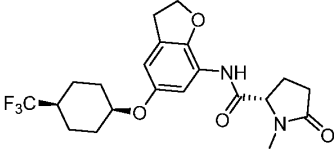
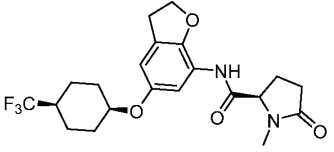
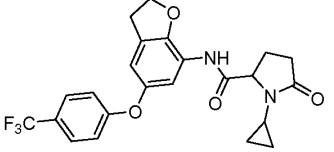
87	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 3-Methyl-2-oxooxazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.83 (s, 1H), 7.91 (d, 1H), 7.71 (d, 2H), 7.15 (d, 1H), 7.08 (d, 2H), 6.97-6.89 (m, 1H), 4.68 (dd, 1H), 4.42 (t, 1H), 4.18 (dd, 1H), 3.89 (s, 3H), 2.73 (s, 3H). LCMS: m/z 411.0 [M+H]⁺
88	 Starting materials: 5-(3,4-Difluorophenoxy)-2-methoxyaniline and 3-Methyl-2-oxooxazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.79 (s, 1H), 7.86 (d, 1H), 7.47-7.35 (m, 1H), 7.15-7.05 (m, 2H), 6.86 (dd, 1H), 6.80-6.72 (m, 1H), 4.68 (dd, 1H), 4.42 (t, 1H), 4.18 (dd, 1H), 3.87 (s, 3H), 2.73 (s, 3H). LCMS: m/z 379.0 [M+H]⁺
89	 Starting materials: 5-((3,4-Difluorophenoxy)methyl)-2-methoxyaniline HCl and 3-Methyl-2-oxooxazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.71 (s, 1H), 8.09 (d, 1H), 7.41-7.30 (m, 1H), 7.29-7.17 (m, 1H), 7.17-7.11 (m, 1H), 7.08 (d, 1H), 6.87-6.78 (m, 1H), 5.00 (s, 2H), 4.66 (dd, 1H), 4.44 (t, 1H), 4.18 (dd, 1H), 3.86 (s, 3H), 2.75 (s, 3H). LCMS: m/z 391.0 [M-H]⁻
90	 Starting materials: 5-((3-Fluorophenoxy)methyl)-2-methoxyaniline HCl and 3-Methyl-2-oxooxazolidine-4-carboxylic acid	Purification method C. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.71 (s, 1H), 8.10 (s, 1H), 7.31 (d, 1H), 7.25-7.20 (m, 1H), 7.08 (d, 1H), 6.91-6.82 (m, 2H), 6.80-6.72 (m, 1H), 5.02 (s, 2H), 4.69-4.63 (m, 1H), 4.49-4.41 (m, 1H), 4.23-4.15 (m, 1H), 3.86 (s, 3H), 2.75 (s, 3H). LCMS: m/z 375.2 [M+H]⁺

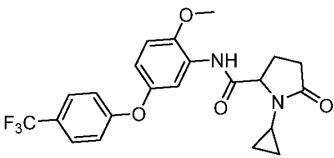
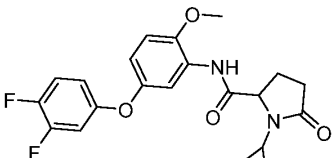
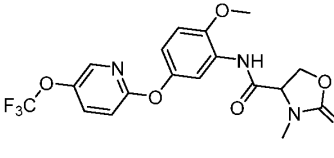
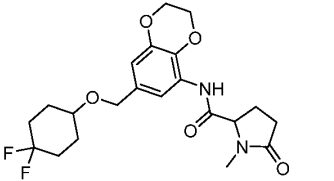
91	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-Methyl-5-thioxopyrrolidine-2-carboxylic acid	Purification method C. ^1H NMR (400 MHz, DMSO-d_6) δ: 9.84 (s, 1H), 7.90-7.82 (m, 1H), 7.71 (d, 2H), 7.15 (d, 1H), 7.07 (d, 2H), 6.94 (dd, 1H), 5.00-4.92 (m, 1H), 3.89 (s, 3H), 3.07 (s, 3H), 2.94-2.83 (m, 2H), 2.36-2.29 (m, 1H), 2.06-1.91 (m, 1H). LCMS: m/z 425.0 $[\text{M}+\text{H}]^+$
92	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and Lithium 5-thioxopyrrolidine-2-carboxylate	Purification method A. ^1H NMR (400 MHz, DMSO-d_6) δ: 10.30 (s, 1H), 9.61 (s, 1H), 7.91-7.85 (m, 1H), 7.71 (d, 2H), 7.13 (s, 1H), 7.08 (d, 2H), 6.92 (dd, 1H), 4.84-4.72 (m, 1H), 3.88 (s, 3H), 2.75 (q, 2H), 2.44-2.31 (m, 1H), 2.13-2.01 (m, 1H). LCMS: m/z 411.1 $[\text{M}+\text{H}]^+$
93	 Starting materials: 5-(3,4-Difluorophenoxy)-2-methoxyaniline and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ^1H NMR (400 MHz, DMSO-d_6) δ: 9.62 (s, 1H), 7.83 (d, 1H), 7.48-7.36 (m, 1H), 7.14-7.05 (m, 2H), 6.84 (dd, 1H), 6.76 (d, 1H), 4.50-4.41 (m, 1H), 3.86 (s, 3H), 2.64 (s, 3H), 2.35-2.13 (m, 3H), 1.94-1.81 (m, 1H). LCMS: m/z 377.2 $[\text{M}+\text{H}]^+$
94	 Starting materials: 5-(3,4-Difluorophenoxy)-2-methoxyaniline and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ^1H NMR (400 MHz, DMSO-d_6) δ: 9.62 (s, 1H), 7.83 (d, 1H), 7.47-7.38 (m, 1H), 7.12-7.04 (m, 2H), 6.84 (dd, 1H), 6.76 (d, 1H), 4.50-4.41 (m, 1H), 3.86 (s, 3H), 2.64 (s, 3H), 2.30-2.14 (m, 3H), 1.92-1.77 (m, 1H). LCMS: m/z 377.2 $[\text{M}+\text{H}]^+$

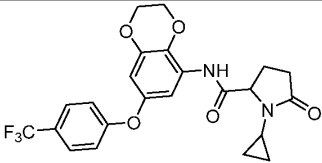
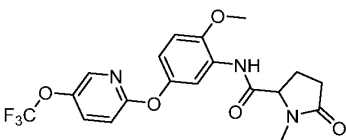
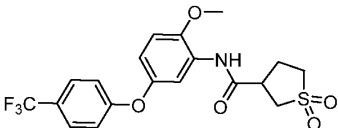
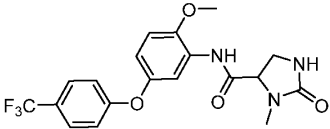
95	 Starting materials: 5-((3,4-Difluorophenyl)methyl)-2-methoxyaniline HCl and 5-Oxopyrrolidine-2-carboxylic acid	Purification method A. ^1H NMR (500 MHz, DMSO-d_6) δ: 9.50 (s, 1H), 8.03 (d, 1H), 7.38-7.25 (m, 1H), 7.18 (dd, 1H), 7.15-7.09 (m, 1H), 7.05 (d, 1H), 6.82-6.75 (m, 1H), 4.98 (s, 2H), 4.46-4.38 (m, 1H), 3.84 (s, 3H), 2.65 (s, 3H), 2.33-2.12 (m, 3H), 1.93-1.82 (m, 1H). LCMS: m/z 391.2 $[\text{M}+\text{H}]^+$
96	 Starting materials: 5-(Bicyclo[2.2.1]heptan-2-yloxy)-2-methoxyaniline HCl and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ^1H NMR (400 MHz, DMSO-d_6) δ: 9.45 (s, 1H), 7.68-7.61 (m, 1H), 6.94 (d, 1H), 6.60 (dd, 1H), 4.50-4.38 (m, 1H), 4.11 (d, 1H), 3.78 (s, 3H), 2.66 (s, 3H), 2.36-2.15 (m, 5H), 1.96-1.84 (m, 1H), 1.80-1.67 (m, 1H), 1.61-1.33 (m, 4H), 1.24-1.02 (m, 3H). LCMS: m/z 359.2 $[\text{M}+\text{H}]^+$
97	 Starting materials: 7-(3,4-Difluorophenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine HCl and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ^1H NMR (400 MHz, DMSO-d_6) δ: 9.52 (s, 1H), 7.46-7.28 (m, 2H), 7.12-7.01 (m, 1H), 6.79 (d, 1H), 6.41 (d, 1H), 4.44 (dd, 1H), 4.35-4.24 (m, 4H), 2.65 (s, 3H), 2.34-2.13 (m, 3H), 1.96-1.85 (m, 1H). LCMS: m/z 405.0 $[\text{M}+\text{H}]^+$
98	 Starting materials: 7-(3,4-Difluorophenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine HCl and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ^1H NMR (600 MHz, DMSO-d_6) δ 9.64 (s, 1H), 7.44-7.37 (m, 1H), 7.35 (d, 1H), 7.14-6.99 (m, 1H), 6.77 (dd, 1H), 6.41 (d, 1H), 4.43 (dd, 1H), 4.36-4.22

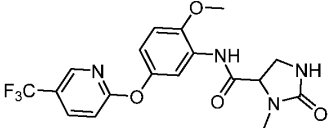
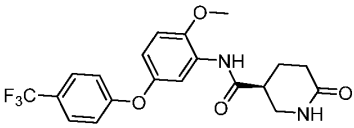
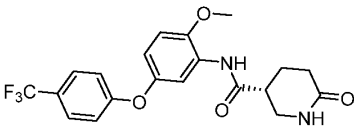
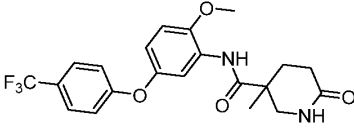
	phenoxy)-2,3-dihydrobenzo[b][1,4]-dioxin-5-amine HCl and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	(m, 4H), 2.61 (s, 3H), 2.28-2.14 (m, 3H), 1.90-1.81 (m, 1H). LCMS: m/z 405.0 [M+H] ⁺
99	 Starting materials: 5-(4-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-amine HCl and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.95 (s, 1H), 7.70 (d, 2H), 7.57 (d, 1H), 7.07 (d, 2H), 6.88 (s, 1H), 4.65 (t, 2H), 4.40 (d, 1H), 3.25 (t, 2H), 2.63 (s, 3H), 2.24-2.17 (m, 3H), 1.90-1.80 (m, 1H). LCMS: m/z 421.2 [M+H]⁺
100	 Starting materials: 5-(3,4-Difluorophenoxy)-2,3-dihydrobenzofuran-7-amine HCl and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method F. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.91 (s, 1H), 7.52 (d, 1H), 7.40 (q, 1H), 7.14-6.97 (m, 1H), 6.81 (d, 1H), 6.78-6.70 (m, 1H), 4.63 (t, 2H), 4.43-4.36 (m, 1H), 3.28-3.19 (m, 2H), 2.63 (s, 3H), 2.29-2.13 (m, 3H), 1.93-1.81 (m, 1H). LCMS: m/z 389.0 [M+H]⁺
101	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and Lithium (R)-3-methyl-2-oxo-oxazolidine-4-carboxylate	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.83 (s, 1H), 7.94-7.88 (m, 1H), 7.71 (d, 2H), 7.15 (d, 1H), 7.08 (d, 2H), 6.94 (dd, 1H), 4.73-4.65 (m, 1H), 4.42 (t, 1H), 4.18 (dd, 1H), 2.73 (s, 3H). LCMS: m/z 411.0 [M+H]⁺
102		Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.83 (s, 1H), 7.96-7.86 (m, 1H), 7.71

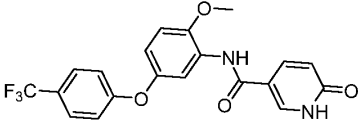
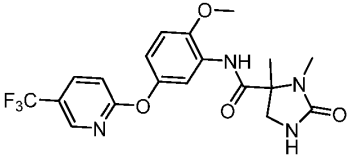
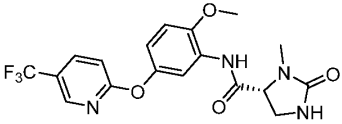
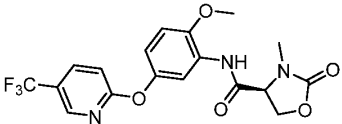
	Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and Lithium (S)-3-methyl-2-oxo-oxazolidine-4-carboxylate	(d, 2H), 7.15 (d, 1H), 7.08 (d, 2H), 6.94 (dd, 1H), 4.68 (dd, 1H), 4.42 (t, 1H), 4.18 (dd, 1H), 3.89 (s, 3H), 2.73 (s, 3H). LCMS: m/z 411.0 [M+H] ⁺
103	 Starting materials: 2-Methoxy-5-(((trans)-4-(trifluoromethyl)cyclohexyl)oxy)aniline and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method C. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.46 (s, 1H), 7.65 (d, 1H), 6.95 (d, 1H), 6.71 (dd, 1H), 4.50-4.41 (m, 1H), 4.19-4.08 (m, 1H), 2.66 (s, 3H), 2.37-2.15 (m, 4H), 2.10 (d, 2H), 1.97-1.84 (m, 3H), 1.49-1.31 (m, 4H). LCMS: m/z 415.0 [M+H]⁺
104	 Starting materials: 5-(((4,4-Difluorocyclohexyl)oxy)-2-methoxyaniline HCl and 3-Methyl-2-oxooxazolidine-4-carboxylic acid	Purification method C. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.68 (s, 1H), 7.74 (s, 1H), 6.98 (d, 1H), 6.77 (d, 1H), 4.74-4.62 (m, 1H), 4.49-4.37 (m, 2H), 4.19 (dd, 1H), 3.80 (s, 3H), 2.74 (s, 3H), 2.06-1.76 (m, 8H). LCMS: m/z 385.2 [M+H]⁺
105	 Starting materials: 2-Methoxy-5-(((trans)-4-(trifluoromethyl)cyclohexyl)oxy)aniline and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method C. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.46 (s, 1H), 7.65 (d, 1H), 6.95 (d, 1H), 6.71 (dd, 1H), 4.49-4.41 (m, 1H), 4.22-4.09 (m, 1H), 3.78 (s, 3H), 2.66 (s, 3H), 2.35-2.16 (m, 4H), 2.10 (d, 2H), 1.95-1.84 (m, 3H), 1.39 (q, 4H). LCMS: m/z 415.0 [M+H]⁺
106		Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.40 (s, 1H), 9.65 (s, 1H), 7.65-7.58 (m, 2H), 7.47 (d, 2H), 7.28 (d, 3H), 7.11 (d, 1H), 6.68 (d, 1H), 4.61 (s,

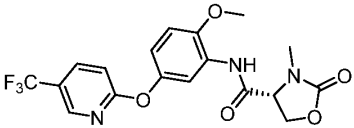
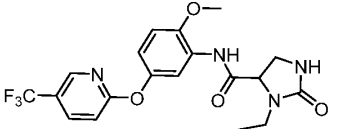
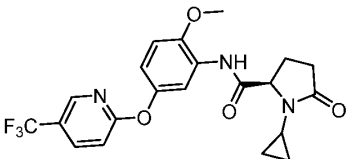
	Starting materials: 5-Amino-7-(3-(trifluoromethyl)phenoxy)-2H-benzo[b][1,4]oxazin-3(4H)-one and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	3H), 4.32-4.26 (m, 1H), 2.67 (s, 3H), 2.33-2.11 (m, 5H), 2.07-1.94 (m, 1H). LCMS: m/z 450.0 [M+H] ⁺
107	 Starting materials: 5-(((cis)-4-(Trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran-7-amine HCl and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.75 (s, 1H), 7.37 (d, 1H), 6.70 (d, 1H), 4.55 (t, 2H), 4.46-4.34 (m, 2H), 3.18 (t, 2H), 2.65 (s, 3H), 2.40-2.16 (m, 4H), 2.03-1.83 (m, 3H), 1.69-1.49 (m, 6H). LCMS: m/z 427.2 [M+H] ⁺
108	 Starting materials: 5-(((cis)-4-(Trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran-7-amine HCl and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.75 (s, 1H), 7.37 (d, 1H), 6.70 (d, 1H), 4.55 (t, 2H), 4.48-4.32 (m, 2H), 3.18 (t, 2H), 2.65 (s, 3H), 2.39-2.17 (m, 5H), 1.97 (d, 2H), 1.89 (d, 1H), 1.68-1.54 (m, 6H). LCMS: m/z 427.2 [M+H] ⁺
109	 Starting materials: 5-(4-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-amine HCl and 1-Cyclopropyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.93 (s, 1H), 7.70 (d, 2H), 7.60 (d, 1H), 7.07 (d, 2H), 6.87 (s, 1H), 4.66 (t, 2H), 4.40 (d, 1H), 3.29-3.20 (m, 2H), 2.36-2.05 (m, 2H), 1.92-1.76 (m, 1H), 0.77-0.40 (m, 4H). LCMS: m/z 447.0 [M+H] ⁺

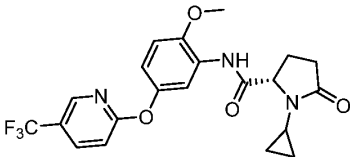
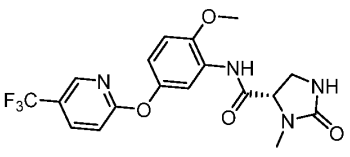
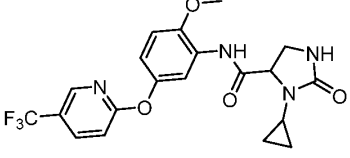
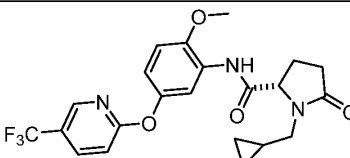
110	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-Cyclopropyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.65 (s, 1H), 7.95-7.84 (m, 1H), 7.71 (d, 2H), 7.14 (d, 1H), 7.08 (d, 2H), 6.92 (dd, 1H), 4.54-4.42 (m, 1H), 3.89 (s, 3H), 2.44-2.37 (m, 1H), 2.32-2.24 (m, 1H), 2.24-2.10 (m, 2H), 1.94-1.78 (m, 1H), 0.74-0.46 (m, 4H). LCMS: m/z 435.2 [M+H]⁺
111	 Starting materials: 5-(3,4-Difluorophenoxy)-2-methoxyaniline and 1-Cyclopropyl-5-oxopyrrolidine-2-carboxylic acid	Purification method E. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.61 (s, 1H), 7.87-7.82 (m, 1H), 7.47-7.35 (m, 1H), 7.13-7.04 (m, 2H), 6.84 (dd, 1H), 6.81-6.70 (m, 1H), 4.51-4.42 (m, 1H), 3.87 (s, 3H), 2.44-2.37 (m, 1H), 2.37-2.22 (m, 1H), 2.22-2.09 (m, 2H), 1.92-1.80 (m, 1H), 0.75-0.48 (m, 4H). LCMS: m/z 403.2 [M+H]⁺
112	 Starting materials: 2-Methoxy-5-((5-(trifluoromethoxy)pyridin-2-yl)oxy)aniline and 3-Methyl-2-oxooxazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.79 (s, 1H), 8.23 (d, 1H), 7.99-7.93 (m, 1H), 7.89 (d, 1H), 7.19-7.08 (m, 2H), 6.95 (dd, 1H), 4.68 (dd, 1H), 4.43 (t, 1H), 4.18 (dd, 1H), 3.87 (s, 3H), 2.73 (s, 3H). LCMS: m/z 428.2 [M+H]⁺
113	 Starting materials: 7-(((4,4-Difluorocyclohexyl)oxy)methyl)-2,3-dihydro-2H-benzofuran and 1-methyl-2-oxopyrrolidine-5-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.54 (s, 1H), 7.49 (s, 1H), 6.64 (s, 1H), 4.47-4.39 (m, 1H), 4.35 (s, 2H), 4.32-4.23 (m, 4H), 3.58-3.52 (m, 1H), 2.66 (s, 3H), 2.33-2.14 (m, 3H), 1.98-1.64

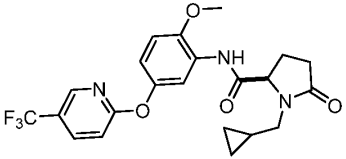
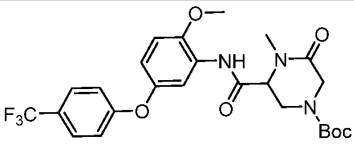
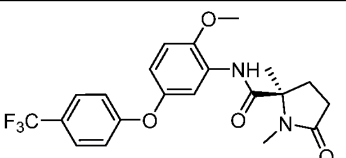
	benzo[b][1,4]dioxin-5-amine and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	(m, 9H). LCMS: m/z 425.0 [M+H] ⁺
114	 Starting materials: 7-(4-(Trifluoromethyl)phenoxy)-2,3-dihydro-benzo[b][1,4]dioxin-5-amine HCl and 1-Cyclopropyl-5-oxopyrrolidine-2-carboxylic acid	Purification method C. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.70 (s, 1H), 7.71 (d, 2H), 7.45 (d, 1H), 7.09 (d, 2H), 6.52 (d, 1H), 4.47 (d, 1H), 4.41-4.27 (m, 4H), 2.41-2.11 (m, 4H), 1.90-1.75 (m, 1H), 0.78-0.43 (m, 4H). LCMS: m/z 463.2 [M+H]⁺
115	 Starting materials: 2-Methoxy-5-((5-(trifluoromethoxy)pyridin-2-yl)oxy)-aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method E. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.62 (s, 1H), 8.23 (d, 1H), 7.98-7.90 (m, 1H), 7.85 (d, 1H), 7.11 (dd, 2H), 6.93 (dd, 1H), 4.53-4.41 (m, 1H), 3.88 (s, 3H), 2.65 (s, 3H), 2.31-2.16 (m, 3H), 1.95-1.81 (m, 1H). LCMS: m/z 426.2 [M+H]⁺
116	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and Tetrahydrothiophene-3-carboxylic acid 1,1-dioxide	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.62 (s, 1H), 8.23 (d, 1H), 7.98-7.90 (m, 1H), 7.85 (d, 1H), 7.11 (dd, 2H), 6.93 (dd, 1H), 4.53-4.41 (m, 1H), 3.88 (s, 3H), 2.65 (s, 3H), 2.31-2.16 (m, 3H), 1.95-1.81 (m, 1H). LCMS: m/z 430.2 [M+H]⁺
117	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.51 (s, 1H), 7.89 (s, 1H), 7.71 (d, 2H), 7.14 (d, 1H), 7.08 (d, 2H), 6.49-

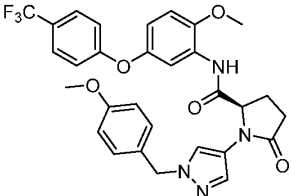
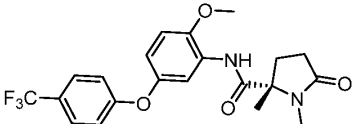
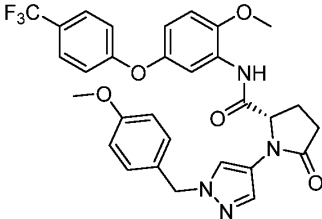
	(trifluoromethyl)phenoxy)aniline and 3-Methyl-2-oxoimi-dazolidine-4-carboxylic acid	6.44 (m, 1H), 4.41-4.35 (m, 1H), 3.88 (s, 3H), 3.19-3.09 (m, 1H), 2.62 (s, 3H). LCMS: m/z 410.2 [M+H] ⁺
118	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and 3-Methyl-2-oxoimi-dazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.49 (s, 1H), 8.55 (s, 1H), 8.21 (d, 1H), 7.90 (s, 1H), 7.20 (d, 1H), 7.13 (d, 1H), 6.96 (d, 1H), 6.47 (s, 1H), 4.43-4.33 (m, 1H), 3.88 (s, 3H), 3.58-3.48 (m, 1H), 3.20-3.10 (m, 1H), 2.62 (s, 3H). LCMS: m/z 411.0 [M+H]⁺
119	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (S)-6-Oxopiperidine-3-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.44 (s, 1H), 7.89-7.84 (m, 1H), 7.70 (d, 2H), 7.48 (d, 1H), 7.09 (dd, 3H), 6.89 (dd, 1H), 3.87 (s, 3H), 3.30-3.18 (m, 2H), 3.09-2.94 (m, 1H), 2.24-2.16 (m, 2H), 1.97-1.90 (m, 1H), 1.86-1.77 (m, 1H). LCMS: m/z 409.2 [M+H]⁺
120	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (R)-6-Oxopiperidine-3-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.45 (s, 1H), 7.91-7.84 (m, 1H), 7.70 (d, 2H), 7.48 (d, 1H), 7.09 (dd, 3H), 6.89 (dd, 1H), 3.87 (s, 3H), 3.31-3.17 (m, 2H), 3.05-2.92 (m, 1H), 2.25-2.15 (m, 2H), 2.00-1.87 (m, 1H), 1.87 – 1.69 (m, 1H). LCMS: m/z 409.2 [M+H]⁺
121	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (S)-6-Oxopiperidine-3-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 8.85 (s, 1H), 7.71 (d, 2H), 7.60 (dd, 1H), 7.52 (s, 1H), 7.13 (d, 1H), 7.08

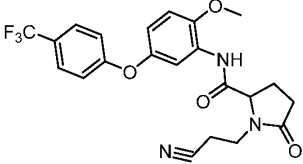
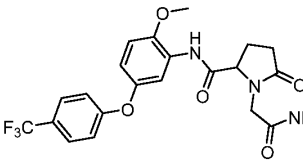
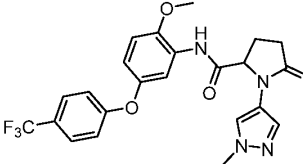
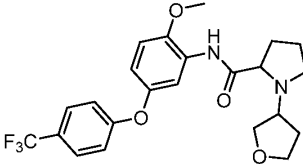
	(trifluoromethyl)phenoxy)aniline and 3-Methyl-6-oxopiperidine-3-carboxylic acid	(d, 2H), 6.95 (dd, 1H), 3.85 (s, 3H), 3.55 (d, 1H), 3.04 (d, 1H), 2.24-2.14 (m, 3H), 1.86-1.75 (m, 1H), 1.26 (s, 3H). LCMS: m/z 423.0 [M+H] ⁺
122	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 6-Oxo-1,6-dihydropyridine-3-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 12.06 (s, 1H), 9.39 (s, 1H), 8.14 (d, 1H), 7.90 (dd, 1H), 7.72 (d, 2H), 7.62 (dd, 1H), 7.15 (d, 1H), 7.10 (d, 2H), 6.97 (dd, 1H), 6.38 (d, 1H), 3.86 (s, 3H). LCMS: m/z 423.0 [M+H]⁺
123	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and 3,4-Dimethyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 8.90 (s, 1H), 8.55 (s, 1H), 8.22 (dd, 1H), 7.83 (d, 1H), 7.17 (dd, 2H), 6.97 (dd, 1H), 3.88 (s, 3H), 3.43 (d, 1H), 3.20 (d, 1H), 2.67 (s, 3H), 1.43 (s, 3H). LCMS: m/z 425.2 [M+H]⁺
124	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and (R)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.47 (s, 1H), 8.55 (s, 1H), 8.23–8.17 (m, 1H), 7.89 (d, 1H), 7.20 (d, 1H), 7.12 (d, 1H), 7.02–6.86 (m, 1H), 6.46 (s, 1H), 4.45–4.25 (m, 1H), 3.88 (s, 3H), 3.54 (t, 1H), 3.18–3.09 (m, 1H), 2.62 (d, 3H). LCMS: m/z 411.0 [M+H]⁺
125	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A ¹H NMR (400 MHz, Acetonitrile-<i>d</i>₃) δ: 8.59 (s, 1H), 8.33 (d, 1H), 8.12 (d, 1H), 7.35 (d, 1H), 7.28 (s, 1H), 7.10 (s, 1H), 6.95 (dd, 1H), 3.85 (s, 3H), 3.55 (d, 1H), 3.04 (d, 1H), 2.24–2.14 (m, 3H), 1.86–1.75 (m, 1H), 1.26 (s, 3H). LCMS: m/z 423.0 [M+H]⁺

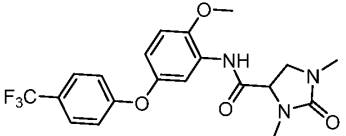
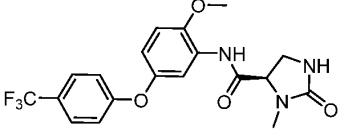
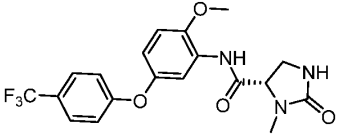
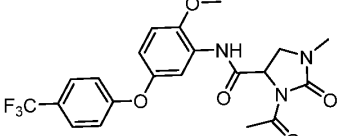
	(trifluoromethyl)pyridin-2-yl)oxy)-aniline and Lithium (S)-3-methyl-2-oxooxazolidine-4-carboxylate	(d, 1H), 6.95 (dd, 1H), 4.54–4.44 (m, 2H), 4.31–4.21 (m, 1H). LCMS: m/z 412.0 [M+H] ⁺
126	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and Lithium (R)-3-methyl-2-oxooxazolidine-4-carboxylate	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.79 (s, 1H), 8.38 (d, 1H), 7.90 (d, 1H), 7.46 (d, 1H), 7.42 (s, 1H), 7.12 (d, 1H), 6.96 (dd, 1H), 4.68 (dd, 1H), 4.43 (t, 1H), 4.18 (dd, 1H), 3.89 (s, 3H), 2.73 (s, 3H). LCMS: m/z 412.0 [M+H]⁺
127	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and 3-ethyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ: 9.46 (s, 1H), 8.36 (d, 1H), 7.87 (d, 1H), 7.44 (d, 1H), 7.39 (s, 1H), 7.10 (d, 1H), 6.93 (dd, 1H), 6.43 (s, 1H), 4.49 (dd, 1H), 3.86 (s, 3H), 3.51 (t, 1H), 3.18–3.13 (m, 1H), 2.87 (dq, 1H), 0.98 (t, 3H). LCMS: m/z 425.0 [M+H]⁺
128	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and (R)-1-Cyclopropyl-5-oxopyrrolidine-2-carboxylic acid	Purification method F. ¹H NMR (400 MHz, Acetonitrile-<i>d</i>₃) δ: 8.51–8.41 (m, 2H), 8.13 (d, 1H), 8.09–8.03 (m, 1H), 7.13 (d, 1H), 7.09 (s, 1H), 6.96–6.89 (m, 1H), 4.30–4.20 (m, 1H), 3.96 (s, 3H), 2.60–2.45 (m, 1H), 2.45–2.35 (m, 1H), 2.35–2.20 (m, 2H), 2.07–2.03 (m, 1H), 0.86 – 0.68 (m, 2H), 0.67 – 0.48 (m, 2H). LCMS: m/z 436.1 [M+H]⁺

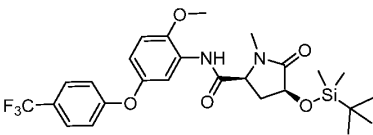
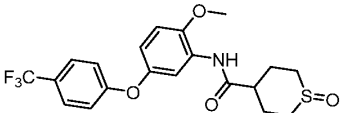
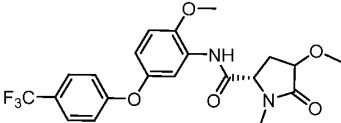
129	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and (S)-1-Cyclopropyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.62 (s, 1H), 8.55 (s, 1H), 8.27–8.15 (m, 1H), 7.90 (d, 1H), 7.20 (d, 1H), 7.12 (d, 1H), 7.00–6.91 (m, 1H), 4.52–4.42 (m, 1H), 3.89 (s, 3H), 2.45–2.38 (m, 2H), 2.36–2.26 (m, 1H), 2.22–2.10 (m, 2H), 1.95–1.75 (m, 1H), 0.79–0.67 (m, 1H), 0.67–0.47 (m, 3H). LCMS: m/z 436.2 [M+H]⁺
130	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and (S)-3-Methyl-2-oxo-imidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.47 (s, 1H), 8.55 (s, 1H), 8.23–8.17 (m, 1H), 7.89 (d, 1H), 7.20 (d, 1H), 7.12 (d, 1H), 7.02–6.86 (m, 1H), 6.46 (s, 1H), 4.45–4.25 (m, 1H), 3.88 (s, 3H), 3.54 (t, 1H), 3.18–3.09 (m, 1H), 2.62 (d, 3H). LCMS: m/z 411.0 [M+H]⁺
131	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and 3-cyclopropyl-2-oxo-imidazolidine-4-carboxylic acid	Purification method A ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.49 (s, 1H), 8.55 (d, 1H), 8.21 (dd, 1H), 7.92 (d, 1H), 7.16 (dd, 2H), 6.95 (dd, 1H), 6.45 (s, 1H), 4.44 (dd, 1H), 3.89 (s, 3H), 3.46 (t, 1H), 3.14 (dd, 1H), 2.43–2.30 (m, 1H), 0.66–0.44 (m, 4H). LCMS: m/z 437.2 [M+H]⁺
132	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and (S)-1-Cyclopropyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A followed by method I. Retention time 14.3 min. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.65 (s, 1H), 8.52 (d, 1H), 8.26–8.13 (m, 1H), 7.82 (d, 1H), 7.17 (d, 1H),

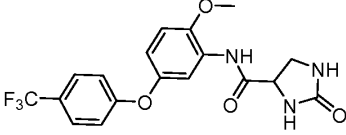
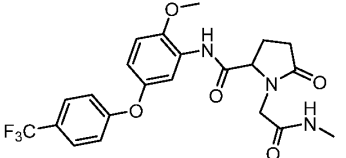
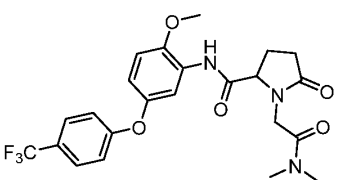
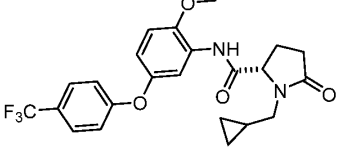
	(trifluoromethyl)pyridin-2-yl)oxy)-aniline and 1-(Cyclopropylmethyl)-5-oxopyrrolidine-2-carboxylic acid (racemic)	7.10 (d, 1H), 6.98–6.92 (m, 1H), 4.77–4.55 (m, 1H), 2.62 (d, 1H), 2.33–2.13 (m, 2H), 1.94–1.74 (m, 1H), 0.81 (dq, 1H), 0.49–0.43 (m, 1H), 0.39–0.27 (m, 1H), 0.19–0.12 (m, 1H), 0.12–0.04 (m, 1H). LCMS: m/z 450.2 [M+H] ⁺
133	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and 1-(Cyclopropylmethyl)-5-oxopyrrolidine-2-carboxylic acid (racemic)	Purification A method followed by method I. Retention time 16.9 min. ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ: 9.65 (s, 1H), 8.52 (d, 1H), 8.26–8.13 (m, 1H), 7.82 (d, 1H), 7.17 (d, 1H), 7.10 (d, 1H), 6.98–6.92 (m, 1H), 4.77–4.55 (m, 1H), 2.62 (d, 1H), 2.33–2.13 (m, 2H), 1.94–1.74 (m, 1H), 0.81 (dq, 1H), 0.49–0.43 (m, 1H), 0.39–0.27 (m, 1H), 0.19–0.12 (m, 1H), 0.12–0.04 (m, 1H). LCMS: m/z 450.2 [M+H] ⁺
Int-279	 (Intermediate) Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and Lithium 4-(tert-butoxycarbonyl)-1-methyl-6-oxopiperazine-2-carboxylate	LCMS: m/z 523.5 [M+H] ⁺
134	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and	Purification method A. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 8.83 (s, 1H), 7.72 (d, 2H), 7.62 (dd, 1H), 7.15 (d, 1H), 7.08 (d, 2H), 6.97 (dd, 1H), 3.85 (s, 3H), 2.69 (s, 3H), 2.30 (d, 2H), 2.00–1.87 (m, 1H), 1.48

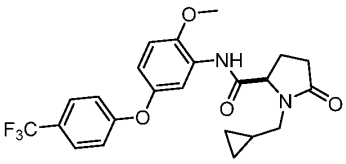
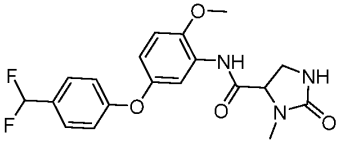
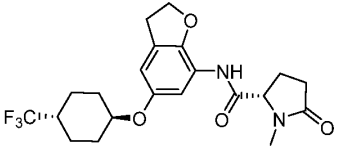
	Lithium (R)-1,2-dimethyl-5-oxo-pyrrolidine-2-carboxylate	(s, 3H). LCMS: m/z 423.2 [M+H] ⁺
Int-280	 (intermediate) Starting materials: (R)-1-(1-(4-Methoxybenzyl)-1H-pyrazol-4-yl)-5-oxopyrrolidine-2-carboxylic acid and 2-Methoxy-5-(4-(trifluoromethyl)-phenoxy)aniline	LCMS: m/z 479.0 [M-H] ⁻
135	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (S)-1,2-Dimethyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 8.82 (s, 1H), 7.71 (d, 2H), 7.61 (d, 1H), 7.14 (d, 1H), 7.08 (d, 2H), 7.01–6.90 (m, 1H), 3.85 (s, 3H), 2.69 (s, 3H), 2.33–2.17 (m, 3H), 2.02–1.85 (m, 1H), 1.48 (s, 3H). LCMS: m/z 423.2 [M+H]⁺
Int-281	 (intermediate) Starting materials: (S)-1-(1-(4-Methoxybenzyl)-1H-pyrazol-4-yl)-5-oxopyrrolidine-2-carboxylic acid and 2-Methoxy-5-(4-(trifluoromethyl)-phenoxy)aniline	LCMS: m/z 579.2 [M-H] ⁻

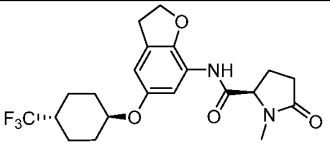
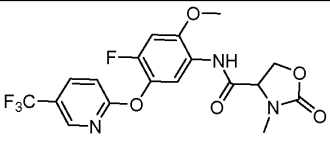
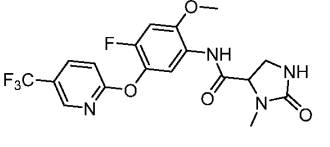
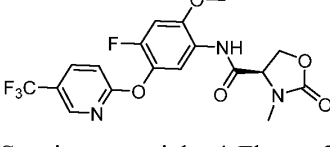
Int-282	 (intermediate) Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-(2-Cyanoethyl)-5-oxopyrrolidine-2-carboxylic acid	LCMS: m/z 446.0 [M-H] ⁻
136	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-(2-Amino-2-oxoethyl)-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.75 (s, 1H), 7.82 (s, 1H), 7.71 (d, 2H), 7.43 (s, 1H), 7.23–7.03 (m, 4H), 6.93 (d, 1H), 4.68–4.58 (m, 1H), 4.15 (d, 1H), 3.86 (s, 3H), 3.24 (d, 1H), 2.42–2.21 (m, 3H), 1.96–1.85 (m, 1H). LCMS: m/z 552.0 [M+H]⁺
137	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-(1-Methyl-1H-pyrazol-4-yl)-5-oxopyrrolidine-2-carboxylic acid HCl	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.82 (s, 1H), 7.93 (d, 1H), 7.81 (d, 1H), 7.69 (d, 2H), 7.45 (s, 1H), 7.15 (d, 1H), 7.06 (d, 2H), 6.92 (dd, 1H), 4.98 (d, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 2.49–2.30 (m, 3H), 2.06 (q, 1H). LCMS: m/z 475.0 [M+H]⁺
138	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.65 (d, 1H), 7.84 (t, 1H), 7.71 (d, 2H), 7.19–7.10 (m, 1H), 7.07 (d, 2H), 6.96–6.87 (m, 1H), 4.76–4.59 (m, 1H), 4.38 (m, 1H), 3.78–3.44 (m, 4H),

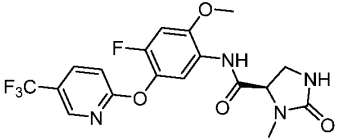
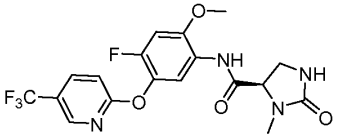
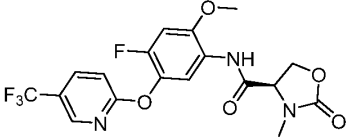
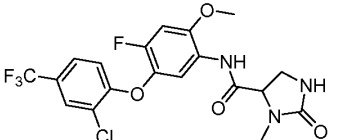
	5-Oxo-1-(tetrahydrofuran-3-yl)-pyrrolidine-2-carboxylic acid	2.41–2.04 (m, 4H), 2.01–1.76 (m, 2H). LCMS: m/z 465.0 [M+H] ⁺
139	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and Lithium 1,3-dimethyl-2-oxoimidazolidine-4-carboxylate	Purification method D. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.57 (s, 1H), 7.88 (d, 1H), 7.71 (d, 2H), 7.11 (dd, 3H), 6.93 (dd, 1H), 4.33 (dd, 1H), 3.88 (s, 3H), 3.54 (t, 1H), 3.19 (dd, 1H), 2.64 (d, 6H). LCMS: m/z 424.0 [M+H]⁺
140	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (R)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.52 (s, 1H), 7.93–7.83 (m, 1H), 7.71 (d, 2H), 7.14 (d, 1H), 7.08 (d, 2H), 6.93 (dd, 1H), 6.47 (s, 1H), 4.46–4.28 (m, 1H), 3.88 (s, 3H), 3.53 (t, 1H), 3.22–3.09 (m, 2H), 2.62 (s, 3H). LCMS: m/z 410.0 [M+H]⁺
141	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.52 (s, 1H), 7.89 (t, 1H), 7.71 (d, 2H), 7.11 (dd, 3H), 6.93 (dd, 1H), 6.47 (s, 1H), 4.47–4.29 (m, 1H), 3.88 (s, 3H), 3.53 (t, 1H), 3.17 (d, 2H), 2.62 (s, 3H). LCMS: m/z 410.1 [M+H]⁺
142	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.79 (s, 1H), 7.89 (d, 1H), 7.70 (d, 2H), 7.14 (d, 1H), 7.06 (d, 2H), 6.91 (dd, 1H), 5.03 (dd, 1H), 3.90 (s, 3H), 3.64 (t, 1H), 3.30 (dd, 1H), 2.74 (s,

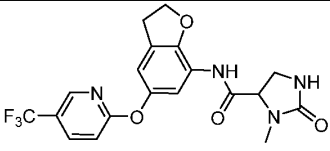
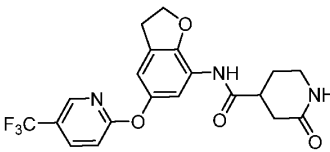
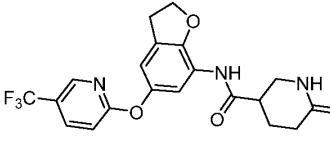
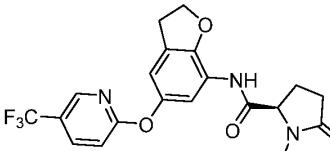
	(trifluoromethyl)phenoxy)aniline and 3-Acetyl-1-methyl-2-oxoimidazolidine-4-carboxylic acid	3H), 2.35 (s, 3H). LCMS: m/z 452.0 [M+H] ⁺
Int-283	 (intermediate) Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (2S,4S)-4-((tert-Butyldimethylsilyl)oxy)-1-methyl-5-oxopyrrolidine-2-carboxylic acid	LCMS: m/z 539.2 [M+H] ⁺
Int-284	 (intermediate) Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and Tetrahydro-2H-thiopyran-4-carboxylic acid 1-oxide	LCMS: m/z 428.2 [M+H] ⁺
143	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (2S)-4-Methoxy-1-methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, Acetonitrile-<i>d</i>₃) δ: 8.72–8.48 (m, 1H), 8.13–8.01 (m, 1H), 7.68 (d, 2H), 7.18–7.03 (m, 2H), 6.95–6.80 (m, 1H), 4.37–4.26 (m, 1H), 4.19–4.06 (m, 1H), 3.94 (s, 3H), 3.50 (s, 2H), 2.84–2.75 (m, 3H), 2.75–2.67 (m, 1H), 2.52–2.36 (m, 1H). LCMS: m/z 439.2 [M+H]⁺

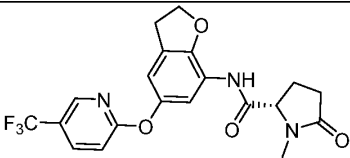
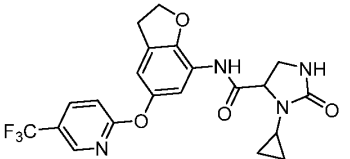
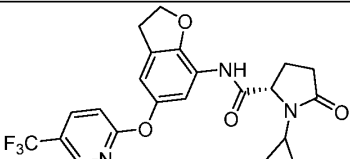
144	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 2-Oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.27 (s, 1H), 7.98 (d, 1H), 7.71 (d, 2H), 7.15 (d, 1H), 7.08 (d, 2H), 6.95–6.84 (m, 1H), 6.80 (s, 1H), 6.49 (s, 1H), 4.38–4.28 (m, 1H), 3.63 (t, 1H), 3.30–3.24 (m, 1H). LCMS: m/z 396.0 [M+H]⁺
145	 Starting materials: 2-Methoxy-4-(4-(trifluoromethyl)phenoxy)aniline and 1-(2-(Methylamino)-2-oxoethyl)-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.73 (s, 1H), 7.88 (d, 1H), 7.83 (s, 1H), 7.70 (d, 2H), 7.13 (d, 1H), 7.07 (d, 2H), 6.92 (dd, 1H), 4.67–4.58 (m, 1H), 4.16 (d, 1H), 3.86 (s, 3H), 3.26 (d, 1H), 2.60–2.55 (m, 3H), 2.41–2.22 (m, 3H), 1.95–1.84 (m, 1H). LCMS: m/z 466.2 [M+H]⁺
146	 Starting materials: 2-Methoxy-4-(4-(trifluoromethyl)phenoxy)aniline and 1-(2-(Dimethylamino)-2-oxoethyl)-5-oxopyrrolidine-2-carboxylic acid	Purification method F. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.67 (s, 1H), 7.84 (s, 1H), 7.71 (d, 2H), 7.12 (d, 1H), 7.07 (d, 2H), 6.91 (dd, 1H), 4.71–4.58 (m, 1H), 4.42 (d, 1H), 3.86 (s, 3H), 3.57 (d, 1H), 2.92 (s, 3H), 2.80 (s, 3H), 2.41–2.20 (m, 3H), 1.99–1.82 (m, 1H). LCMS: m/z 480.2 [M+H]⁺
147	 Starting materials: 2-methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and	Purification method A followed by method I. Retention time 16.48 min. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.67 (s, 1H), 7.81 (d, 1H), 7.69 (d, 2H), 7.12 (d, 1H), 7.06 (d, 2H), 6.94–6.84 (m, 1H), 4.72–4.66 (m, 1H),

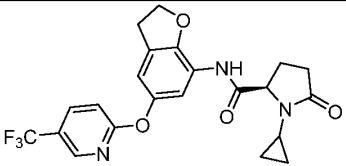
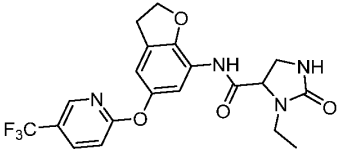
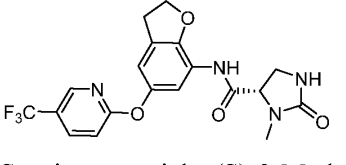
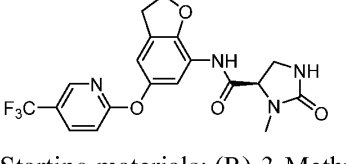
	1-(cyclopropylmethyl)-5-oxo-pyrrolidine-2-carboxylic acid	2.65–2.60 (m, 1H), 2.32–2.15 (m, 2H), 1.96–1.74 (m, 1H), 0.87–0.77 (m, 0H), 0.48–0.41 (m, 1H), 0.40–0.33 (m, 1H), 0.18–0.12 (m, 1H), 0.11–0.05 (m, 1H). LCMS: m/z 449.2 [M+H] ⁺
148	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-(Cyclopropylmethyl)-5-oxo-pyrrolidine-2-carboxylic acid	Purification method A followed by method I. Retention time 26.11 min. ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ: 9.67 (s, 1H), 7.81 (d, 1H), 7.69 (d, 2H), 7.12 (d, 1H), 7.06 (d, 2H), 6.94–6.84 (m, 1H), 4.72–4.66 (m, 1H), 2.65–2.60 (m, 1H), 2.32–2.15 (m, 2H), 1.96–1.74 (m, 1H), 0.87–0.77 (m, 0H), 0.48–0.41 (m, 1H), 0.40–0.33 (m, 1H), 0.18–0.12 (m, 1H), 0.11–0.05 (m, 1H). LCMS: m/z 449.2 [M+H] ⁺
149	 Starting materials: 5-(4-(Difluoromethyl)phenoxy)-2-methoxyaniline and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹ H NMR (400 MHz, Acetonitrile- <i>d</i> ₃) δ: 8.60 (s, 1H), 8.06 (d, 1H), 7.56 (d, 2H), 7.07 (d, 3H), 6.87 (dd, 1H), 6.79 (t, 1H), 5.01 (s, 1H), 4.19 (dd, 1H), 3.68 (t, 1H), 3.32 (t, 1H), 2.78 (s, 3H). LCMS: m/z 390.1 [M-H] [–]
150	 Starting materials: 5-(((trans)-4-(Trifluoromethyl)cyclohexyloxy)-2,3-dihydrobenzofuran-7-amine HCl and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.74 (s, 1H), 7.33 (s, 1H), 6.70 (s, 1H), 4.55 (t, 2H), 4.37 (m, 1H), 4.17–3.89 (m, 1H), 3.18 (t, 2H), 2.31 (s, 3H), 2.09 (m, 4H), 1.89 (m, 2H), 1.55–1.20 (m, 4H). LCMS: m/z 427.2 [M+H] ⁺

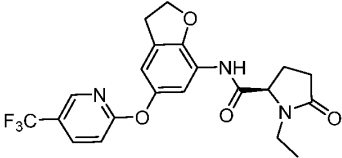
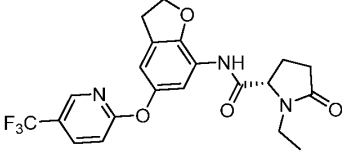
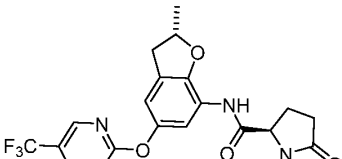
151	 Starting materials: 5-(((trans)-4-(Trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran-7-amine HCl and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.74 (s, 1H), 7.33 (s, 1H), 6.70 (s, 1H), 4.54 (t, 2H), 4.37 (m, 1H), 4.16–4.01 (m, 1H), 3.18 (t, 2H), 2.63 (s, 3H), 2.36–2.13 (m, 4H), 2.10 (m, 2H), 1.89 (s, 3H), 1.51–1.20 (m, 4H). LCMS: m/z 427.2 [M+H]⁺
152	 Starting materials: 4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)-pyridin-2-yl)oxy)aniline HCl and 3-Methyl-2-oxooxazolidine-4-carboxylic acid	Purification method A. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ: 9.80 (s, 1H), 8.53 (s, 1H), 8.24 (d, 1H), 7.95 (d, 1H), 7.32 (d, 1H), 7.22 (d, 1H), 4.69–4.59 (m, 1H), 4.41 (t, 1H), 4.21–4.10 (m, 1H), 3.88 (s, 3H), 2.71 (s, 3H). LCMS: m/z 430.0 [M+H]⁺
153	 Starting materials: 4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)-pyridin-2-yl)oxy)aniline HCl and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.53 (s, 1H), 8.55 (s, 1H), 8.26 (dd, 1H), 7.95 (dd, 1H), 7.34 (d, 1H), 7.23 (d, 1H), 6.45 (s, 1H), 4.43–4.26 (m, 1H), 3.89 (s, 3H), 3.53 (t, 1H), 3.16 (t, 1H), 2.62 (s, 3H). LCMS: m/z 429.2 [M+H]⁺
154	 Starting materials: 4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)-pyridin-2-yl)oxy)aniline HCl and Lithium (R)-3-methyl-2-oxooxa-	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.82 (s, 1H), 8.57–8.50 (m, 1H), 8.26 (dd, 1H), 7.97 (d, 1H), 7.34 (d, 1H), 7.24 (d, 1H), 4.66–4.61 (m, 1H), 4.43 (t, 1H), 4.21–4.15 (m, 1H), 3.90 (s, 3H), 2.73 (s, 3H). LCMS: m/z 430.0

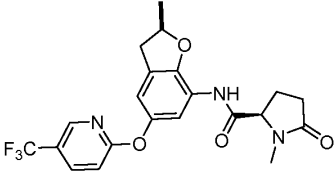
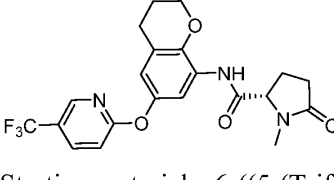
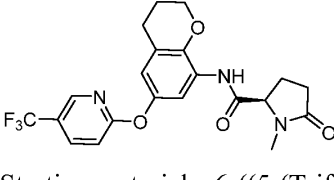
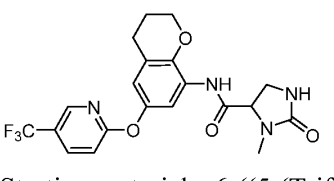
	zolidine-4-carboxylate	[M+H] ⁺
155	 Starting materials: 4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)aniline HCl and (R)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.50 (s, 1H), 8.53 (d, 1H), 8.24 (dd, 1H), 7.92 (d, 1H), 7.32 (d, 1H), 7.21 (d, 1H), 6.42 (s, 1H), 4.33 (dd, 1H), 3.87 (s, 3H), 3.51 (t, 1H), 3.15 (t, 1H), 2.60 (s, 3H). LCMS: m/z 429.2 [M+H]⁺
156	 Starting materials: 4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)aniline HCl and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.50 (s, 1H), 8.55 (s, 1H), 8.26 (dd, 1H), 7.94 (d, 1H), 7.34 (d, 1H), 7.23 (d, 1H), 6.44 (s, 1H), 4.39–4.31 (m, 1H), 3.89 (s, 3H), 3.53 (t, 1H), 3.21–3.13 (m, 1H), 2.62 (s, 3H). LCMS: m/z 429.0 [M+H]⁺
157	 Starting materials: 4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)aniline HCl and Lithium (S)-3-methyl-2-oxoimidazolidine-4-carboxylate	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.82 (s, 1H), 8.58 – 8.49 (m, 1H), 8.26 (d, 1H), 7.97 (d, 1H), 7.34 (d, 1H), 7.23 (d, 1H), 4.69–4.61 (m, 1H), 4.43 (t, 1H), 4.22–4.13 (m, 1H), 3.90 (s, 3H), 2.73 (s, 3H). LCMS: m/z 430.0 [M+H]⁺
158	 Starting materials: 5-(2-Chloro-4-(trifluoromethyl)phenoxy)-4-fluoro-	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.58 (s, 1H), 8.02 (s, 1H), 7.96 (d, 1H), 7.67 (d, 1H), 7.32 (d, 1H), 6.97 (d, 1H), 6.44 (s, 1H), 4.36 (dd, 1H), 3.90 (s, 3H), 3.52 (t, 1H), 3.21–3.10

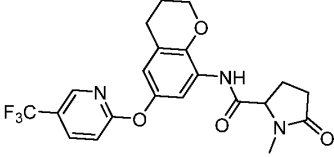
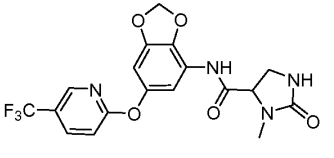
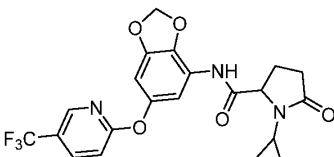
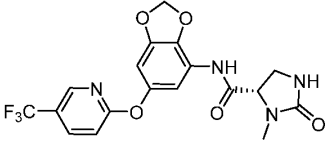
	2-methoxyaniline HCl and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	(m, 1H), 2.61 (s, 3H). LCMS: m/z 462.0 [M+H] ⁺
159	 Starting materials: 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine HCl and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.76 (s, 1H), 8.55 (s, 1H), 8.20 (d, 1H), 7.56 (s, 1H), 7.18 (d, 1H), 6.90 (s, 1H), 6.39 (s, 1H), 4.65 (t, 2H), 4.35 (dd, 1H), 3.51 (t, 1H), 3.25 (t, 2H), 3.18–3.10 (m, 1H), 2.60 (s, 3H). LCMS: m/z 423.0 [M+H]⁺
160	 Starting materials: 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine HCl and 2-Oxopiperidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.62 (s, 1H), 8.55 (s, 1H), 8.19 (d, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 7.16 (d, 1H), 6.85 (s, 1H), 4.63 (t, 2H), 3.24 (t, 2H), 3.19–2.89 (m, 3H), 2.24 (d, 2H), 2.02–1.57 (m, 2H). LCMS: m/z 422.2 [M+H]⁺
161	 Starting materials: 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine HCl and 6-Oxopiperidine-3-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.65 (s, 1H), 8.53 (s, 1H), 8.17 (d, 1H), 7.53 (s, 1H), 7.44 (s, 1H), 7.14 (d, 1H), 6.84 (s, 1H), 4.62 (t, 2H), 3.22 (m, 4H), 2.96–2.85 (m, 1H), 2.23–2.07 (m, 2H), 1.97–1.70 (m, 2H). LCMS: m/z 422.2 [M+H]⁺
162	 Starting materials: 5-((5-(Trifluoro-	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.91 (s, 1H), 8.55 (s, 1H), 8.19 (d, 1H), 7.57 (s, 1H), 7.17 (d, 1H), 6.89 (s, 1H), 4.65 (t, 2H), 4.40 (s, 1H), 3.25

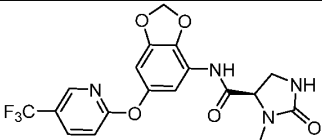
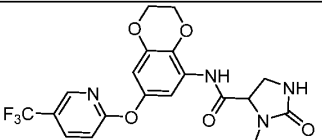
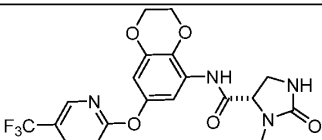
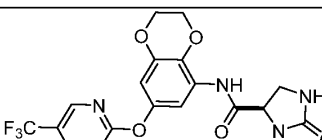
	methylpyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine HCl and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	(t, 2H), 2.63 (s, 3H), 2.36–2.10 (m, 3H), 1.99–1.73 (m, 1H). LCMS: m/z 422.0 [M+H]⁺
163	Starting materials: 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine HCl and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid 	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.91 (s, 1H), 8.55 (s, 1H), 8.19 (d, 1H), 7.57 (s, 1H), 7.17 (d, 1H), 6.89 (s, 1H), 4.65 (t, 1H), 4.40 (s, 1H), 3.24 (d, 1H), 2.63 (s, 3H), 2.33–2.14 (m, 3H), 1.86 (m, 1H). LCMS: m/z 422.0 [M+H]⁺
164	Starting materials: 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine HCl and 3-Cyclopropyl-2-oxoimidazolidine-4-carboxylic acid 	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.79 (s, 1H), 8.55 (d, 1H), 8.20 (dd, 1H), 7.60 (t, 1H), 7.18 (d, 1H), 6.89 (d, 1H), 6.40 (s, 1H), 4.65 (t, 2H), 4.44–4.35 (m, 1H), 3.43 (t, 1H), 3.25 (t, 2H), 3.16–3.09 (m, 1H), 2.34 (s, 1H), 0.62–0.52 (m, 2H), 0.49 (m, 2H). LCMS: m/z 449.0 [M+H]⁺
165	Starting materials: 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine and Lithium (S)-1-cyclopropyl-5-oxopyrrolidine-2-carboxylate 	Purification method A. ¹H NMR (400 MHz, Acetonitrile-<i>d</i>₃) δ: 8.47 (s, 1H), 8.16 (s, 1H), 8.06 (d, 1H), 7.72 (s, 1H), 7.11 (d, 1H), 6.87 (s, 1H), 4.70 (t, 2H), 4.22 (d, 1H), 3.31 (t, 2H), 2.60–2.22 (m, 4H), 0.89–0.66 (m, 2H), 0.60 (m, 2H). LCMS: m/z 448.0 [M+H]⁺

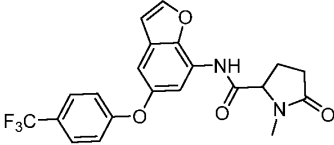
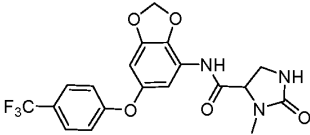
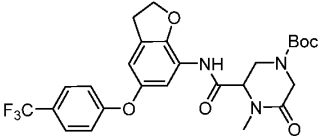
166	 Starting materials: 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine and Lithium (R)-1-cyclopropyl-5-oxo-pyrrolidine-2-carboxylate	Purification method A. ¹H NMR (400 MHz, Acetonitrile-<i>d</i>₃) δ: 8.47 (s, 1H), 8.16 (s, 1H), 8.06 (d, 1H), 7.72 (s, 1H), 7.11 (d, 1H), 6.87 (s, 1H), 4.70 (t, 2H), 4.22 (d, 1H), 3.31 (t, 2H), 2.60–2.22 (m, 4H), 0.89–0.66 (m, 2H), 0.60 (m, 2H). LCMS: m/z 448.2 [M+H]⁺
167	 Starting materials: 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine HCl and 3-Ethyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.80 (s, 1H), 8.55 (s, 1H), 8.20 (d, 1H), 7.56 (s, 1H), 7.18 (d, 1H), 6.90 (s, 1H), 6.39 (s, 1H), 4.65 (t, 2H), 4.49 (dd, 1H), 3.49 (t, 1H), 3.38–3.20 (m, 3H), 3.20–3.11 (m, 1H), 2.84 (dq, 1H), 0.98 (t, 3H). LCMS: m/z 437.2 [M+H]⁺
168	 Starting materials: (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid and 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.75 (s, 1H), 8.53 (d, 1H), 8.18 (dd, 1H), 7.54 (d, 1H), 7.16 (d, 1H), 6.92–6.82 (m, 1H), 6.38 (s, 1H), 4.63 (t, 2H), 4.33 (dd, 1H), 3.49 (t, 1H), 3.23 (t, 2H), 3.17–3.08 (m, 1H), 2.59 (s, 4H). LCMS: m/z 423.0 [M+H]⁺
169	 Starting materials: (R)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.75 (s, 1H), 8.53 (d, 1H), 8.18 (dd, 1H), 7.54 (d, 1H), 7.16 (d, 1H), 6.92–6.83 (m, 1H), 6.38 (s, 1H), 4.63 (t, 2H), 4.33 (dd, 1H), 3.49 (t, 1H), 3.23

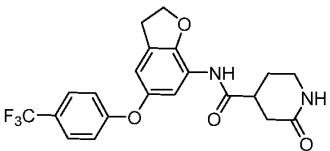
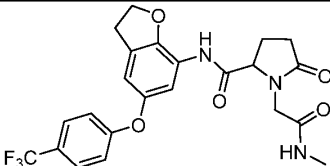
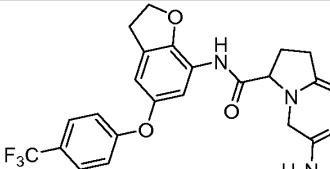
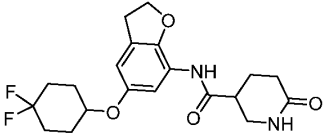
	and 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine	(t, 3H), 3.13 (dd, 1H), 2.58 (s, 3H). LCMS: m/z 423.0 [M+H] ⁺
170	 Starting materials: 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine and (R)-1-Ethyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.91 (s, 1H), 8.67–8.48 (m, 1H), 8.18 (dd, 1H), 7.55 (d, 1H), 7.15 (d, 1H), 6.88 (d, 1H), 4.64 (t, 1H), 4.53–4.39 (m, 1H), 3.45 (m, 1H), 3.23 (t, 2H), 2.78 (m, 1H), 2.33–2.05 (m, 3H), 1.97–1.75 (m, 1H), 0.98 (t, 3H). LCMS: m/z 436.2 [M+H]⁺
171	 Starting materials: 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine and 1-(S)-1-Ethyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.91 (s, 1H), 8.53 (t, 1H), 8.18 (dd, 1H), 7.55 (d, 1H), 7.15 (d, 1H), 6.88 (s, 1H), 4.64 (t, 2H), 4.51 (m, 1H), 3.46 (m, 1H), 3.23 (t, 2H), 2.78 (m, 1H), 2.32–2.05 (m, 3H), 1.86 (m, 1H), 0.98 (t, 3H). LCMS: m/z 436.2 [M+H]⁺
172	 Starting materials: 2-Methyl-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine and (R)-1-methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A followed by method I. Retention time 7.23 min. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.85 (s, 1H), 8.53 (s, 1H), 8.17 (d, 1H), 7.56 (s, 1H), 7.15 (d, 1H), 6.84 (s, 1H), 5.02 (q, 1H), 4.40 (d, 1H), 3.39–3.33 (m, 1H), 2.88–2.80 (m, 1H), 2.61 (s, 3H), 2.29–2.12 (m, 3H), 1.91–1.82 (m, 1H), 1.46 (d, 3H). LCMS: m/z 436.2 [M+H]⁺

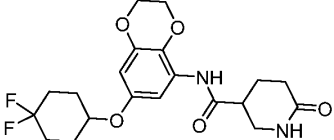
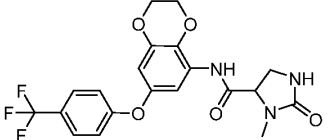
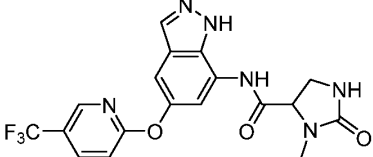
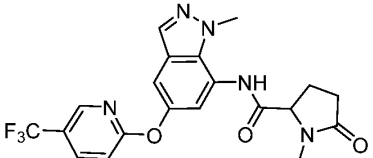
173	 Starting materials: 2-Methyl-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-amine and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A followed by method I. Retention time 11.33 min. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.84 (s, 1H), 8.53 (s, 1H), 8.17 (d, 1H), 7.56 (s, 1H), 7.15 (d, 1H), 6.83 (s, 1H), 5.02 (q, 1H), 4.40 (d, 1H), 3.39–3.33 (m, 1H), 2.85 (dd, 1H), 2.62 (s, 3H), 2.28–2.15 (m, 3H), 1.90–1.81 (m, 1H), 1.45 (d, 3H). LCMS: m/z 436.2 [M+H]⁺
174	 Starting materials: 6-((5-(Trifluoromethyl)pyridin-2-yl)oxy)chroman-8-amine and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, Methanol-<i>d</i>₄) δ: 8.42 (s, 1H), 8.07 (dd, 1H), 7.76 (d, 1H), 7.09 (d, 1H), 6.71 (d, 1H), 4.45 (dd, 1H), 4.32 (t, 2H), 2.85 (m, 5H), 2.55–2.34 (m, 3H), 2.13–2.00 (m, 3H). LCMS: m/z 436.0 [M+H]⁺
175	 Starting materials: 6-((5-(Trifluoromethyl)pyridin-2-yl)oxy)chroman-8-amine and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, Methanol-<i>d</i>₄) δ: 8.42 (s, 1H), 8.07 (dd, 1H), 7.76 (d, 1H), 7.09 (d, 1H), 6.71 (d, 1H), 4.45 (dd, 1H), 4.32 (t, 2H), 2.85 (m, 5H), 2.55–2.34 (m, 3H), 2.13–2.00 (m, 3H). LCMS: m/z 436.0 [M+H]⁺
176	 Starting materials: 6-((5-(Trifluoromethyl)pyridin-2-yl)oxy)chroman-8-amine and 3-Methyl-2-oxoimidazolidine	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.37 (s, 1H), 8.55 (s, 1H), 8.20 (dd, 1H), 7.72 (d, 1H), 7.18 (d, 1H), 6.72 (d, 1H), 6.46 (s, 1H), 4.37 (dd, 1H), 4.26 (t, 2H), 3.53 (t, 1H), 3.14 (t, 1H), 2.76 (t, 2H), 2.61 (s, 3H), 1.96 (t, 2H).

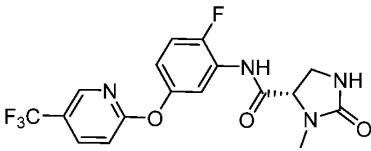
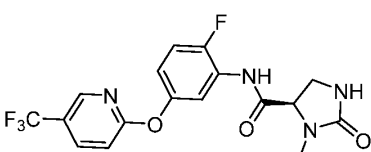
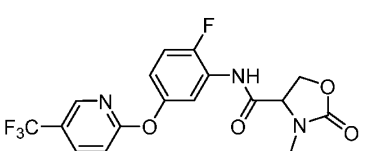
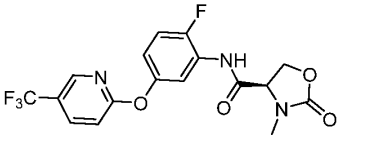
	dine-4-carboxylic acid	LCMS: m/z 437.2 [M+H] ⁺
177	 Starting materials: 6-((5-(Trifluoromethyl)pyridin-2-yl)oxy)chroman-8-amine and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, Methanol-d₄) δ: 8.42 (s, 1H), 8.06 (dd, 1H), 7.76 (d, 1H), 7.08 (d, 1H), 6.71 (d, 1H), 4.45 (dd, 1H), 4.35–4.28 (m, 2H), 2.83 (m, 5H), 2.55–2.33 (m, 3H), 2.11–2.00 (m, 3H). LCMS: m/z 436.4 [M+H]⁺
178	 Starting materials: 6-((5-(Trifluoromethyl)pyridin-2-yl)oxy)benzo[d][1,3]dioxol-4-amine and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-d₆) δ: 10.10 (s, 1H), 8.57 (d, 1H), 8.25–8.16 (m, 1H), 7.26–7.11 (m, 2H), 6.74 (d, 1H), 6.43 (s, 1H), 6.12 (s, 2H), 4.35–4.24 (m, 1H), 3.57–3.47 (m, 1H), 3.22–3.11 (m, 1H), 2.61 (s, 3H). LCMS: m/z 425.0 [M+H]⁺
179	 Starting materials: 6-((5-(Trifluoromethyl)pyridin-2-yl)oxy)benzo[d][1,3]dioxol-4-amine and 1-Cyclopropyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-d₆) δ: 10.17 (s, 1H), 8.57 (d, 1H), 8.27–8.14 (m, 1H), 7.27–7.14 (m, 2H), 6.74 (d, 1H), 6.14 (d, 2H), 4.47–4.17 (m, 1H), 2.46–2.36 (m, 1H), 2.35–2.23 (m, 1H), 2.23–2.12 (m, 2H), 1.93–1.82 (m, 1H), 0.77–0.67 (m, 1H), 0.66–0.58 (m, 1H), 0.57–0.46 (m, 2H). LCMS: m/z 450.2 [M+H]⁺
180	 Starting materials: 6-((5-(Trifluoromethyl)pyridin-2-yl)oxy)benzo[d][1,3]dioxol-4-amine and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-d₆) δ: 10.06 (s, 1H), 8.64–8.53 (m, 1H), 8.25–8.08 (m, 1H), 7.28–7.11 (m, 2H), 6.74 (d, 1H), 6.41 (s, 1H), 6.12 (s,

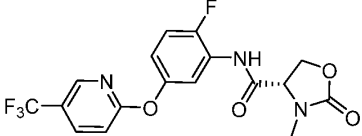
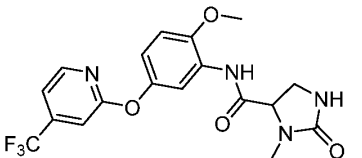
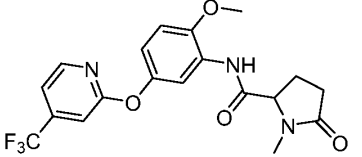
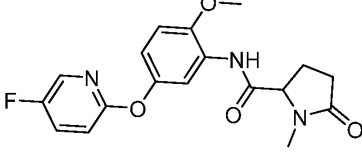
	[1,3]dioxol-4-amine and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	2H), 4.47–4.14 (m, 1H), 3.69–3.47 (m, 1H), 3.21–3.11 (m, 1H), 2.61 (s, 3H). LCMS: m/z 425.0 [M+H] ⁺
181	 Starting materials: 6-((5-(Trifluoromethyl)pyridin-2-yl)oxy)benzo[d]-[1,3]dioxol-4-amine and (R)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.08 (s, 1H), 8.57 (d, 1H), 8.29–8.10 (m, 1H), 7.28–7.07 (m, 2H), 6.74 (d, 1H), 6.42 (s, 1H), 6.12 (s, 2H), 4.35–4.21 (m, 1H), 3.51 (d, 1H), 3.16 (t, 1H), 2.61 (s, 3H). LCMS: m/z 425.5 [M+H]⁺
182	 Starting materials: 7-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine HCl and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method B. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.53 (s, 1H), 8.56 (s, 1H), 8.21 (d, 1H), 7.45 (s, 1H), 7.18 (d, 1H), 6.58 (s, 1H), 6.46 (s, 1H), 4.43–4.26 (m, 5H), 3.59–3.45 (m, 1H), 3.20–3.08 (m, 1H), 2.61 (s, 3H). LCMS: m/z 439.0 [M+H]⁺
183	 Starting materials: 7-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine HCl and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method B followed by method H. Retention time 8.02 min. LCMS: m/z 439.0 [M+H]⁺
184		Purification method B followed by method H. Retention time 12.86 min. LCMS: m/z 439.0 [M+H]⁺

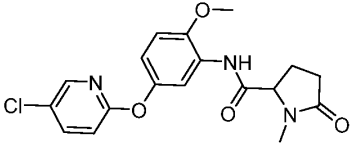
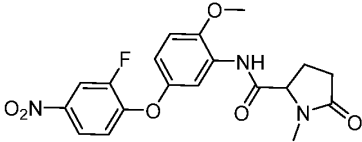
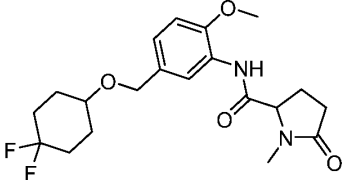
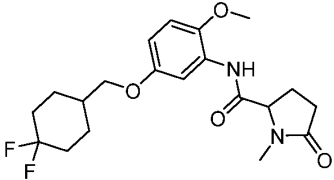
	Starting materials: 7-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine HCl and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	
185	 Starting materials: 5-(4-(Trifluoromethyl)phenoxy)benzofuran-7-amine and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.62 (s, 1H), 8.15 (d, 1H), 7.77–7.65 (m, 3H), 7.23 (d, 1H), 7.12 (d, 2H), 7.02 (d, 1H), 4.52–4.44 (m, 1H), 2.68 (s, 3H), 2.35–2.19 (m, 3H), 2.01–1.90 (m, 1H). LCMS: m/z 419.2 [M+H]⁺
186	 Starting materials: 6-(4-(Trifluoromethyl)phenoxy)benzo[d][1,3]-dioxol-4-amine and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.10 (s, 1H), 7.71 (d, 2H), 7.15 (s, 1H), 7.11 (d, 2H), 6.71 (d, 1H), 6.42 (s, 1H), 6.13 (s, 2H), 4.36–4.20 (m, 1H), 3.51 (t, 1H), 3.16 (t, 1H), 2.60 (s, 3H). LCMS: m/z 424.0 [M+H]⁺
Int-285	 (intermediate) Starting materials: 5-(4-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-amine HCl and Lithium 4-(tert-butoxycarbonyl)-1-methyl-6-oxopiperazine-2-carboxylate	LCMS: m/z 534.2 [M-H] ⁻

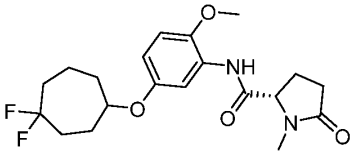
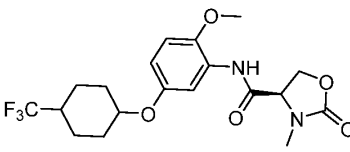
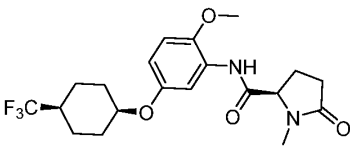
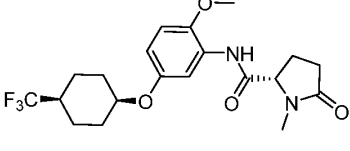
187	 Starting materials: 5-(4-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-amine HCl and 2-Oxopiperidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.65 (s, 1H), 7.69 (d, 2H), 7.57 (s, 1H), 7.48 (s, 1H), 7.06 (d, 2H), 6.84 (s, 1H), 4.64 (t, 2H), 3.24 (t, 2H), 3.16–2.92 (m, 3H), 2.25 (d, 2H), 2.03–1.80 (m, 1H), 1.74–1.55 (m, 1H). LCMS: m/z 421.2 [M+H]⁺
188	 Starting materials: 5-(4-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-amine HCl and 1-(2-(Methylamino)-2-oxoethyl)-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.99 (s, 1H), 7.94–7.81 (m, 1H), 7.70 (d, 2H), 7.52 (s, 1H), 7.07 (d, 2H), 6.87 (s, 1H), 4.64 (t, 2H), 4.59–4.51 (m, 1H), 4.15 (d, 1H), 3.28–3.20 (m, 3H), 2.57 (d, 3H), 2.36–2.22 (m, 3H), 1.95–1.83 (m, 1H). LCMS: m/z 478.0 [M+H]⁺
189	 Starting materials: 5-(4-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-amine HCl and 1-(2-Amino-2-oxoethyl)-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.99 (s, 1H), 7.68 (d, 2H), 7.50 (s, 1H), 7.40 (s, 1H), 7.12–7.02 (m, 3H), 6.85 (s, 1H), 4.62 (t, 2H), 4.58–4.51 (m, 1H), 4.12 (d, 1H), 3.27–3.15 (m, 3H), 2.34–2.17 (m, 3H), 1.93–1.80 (m, 1H). LCMS: m/z 464.0 [M+H]⁺
190	 Starting materials: 5-((4,4-Difluorocyclohexyl)oxy)-2,3-dihydrobenzofuran-7-amine HCl and 6-Oxopiperidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.52 (s, 1H), 7.47 (s, 1H), 7.36 (s, 1H), 6.70 (s, 1H), 4.54 (t, 2H), 4.36 (s, 1H), 3.25 (s, 2H), 3.17 (t, 2H), 2.91 (m, 1H), 2.27–1.62 (m, 12H). LCMS:

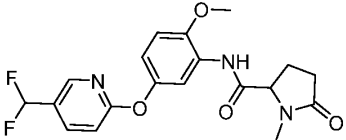
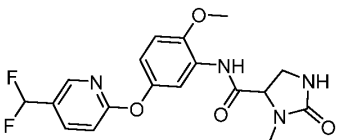
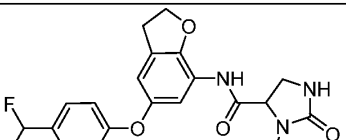
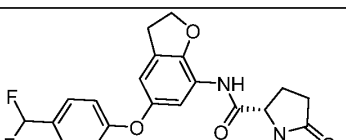
	dine-3-carboxylic acid	m/z 395.2 [M+H] ⁺
191	 Starting materials: 7-((4,4-Difluorocyclohexyloxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine HCl and 6-Oxopiperidine-3-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.30 (s, 1H), 7.48 (s, 1H), 7.23 (s, 1H), 6.33 (s, 1H), 4.39 (s, 1H), 4.24 (s, 4H), 3.28–3.17 (m, 2H), 2.95 (m, 1H), 2.20 (m, 2H), 2.08–1.67 (m, 8H). LCMS: m/z 411.2 [M+H]⁺
192	 Starting materials: 7-(4-(Trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-amine HCl and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.57 (s, 1H), 7.71 (d, 2H), 7.43 (s, 1H), 7.09 (d, 2H), 6.53 (s, 1H), 6.46 (s, 1H), 4.43–4.26 (m, 5H), 3.57–3.48 (m, 1H), 3.19–3.09 (m, 1H), 2.60 (s, 3H). LCMS: m/z 438.0 [M+H]⁺
193	 Starting materials: 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-1H-indazol-7-amine and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, Methanol-<i>d</i>₄) δ: 8.43 (s, 1H), 8.15–8.07 (m, 2H), 7.46 (s, 1H), 7.41 (s, 1H), 7.17 (d, 1H), 4.47–4.37 (m, 1H), 3.80 (t, 1H), 3.56 (t, 1H), 2.87 (s, 3H). LCMS: m/z 421.0 [M+H]⁺
194	 Starting materials: 1-Methyl-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-indazol-7-amine and 1-Methyl-5-	Purification method A. ¹H NMR (400 MHz, Methanol-<i>d</i>₄) δ: 8.43 (s, 1H), 8.22 (s, 1H), 8.14–8.06 (m, 1H), 7.90 (d, 1H), 7.25 (d, 1H), 7.14 (d, 1H), 4.56–4.47 (m, 1H), 4.27 (s, 3H), 2.86 (s, 3H), 2.63–2.35 (m, 3H), 2.26–2.05 (m, 2H).

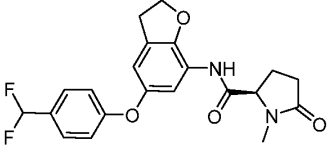
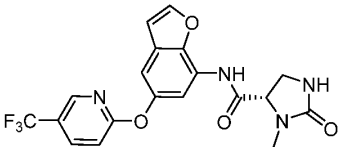
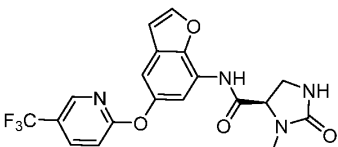
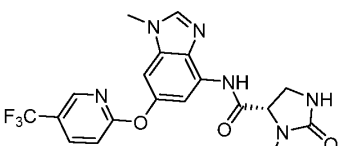
	oxopyrrolidine-2-carboxylic acid	LCMS: m/z 434.0 [M+H] ⁺
195	 Starting materials: 2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 10.10 (s, 1H), 8.55 (s, 1H), 8.22 (dd, 1H), 7.84–7.75 (m, 1H), 7.39–7.31 (m, 1H), 7.25 (d, 1H), 7.09–6.96 (m, 1H), 6.42 (s, 1H), 4.34 (dd, 1H), 3.53 (t, 1H), 3.18 (t, 1H), 2.61 (s, 3H). LCMS: m/z 399.0 [M+H]⁺
196	 Starting materials: 2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and (R)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 10.10 (s, 1H), 8.55 (s, 1H), 8.22 (dd, 1H), 7.84–7.72 (m, 1H), 7.43–7.31 (m, 1H), 7.25 (d, 1H), 7.08–6.98 (m, 1H), 6.42 (s, 1H), 4.34 (dd, 1H), 3.53 (t, 1H), 3.18 (t, 1H), 2.65 – 2.56 (m, 3H). LCMS: m/z 399.1 [M+H]⁺
197	 Starting materials: 2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline HCl and 3-Methyl-2-oxooxazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.32 (s, 1H), 8.56 (s, 1H), 8.28–8.21 (m, 1H), 7.92–7.85 (m, 1H), 7.38 (t, 1H), 7.27 (d, 1H), 7.05 (m, 1H), 4.63 (dd, 1H), 4.45 (t, 1H), 4.23 (dd, 1H), 2.75 (s, 3H). LCMS: m/z 400.0 [M+H]⁺
198	 Starting materials: 2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline HCl and (R)-3-methyl-2-oxooxazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.32 (s, 1H), 8.56 (s, 1H), 8.25 (d, 1H), 7.93–7.81 (m, 1H), 7.43–7.32 (m, 1H), 7.27 (d, 1H), 7.11–6.99 (m, 1H), 4.63 (dd, 1H), 4.45 (t, 1H), 4.23 (dd, 1H), 2.75 (s, 3H). LCMS: m/z 400.0

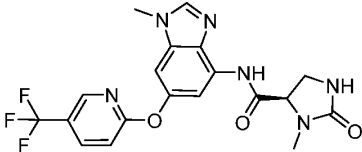
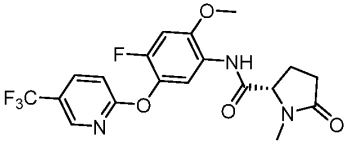
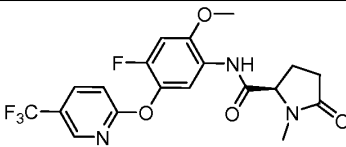
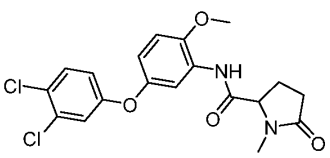
		[M+H] ⁺
199	 Starting materials: 2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline HCl and (S)-3-Methyl-2-oxooxazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.32 (s, 1H), 8.56 (s, 1H), 8.28–8.21 (m, 1H), 7.92–7.85 (m, 1H), 7.38 (t, 1H), 7.27 (d, 1H), 7.05 (m, 1H), 4.63 (dd, 1H), 4.45 (t, 1H), 4.23 (dd, 1H), 2.75 (s, 3H). LCMS: m/z 400.0 [M+H]⁺
200	 Starting materials: 2-Methoxy-5-((4-(trifluoromethyl)pyridin-2-yl)oxy)aniline and 3-methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method B. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.47 (s, 1H), 8.38 (d, 1H), 7.89 (d, 1H), 7.46 (d, 1H), 7.41 (s, 1H), 7.12 (d, 1H), 6.95 (dd, 1H), 6.46 (s, 1H), 4.38 (dd, 1H), 3.88 (s, 3H), 3.54 (t, 1H), 3.16 (t, 1H), 2.62 (s, 3H). LCMS: m/z 411.0 [M+H]⁺
201	 Starting materials: 2-Methoxy-5-((4-(trifluoromethyl)pyridin-2-yl)oxy)aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.62 (s, 1H), 8.38 (d, 1H), 7.87 (d, 1H), 7.46 (d, 1H), 7.41 (s, 1H), 7.11 (d, 1H), 6.95 (dd, 1H), 4.46 (d, 1H), 3.88 (s, 3H), 2.65 (s, 3H), 2.30–2.15 (m, 3H), 1.92–1.85 (m, 1H). LCMS: m/z 410.0 [M+H]⁺
202	 Starting materials: 5-((5-Fluoropyridin-2-yl)oxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.59 (s, 1H), 8.12 (d, 1H), 7.87–7.77 (m, 2H), 7.11–7.03 (m, 2H), 6.88 (dd, 1H), 4.51–4.42 (m, 1H), 3.87 (s, 3H), 2.64 (s, 3H), 2.31–2.13 (m, 3H), 1.96–1.83 (m, 1H). LCMS: m/z 358.0 [M-

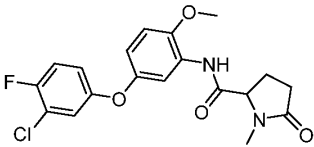
	carboxylic acid	H^-
203	 Starting materials: 5-((5-Chloropyridin-2-yl)oxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ^1H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.61 (s, 1H), 8.17 (d, 1H), 7.93 (dd, 1H), 7.84 (dd, 1H), 7.07 (dd, 2H), 6.90 (dd, 1H), 4.54–4.38 (m, 1H), 3.87 (s, 3H), 2.64 (s, 3H), 2.36–2.11 (m, 3H), 1.99–1.78 (m, 1H). LCMS: m/z 376.0 $[\text{M}+\text{H}]^+$
204	 Starting materials: 5-(2-Fluoro-4-nitrophenoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. LCMS: m/z 404.0 $[\text{M}+\text{H}]^+$
205	 Starting materials: 5-(((4,4-Difluorocyclohexyl)oxy)methyl)-2-methoxyaniline HCl and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method F. ^1H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.45 (s, 1H), 7.91 (s, 1H), 7.06 (d, 1H), 7.01 (d, 1H), 4.43–4.40 (m, 1H), 4.39 (s, 2H), 3.82 (s, 3H), 3.56 (m, 1H), 2.65 (s, 3H), 2.31–2.15 (m, 3H), 2.01–1.64 (m, 9H). LCMS: m/z 397.2 $[\text{M}+\text{H}]^+$
206	 Starting materials: 5-((4,4-Difluorocyclohexyl)methoxy)-2-methoxyaniline HCl and 1-Methyl-5-oxo-	Purification method A. ^1H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.46 (s, 1H), 7.68 (d, 1H), 6.96 (d, 1H), 6.67 (dd, 1H), 4.49–4.40 (m, 1H), 3.79 (s, 4H), 3.76 (d, 4H), 2.66 (s, 3H), 2.34–2.15 (m, 3H), 2.09–1.98 (m, 2H), 1.94–1.73 (m, 6H), 1.31 (q, 2H).

	pyrrolidine-2-carboxylic acid	LCMS: m/z 397.2 [M+H] ⁺
207	 Starting materials: 5-((4,4-Difluorocycloheptyl)oxy)-2-methoxyaniline and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, Acetonitrile-<i>d</i>₃) δ: 8.35 (s, 1H), 7.93 (d, 1H), 6.95 (d, 1H), 6.68 (dd, 1H), 4.56–4.41 (m, 1H), 4.31–4.19 (m, 1H), 3.87 (s, 3H), 2.79 (s, 3H), 2.46–2.03 (m, 11H), 1.92–1.72 (m, 2H), 1.61–1.49 (m, 1H). LCMS: m/z 397.2 [M+H]⁺
208	 Starting materials: 2-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)aniline and Lithium (R)-3-methyl-2-oxooxazolidine-4-carboxylate	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.54 (s, 1H), 7.69 (d, 1H), 7.03–6.92 (m, 1H), 6.73 (dd, 1H), 4.69–4.61 (m, 1H), 4.50–4.09 (m, 3H), 3.80 (s, 3H), 2.76 (s, 3H), 2.15–2.04 (m, 1H), 2.04–1.87 (m, 2H), 1.73–1.53 (m, 3H), 1.41 (q, 2H). LCMS: m/z 417.2 [M+H]⁺
209	 Starting materials: 2-Methoxy-5-(((cis)-4-(trifluoromethyl)cyclohexyl)oxy)aniline and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.46 (s, 1H), 7.76–7.63 (m, 1H), 6.96 (d, 1H), 6.71 (dd, 1H), 4.52–4.39 (m, 2H), 3.80 (s, 3H), 2.66 (s, 3H), 2.42–2.15 (m, 4H), 2.01–1.94 (m, 2H), 1.94–1.86 (m, 1H), 1.72–1.51 (m, 6H). LCMS: m/z 415.0 [M+H]⁺
210	 Starting materials: 2-Methoxy-5-(((cis)-4-(trifluoromethyl)cyclohexyl)oxy)aniline and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.43 (s, 1H), 7.69 (d, 1H), 6.96 (d, 1H), 6.71 (dd, 1H), 4.48 (s, 1H), 4.44 (q, 1H), 3.80 (s, 3H), 2.67 (s, 3H), 2.44–2.14 (m, 4H), 2.02–1.84 (m, 3H), 1.72–1.51 (m, 6H). LCMS: m/z 413.1

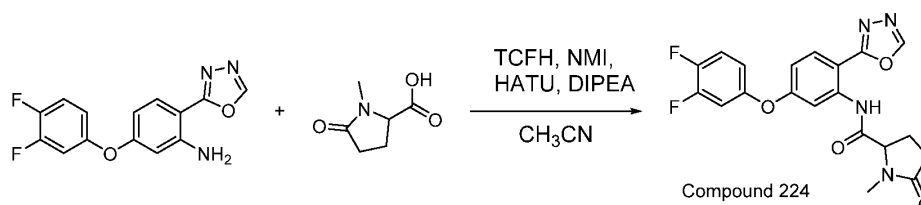
		[M-H] ⁻
211	 Starting materials: 5-((5-(Difluoromethyl)pyridin-2-yl)oxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.63 (s, 1H), 8.34 (s, 1H), 8.04 (d, 1H), 7.87 (s, 1H), 7.27–6.88 (m, 4H), 4.56–4.40 (m, 1H), 3.88 (s, 3H), 2.65 (s, 3H), 2.37–2.11 (m, 3H), 1.98–1.77 (m, 1H). LCMS: m/z 392.0 [M+H]⁺
212	 Starting materials: 5-((5-(Difluoromethyl)pyridin-2-yl)oxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.48 (s, 1H), 8.35 (s, 1H), 8.10–7.99 (m, 1H), 7.88 (s, 1H), 7.26–6.89 (m, 4H), 6.47 (s, 1H), 4.45–4.32 (m, 1H), 3.88 (s, 3H), 3.53 (t, 1H), 3.23–3.11 (m, 1H), 2.62 (s, 3H). LCMS: m/z 393.1 [M+H]⁺
213	 Starting materials: 5-(4-(Difluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-amine HCl and 3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.77 (s, 1H), 7.54 (m, 3H), 7.18–6.77 (m, 4H), 6.40 (s, 1H), 4.64 (t, 2H), 4.44–4.25 (m, 1H), 3.62–3.39 (m, 1H), 3.24 (t, 2H), 3.14 (t, 1H), 2.59 (s, 3H). LCMS: m/z 402.2 [M-H]⁻
214	 Starting materials: 5-(4-(Difluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-amine HCl and (S)-1-Methyl-5-oxopyrrolidine-2-	Purification method A. ¹H NMR (400 MHz, Acetonitrile-<i>d</i>₃) δ: 8.14 (s, 1H), 7.65 (d, 1H), 7.55 (d, 2H), 7.06 (d, 2H), 6.9–6.55 (m, 2H), 4.68 (t, 2H), 4.24 (dd, 1H), 3.29 (t, 2H), 2.76 (s, 3H), 2.4–2.21 (m, 4H). LCMS: m/z 401.2 [M-H]⁻

	carboxylic acid	
215	 Starting materials: 5-(4-(Difluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-amine HCl and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.91 (s, 1H), 7.54 (m, 3H), 7.23–6.73 (m, 4H), 4.64 (t, 2H), 4.49–4.30 (m, 1H), 3.28–3.18 (m, 3H), 2.63 (s, 3H), 2.35–2.17 (m, 4H). LCMS: m/z 403.0 [M+H]⁺
216	 Starting materials: 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)benzofuran-7-amine and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.49 (s, 1H), 8.55 (s, 1H), 8.23 (dd, 1H), 8.14 (d, 1H), 7.70 (dd, 1H), 7.29 (d, 1H), 7.24 (d, 1H), 7.02 (d, 1H), 6.45 (s, 1H), 4.43 (dd, 1H), 3.57 (t, 1H), 3.23 (t, 1H), 2.65 (s, 3H). LCMS: m/z 421.2 [M+H]⁺
217	 Starting materials: 5-((5-(Trifluoromethyl)pyridin-2-yl)oxy)benzofuran-7-amine and (R)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.49 (s, 1H), 8.55 (s, 1H), 8.23 (dd, 1H), 8.14 (s, 1H), 7.70 (d, 1H), 7.29 (d, 1H), 7.25 (d, 1H), 7.02 (d, 1H), 6.45 (s, 1H), 5.76 (s, 1H), 4.44 (t, 1H), 3.57 (t, 1H), 3.23 (t, 1H), 2.65 (s, 3H). LCMS: m/z 421.0 [M+H]⁺
218	 Starting materials: 1-Methyl-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-benzo[d]imidazol-4-amine and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.27 (s, 1H), 8.56 (s, 1H), 8.31–8.20 (m, 2H), 7.87 (s, 1H), 7.27 (d, 1H), 7.23 (d, 1H), 6.47 (s, 1H), 4.60–4.47 (m, 1H), 3.82 (s, 3H), 3.61–3.52 (m, 1H), 3.44–3.38 (m, 1H). LCMS: m/z

	(S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	435.2 [M+H] ⁺
219	 Starting materials: 1-Methyl-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-benzo[d]imidazol-4-amine and (R)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.27 (s, 1H), 8.56 (s, 1H), 8.31–8.20 (m, 2H), 7.87 (s, 1H), 7.27 (d, 1H), 7.23 (d, 1H), 6.47 (s, 1H), 4.60–4.47 (m, 1H), 3.82 (s, 3H), 3.61–3.52 (m, 1H), 3.44–3.38 (m, 1H). LCMS: m/z 435.2 [M+H]⁺
220	 Starting materials: 4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)aniline and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.68 (s, 1H), 8.55 (s, 1H), 8.26 (dd, 1H), 7.93 (d, 1H), 7.34 (d, 1H), 7.23 (d, 1H), 4.51–4.40 (m, 1H), 3.89 (s, 3H), 2.64 (s, 3H), 2.29–2.14 (m, 3H), 1.97–1.79 (m, 1H). LCMS: m/z 428.0 [M+H]⁺
221	 Starting materials: 4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)aniline and (R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.68 (s, 1H), 8.55 (s, 1H), 8.26 (dd, 1H), 7.93 (d, 1H), 7.34 (d, 1H), 7.23 (d, 1H), 4.48–4.33 (m, 1H), 3.89 (s, 3H), 2.65 (s, 3H), 2.31–2.13 (m, 3H), 1.93–1.78 (m, 1H). LCMS: m/z 428.2 [M+H]⁺
222	 Starting material: 5-(3,4-Dichloro-	Purification method Column chromatography. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.86 - 1.92 (1 H, m), 2.15 - 2.31 (3 H, m), 2.64 (3 H, s), 3.87 (3 H, s), 4.47 (1

	phenoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	H, m), 6.89 (1 H, m), 6.93 (1 H, m), 7.12 (1 H, d), 7.19 (1 H, d), 7.59 (1 H, d), 7.84 (1 H, d), 9.64 (1 H, s). LCMS: m/z 409.0 [M+H] ⁺
223	 Starting material: 5-(3-Chloro-4-fluorophenoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method Column chromatography. ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ: 1.86 - 1.92 (1 H, m), 2.15 - 2.31 (3 H, m), 2.64 (3 H, s), 3.86 (3 H, s), 4.46 (1 H, m), 6.84 (1 H, m), 6.95 (1 H, m), 7.10 (1 H, d), 7.16 (1 H, m), 7.40 (1 H, t), 7.82 (1 H, d), 9.62 (1 H, s). LCMS: m/z 393.0 [M+H] ⁺

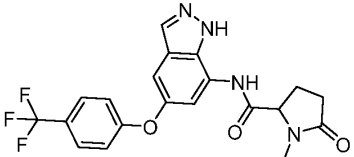
Example 2. N-(5-(3,4-Difluorophenoxy)-2-(1,3,4-oxadiazol-2-yl)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 224)



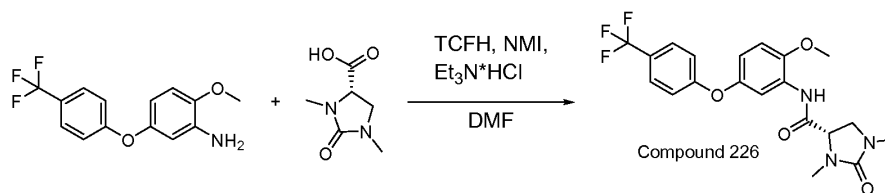
- 5 To a solution of 5-(3,4-difluorophenoxy)-2-(1,3,4-oxadiazol-2-yl)aniline (0.122 g, 1 eq., 422 μmol) in acetonitrile (3 mL) was added 1-methyl-5-oxopyrrolidine-2-carboxylic acid (72.5 mg, 1.2 eq., 506 μmol) and DIPEA (218 mg, 294 μL, 4 eq., 1.69 mmol). HATU (321 mg, 2 eq., 844 μmol) was then added and the mixture was stirred overnight at RT. N-(Chloro(dimethylamino)methylene)-N-methylmethanaminium
- 10 hexafluorophosphate(V) (237 mg, 2 eq., 844 μmol) and 1-methyl-1H-imidazole (208 mg, 202 μL, 6 eq., 2.53 mmol) were added and the mixture was stirred overnight. The mixture was concentrated in vacuum, diluted with EtOAc (10 mL), washed with NaHSO₄ (2 mL, 10 %), K₂CO₃ (2 mL, 10 %) and water (2 mL) followed by drying over Na₂SO₄. EtOAc was evaporated. The residue was purified by HPLC (2-10 min 0-55 %
- 15 of MeCN, flow rate: 30 mL/min) to afford the title compound (0.0242 g, 58.4 μmol, 13.8 %, 100 % purity). ¹H NMR (600 MHz, DMSO-*d*₆) δ: 10.89 (s, 1H), 9.38 (s, 1H),

8.01 – 7.89 (m, 2H), 7.57 – 7.50 (m, 1H), 7.45 – 7.38 (m, 1H), 7.04 (dd, $J = 8.0, 4.8$ Hz, 1H), 6.96 (dd, $J = 8.8, 2.5$ Hz, 1H), 4.26 (dd, $J = 9.1, 3.9$ Hz, 1H), 2.70 (s, 3H), 2.38 – 2.21 (m, 3H), 2.01 – 1.93 (m, 1H). LCMS: m/z 415.0 $[M+H]^+$.

- 5 The following compounds were prepared according to the procedure described for compound 224. The compound code, structure, starting materials, purification method and characterization data are indicated in the table.

No	Structure and starting material	Purification method and characterization data
225	 Starting materials: 5-(4-(Trifluoromethyl)phenoxy)-1H-indazol-7-amine and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ^1H NMR (400 MHz, Methanol-d_4) δ: 8.10 (s, 1H), 7.64 (d, 2H), 7.43–7.28 (m, 2H), 7.11 (d, 2H), 4.49–4.37 (m, 1H), 2.90 (s, 3H), 2.63–2.34 (m, 3H), 2.29–2.18 (m, 1H). LCMS: m/z 419.0 $[M+H]^+$

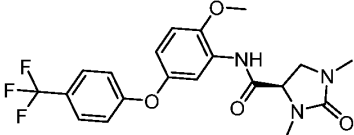
- 10 **Example 3.** (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1,3-dimethyl-2-oxoimidazolidine-4-carboxamide (Compound 226)



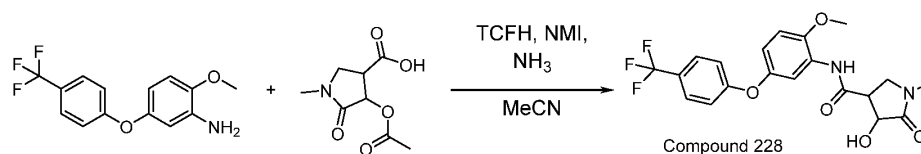
- 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline (0.07 g, 1 eq., 0.25 mmol), (S)-1,3-dimethyl-2-oxoimidazolidine-4-carboxylic acid (39 mg, 1 eq., 0.25 mmol) and triethylamine hydrochloride (34 mg, 1 eq., 0.25 mmol) were dissolved in DMF (3 mL) followed by stirring for 10 min. Then 1-methyl-1H-imidazole (0.1 g, 99 μL , 5 eq., 1.2 mmol) was added followed by stirring for 10 min. N-(Chloro(dimethylamino)methylene)-N-methylmethanaminium hexafluorophosphate(V) (76 mg, 1.1 eq., 0.27 mmol) was then added in a single portion followed by stirring at 20 °C for 10 h.

The mixture was filtered and the filtrate was purified by HPLC (Method A) to give the title compound (0.0314 g, 74.2 μ mol, 30 %, 100 % purity). ^1H NMR (400 MHz, DMSO-*d*6) δ : 9.57 (s, 1H), 7.88 (t, 1H), 7.71 (d, 2H), 7.15 (d, 1H), 7.08 (d, 2H), 7.00 – 6.88 (m, 1H), 4.40 – 4.26 (m, 1H), 3.88 (s, 3H), 3.54 (t, 1H), 3.26 – 3.16 (m, 1H), 2.64 (d, 6H). LCMS: m/z 424.2 $[\text{M}+\text{H}]^+$.

The following compounds were prepared according to the procedure described for compound 226. The compound code, structure, starting materials, purification method and characterization data are indicated in the table.

No	Structure and starting material	Purification method and characterization data
227	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and Lithium (R)-1,3-dimethyl-2-oxoimidazolidine-4-carboxylate	Purification method A. ^1H NMR (400 MHz, DMSO-<i>d</i>6) δ: 9.58 (s, 1H), 7.88 (d, 1H), 7.71 (d, 2H), 7.15 (d, 1H), 7.08 (d, 2H), 6.93 (dd, 1H), 4.33 (dd, 1H), 3.88 (s, 3H), 3.54 (t, 1H), 3.19 (dd, 1H), 2.64 (d, 6H). LCMS: m/z 424.2 $[\text{M}+\text{H}]^+$

Example 4. 4-Hydroxy-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-3-carboxamide (Compound 228)



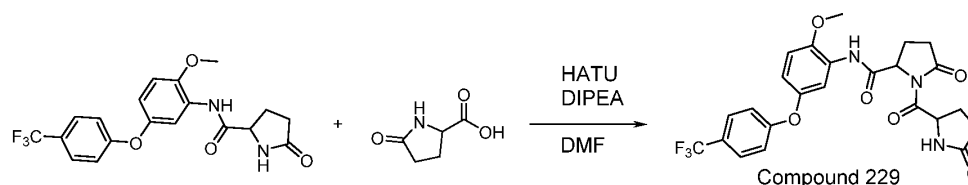
2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline (100 mg, 1 eq., 353 μ mol), 4-acetoxy-1-methyl-5-oxopyrrolidine-3-carboxylic acid (92.3 mg, 1.3 eq., 459 μ mol) and 1-methyl-1H-imidazole (174 mg, 169 μ L, 6 eq., 2.12 mmol) were dissolved in acetonitrile (2 mL) followed by stirring the mixture at 22 $^{\circ}\text{C}$ for 10 min. Then N-(chloro(dimethylamino)methylene)-N-methylmethanaminium hexafluorophosphate(V) (198 mg, 2 eq., 706 μ mol) was added. The mixture was stirred at 22 $^{\circ}\text{C}$ for 16 h. 4-Acetoxy-1-methyl-5-oxopyrrolidine-3-carboxylic acid (92.3 mg, 1.3 eq., 459 μ mol)

and N-(chloro(dimethylamino)methylene)-N-methylmethanaminium hexafluoro-phosphate(V) (198 mg, 2 eq., 706 μ mol) were added to the mixture followed by stirring at 22 °C for 16 h. The mixture was concentrated and ammonia (60.1 mg, 10 eq., 3.53 mmol) in methanol solution was added. The reaction mass was stirred at 22 °C for 16 h.

5 The solution was purified by reverse phase HPLC (purification method A) to afford the title compound (5 mg, 0.01 mmol, 3 %, 95 % purity). ¹H NMR (400 MHz, Methanol-d₄) δ : 8.03 – 8.00 (m, 1H), 7.65 – 7.57 (m, 2H), 7.10 – 7.03 (m, 3H), 6.85 (m, 1H), 4.54 (dd, 1H), 3.93 (d, 3H), 3.77 – 3.67 (m, 1H), 3.58 – 3.47 (m, 2H), 3.31 – 3.25 (m, 1H), 2.88 (s, 3H). LCMS: m/z 425.1 [M+H]⁺.

10

Example 5. N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-1-(5-oxopyrrolidine-2-carbonyl)pyrrolidine-2-carboxamide (Compound 229)



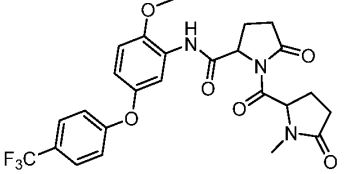
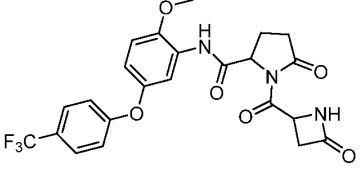
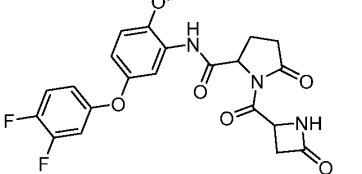
To a solution of N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-pyrrolidine-2-carboxamide (0.047 g, 1 eq., 0.12 mmol) in DMF (2 mL) was added 5-oxopyrrolidine-2-carboxylic acid (15 mg, 1 eq., 0.12 mmol) and diisopropylethylamine (46 mg, 62 μ L, 3 eq., 0.36 mmol). The mixture was stirred at RT for 15 minutes and HATU (68 mg, 1.5 eq., 0.18 mmol) was added in a single portion. The resulting solution was stirred at RT for 10 h. The mixture was concentrated in vacuum, diluted

15 with ethylacetate (10 mL), washed with NaHSO₄ (2 mL, 10 %), K₂CO₃ (2 mL, 10 %) and water (2 mL) followed by drying over Na₂SO₄. Ethyl acetate was evaporated and the residue was purified by method A to afford the title compound (0.0117 g). ¹H NMR (400 MHz, DMSO-d₆) δ : 9.78 (s, 1H), 7.87 (d, 1H), 7.77 (s, 1H), 7.69 (d, 2H), 7.14 (d, 1H), 7.06 (d, 2H), 6.90 (dd, 1H), 5.16 – 5.07 (m, 1H), 5.07 – 5.00 (m, 1H), 3.90 (s, 3H),

20 2.70 – 2.56 (m, 1H), 2.46 – 2.30 (m, 3H), 2.05 – 1.89 (m, 4H). LCMS: m/z 506.0 [M+H]⁺.

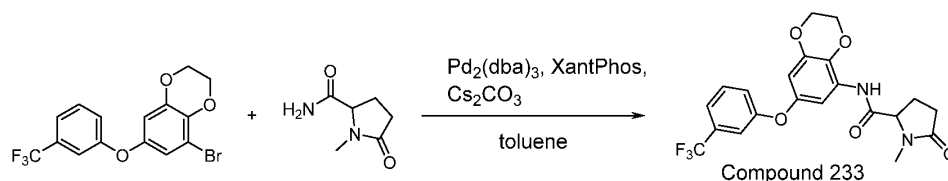
25

The following compounds were prepared according to the procedure described for Compound 229. The compound code, structure, starting materials, purification method and characterization data are indicated in the table.

No	Structure and starting material	Purification method and characterization data
230	 Starting materials: N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)-phenyl)-5-oxopyrrolidine-2-carboxamide and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method C. ¹H NMR (400 MHz, Acetonitrile-<i>d</i>₃) δ: 8.64 (d, 1H), 8.06-7.97 (m, 1H), 7.67 (d, 2H), 7.12-7.03 (m, 3H), 6.92-6.81 (m, 1H), 5.19 (td, 1H), 4.93 (dd, 1H), 3.95 (d, 3H), 2.78-2.69 (m, 3H), 2.67 (s, 1H), 2.62-2.52 (m, 1H), 2.50-2.38 (m, 2H), 2.20-2.12 (m, 4H). LCMS: m/z 520.2 [M+H]⁺
231	 Starting materials: N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)-phenyl)-5-oxopyrrolidine-2-carboxamide and 4-Oxoazetidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, Acetonitrile-<i>d</i>₃) δ: 8.63 (s, 1H), 8.03 (d, 1H), 7.67 (d, 2H), 7.09 (d, 3H), 6.88 (dd, 1H), 6.67-6.60 (m, 1H), 4.98-4.80 (m, 2H), 3.96 (s, 3H), 3.39-3.31 (m, 1H), 2.91-2.80 (m, 1H), 2.77-2.65 (m, 1H), 2.63-2.38 (m, 2H), 1.83-1.78 (m, 1H). LCMS: m/z 493.2 [M+H]⁺
232	 Starting materials: N-(5-(3,4-Difluorophenoxy)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide and 4-Oxoazetidine-2-carboxylic acid	Purification method A. ¹H NMR (400 MHz, Acetonitrile-<i>d</i>₃) δ: 8.61 (s, 1H), 7.99 (d, 1H), 7.30-7.18 (m, 1H), 7.05 (d, 1H), 6.98-6.91 (m, 1H), 6.85-6.74 (m, 2H), 6.64 (s, 1H), 4.96-4.85 (m, 2H), 3.94 (s, 3H), 3.43-3.32 (m, 1H), 2.91-2.83 (m, 1H), 2.79-2.63 (m, 1H), 2.58-2.40 (m, 3H). LCMS: m/z

	acid	458.0 [M-H] ⁻
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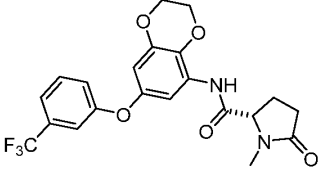
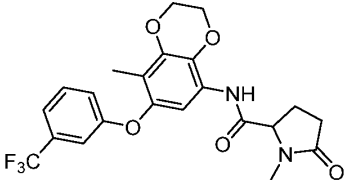
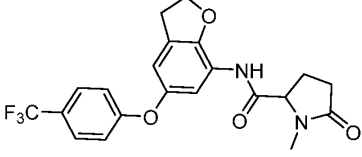
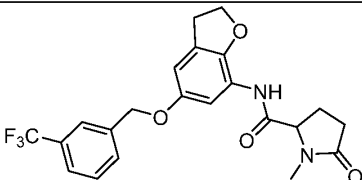
Example 6. 1-Methyl-5-oxo-N-(7-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)pyrrolidine-2-carboxamide (Compound 233)

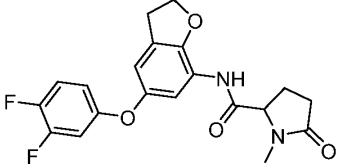
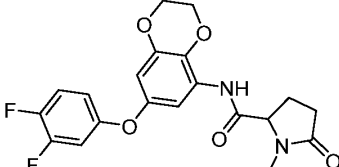
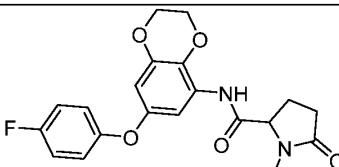


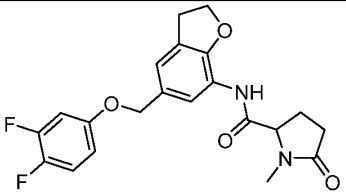
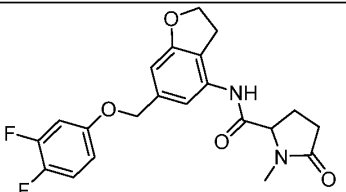
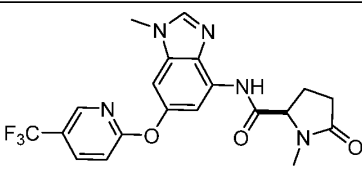
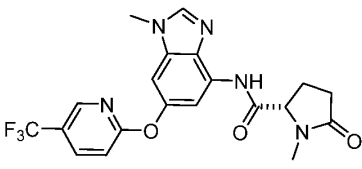
- 5 To a mixture of 5-bromo-7-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b]-[1,4]dioxine (217.2 mg, 1 eq., 579.0 μ mol), 1-methyl-5-oxopyrrolidine-2-carboxamide (123.5 mg, 1.5 eq., 868.5 μ mol) and cesium carbonate (565.9 mg, 3 eq., 1.737 mmol) in toluene (4 mL) under argon $\text{Pd}_2(\text{dba})_3$ (26.51 mg, 0.05 eq., 28.95 μ mol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (50.25 mg, 0.15 eq., 86.85 μ mol) were added
- 10 and the mixture was heated at 110 °C for 18 h. After cooling to RT the mixture was concentrated and the residue was purified by method A to afford the title compound (0.0286 g). ¹H NMR (600 MHz, DMSO-*d*₆) δ : 9.68 (s, 1H), 7.59 – 7.54 (m, 1H), 7.42 (d, 1H), 7.39 (d, 1H), 7.25 – 7.19 (m, 2H), 6.47 (d, 1H), 4.44 (dd, 1H), 4.35 – 4.27 (m, 4H), 2.61 (s, 3H), 2.27 – 2.12 (m, 3H), 1.89 – 1.82 (m, 1H). LCMS: *m/z* 437.0 [M+H]⁺.
- 15

The following compounds were prepared according to the procedure described for Compound 233. The compound code, structure, starting materials, purification method and characterization data are indicated in the table.

No	Structure and starting material	Purification method and characterization data
234	Starting material: 1-Methyl-5-oxo-N-(7-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-	Purification method A followed by method G. Retention time 10.09 min. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.68 (s, 1H), 7.57 (t, 1H), 7.46-7.34 (m, 2H), 7.25-7.19 (m, 2H), 6.48 (s, 1H), 4.44 (d, 1H), 4.31 (d, 4H), 2.61 (s, 3H), 2.30-2.11 (m, 3H), 1.92-1.80

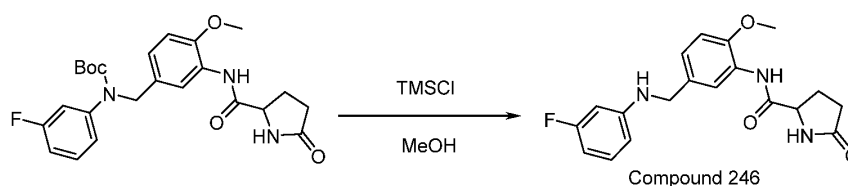
	pyrrolidine-2-carboxamide (racemic)	(m, 1H). LCMS: m/z 437.2 [M+H] ⁺
235	 Starting material: 1-Methyl-5-oxo-N-(7-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-pyrrolidine-2-carboxamide (racemic)	Purification method A followed by method G. Retention time 27.41 min. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.68 (s, 1H), 7.57 (t, 1H), 7.46-7.34 (m, 2H), 7.25-7.19 (m, 2H), 6.48 (s, 1H), 4.44 (d, 1H), 4.31 (d, 4H), 2.61 (s, 3H), 2.30-2.11 (m, 3H), 1.92-1.80 (m, 1H). LCMS: m/z 437.2 [M+H]⁺
236	 Starting material: 8-Bromo-5-methyl-6-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxine and 1-Methyl-5-oxopyrrolidine-2-carboxamide	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.64 (s, 1H), 7.60-7.53 (m, 1H), 7.39 (d, 1H), 7.34 (s, 1H), 7.15 (d, 1H), 7.09 (dd, 1H), 4.42 (d, 1H), 4.39-4.28 (m, 4H), 2.62 (s, 3H), 2.30-2.13 (m, 3H), 1.93 (d, 3H), 1.91-1.83 (m, 1H). LCMS: m/z 451.4 [M+H]⁺
237	 Starting material: 7-Bromo-5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran and 1-Methyl-5-oxopyrrolidine-2-carboxamide	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.94 (s, 1H), 7.70 (d, 2H), 7.57 (d, 1H), 7.07 (d, 2H), 6.88 (d, 1H), 4.65 (t, 2H), 4.43-4.36 (m, 1H), 3.25 (t, 2H), 2.63 (s, 3H), 2.29-2.15 (m, 3H), 1.93-1.81 (m, 1H). LCMS: m/z 421.2 [M+H]⁺
238	 Starting material: 7-Bromo-5-((3-(trifluoromethyl)phenoxy)methyl)-2,3-dihydrobenzofuran and 1-Methyl-5-oxopyrrolidine-2-carboxamide	Purification method C. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.77 (s, 1H), 7.81-7.60 (m, 4H), 7.50-7.45 (m, 1H), 6.79-6.74 (m, 1H), 5.10 (s, 2H), 4.56 (t, 2H), 4.42-4.34 (m,

	(trifluoromethyl)benzyl)oxy)-2,3-dihydrobenzofuran and 1-Methyl-5-oxopyrrolidine-2-carboxamide	1H), 3.19 (t, 2H), 2.68-2.65(m, 1H), 2.65 (s, 3H), 2.34-2.18 (m, 3H), 1.91-1.84 (m, 1H). LCMS: m/z 435.0 [M+H] ⁺
239	 Starting material: 7-Bromo-5-(3,4-difluorophenoxy)-2,3-dihydrobenzofuran and 1-Methyl-5-oxopyrrolidine-2-carboxamide	Purification method A. ¹ H NMR (400 MHz, Acetonitrile- <i>d</i> ₃) δ: 8.13 (s, 1H), 7.64 (d, 1H), 7.31-7.20 (m, 1H), 6.96-6.89 (m, 1H), 6.83-6.74 (m, 2H), 4.68 (t, 2H), 4.24 (dd, 1H), 3.28 (t, 2H), 2.44-2.23 (m, 3H). LCMS: m/z 389.2 [M+H] ⁺
240	 Starting material: 5-Bromo-7-(3,4-difluorophenoxy)-2,3-dihydrobenzobenzodioxine and 1-Methyl-5-oxopyrrolidine-2-carboxamide	Purification method A. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.67 (s, 1H), 7.48-7.32 (m, 2H), 7.16-7.06 (m, 1H), 6.78 (d, 1H), 6.43 (d, 1H), 4.45 (d, 1H), 4.37-4.26 (m, 4H), 2.64 (d, 3H), 2.31-2.15 (m, 3H), 1.92-1.79 (m, 1H). LCMS: m/z 405.2 [M+H] ⁺
241	 Starting material: 5-Bromo-7-(4-fluorophenoxy)-2,3-dihydrobenzobenzodioxine and 1-Methyl-5-oxopyrrolidine-2-carboxamide	Purification method A. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 9.63 (s, 1H), 7.33 (d, 1H), 7.23-7.15 (m, 2H), 7.05-6.93 (m, 2H), 6.35 (d, 1H), 4.48-4.40 (m, 1H), 4.34-4.24 (m, 4H), 2.63 (s, 3H), 2.33-2.12 (m, 3H), 1.94-1.80 (m, 1H). LCMS: m/z 387.2 [M+H] ⁺

242	 Starting material: 7-Bromo-5-((3,4-difluorophenoxy)methyl)-2,3-dihydrobenzofuran and 1-Methyl-5-oxopyrrolidine-2-carboxamide	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.79 (s, 1H), 7.75 (d, 1H), 7.39-7.28 (m, 1H), 7.18-7.06 (m, 2H), 6.85-6.73 (m, 1H), 4.95 (s, 2H), 4.62 (t, 2H), 4.43-4.34 (m, 1H), 3.23 (t, 2H), 2.66 (s, 3H), 2.34-2.17 (m, 3H), 1.95-1.79 (m, 1H). LCMS: m/z 403.0 [M+H]⁺
243	 Starting material: 6-((3,4-Difluorophenoxy)methyl)-2,3-dihydrobenzofuran-4-yl trifluoromethanesulfonate and 1-methyl-5-oxopyrrolidine-2-carboxamide	Purification method A. ¹H NMR (500 MHz, DMSO-<i>d</i>₆) δ: 9.84 (s, 1H), 7.32 (q, 1H), 7.16 (s, 1H), 7.14-7.05 (m, 1H), 6.79 (d, 1H), 6.64 (s, 1H), 4.99 (s, 2H), 4.52 (t, 2H), 4.33-4.22 (m, 1H), 3.09 (t, 2H), 2.66 (s, 3H), 2.31-2.15 (m, 3H), 1.97-1.81 (m, 1H). LCMS: m/z 403.0 [M+H]⁺
244	 Starting material: 4-Bromo-1-methyl-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-benzo[d]imidazole and 1-methyl-5-oxopyrrolidine-2-carboxamide	Purification method A followed by method I. Retention time 16.32 min. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 10.43 (s, 1H), 8.54 (s, 1H), 8.24 (s, 1H), 8.21 (dd, 1H), 7.84 (s, 1H), 7.25 (d, 1H), 7.21 (d, 1H), 4.60 (dd, 1H), 3.80 (s, 3H), 2.65 (s, 3H), 2.31-2.17 (m, 3H), 1.93-1.87 (m, 1H). LCMS: m/z 434.0 [M+H]⁺
245	 Starting material: 4-Bromo-1-	Purification method A followed by method I. Retention time 18.97 min. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 10.43 (s, 1H), 8.54 (s, 1H), 8.24 (s, 1H), 8.21 (dd, 1H), 7.84 (s, 1H), 7.25

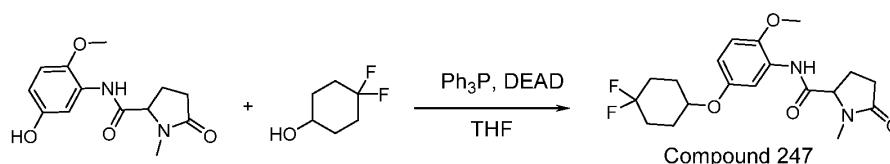
methyl-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-1H-benzo[d]imidazole and 1-methyl-5-oxopyrrolidine-2-carboxamide	(d, 1H), 7.21 (d, 1H), 4.60 (dd, 1H), 3.80 (s, 3H), 2.65 (s, 3H), 2.31–2.17 (m, 3H), 1.93–1.87 (m, 1H). LCMS: m/z 434.0 [M+H] ⁺
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Example 7. N-(5-(((3-Fluorophenyl)amino)methyl)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 246)



- 5 Chlorotrimethylsilane (210 mg, 245 μ L, 5 eq., 1.93 mmol) was added slowly to methanol (5 mL) at 0 °C and the mixture was stirred at 0 °C for 30 min. To the obtained solution tert-butyl (3-(3-fluorophenyl)(4-methoxy-3-(5-oxopyrrolidine-2-carboxamido)-benzyl)carbamate (300 mg, 58.89 %, 1 eq., 386 μ mol) was added and the mixture was stirred at RT for 18 h. The mixture was treated with aqueous NaHCO₃ solution (10 mL)
- 10 and extracted with ethyl acetate (2 $\times$ 20 mL). Combined organic phases were washed with brine (2 $\times$ 15 mL), dried over sodium sulfate, filtered, concentrated and the residue was purified by reverse phase HPLC (water-acetonitrile) to afford the title compound (0.0201 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.17 (s, 1H), 8.04 – 7.90 (m, 2H), 7.12 – 6.96 (m, 3H), 6.58 – 6.49 (m, 1H), 6.39 (dd, 1H), 6.32 – 6.18 (m, 2H), 4.34 (dd, 1H),
- 15 4.16 (d, 2H), 3.82 (s, 3H), 2.38 – 2.28 (m, 1H), 2.28 – 2.02 (m, 2H), 2.03 – 1.85 (m, 1H). LCMS: m/z 358.2 [M+H]⁺.

Example 8. N-(5-((4,4-Difluorocyclohexyl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 247)

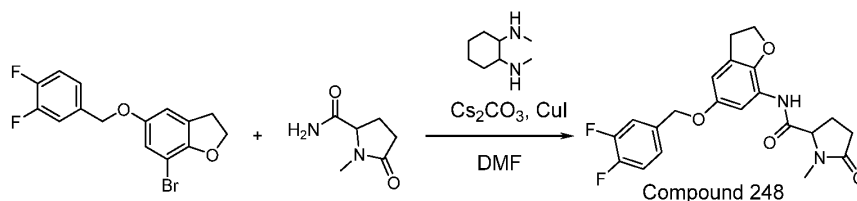


20

N-(5-hydroxy-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (0.0667 g, 1 eq., 252 μ mol), triphenylphosphine (86.1 mg, 1.3 eq., 328 μ mol) and

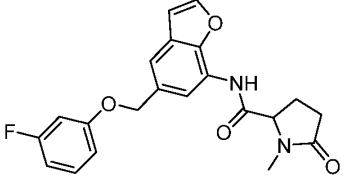
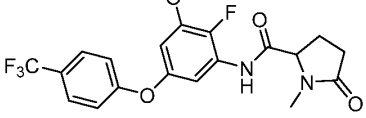
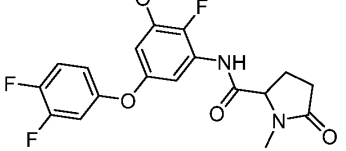
DEAD (54.9 mg, 49.5 μ L, 1.25 eq., 315 μ mol) were dissolved in THF (5.5 mL). The mixture was stirred at RT for 30 min. 4,4-Difluorocyclohexan-1-ol (48.1 mg, 1.4 eq., 353 μ mol) was added to the mixture at RT and stirred for 58 h. The mixture was purified by column chromatography to give the title compound (0.0032 g, 7.9 μ mol, 3.1 %, 95 % purity). Purification method C. ^1H NMR (400 MHz, Methanol- d_4) δ : 7.75 (d, 1H), 6.97 (d, 1H), 6.77 (dd, 1H), 4.48 – 4.40 (m, 2H), 3.87 (s, 3H), 2.85 (s, 3H), 2.59 – 2.47 (m, 1H), 2.47 – 2.34 (m, 2H), 2.19 – 2.04 (m, 3H), 1.99 – 1.84 (m, 6H). LCMS: m/z 383.2 $[\text{M}+\text{H}]^+$.

Example 9. N-(5-((3,4-Difluorobenzyl)oxy)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 248)

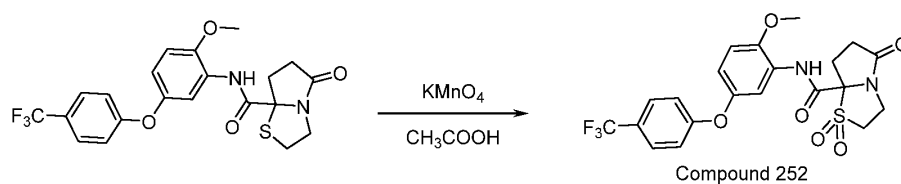


7-Bromo-5-((3,4-difluorobenzyl)oxy)-2,3-dihydrobenzofuran (0.100 g, 1 eq., 293 μ mol), 1-methyl-5-oxopyrrolidine-2-carboxamide (50.0 mg, 1.2 eq., 352 μ mol), cesium carbonate (95.5 mg, 1 eq., 293 μ mol), copper (I) iodide (16.7 mg, 0.3 eq., 87.9 μ mol) and N1,N2-dimethylcyclohexane-1,2-diamine (25.0 mg, 0.6 eq., 176 μ mol) were mixed in N,N-dimethylformamide (2 mL). The mixture was heated at 100 $^{\circ}\text{C}$ under argon atmosphere for 12 h. Then N,N-dimethylformamide was evaporated and the residue was diluted with EtOAc (10 mL), washed with water (2 $\times$ 2 mL), dried over Na_2SO_4 and concentrated in vacuum. A sample of reaction mixture was analyzed by LCMS. Residue was purified by method A to afford the title compound (0.0035 g). ^1H NMR (400 MHz, Acetonitrile- d_3) δ : 8.03 (s, 1H), 7.59 (d, 1H), 7.46 – 7.36 (m, 1H), 7.36 – 7.24 (m, 2H), 6.74 (d, 1H), 5.01 (s, 2H), 4.61 (t, 2H), 4.23 (dd, 1H), 3.24 (t, 2H), 2.78 (s, 3H), 2.45 – 2.24 (m, 3H). LCMS: m/z 403.0 $[\text{M}+\text{H}]^+$.

The following compounds were prepared according to the procedure described for Compound 248. The compound number, structure, starting materials, purification method and characterization data are indicated in the table.

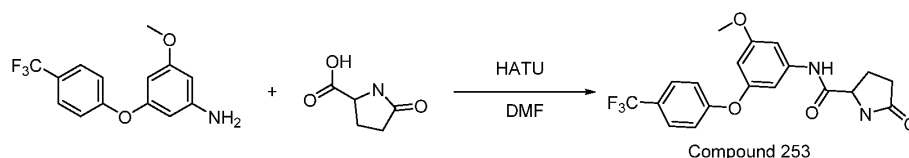
No	Structure and starting material	Purification method and characterization data
249	 Starting material: 7-Bromo-5-((3-fluorophenoxy)methyl)benzofuran and 1-Methyl-5-oxopyrrolidine-2-carboxamide	Purification method B. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 10.45 (s, 1H), 8.08 (d, 1H), 7.89 (s, 1H), 7.54 (s, 1H), 7.36-7.26 (m, 1H), 7.06-6.98 (m, 1H), 6.95-6.83 (m, 2H), 6.78 (d, 1H), 5.17 (s, 2H), 4.51-4.42 (m, 1H), 2.71 (s, 3H), 2.38-2.20 (m, 3H), 2.03-1.79 (m, 1H). LCMS: m/z 383.0 [M+H]⁺
250	 Starting material: 2-Fluoro-1-iodo-3-methoxy-5-(4-(trifluoromethyl)phenoxy)benzene and 1-Methyl-5-oxopyrrolidine-2-carboxamide	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 9.77 (s, 1H), 7.68 (d, 2H), 7.40-7.30 (m, 1H), 7.01 (d, 3H), 4.11-4.04 (m, 1H), 3.86 (s, 3H), 2.45 (s, 3H), 2.14-2.01 (m, 3H), 1.49-1.40 (m, 1H). LCMS: m/z 427.2 [M+H]⁺
251	 Starting material: 5-(3,4-Difluorophenoxy)-2-fluoro-1-iodo-3-methoxybenzene and 1-Methyl-5-oxopyrrolidine-2-carboxamide	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 7.51-7.36 (m, 1H), 7.27-7.08 (m, 2H), 6.86 (d, 1H), 6.76 (dd, 1H), 4.44-4.29 (m, 1H), 2.64 (s, 3H), 2.30-2.17 (m, 3H), 1.94-1.82 (m, 1H). LCMS: m/z 395.0 [M+H]⁺

Example 10. N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxotetrahydropyrrolo[2,1-b]thiazole-7a(5H)-carboxamide 1,1-dioxide (Compound 252)



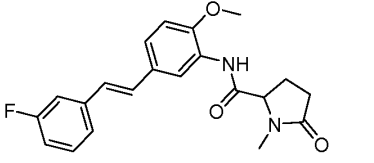
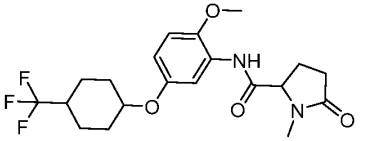
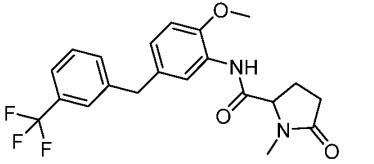
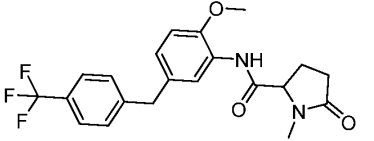
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxotetrahydropyrrolo-[2,1-b]thiazole-7a(5H)-carboxamide (100 mg, 1 eq., 221 μmol) was dissolved in acetic acid (3 mL) and potassium permanganate (55.9 mg, eq., 354 μmol) was added at RT.
- 5 The mixture was stirred at RT for 24 h. The mixture was poured into sodium hydro-carbonate saturated solution (30 mL) followed by extraction with ethyl acetate (3 $\times$ 30 mL). Combined organic phases were washed with brine (2 $\times$ 30 mL), dried over sodium sulfate, filtered, concentrated and the residue was purified by purification method A to afford the title compound (0.0079 g). ^1H NMR (400 MHz, Acetonitrile- d_3) δ : 8.77 (s, 1H), 7.99 (d, 1H), 7.70 (d, 2H), 7.15 – 7.05 (m, 3H), 6.96 (dd, 1H), 4.52 – 4.38 (m, 1H), 3.95 (s, 3H), 3.73 – 3.64 (m, 1H), 3.45 – 3.26 (m, 2H), 2.87 – 2.66 (m, 3H), 2.57 – 2.42 (m, 1H). LCMS: m/z 485.2 $[\text{M}+\text{H}]^+$.
- 10

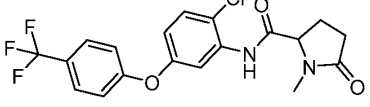
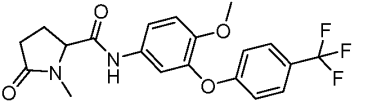
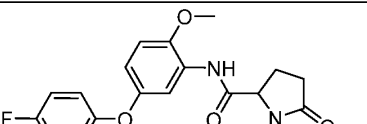
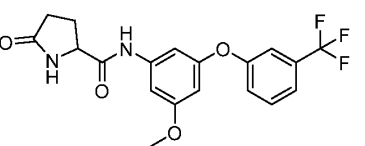
- Example 11.** N-(3-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 253)
- 15

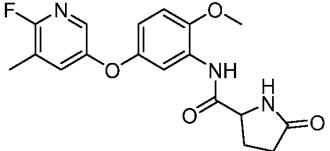
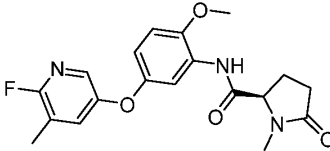
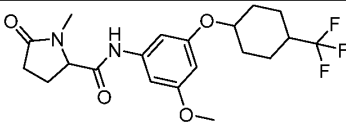
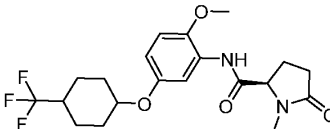


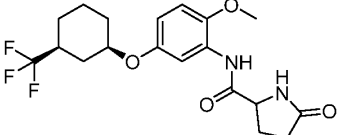
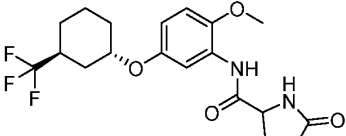
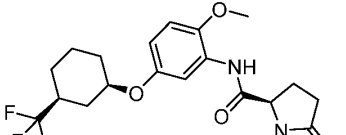
- To a solution of 5-oxopyrrolidine-2-carboxylic acid (51.1 mg, 0.40 mmol), 3-methoxy-5-(4-(trifluoromethyl)phenoxy)aniline (112 mg, 0.40 mmol), HATU (226 mg, 0.60 mmol) and dry DMF (2 mL) was added DIPEA (0.34 mL, 2.0 mmol). The mixture
- 20 was stirred at RT overnight. The reaction mixture was quenched with water (10 mL) followed by extraction with ethyl acetate (2 $\times$ 10 mL). The combined organic layers were washed with water, dried, evaporated and then purified by reverse phase chromatography to yield 0.074 g the title compound. ^1H NMR (600 MHz, DMSO- d_6) δ : 1.93 – 2.00 (m, 1 H), 2.08 – 2.22 (m, 2 H), 2.28 – 2.36 (m, 1 H), 3.75 (s, 3 H), 4.14 (dd, 1 H), 6.48 (t, 1 H), 6.97 (t, 1 H), 7.15 – 7.21 (m, 3 H), 7.76 (d, 2 H), 7.86 (s, 1 H), 10.14 (s, 1 H). LCMS: m/z 395.2 $[\text{M}+\text{H}]^+$
- 25

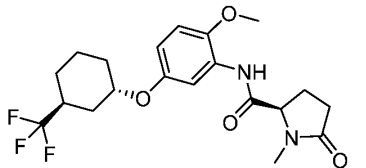
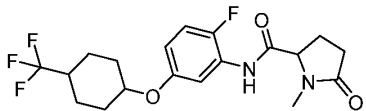
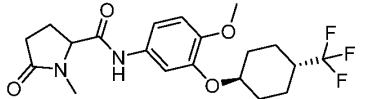
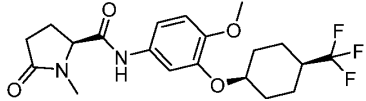
The following compounds were prepared according to the procedure described for Compound 253. The compound number, structure, starting materials, purification method and characterization data are indicated in the table.

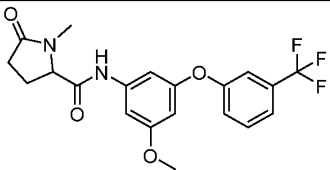
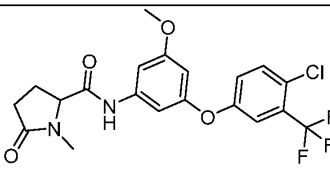
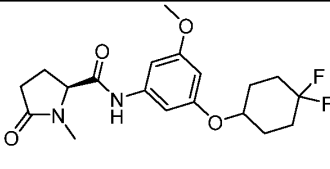
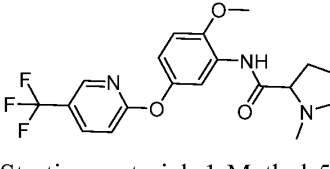
No	Structure and starting material	Purification method and characterization data
254	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and (E)-5-(3-Fluorostyryl)-2-methoxyaniline	Purification method A. ¹H NMR (DMSO-<i>d</i>₆, 600 MHz) δ: 9.55 (s, 1H), 8.21 (d, 1H), 7.4-7.5 (m, 4H), 7.28 (d, 1H), 7.0-7.1 (m, 3H), 4.45 (dd, 1H), 3.88 (s, 3H), 2.69 (s, 3H), 2.2-2.4 (m, 3H), 1.9-2.0 (m, 1H). LCMS: <i>m/z</i> 369.3 [M+H]⁺
255	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 2-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)aniline	Purification method A. ¹H NMR (400 MHz, Chloroform-<i>d</i>) δ: 1.21-1.49 (m, 4H), 1.80 (br s, 1H), 1.98-2.26 (m, 6H), 2.38-2.66 (m, 3H), 2.93 (s, 3H), 3.70-3.93 (m, 3H), 4.01-4.26 (m, 2H), 6.63 (dd, 1H), 6.80 (d, 1H), 8.02-8.10 (m, 2H). LCMS: <i>m/z</i> 414.3 [M+H]⁺
256	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 2-Methoxy-5-(3-(trifluoromethyl)benzyl)aniline	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.85-1.93 (m, 1H), 2.16-2.33 (m, 3H), 2.65 (s, 3H), 3.33 (s, 6H), 3.79-3.85 (m, 3H), 3.96 (s, 2H), 4.39-4.47 (m, 1H), 7.00 (s, 2H), 7.42 (m, 2H), 7.64 (m, 2H), 7.86 (s, 1H), 9.45 (s, 1H). LCMS: <i>m/z</i> 407.2 [M+H]⁺
257		Purification method A. ¹H NMR (400 MHz, Chloroform-<i>d</i>) δ: 2.09-2.22 (m, 1H), 2.38-2.64 (m, 3H), 2.93 (s, 3H), 3.79-4.00

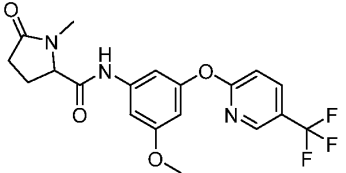
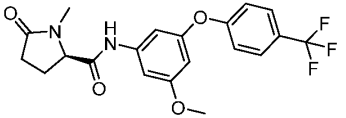
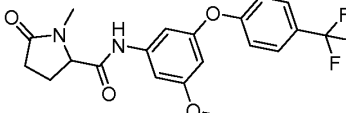
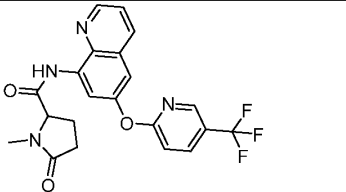
	Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 2-Methoxy-5-(4-(trifluoromethyl)benzyl)aniline	(m, 5H), 4.03-4.17 (m, 1H), 6.78-6.92 (m, 2H), 7.34-7.48 (m, 4H), 8.01 (s, 1H), 8.26 (d, 1H). LCMS: m/z 407.3 [M+H] ⁺
258	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 2-Chloro-5-(4-(trifluoromethyl)phenoxy)aniline	Purification method A. ¹H NMR (400 MHz, Chloroform-<i>d</i>) δ: 2.10-2.23 (m, 1H), 2.38-2.66 (m, 3H), 2.98 (s, 3H), 4.09-4.18 (m, 1H), 6.80 (dd, 1H), 7.07 (d, 2H), 7.36-7.42 (m, 1H), 7.60 (d, 2H), 8.03 (s, 1H), 8.19 (d, 1H). LCMS: m/z 413.2 [M+H]⁺
259	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 4-Methoxy-3-(4-(trifluoromethyl)phenoxy)aniline	Purification method A. ¹H NMR (400 MHz, Chloroform-<i>d</i>) δ: 2.10-2.17 (m, 1H), 2.37-2.60 (m, 3H), 2.91 (s, 3H), 3.80 (s, 3H), 4.09 (dd, 1H), 6.94-7.03 (m, 3H), 7.36 (d, 1H), 7.40 (dd, 1H), 7.48-7.61 (m, 2H), 7.69 (br s, 1H). LCMS: m/z 409.3 [M+H]⁺
260	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 5-(4-Fluorophenoxy)-2-methoxyaniline	Purification method A. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.82-1.94 (m, 1H), 2.14-2.34 (m, 3H), 2.52-2.69 (m, 3H), 3.80-3.87 (m, 3H), 4.42-4.51 (m, 1H), 6.79 (dd, 1H), 6.92-7.04 (m, 2H), 7.08 (d, 1H), 7.19 (t, 2H), 7.80 (d, 1H), 9.61 (s, 1H). LCMS: m/z 359.2 [M+H]⁺
261	 Starting material: 5-Oxopyrrolidine-2-carboxylic acid and 3-Methoxy-5-(3-(trifluoromethyl)-	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.93-1.99 (m, 1H), 2.07-2.22 (m, 2H), 2.28-2.35 (m, 1H), 3.74 (s, 3H), 4.13 (dd, 1H), 6.44 (t, 1H), 6.92 (t, 1H), 7.14 (t, 1H), 7.34 (dd, 1H), 7.37 (s, 1H), 7.53 (d, 1H), 7.65 (t, 1H), 7.85 (s, 1H), 10.12 (s, 1H). LCMS:

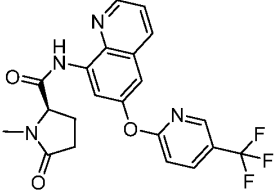
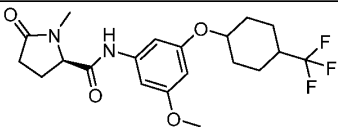
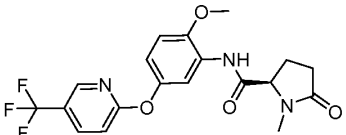
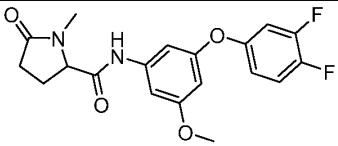
	phenoxy)aniline	m/z 395.2 [M+H] ⁺
262	 Starting material: 5-Oxopyrrolidine-2-carboxylic acid and 5-((6-Fluoro-5-methylpyridin-3-yl)oxy)-2-methoxyaniline	Purification method A. ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ: 1.95 (ddt, 1H), 2.07-2.22 (m, 5H), 2.27-2.36 (m, 1H), 3.85 (s, 3H), 4.38 (dd, 1H), 6.82 (dd, 1H), 7.08 (d, 1H), 7.51 (dd, 1H), 7.75 (br s, 1H), 7.87 (d, 1H), 7.92 (s, 1H), 9.32 (s, 1H). LCMS: m/z 374.2 [M+H] ⁺
263	 Starting material: (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 5-((6-Fluoro-5-methylpyridin-3-yl)oxy)-2-methoxyaniline	Purification method A. ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ: 1.85-1.92 (m, 1H), 2.16-2.32 (m, 6H), 2.64 (s, 3H), 3.32 (s, 6H), 3.86 (s, 3H), 4.47 (dd, 1H), 6.83 (dd, 1H), 7.08 (d, 1H), 7.51 (dd, 1H), 7.74 (br s, 1H), 7.84 (d, 1H), 9.61 (s, 1H). LCMS: m/z 374.1 [M+H] ⁺
264	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 3-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)aniline	Purification method A. ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ: 1.36-1.49 (m, 4H), 1.87-1.95 (m, 3H), 2.08-2.16 (m, 2H), 2.20-2.40 (m, 4H), 2.67 (s, 3H), 3.71 (s, 3H), 4.17-4.28 (m, 2H), 6.27 (t, 1H), 6.87 (d, 2H), 10.13 (s, 1H). LCMS: m/z 415.2 [M+H] ⁺
265	 Starting material: (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 2-Methoxy-5-((4-(trifluoromethyl)-	Purification method A. ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ: 1.34-1.46 (m, 3H), 1.55-1.69 (m, 2H), 1.86-2.00 (m, 3H), 2.10 (br d, 1H), 2.19-2.37 (m, 4H), 2.67 (s, 3H), 3.79-3.81 (m, 3H), 4.11-4.18 (m, 1H), 4.43-4.50 (m, 1H), 6.72 (dd, 1H), 6.94-6.98 (m, 1H), 7.66 (d, 1H), 9.43-9.49 (m, 1H). LCMS: m/z 415.2 [M+H] ⁺

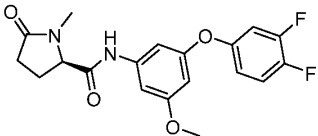
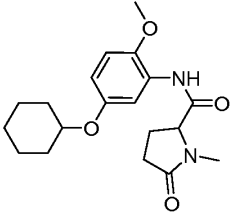
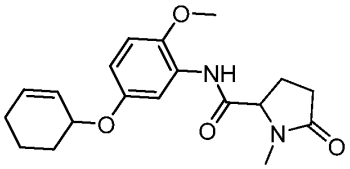
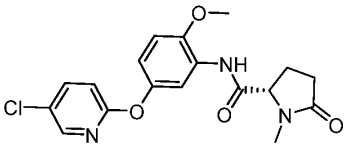
	cyclohexyl)oxy)aniline	
266	 Starting material: 5-Oxopyrrolidine-2-carboxylic acid and 2-Methoxy-5-((3-(trifluoromethyl)cyclohexyl)oxy)aniline	Purification method B. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ: 1.16-1.30 (m, 3H), 1.35-1.44 (m, 1H), 1.78-1.86 (m, 2H), 1.93-1.99 (m, 1H), 2.04-2.15 (m, 2H), 2.16-2.24 (m, 2H), 2.29-2.37 (m, 1H), 3.79 (s, 3H), 4.19 (tt, 1H), 4.36 (dd, 1H), 6.70 (dd, 1H), 6.96 (d, 1H), 7.71-7.74 (m, 1H), 7.94 (s, 1H), 9.17 (s, 1H). LCMS: m/z 401.2 $[\text{M}+\text{H}]^+$
267	 Starting material: 5-Oxopyrrolidine-2-carboxylic acid and 2-Methoxy-5-((3-(trifluoromethyl)cyclohexyl)oxy)aniline	Purification method B. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ: 1.23-1.36 (m, 1H), 1.43-1.50 (m, 1H), 1.52-1.67 (m, 3H), 1.85-1.90 (m, 2H), 1.94-2.00 (m, 1H), 2.03-2.15 (m, 2H), 2.18-2.24 (m, 1H), 2.29-2.36 (m, 1H), 2.51-2.58 (m, 1H), 3.79 (s, 3H), 4.36 (dd, 1H), 4.62 (br s, 1H), 6.72 (dd, 1H), 6.96 (d, 1H), 7.76 (dd, 1H), 7.94 (s, 1H), 9.19 (s, 1H). LCMS: m/z 401.2 $[\text{M}+\text{H}]^+$
268	 Starting material: (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 2-Methoxy-5-((3-(trifluoromethyl)cyclohexyl)oxy)aniline	Purification method B. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ: 1.15-1.29 (m, 3H), 1.35-1.44 (m, 1H), 1.78-1.92 (m, 3H), 2.05 (br d, 1H), 2.16-2.33 (m, 4H), 2.66 (s, 3H), 3.32 (s, 1H), 3.80 (s, 3H), 4.17-4.23 (m, 1H), 4.42-4.46 (m, 1H), 6.72 (dd, 1H), 6.96 (d, 1H), 7.67 (t, 1H), 9.46 (s, 1H). LCMS: m/z 415.2 $[\text{M}+\text{H}]^+$

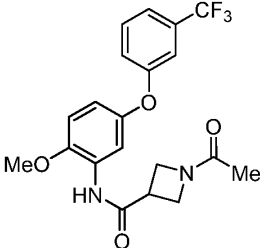
269	 Starting material: (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 2-Methoxy-5-((3-(trifluoromethyl)cyclohexyl)oxy)aniline	Purification method B. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.21-1.36 (m, 1H), 1.42-1.50 (m, 1H), 1.53-1.67 (m, 3H), 1.86-1.94 (m, 3H), 2.06 (br d, 1H), 2.18-2.35 (m, 3H), 2.52-2.60 (m, 1H), 2.67 (s, 3H), 3.33 (s, 9H), 3.81 (s, 3H), 4.45 (dd, 1H), 4.63 (br s, 1H), 6.74 (dd, 1H), 6.98 (d, 1H), 7.72 (dd, 1H), 9.49 (s, 1H). LCMS: m/z 415.2 [M+H]⁺
270	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 2-Fluoro-5-((4-(trifluoromethyl)cyclohexyl)oxy)aniline	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.28-1.48 (m, 4H), 1.88-1.97 (m, 3H), 2.11 (br d, 2H), 2.20-2.39 (m, 4H), 2.67-2.70 (m, 3H), 4.20-4.26 (m, 1H), 4.36-4.41 (m, 1H), 6.77 (dt, 1H), 7.17 (dd, 1H), 7.53 (dd, 1H), 10.03 (s, 1H). LCMS: m/z 403.2 [M+H]⁺
271	 Starting material: (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 4-Methoxy-3-(((1<i>r</i>,4<i>r</i>)-4-(trifluoromethyl)cyclohexyl)oxy)aniline	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.34-1.48 (m, 4H), 1.81-2.00 (m, 3H), 2.07-2.16 (m, 2H), 2.19-2.38 (m, 4H), 2.66-2.69 (m, 3H), 3.71 (s, 3H), 4.08-4.21 (m, 2H), 6.92 (d, 1H), 7.16 (dd, 1H), 7.33 (d, 1H), 10.03 (s, 1H). LCMS: m/z 415.2 [M+H]⁺
272	 Starting material: (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 4-Methoxy-3-(((1<i>s</i>,4<i>s</i>)-4-(trifluoromethyl)cyclohexyl)oxy)aniline	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.56-1.71 (m, 7H), 1.77-2.00 (m, 3H), 2.20-2.39 (m, 4H), 2.66 (s, 3H), 3.70-3.80 (m, 3H), 4.16 (dd, 1H), 6.94 (d, 1H), 7.17 (dd, 1H), 7.34 (d, 1H), 10.05 (s, 1H). LCMS: m/z 415.2 [M+H]⁺

273	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 3-Methoxy-5-(3-(trifluoromethyl)phenoxy)aniline	Purification method A. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ: 1.87-1.93 (m, 1H), 2.18-2.33 (m, 3H), 2.65 (s, 3H), 3.75 (s, 3H), 4.15-4.20 (m, 1H), 6.45 (t, 1H), 6.90 (t, 1H), 7.16 (t, 1H), 7.34 (dd, 1H), 7.37 (s, 1H), 7.53 (d, 1H), 7.65 (t, 1H), 10.30 (br s, 1H). LCMS: m/z 409.1 $[\text{M}+\text{H}]^+$
274	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 3-(4-Chloro-3-(trifluoromethyl)phenoxy)-5-methoxyaniline	Purification method A. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ: 1.86-1.93 (m, 1H), 2.18-2.30 (m, 3H), 2.65 (s, 3H), 3.74 (s, 3H), 4.17 (dd, 1H), 6.47 (t, 1H), 6.90 (t, 1H), 7.16 (t, 1H), 7.33 (dd, 1H), 7.50 (d, 1H), 7.74 (d, 1H), 10.30 (s, 1H). LCMS: m/z 443.1 $[\text{M}+\text{H}]^+$
275	 Starting material: (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 3-((4,4-Difluorocyclohexyl)oxy)-5-methoxyaniline	Purification method A. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ: 1.79-1.85 (m, 2H), 1.87-2.07 (m, 7H), 2.18-2.35 (m, 3H), 2.67 (s, 3H), 3.72 (s, 3H), 4.14-4.22 (m, 1H), 6.32 (t, 1H), 6.86 (t, 1H), 6.94 (t, 1H), 10.16 (s, 1H). LCMS: m/z 383.2 $[\text{M}+\text{H}]^+$
276	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)aniline	Purification method A. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ: 1.79-1.86 (m, 1H), 2.09-2.23 (m, 3H), 2.58 (s, 3H), 3.82 (s, 3H), 4.37-4.43 (m, 1H), 6.89 (dd, 1H), 7.05 (d, 1H), 7.13 (d, 1H), 7.81 (d, 1H), 8.14 (dd, 1H), 8.48 (dd, 1H), 9.56 (s, 1H). LCMS: m/z 410.3 $[\text{M}+\text{H}]^+$

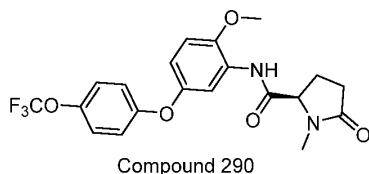
	methylpyridin-2-yl)oxy)aniline	
277	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 3-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)aniline	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.82-1.88 (m, 1H), 2.12-2.25 (m, 3H), 2.59 (s, 3H), 3.67 (s, 3H), 4.10-4.14 (m, 1H), 6.49 (t, 1H), 7.02 (t, 1H), 7.08 (t, 1H), 7.17 (d, 1H), 8.17 (dd, 1H), 8.53 (dd, 1H), 10.26 (s, 1H). LCMS: m/z 410.3 [M+H]⁺
278	 Starting material: (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 3-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline	¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.85-1.98 (m, 1H), 2.17-2.33 (m, 3H), 2.65 (s, 3H), 3.70-3.75 (m, 3H), 4.08-4.19 (m, 1H), 6.48 (s, 1H), 6.94 (t, 1H), 7.15-7.20 (m, 3H), 7.75 (d, 2H), 10.30 (s, 1H). LCMS: m/z 409.1 [M+H]⁺
279	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 3-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.87-1.93 (m, 1H), 2.18-2.33 (m, 3H), 2.65 (s, 3H), 3.74 (s, 3H), 4.15-4.23 (m, 1H), 6.48 (t, 1H), 6.94 (t, 1H), 7.16-7.21 (m, 3H), 7.75 (d, 2H), 10.30 (s, 1H). LCMS: m/z 409.1 [M+H]⁺
280	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 6-((5-(Trifluoromethyl)pyridin-2-yl)oxy)quinolin-8-	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.86-2.09 (m, 1H), 2.18-2.43 (m, 3H), 2.72 (s, 3H), 4.69-4.72 (m, 1H), 7.55 (s, 1H), 7.62 (s, 1H), 7.68 (dd, 1H), 8.40-8.44 (m, 2H), 8.49 (d, 1H), 8.95 (dd, 1H), 10.60 (s, 1H). LCMS: m/z 431.1 [M+H]⁺

	amine	
281	 Starting material: (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 6-((5-(Trifluoromethyl)pyridin-2-yl)oxy)-quinolin-8-amine	Purification method A. ^1H NMR (600 MHz, DMSO-d_6) δ: 1.86-2.46 (m, 4H), 2.72 (s, 3H), 4.71 (dd, 1H), 7.55 (s, 1H), 7.62 (s, 1H), 7.68 (dd, 1H), 8.40-8.44 (m, 2H), 8.49 (d, 1H), 8.95 (dd, 1H), 10.60 (s, 1H). LCMS: m/z 431.1 $[\text{M}+\text{H}]^+$
282	 Starting material: (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 3-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)aniline	Purification method A. ^1H NMR (600 MHz, DMSO-d_6) δ: 1.36-1.49 (m, 4H), 1.87-1.95 (m, 4H), 2.11-2.40 (m, 5H), 2.67 (s, 3H), 3.71 (s, 3H), 4.14-4.28 (m, 2H), 6.27 (t, 1H), 6.86 (d, 2H), 10.13 (s, 1H). LCMS: m/z 415.2 $[\text{M}+\text{H}]^+$
283	 Starting material: (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)aniline	Purification method A. ^1H NMR (600 MHz, DMSO-d_6) δ: 1.85-1.92 (m, 1H), 2.16-2.35 (m, 3H), 2.65 (s, 3H), 3.89 (s, 3H), 4.44-4.49 (m, 1H), 6.96 (dd, 1H), 7.12 (d, 1H), 7.19 (d, 1H), 7.88 (d, 1H), 8.21 (dd, 1H), 8.54-8.55 (m, 1H), 9.63 (s, 1H). LCMS: m/z 410.2 $[\text{M}+\text{H}]^+$
284	 Starting material: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ^1H NMR (600 MHz, DMSO-d_6) δ: 1.84-1.92 (m, 1H), 2.18-2.32 (m, 3H), 2.64 (s, 3H), 3.73 (s, 3H), 4.13-4.19 (m, 1H), 6.38 (t, 1H), 6.85 (t, 1H), 6.91 (dtd, 1H), 7.11

	and 3-(3,4-Difluorophenoxy)-5-methoxyaniline	(s, 1H), 7.25 (ddd, 1H), 7.48 (dt, 1H), 10.25 (s, 1H). LCMS: m/z 377.2 [M+H] ⁺
285	 Starting material: (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 3-(3,4-Difluorophenoxy)-5-methoxyaniline	Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.84-1.97 (m, 1H), 2.16-2.33 (m, 3H), 2.61-2.69 (m, 3H), 3.73 (s, 3H), 4.03-4.19 (m, 1H), 6.38 (t, 1H), 6.85 (t, 1H), 6.91 (d, 1H), 7.11 (s, 1H), 7.25 (ddd, 1H), 7.48 (dt, 1H), 10.25 (s, 1H). LCMS: m/z 377.2 [M+H]⁺
286	 Starting materials: 1-Methyl-5-oxopyrrolidine-2-carboxylic acid and 5-(Cyclohexyloxy)-2-methoxyaniline	Purification method A. ¹H NMR (400 MHz, CDCl₃) δ: 8.06 (d, 1H), 8.01 (br s, 1H), 6.78 (d, 1H), 6.63 (dd, 1H), 4.16 (tt, 1H), 4.09 (dd, 1H), 3.83 (s, 3H), 2.93 (s, 3H), 2.65-2.53 (m, 1H), 2.53-2.35 (m, 2H), 2.20-2.12 (m, 1H), 1.95 (m, 2H), 1.77 (m, 2H), 1.57-1.45 (m, 3H), 1.40-1.27 (m, 3H). LCMS: m/z 347.3 [M+H]⁺
287	 Starting materials: 5-(Cyclohex-2-en-1-yloxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method A. ¹H NMR (CDCl₃, 400 MHz) δ: 8.06-8.14 (m, 1H), 8.03 (s, 1H), 6.76-6.81 (m, 1H), 6.61-6.69 (m, 1H), 5.90-6.01 (m, 1H), 5.80-5.90 (m, 1H), 4.72 (br s, 1H), 4.06-4.14 (m, 1H), 3.81-3.88 (m, 3H), 2.93 (s, 3H), 2.51-2.65 (m, 1H), 2.36-2.52 (m, 2H), 1.54-1.66 (m, 1H), 1.54-2.23 (m, 7H). LCMS: m/z 345.240 (M+H)⁺
288		Purification method A. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 9.60 (br. s, 1H), 8.18 (dd, 1H), 7.93 (dd, 1H), 7.83 (d, 1H), 7.09 (d, 1H), 7.05 (dd, 1H),

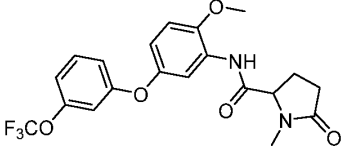
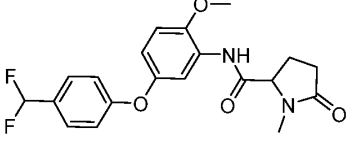
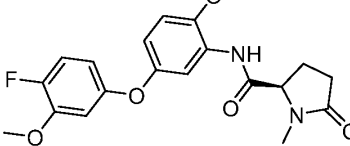
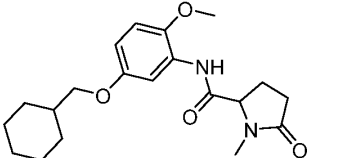
	Starting materials: 5-((5-Chloro-pyridin-2-yl)oxy)-2-methoxy-aniline and (S)-1-Methyl-5-oxo-pyrrolidine-2-carboxylic acid	6.90 (dd, 1H), 4.46 (m, 1H), 3.87 (s, 3H), 2.65 (s, 3H), 2.30-2.16 (m, 3H), 1.92-1.86 (m, 1H). LCMS: m/z 376.126 (M+H) ⁺
289	 Starting materials: 2-Methoxy-5-(3-(trifluoromethyl)phenoxy)-aniline and 1-Acetylazetidine-3-carboxylic acid	Purification method C. ¹H NMR (CDCl₃, 400 MHz) δ: 8.22 (d, 1H), 7.89 (br s, 1H), 7.40 (app t, 1H), 7.29 (app dt, 1H), 7.16 (m, 1H), 7.12 (m, 1H), 6.88 (d, 1H), 6.77 (dd, 1H), 4.45 (dd, 1H), 4.16-4.32 (m, 3H), 3.91 (s, 3H), 3.45 (tt, 1H), 1.88 (s, 3H). LCMS: m/z 409.159 (M+H)⁺

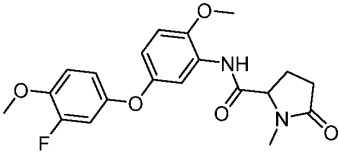
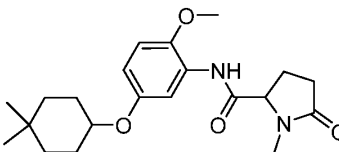
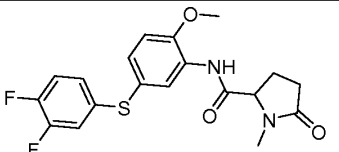
Example 12. (*R*)-*N*-(2-methoxy-5-(4-(trifluoromethoxy)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 290)

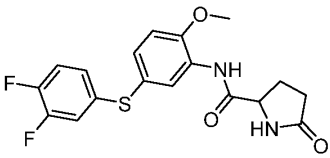
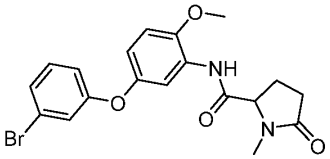
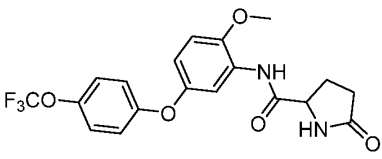
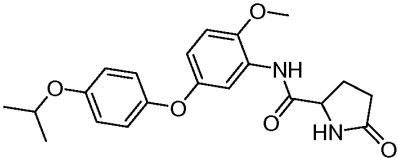


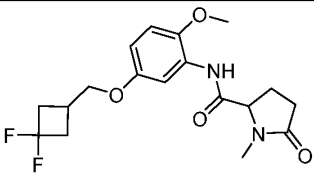
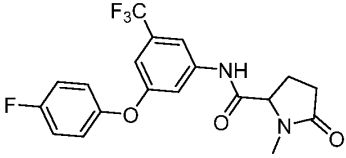
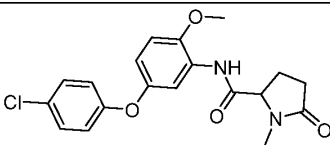
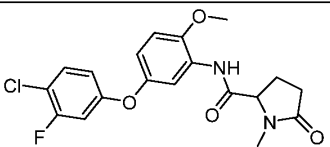
- 5 To a mixture of 2-methoxy-5-(4-(trifluoromethoxy)phenoxy)aniline (0.060 g, 0.20 mmol), (2R)-1-methyl-5-oxopyrrolidine-2-carboxylic acid (0.029 g, 0.20 mmol) and HATU (0.114 g, 0.30 mmol) in dry DMF (1.0 ml) was added DIPEA (0.174 ml, 1.00 mmol). The mixture was stirred overnight at RT. The mixture was diluted with EtOAc and washed with water and brine. Organic phase was dried and evaporated. The
- 10 crude product was purified by reverse phase flash chromatography to afford 0.056 g of the of the title compound. ¹H NMR (400 MHz, CDCl₃) δ : 8.17 (d, 1H), 8.07 (s, 1H), 7.11-7.18 (m, 2H), 6.91-6.98 (m, 2H), 6.87 (d, 1H), 6.77 (dd, 1H), 4.07-4.14 (m, 1H), 3.90 (s, 3H), 2.94 (s, 3H), 2.37-2.63 (m, 3H), 2.10-2.20 (m, 1H). LCMS: m/z 425.0 [M+H]⁺

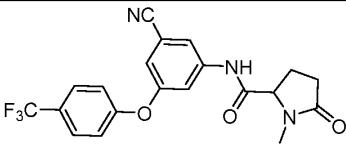
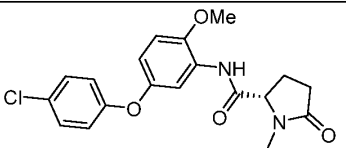
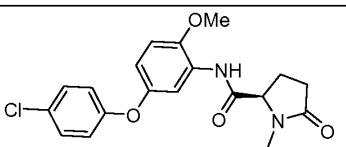
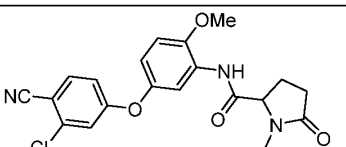
The following compounds were prepared according to the procedure described for Compound 290. The compound number, structure, starting materials, purification method and characterization data are indicated in the table.

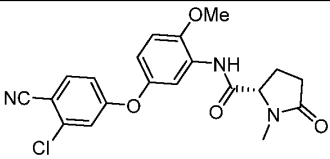
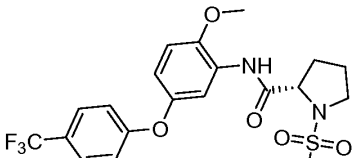
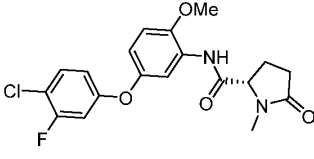
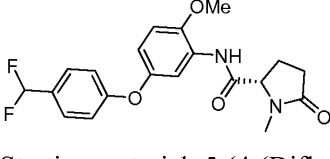
No	Structure and starting material	Characterization data
291	 Starting material: 2-Methoxy-5-(3-(trifluoromethoxy)-phenoxy)aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.19 (d, 1H), 8.08 (s, 1H), 7.29 (t, 1H), 6.85-6.92 (m, 3H), 6.77-6.82 (m, 2H), 4.08-4.14 (m, 1H), 3.91 (s, 3H), 2.94 (s, 3H), 2.37-2.63 (m, 3H), 2.11-2.20 (m, 1H). LCMS: <i>m/z</i> 425.1 [M+H] ⁺
292	 Starting material: 5-(4-(Difluoromethyl)phenoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.18 (d, 1H), 8.07 (s, 1H), 7.40-7.48 (m, 2H), 6.95-7.05 (m, 2H), 6.89 (d, 1H), 6.80 (dd, 1H), 6.61 (t, 1H), 4.07-4.14 (m, 1H), 3.91 (s, 3H), 2.94 (s, 3H), 2.37-2.63 (m, 3H), 2.11-2.20 (m, 1H). LCMS: <i>m/z</i> 391.1 [M+H] ⁺
293	 Starting material: 5-(4-Fluoro-3-methoxyphenoxy)-2-methoxyaniline and (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.13 (d, 1H), 8.05 (s, 1H), 6.98 (dd, 1H), 6.85 (d, 1H), 6.74 (dd, 1H), 6.66 (dd, 1H), 6.39-6.46 (m, 1H), 4.07-4.13 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 2.94 (s, 3H), 2.37-2.63 (m, 3H), 2.10-2.20 (m, 1H). LCMS: <i>m/z</i> 389.1 [M+H] ⁺
294		¹ H NMR (400 MHz, CDCl ₃) δ: 8.05 (d, 1H), 8.03 (s, 1H), 6.80 (d, 1H), 6.61 (dd, 1H), 4.11 (dd, 1H), 3.84 (s, 3H), 3.72 (d, 2H), 2.93 (s, 3H), 2.54-

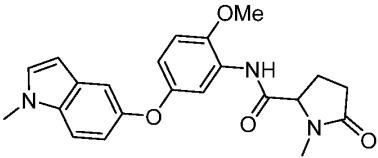
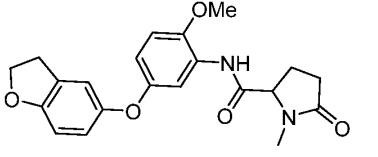
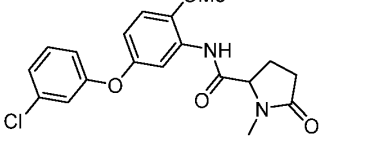
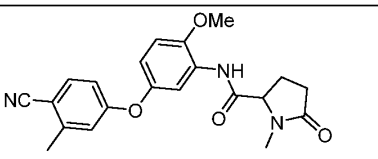
	Starting material: 5-(Cyclohexyl-methoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	2.66 (m, 1H), 2.36-2.54 (m, 2H), 2.11-2.21 (m, 1H), 1.81-1.91 (m, 2H), 1.63-1.81 (m, 4H), 1.12-1.36 (m, 3H), 0.96-1.10 (m, 2H). LCMS: m/z 361.1 $[M+H]^+$
295	 Starting material: 5-(3-Fluoro-4-methoxyphenoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	^1H NMR (400 MHz, CDCl_3) δ : 8.12 (d, 1H), 8.05 (s, 1H), 6.81-6.95 (m, 2H), 6.67-6.79 (m, 3H), 4.06-4.14 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.93 (s, 3H), 2.36-2.64 (m, 3H), 2.10-2.21 (m, 1H). LCMS: m/z 389.0 $[M+H]^+$
296	 Starting material: 5-((4,4-Dimethylcyclohexyl)oxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	^1H NMR (400 MHz, CDCl_3) δ : 8.07 (d, 1H), 8.03 (s, 1H), 6.79 (d, 1H), 6.64 (dd, 1H), 4.06-4.22 (m, 2H), 3.84 (s, 3H), 2.93 (s, 3H), 2.36-2.67 (m, 3H), 2.11-2.23 (m, 1H), 1.78-1.91 (m, 2H), 1.58-1.70 (m, 2H), 1.43-1.57 (m, 2H), 1.18-1.32 (m, 2H), 0.96 (s, 3H), 0.93 (s, 3H). LCMS: m/z 375.4 $[M+H]^+$
297	 Starting material: 5-((3,4-Difluorophenyl)thio)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	^1H NMR (400 MHz, CDCl_3) δ : 8.51 (d, 1H), 8.02 (s, 1H), 7.21 (dd, 1H), 6.94-7.10 (m, 3H), 6.90 (d, 1H), 4.08-4.14 (m, 1H), 3.92 (s, 3H), 2.94 (s, 3H), 2.37-2.65 (m, 3H), 2.11-2.20 (m, 1H). LCMS: m/z 393.3 $[M+H]^+$

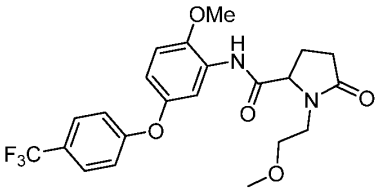
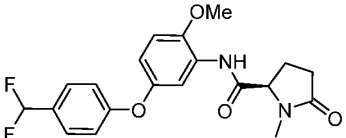
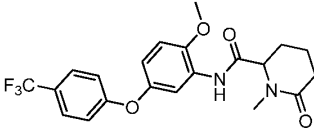
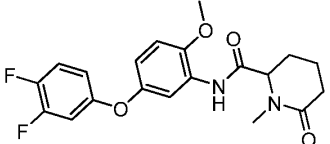
298	 Starting material: 5-((3,4-Difluorophenyl)thio)-2-methoxyaniline and 5-Oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.51 (d, 1H), 8.30 (s, 1H), 7.20 (dd, 1H), 6.92-7.10 (m, 1H), 6.89 (d, 1H), 6.36 (s, 1H), 4.30 (ddd, 1H), 3.92 (s, 3H), 2.57-2.70 (m, 1H), 2.45-2.57 (m, 1H), 2.22-2.45 (m, 2H). LCMS: <i>m/z</i> 379.2 [M+H] ⁺
299	 Starting material: 5-(3-Bromophenoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (600 MHz, CDCl ₃) δ: 8.16 (d, 1H), 8.06 (s, 1H), 7.13-7.18 (m, 2H), 7.04-7.07 (m, 1H), 6.89-6.92 (m, 1H), 6.87 (d, 1H), 6.77 (dd, 1H), 4.10 (dd, 1H), 3.91 (s, 3H), 2.94 (s, 3H), 2.54-2.62 (m, 1H), 2.38-2.52 (m, 2H), 2.12-2.19 (m, 1H). LCMS: <i>m/z</i> 419.2 [M+H] ⁺
300	 Starting material: 2-Methoxy-5-(4-(trifluoromethoxy)-phenoxy)aniline and 5-Oxopyrrolidine-2-carboxylic acid	¹ H NMR (600 MHz, CDCl ₃) δ: 8.34 (s, 1H), 8.16 (d, 1H), 7.11-7.16 (m, 2H), 6.91-6.96 (m, 2H), 6.86 (d, 1H), 6.76 (dd, 1H), 6.39 (s, 1H), 4.29 (ddd, 1H), 3.89 (s, 3H), 2.58-2.67 (m, 1H), 2.46-2.54 (m, 1H), 2.34-2.42 (m, 1H), 2.24-2.32 (m, 1H). LCMS: <i>m/z</i> 411.3 [M+H] ⁺
301	 Starting material: 5-(4-Isopropoxyphenoxy)-2-methoxyaniline and 5-Oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.30 (s, 1H), 8.11 (d, 1H), 6.87-6.93 (m, 2H), 6.78-6.87 (m, 3H), 6.69 (dd, 1H), 6.22 (s, 1H), 4.46 (sept, 1H), 4.28 (ddd, 1H), 3.87 (s, 3H), 2.56-2.68 (m, 1H), 2.44-2.56 (m, 1H), 2.33-2.44 (m, 1H), 2.22-2.33 (m, 1H), 1.32 (d, 6H). LCMS: <i>m/z</i> 385.2 [M+H] ⁺

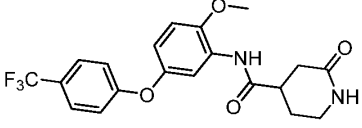
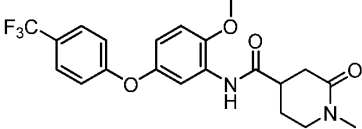
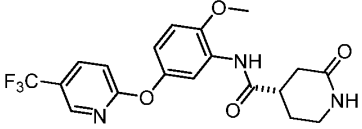
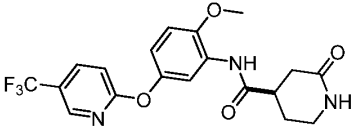
302	 Starting material: 5-((3,3-Difluorocyclobutyl)methoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (600 MHz, CDCl ₃) δ: 8.07 (d, 1H), 8.04 (s, 1H), 6.81 (d, 1H), 6.62 (dd, 1H), 4.09-4.13 (m, 1H), 3.97 (d, 2H), 3.85 (s, 3H), 2.93 (s, 3H), 2.65-2.75 (m, 2H), 2.54-2.63 (m, 2H), 2.38-2.53 (m, 4H), 2.12-2.19 (m, 1H). LCMS: <i>m/z</i> 369.3 [M+H] ⁺
303	 Starting material: 5-((3,3-Difluorocyclobutyl)methoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 9.23 (s, 1H), 7.78-7.85 (m, 1H), 7.48-7.55 (m, 1H), 6.99-7.12 (m, 4H), 6.94-6.99 (m, 1H), 4.16 (dd, 1H), 2.84 (s, 3H), 2.44-2.60 (m, 2H), 2.24-2.39 (m, 1H), 2.09-2.22 (m, 1H). LCMS: <i>m/z</i> 397.5 [M+H] ⁺
304	 Starting material: 5-(4-Chlorophenoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.14 (d, 1H), 8.05 (s, 1H), 7.21-7.28 (m, 2H), 6.82-6.92 (m, 3H), 6.75 (dd, 1H), 4.09 (dd, 1H), 3.89 (s, 3H), 2.93 (s, 3H), 2.36-2.65 (m, 3H), 2.09-2.22 (m, 1H). LCMS: <i>m/z</i> 375.0 [M+H] ⁺
305	 Starting material: 5-(4-Chloro-3-fluorophenoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.17 (d, 1H), 8.07 (s, 1H), 7.22-7.34 (m, 1H), 6.88 (d, 1H), 6.78 (dd, 1H), 6.63-6.75 (m, 2H), 4.04-4.16 (m, 1H), 3.91 (s, 3H), 2.94 (s, 3H), 2.34-2.65 (m, 3H), 2.08-2.22 (m, 1H). LCMS: <i>m/z</i> 393.1 [M+H] ⁺

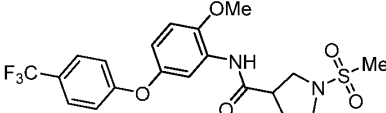
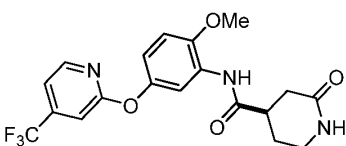
306	 Starting material: 3-Amino-5-(4-(trifluoromethyl)-phenoxy)benzonitrile and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, d ₆ -DMSO) δ: 10.6 (s, 1H), 7.94 (s, 1H), 7.75-7.86 (m, 2H), 7.53-7.61 (m, 1H), 7.39-7.47 (m, 1H), 7.23-7.34 (m, 2H), 4.15-4.25 (m, 1H), 2.67 (s, 3H), 2.16-2.38 (m, 3H), 1.85-1.99 (m, 1H). LCMS: <i>m/z</i> 404.4 [M+H] ⁺
307	 Starting material: 5-(4-Chlorophenoxy)-2-methoxyaniline and (<i>S</i>)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.14 (d, 1H), 8.05 (s, 1H), 7.21-7.28 (m, 2H), 6.86-6.92 (m, 2H), 6.86 (d, 1H), 6.75 (dd, 1H), 4.09 (dd, 1H), 3.89 (s, 3H), 2.93 (s, 3H), 2.36-2.63 (m, 3H), 2.09-2.19 (m, 1H). LCMS: <i>m/z</i> 375.1 [M+H] ⁺
308	 Starting material: 5-(4-Chlorophenoxy)-2-methoxyaniline and (<i>R</i>)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.14 (d, 1H), 8.05 (s, 1H), 7.21-7.28 (m, 2H), 6.86-6.92 (m, 2H), 6.86 (d, 1H), 6.75 (dd, 1H), 4.09 (dd, 1H), 3.89 (s, 3H), 2.93 (s, 3H), 2.36-2.63 (m, 3H), 2.09-2.19 (m, 1H). LCMS: <i>m/z</i> 375.1 [M+H] ⁺
309	 Starting material: 4-(3-Amino-4-methoxyphenoxy)-2-chlorobenzonitrile and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.20 (d, 1H), 8.11 (s, 1H), 7.57 (d, 1H), 6.98 (d, 1H), 6.93 (d, 1H), 6.90 (dd, 1H), 6.82 (dd, 1H), 4.12 (dd, 1H), 3.94 (s, 3H), 2.94 (s, 3H), 2.37-2.65 (m, 3H), 2.10-2.21 (m, 1H). LCMS: <i>m/z</i> 400.1 [M+H] ⁺

310	 Starting material: 4-(3-Amino-4-methoxyphenoxy)-2-chlorobenzonitrile and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.20 (d, 1H), 8.11 (s, 1H), 7.57 (d, 1H), 6.98 (d, 1H), 6.93 (d, 1H), 6.90 (dd, 1H), 6.82 (dd, 1H), 4.12 (dd, 1H), 3.94 (s, 3H), 2.94 (s, 3H), 2.37-2.65 (m, 3H), 2.10-2.21 (m, 1H). LCMS: <i>m/z</i> 400.1 [M+H] ⁺
311	 Starting material: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (Methylsulfonyl)-L-proline	¹ H NMR (400 MHz, CDCl ₃) δ: 9.08 (s, 1H), 8.19 (d, 1H), 7.46-7.60 (m, 2H), 6.93-7.06 (m, 2H), 6.87 (d, 1H), 6.78 (dd, 1H), 4.34 (dd, 1H), 3.92 (s, 3H), 3.55-3.66 (m, 1H), 3.38-3.49 (m, 1H), 2.94 (s, 3H), 2.38-2.49 (m, 1H), 2.08-2.22 (m, 1H), 1.94-2.07 (m, 2H). LCMS: <i>m/z</i> 459.6 [M+H] ⁺
312	 Starting material: 5-(4-Chloro-3-fluorophenoxy)-2-methoxyaniline and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.17 (d, 1H), 8.07 (s, 1H), 7.24-7.32 (m, 1H), 6.88 (d, 1H), 6.78 (dd, 1H), 6.67-6.75 (m, 2H), 4.10 (dd, 1H), 3.91 (s, 3H), 2.94 (s, 3H), 2.36-2.64 (m, 3H), 2.10-2.21 (m, 1H). LCMS: <i>m/z</i> 393.1 [M+H] ⁺
313	 Starting material: 5-(4-(Difluoromethyl)phenoxy)-2-methoxyaniline and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.18 (d, 1H), 8.07 (s, 1H), 7.38-7.48 (m, 2H), 6.94-7.04 (m, 2H), 6.88 (d, 1H), 6.79 (dd, 1H), 6.61 (t, 1H), 4.10 (dd, 1H), 3.91 (s, 3H), 2.93 (s, 3H), 2.36-2.64 (m, 3H), 2.09-2.20 (m, 1H). LCMS: <i>m/z</i> 391.3 [M+H] ⁺

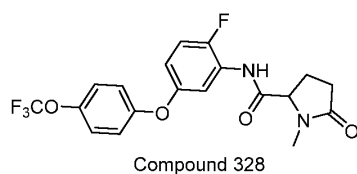
314	 Starting material: 2-Methoxy-5-((1-methyl-1H-indol-5-yl)oxy)aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.11 (d, 1H), 8.01 (s, 1H), 7.26 (d, 1H), 7.22 (d, 1H), 7.05 (d, 1H), 6.97 (dd, 1H), 6.79 (d, 1H), 6.69 (dd, 1H), 6.39 (d, 1H), 4.03-4.10 (m, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 2.92 (s, 3H), 2.33-2.64 (m, 3H), 2.07-2.19 (m, 1H). LCMS: <i>m/z</i> 394.4 [M+H] ⁺
315	 Starting material: 5-((2,3-Dihydrobenzofuran-5-yl)oxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.09 (d, 1H), 8.03 (s, 1H), 6.84-6.89 (m, 1H), 6.81 (d, 1H), 6.75 (dd, 1H), 6.70 (d, 1H), 6.68 (dd, 1H), 4.57 (t, 2H), 4.09 (dd, 1H), 3.87 (s, 3H), 3.18 (t, 2H), 2.93 (s, 3H), 2.35-2.64 (m, 3H), 2.10-2.20 (m, 1H). LCMS: <i>m/z</i> 393.4 [M+H] ⁺
316	 Starting material: 5-(3-Chlorophenoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.16 (d, 1H), 8.07 (s, 1H), 7.21 (t, 1H), 7.01 (d, 1H), 6.82-6.95 (m, 3H), 6.78 (dd, 1H), 4.06-4.15 (m, 1H), 3.91 (s, 3H), 2.94 (s, 3H), 2.35-2.66 (m, 3H), 2.09-2.22 (m, 1H). LCMS: <i>m/z</i> 375.1 [M+H] ⁺
317	 Starting material: 4-(3-Amino-4-methoxyphenoxy)-2-methylbenzonitrile and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.18 (d, 1H), 8.09 (s, 1H), 7.50 (d, 1H), 6.91 (d, 1H), 6.74-6.84 (m, 3H), 4.11 (dd, 1H), 3.92 (s, 3H), 2.94 (s, 3H), 2.48 (s, 3H), 2.37-2.65 (m, 3H), 2.10-2.20 (m, 1H). LCMS: <i>m/z</i> 380.4 [M+H] ⁺

318	 Starting material: 2-Methoxy-5-(4-(trifluoromethyl)-phenoxy)aniline and 1-(2-Methoxyethyl)-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) :δ 8.33 (s, 1H), 8.22 (d, 1H), 7.49-7.58 (m, 2H), 6.95-7.03 (m, 2H), 6.90 (d, 1H), 6.79 (dd, 1H), 4.36-4.44 (m, 1H), 3.92 (s, 3H), 3.80-3.89 (m, 1H), 3.49-3.61 (m, 1H), 3.31 (s, 3H), 3.25-3.36 (m, 1H), 2.53-2.67 (m, 1H), 2.29-2.47 (m, 2H), 2.14-2.27 (m, 1H). LCMS: <i>m/z</i> 453.6 [M+H] ⁺
319	 Starting material: 5-(4-(Difluoro-methyl)phenoxy)-2-methoxyaniline and (<i>R</i>)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.18 (d, 1H), 8.07 (s, 1H), 7.38-7.48 (m, 2H), 6.94-7.04 (m, 2H), 6.88 (d, 1H), 6.79 (dd, 1H), 6.61 (t, 1H), 4.10 (dd, 1H), 3.91 (s, 3H), 2.93 (s, 3H), 2.36-2.64 (m, 3H), 2.09-2.20 (m, 1H). LCMS: <i>m/z</i> 391.3 [M+H] ⁺
320	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-Methyl-6-oxopiperidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.24 (br. s, 1H), 8.17 (d, 1H), 7.54 (m, 2H), 7.00 (m, 2H), 6.90 (d, 1H), 6.81 (dd, 1H), 4.04 (dd, 1H), 3.91 (s, 3H), 3.04 (s, 3H), 2.57 (dt, 1H), 2.44 (m, 1H), 2.25 (m, 1H), 2.15-2.06 (m, 1H), 1.86-1.80 (m, 2H). LCMS: <i>m/z</i> 423.5 [M+H] ⁺
321	 Starting materials: 5-(3,4-Difluoro-phenoxy)-2-methoxyaniline and 1-Methyl-6-oxopiperidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.22 (br. s, 1H), 8.13 (d, 1H), 7.07 (m, 1H), 6.86 (d, 1H), 6.78-6.73 (m, 2H), 6.70-6.66 (m, 1H), 4.04 (dd, 1H), 3.89 (s, 3H), 3.04 (s, 3H), 2.56 (dt, 1H), 2.44 (m, 1H), 2.25 (m, 1H), 2.10 (m, 1H), 1.88-1.80 (m, 2H). LCMS: <i>m/z</i> 391.2 [M+H] ⁺

322	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 2-Oxopiperidine-4-carboxylic acid	¹ H NMR (600 MHz, CDCl ₃) δ: 8.22 (d, 1H), 7.89 (br. s, 1H), 7.53 (m, 2H), 6.98 (m, 2H), 6.88 (d, 1H), 6.78 (dd, 1H), 5.88 (br. s, 1H), 3.92 (s, 3H), 3.48 (m, 1H), 3.37 (td, 1H), 2.82 (m, 1H) 2.71-2.61 (m, 2H), 2.15 (m, 1H), 2.02 (m, 1H). LCMS: m/z 409.2 [M+H] ⁺
323	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-Methyl-2-oxopiperidine-4-carboxylic acid	¹ H NMR (600 MHz, CDCl ₃) δ: 8.21 (d, 1H), 7.87 (br. s, 1H), 7.53 (m, 2H), 6.98 (m, 2H), 6.88 (d, 1H), 6.78 (dd, 1H), 3.92 (s, 3H), 3.43-3.34 (m, 2H), 2.97 (s, 3H), 2.80 (m, 1H), 2.70-2.63 (m, 2H), 2.17 (m, 1H), 2.06 (m, 1H). LCMS: m/z 423.3 [M+H] ⁺
324	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and 2-Oxopiperidine-4-carboxylic acid	Mixture of enantiomers separated with optical HPLC purification. ¹ H NMR (400 MHz, CDCl ₃) δ: 8.42 (s, 1H), 8.28 (d, 1H), 7.90 (br. s, 1H), 7.87 (dd, 1H), 7.00 (d, 1H), 6.92 (d, 1H), 6.87 (dd, 1H), 5.87 (s, 1H), 3.92 (s, 3H), 3.48 (m, 1H), 3.37 (td, 1H), 2.82 (m, 1H), 2.73-2.60 (m, 2H), 2.15 (m, 1H), 2.01 (m, 1H). LCMS: m/z 408.602 (M-H) ⁻ [M+H] ⁺
325	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and 2-Oxopiperidine-4-carboxylic acid	Mixture of enantiomers separated with optical HPLC purification. ¹ H NMR (400 MHz, CDCl ₃) δ: 8.42 (s, 1H), 8.28 (d, 1H), 7.90 (br. s, 1H), 7.87 (dd, 1H), 7.00 (d, 1H), 6.92 (d, 1H), 6.87 (dd, 1H), 5.86 (s, 1H), 3.92 (s, 3H), 3.48 (m, 1H), 3.37 (td, 1H), 2.82 (m, 1H)

		1H), 2.73-2.60 (m, 2H), 2.15 (m, 1H), 2.01 (m, 1H). LCMS: m/z 408.532 (M-H) ⁻
326	 Starting materials: N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)pyrrolidine-3-carboxamide and Methanesulfonyl chloride	¹ H NMR (600 MHz, CDCl ₃) δ: 2.24 - 2.36 (m, 2H), 2.91 (s, 3H), 3.14 (ddd, 1H), 3.42 - 3.48 (m, 1H), 3.52 (ddd, 1H), 3.59 (dd, 1H), 3.68 (dd, 1H), 3.93 (s, 3H), 6.78 (dd, 1H), 6.89 (d, 1H), 6.98 (m, 1H), 7.00 (m, 1H), 7.53 (m, 1H), 7.54 (m, 1H), 7.96 (brs, 1H), 8.17 (d, 1H). LCMS: m/z 459.168 (M+H) ⁺
327	 Starting materials: 2-Methoxy-5-((4-(trifluoromethyl)pyridin-2-yl)oxy)aniline and 2-Oxopiperidine-4-carboxylic acid	Enantiomer obtained with preparative chiral HPLC (methanol, 12 mL/min, column: 10 x 250 mm LuxCell). ¹ H NMR (600 MHz, DMSO-d ₆) δ: 9.34 (s, 1H), 8.38 (d, 1H), 7.88 (d, 1H), 7.49 (br. s, 1H), 7.46 (m, 1H), 7.40 (m, 1H), 7.09 (d, 1H), 6.91 (dd, 1H), 3.87 (s, 3H), 3.20-3.06 (m, 3H), 2.27 (d, 2H), 1.93 (m, 1H), 1.68 (m, 1H). LCMS: m/z 410.228 (M+H) ⁺

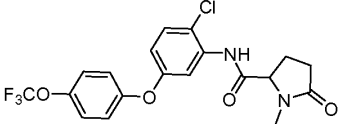
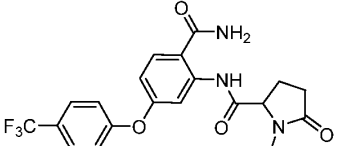
Example 13. *N*-(2-Fluoro-5-(4-(trifluoromethoxy)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 328)



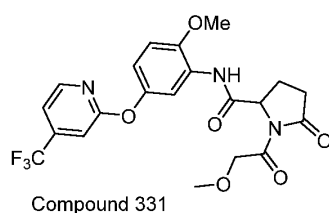
- 5 To a mixture of 2-fluoro-5-(4-(trifluoromethoxy)phenoxy)aniline (0.069 g, 0.24 mmol), 1-methyl-5-oxopyrrolidine-2-carboxylic acid (0.034 g, 0.24 mmol) and 1-methylimidazole (0.071 ml, 0.89 mmol) in dry acetonitrile (1.0 ml) was added N,N,N',N'-tetramethylchloroformamidinium-hexafluorophosphate (0.081 g, 0.288

mmol). The mixture was stirred overnight at RT. The mixture was diluted with EtOAc and washed with water and brine. Organic phase was dried and evaporated. Crude product was purified by reverse phase flash chromatography to afford 0.028 g of the title compound. ¹H NMR (400 MHz, CDCl₃) δ: 8.05 (dd, 1H), 7.81 (s, 1H), 7.14-7.23 (m, 2H), 7.05-7.14 (m, 1H), 6.92-7.03 (m, 2H), 6.71-6.80 (m, 1H), 4.10-4.19 (m, 1H), 2.93 (s, 3H), 2.37-2.64 (m, 3H), 2.10-2.21 (m, 1H). LCMS: *m/z* 413.0 [M+H]⁺.

The following compounds were prepared according to the procedure described for Compound 328. The compound number, structure, starting materials and characterization data are indicated in the table.

No	Structure and starting material	Characterization data
329	 Starting material: 2-Chloro-5-(4-(trifluoromethoxy)-phenoxy)aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.14 (d, 1H), 8.00 (s, 1H), 7.36 (d, 1H), 7.17-7.24 (m, 2H), 6.99-7.06 (m, 2H), 6.75 (dd, 1H), 4.10-4.16 (m, 1H), 2.97 (s, 3H), 2.39-2.65 (m, 3H), 2.12-2.21 (m, 1H). LCMS: <i>m/z</i> 429.2 [M+H] ⁺
330	 Starting materials: 2-Amino-4-(4-(trifluoromethyl)-phenoxy)-benzamide and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 12.5 (s, 1H), 8.50 (d, 1H), 7.58-7.74 (m, 3H), 7.44 (br s, 1H), 7.10-7.19 (m, 2H), 6.77 (dd, 1H), 6.66 (br s, 1H), 4.11 (dd, 1H), 2.94 (s, 3H), 2.34-2.66 (m, 3H), 2.09-2.21 (m, 1H). LCMS: <i>m/z</i> 422.1 [M+H] ⁺

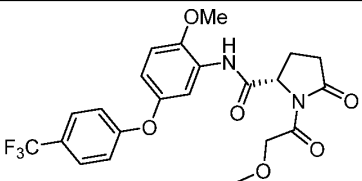
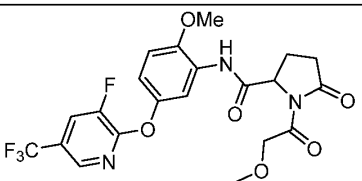
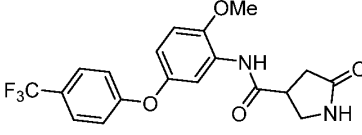
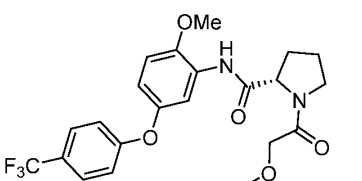
Example 14. *N*-(2-Methoxy-5-((4-(trifluoromethyl)-pyridin-2-yl)oxy)phenyl)-1-(2-methoxyacetyl)-5-oxopyrrolidine-2-carboxamide (Compound 331)

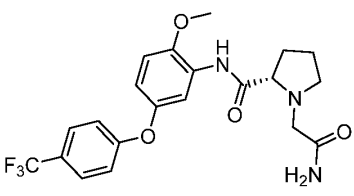
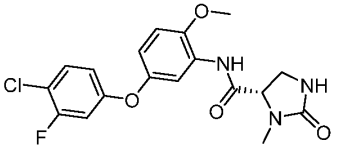
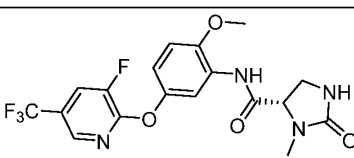
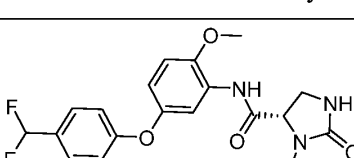


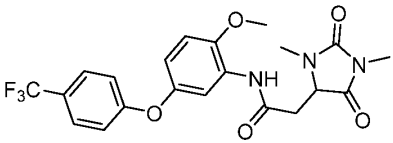
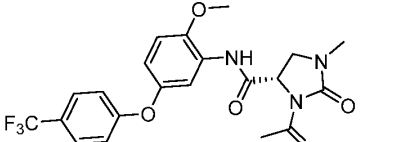
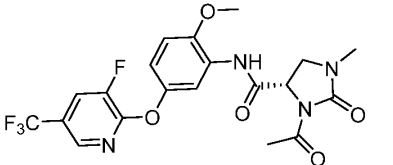
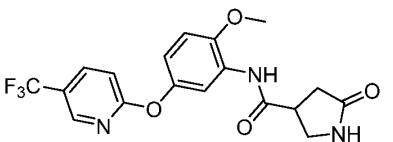
- To a mixture of 2-methoxy-5-((4-(trifluoromethyl)pyridin-2-yl)oxy)aniline (0.071 g, 0.25 mmol), 1-(2-methoxyacetyl)-5-oxopyrrolidine-2-carboxylic acid (0.053 g, 0.25 mmol) in EtOAc (0.30 ml) and pyridine (0.15 ml) was added 1-
- 5 propanephosphonic acid cyclic anhydride, 50 wt-% in EtOAc (0.25 ml, 0.424 mmol). The mixture was stirred at RT overnight. Reaction was quenched with 0.5 % HCl-solution and diluted with water and EtOAc. Phases were separated and organic phase was washed with 0.5 % HCl-solution, water and brine, dried and evaporated. Crude product was purified by reverse phase flash chromatography to afford the title
- 10 compound. Yield: 0.046 g. ¹H NMR (400 MHz, CDCl₃) δ: 8.45 (s, 1H), 8.30 (d, 1H), 8.20 (s, 1H), 7.04-7.22 (m, 2H), 6.82-7.00 (m, 2H), 4.88 (d, 1H), 4.52-4.74 (m, 2H), 3.93 (s, 3H), 3.47 (s, 3H), 2.84-3.03 (m, 1H), 2.47-2.64 (m, 1H), 2.22-2.47 (m, 2H). LCMS: *m/z* 468.5 [M+H]⁺

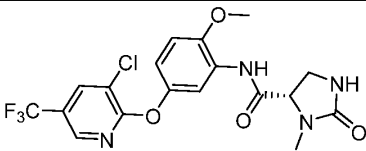
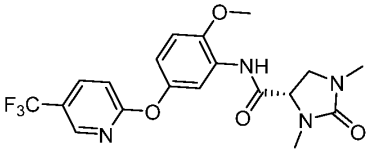
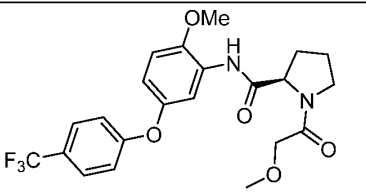
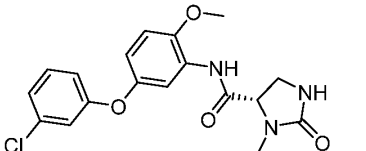
- 15 The following compounds were prepared according to the procedure described for Compound 331. The compound number, structure, starting materials and characterization data are indicated in the table.

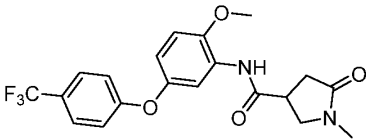
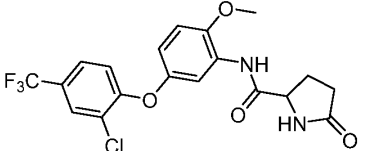
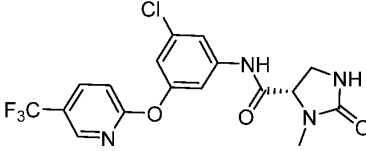
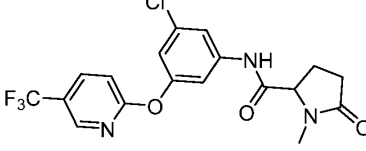
No	Structure and starting material	Characterization data
332	Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (<i>S</i>)-1-Methyl-2-oxoimidazolidine-4-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 9.05 (s, 1H), 8.21 (d, 1H), 7.50-7.57 (m, 2H), 6.96-7.02 (m, 2H), 6.88 (d, 1H), 6.80 (dd, 1H), 5.33 (d, 1H), 4.29-4.36 (m, 1H), 3.89 (s, 3H), 3.85-3.92 (m, 1H), 3.53 (dd, 1H), 2.83 (s, 3H). LCMS: <i>m/z</i> 410.2 [M+H] ⁺

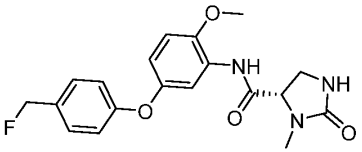
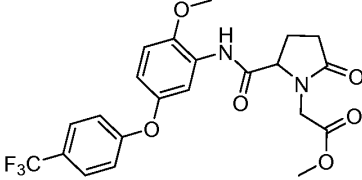
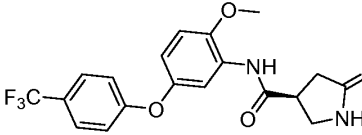
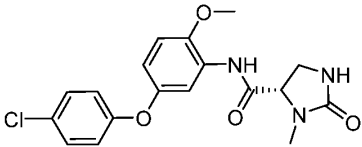
333	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)-phenoxy)aniline and (S)-1-(2-Methoxyacetyl)-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.44 (s, 1H), 8.14 (d, 1H), 7.49-7.56 (m, 2H), 6.94-7.00 (m, 2H), 6.88 (d, 1H), 6.79 (dd, 1H), 4.86 (dd, 1H), 4.57-4.69 (m, 2H), 3.92 (s, 3H), 3.47 (s, 3H), 2.88-3.01 (m, 1H), 2.49-2.59 (m, 1H), 2.25-2.45 (m, 2H). LCMS: <i>m/z</i> 467.5 [M+H] ⁺
334	 Starting materials: 5-((3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyaniline and 1-(2-Methoxyacetyl)-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (600 MHz, d ₆ -DMSO) δ: 9.80 (s, 1H), 8.38 (dd, 1H), 8.34-8.37 (m, 1H), 7.93 (d, 1H), 7.13 (d, 1H), 7.00 (dd, 1H), 5.09 (dd, 1H), 4.48 (q, 2H), 3.91 (s, 3H), 3.29 (s, 3H), 2.54-2.62 (m, 1H), 2.45-2.52 (m, 1H), 2.31-2.40 (m, 1H), 1.96-2.02 (m, 1H). LCMS: <i>m/z</i> 486.5 [M+H] ⁺
335	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)-phenoxy)aniline and 5-Oxopyrrolidine-3-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.20 (d, 1H), 7.91 (s, 1H), 7.49-7.57 (m, 2H), 6.95-7.03 (m, 2H), 6.89 (d, 1H), 6.79 (dd, 1H), 6.14 (s, 1H), 3.92 (s, 3H), 3.60-3.76 (m, 2H), 3.38 (quint., 1H), 2.75 (dd, 1H), 2.61 (dd, 1H). LC-MS: <i>m/z</i> 395.2 [M+H] ⁺
336	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (2-Methoxyacetyl)-L-proline	¹ H NMR (400 MHz, CDCl ₃) δ: 9.26 (s, 1H), 8.16 (d, 1H), 7.48-7.55 (m, 2H), 6.93-7.00 (m, 2H), 6.85 (d, 1H), 6.74 (dd, 1H), 4.78 (dd, 1H), 4.07-4.18 (m, 2H), 3.91 (s, 3H), 3.54-3.63 (m, 1H), 3.48 (s, 3H), 3.42-3.52 (m, 1H), 2.40-2.51 (m, 1H), 2.09-2.24 (m, 1H), 1.83-2.09 (m, 1H). LCMS:

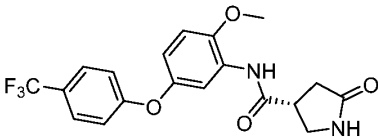
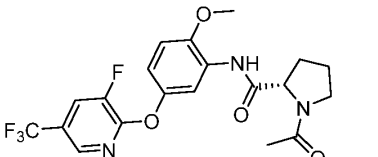
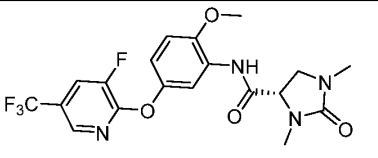
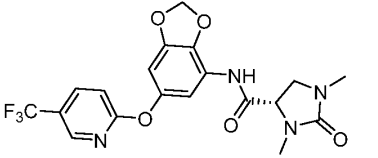
		m/z 453.6 $[M+H]^+$
337	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (2-Amino-2-oxoethyl)-L-proline	1H NMR (400 MHz, $CDCl_3$) δ : 9.46 (s, 1H), 8.23 (d, 1H), 7.49-7.57 (m, 2H), 6.95-7.03 (m, 2H), 6.89 (d, 1H), 6.77 (dd, 1H), 6.58 (bs, 1H), 5.81 (bs, 1H), 3.90 (s, 3H), 3.54 (d, 1H), 3.33-3.43 (m, 2H), 3.19 (d, 1H), 2.49-2.59 (m, 1H), 2.26-2.39 (m, 1H), 1.85-2.07 (m, 3H). LCMS: m/z 438.8 $[M+H]^+$
338	 Starting materials: 5-(4-Chloro-3-fluorophenoxy)-2-methoxyaniline and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	1H NMR (400 MHz, $CDCl_3$) δ : 8.59 (s, 1H), 8.16 (d, 1H), 7.28 (t, 1H), 6.89 (d, 1H), 6.79 (dd, 1H), 6.66-6.76 (m, 2H), 5.15 (s, 1H), 4.13 (dd, 1H), 3.91 (s, 3H), 3.86 (t, 1H), 3.46 (t, 1H), 2.92 (s, 3H). LCMS: m/z 394.2 $[M+H]^+$
339	 Starting materials: 5-((3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyaniline and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	1H NMR (400 MHz, $CDCl_3$) δ : 8.62 (s, 1H), 8.28-8.31 (m, 1H), 8.15-8.19 (m, 1H), 7.67 (dd, 1H), 6.91-6.97 (m, 2H), 4.94 (s, 1H), 4.13 (dd, 1H), 3.93 (s, 3H), 3.85 (t, 1H), 3.41-3.48 (m, 1H), 2.92 (s, 3H). LCMS: m/z 429.4 $[M+H]^+$
340	 Starting materials: 5-(4-(Difluoromethyl)phenoxy)-2-methoxyaniline	1H NMR (400 MHz, $CDCl_3$) δ : 8.58 (s, 1H), 8.17 (d, 1H), 7.40-7.47 (m, 2H), 6.96-7.03 (m, 2H), 6.89 (d, 1H), 6.80 (dd, 1H), 6.61 (t, 1H), 4.93 (s, 1H), 4.12 (dd, 1H), 3.01 (s, 3H), 3.85 (t, 1H), 3.45 (t, 1H), 2.91 (s, 3H).

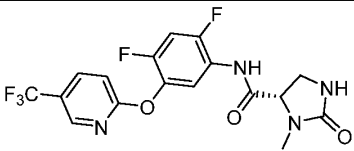
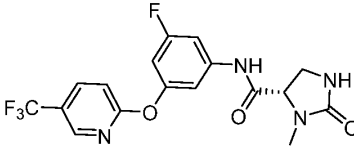
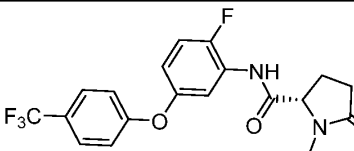
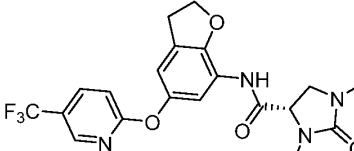
	and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	LCMS: m/z 392.2 $[M+H]^+$
341	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)-phenoxy)aniline and 2-(1,3-Dimethyl-2,5-dioxoimidazolidin-4-yl)acetic acid	^1H NMR (400 MHz, CDCl_3): δ 8.16 (d, 1H), 7.99 (s, 1H), 7.49-7.58 (m, 2H), 6.94-7.03 (m, 2H), 6.88 (d, 1H), 6.77 (dd, 1H), 4.34 (dd, 1H), 3.91 (s, 3H), 3.06 (dd, 1H), 3.04 (s, 3H), 2.98 (s, 3H), 2.80 (dd, 1H). LCMS: m/z 452.6 $[M+H]^+$
342	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)-phenoxy)aniline and (S)-3-Acetyl-1-methyl-2-oxoimidazolidine-4-carboxylic acid	^1H NMR (400 MHz, CDCl_3) δ : 9.06 (s, 1H), 8.14 (d, 1H), 7.47-7.58 (m, 2H), 6.93-7.04 (m, 2H), 6.88 (d, 1H), 6.78 (dd, 1H), 4.94 (dd, 1H), 3.92 (s, 3H), 3.87-3.98 (m, 1H), 3.56 (t, 1H), 2.91 (s, 3H), 2.59 (s, 3H). LCMS: m/z 452.5 $[M+H]^+$
343	 Starting materials: 5-((3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyaniline and (S)-3-Acetyl-1-methyl-2-oxoimidazolidine-4-carboxylic acid	^1H NMR (400 MHz, CDCl_3) δ : 9.07 (s, 1H), 8.24 (d, 1H), 8.14-8.18 (m, 1H), 7.65 (dd, 1H), 6.88-6.95 (m, 2H), 4.95 (dd, 1H), 3.93 (s, 3H), 3.90-3.95 (m, 1H), 3.56 (t, 1H), 2.91 (s, 3H), 2.58 (s, 3H). LCMS: m/z 471.4 $[M+H]^+$
344	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)aniline and (S)-3-Acetyl-1-methyl-2-oxoimidazolidine-4-carboxylic acid	^1H NMR (600 MHz, CDCl_3) δ : 8.40-8.43 (m, 1H), 8.26 (d, 1H), 7.92 (s, 1H), 7.88 (dd, 1H), 7.00 (d, 1H), 6.92 (d, 1H), 6.88 (dd, 1H), 5.89 (s, 1H), 3.92 (s, 3H), 3.70 (dd, 1H), 3.64 (t, 1H), 3.35-3.42 (m, 1H), 2.75 (dd,

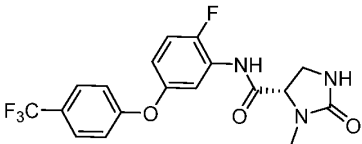
	(trifluoromethyl)pyridin-2-yl)oxy)-aniline and 5-Oxopyrrolidine-3-carboxylic acid	¹ H), 2.60 (dd, 1H). LCMS: <i>m/z</i> 396.7 [M+H] ⁺
345	 Starting materials: 5-((3-Chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyaniline and (<i>S</i>)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	¹ H NMR (600 MHz, CDCl ₃) δ: 8.62 (s, 1H), 8.24-8.29 (m, 2H), 7.97 (d, 1H), 6.95 (d, 1H), 6.92 (dd, 1H), 5.09 (s, 1H), 4.13 (dd, 1H), 3.93 (s, 3H), 3.85 (t, 1H), 3.44 (dd, 1H), 2.92 (s, 3H). LCMS: <i>m/z</i> 445.5 [M+H] ⁺
346	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and (<i>S</i>)-1,3-Dimethyl-2-oxoimidazolidine-4-carboxylic acid	¹ H NMR (600 MHz, CDCl ₃) δ: 8.67 (s, 1H), 8.40-8.44 (m, 1H), 8.25 (d, 1H), 7.88 (dd, 1H), 7.02 (d, 1H), 6.93 (d, 1H), 6.90 (dd, 1H), 3.96 (dd, 1H), 3.92 (s, 3H), 3.76 (t, 1H), 3.30 (dd, 1H), 2.91 (s, 3H), 2.85 (s, 3H). LCMS: <i>m/z</i> 425.8 [M+H] ⁺
347	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (2-Methoxyacetyl)-<i>D</i>-proline	¹ H NMR (600 MHz, d ₆ -DMSO) δ: 9.45 (s, 1H), 7.92 (d, 1H), 7.67-7.73 (m, 2H), 7.12 (d, 1H), 7.05-7.09 (m, 2H), 6.87 (dd, 1H), 4.69 (dd, 1H), 4.03-4.10 (m, 2H), 3.87 (s, 3H), 3.41-3.52 (m, 2H), 3.30 (s, 3H), 1.97-2.07 (m, 1H), 1.83-1.97 (m, 3H). LCMS: <i>m/z</i> 453.8 [M+H] ⁺
348	 Starting materials: 5-(3-Chlorophenoxy)-2-methoxyaniline and (<i>S</i>)-3-	¹ H NMR (600 MHz, d ₆ -DMSO) δ: 9.47 (s, 1H), 7.85 (d, 1H), 7.37 (t, 1H), 7.14 (ddd, 1H), 7.12 (d, 1H), 6.97 (t, 1H), 6.91 (ddd, 1H), 6.87 (dd, 1H), 6.46 (s, 1H), 4.38 (dd, 1H), 3.87 (s, 3H), 3.53 (t, 1H), 3.17 (ddd,

	Methyl-2-oxoimidazolidine-4-carboxylic acid	¹ H), 2.62 (s, 3H). LCMS: <i>m/z</i> 376.2 [M+H] ⁺
349	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)-phenoxy)aniline and 1-Methyl-5-oxopyrrolidine-3-carboxylic acid	¹ H NMR (600 MHz, d ₆ -DMSO) δ: 9.52 (s, 1H), 7.87 (d, 1H), 7.69-7.72 (m, 2H), 7.12 (d, 1H), 7.05-7.09 (m, 2H), 6.90 (d, 1H), 3.88 (s, 3H), 3.50-3.59 (m, 2H), 3.37-3.42 (m, 1H), 2.70 (s, 3H), 2.38-2.44 (m, 1H), 2.45-2.5 (m, 1H). LCMS: <i>m/z</i> 409.5 [M+H] ⁺
350	 Starting materials: 5-(2-Chloro-4-(trifluoromethyl)phenoxy)-2-methoxyaniline and 5-Oxopyrrolidine-2-carboxylic acid	¹ H NMR (600 MHz, d ₆ -DMSO) δ: 9.39 (s, 1H), 8.00 (d, 1H), 7.89-7.93 (m, 2H), 7.65-7.69 (m, 1H), 7.15 (d, 1H), 6.99 (d, 1H), 6.92 (dd, 1H), 4.39 (dd, 1H), 3.88 (s, 3H), 2.28-2.36 (m, 1H), 2.15-2.23 (m, 1H), 2.07-2.14 (m, 1H), 1.92-1.99 (m, 1H). LCMS: <i>m/z</i> 429.1 [M+H] ⁺
351	 Starting materials: 3-Chloro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)aniline and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	¹ H NMR (600 MHz, d ₆ -DMSO) δ: 10.42 (s, 1H), 8.60-8.63 (m, 1H), 8.28 (dd, 1H), 7.68 (t, 1H), 7.45 (t, 1H), 7.32 (d, 1H), 7.12 (d, 1H), 6.49 (s, 1H), 4.18 (dd, 1H), 3.55 (td, 1H), 3.18-3.23 (m, 1H), 2.63 (s, 3H). LCMS: <i>m/z</i> 415.3 [M+H] ⁺
352	 Starting materials: 3-Chloro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-	¹ H NMR (400 MHz, CDCl ₃) δ: 8.82 (s, 1H), 8.45 (s, 1H), 7.93 (dd, 1H), 7.55-7.62 (m, 2H), 7.06 (d, 1H), 6.95 (s, 1H), 4.14 (dd, 1H), 2.90 (s, 3H), 2.35-2.62 (m, 3H), 2.11-2.23 (m, 1H). LCMS: <i>m/z</i> 414.4 [M+H] ⁺

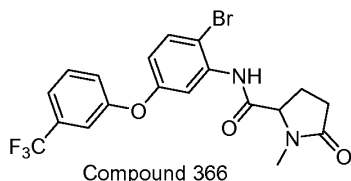
	aniline and 1-Methyl-5-oxo-pyrrolidine-2-carboxylic acid	
353	 Starting materials: 5-(4-(Fluoro-methyl)phenoxy)-2-methoxyaniline and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.57 (s, 1H), 8.15 (d, 1H), 7.28-7.37 (m, 2H), 6.92-7.02 (m, 2H), 6.87 (d, 1H), 6.78 (dd, 1H), 5.32 (d, 2H), 4.86 (s, 1H), 4.12 (dd, 1H), 3.90 (s, 3H), 3.84 (t, 1H), 3.45 (t, 1H), 2.92 (s, 3H). LCMS: <i>m/z</i> 372.4 [M+H] ⁺
354	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1-(2-Methoxy-2-oxoethyl)-5-oxo-pyrrolidine-2-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.20 (s, 1H), 8.15 (d, 1H), 7.50-7.58 (m, 2H), 6.96-7.03 (m, 2H), 6.90 (d, 1H), 6.81 (dd, 1H), 4.62 (d, 1H), 4.41-4.48 (m, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.70 (d, 1H), 2.43-2.65 (m, 3H), 2.13-2.25 (m, 1H). LCMS: <i>m/z</i> 467.5 [M+H] ⁺
355	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (S)-5-Oxopyrrolidine-3-carboxylic acid	¹ H NMR (400 MHz, CDCl ₃) δ: 8.20 (d, 1H), 7.91 (s, 1H), 7.50-7.57 (m, 2H), 6.95-7.02 (m, 2H), 6.89 (d, 1H), 6.79 (dd, 1H), 6.09 (s, 1H), 3.92 (s, 3H), 3.60-3.75 (m, 2H), 3.33-3.44 (m, 1H), 2.75 (dd, 1H), 2.61 (dd, 1H). LCMS: <i>m/z</i> 395.2 [M+H] ⁺
356	 Starting materials: 5-(4-Chloro-phenoxy)-2-methoxyaniline and (S)-3-	¹ H NMR (400 MHz, CDCl ₃) δ: 8.57 (s, 1H), 8.13 (d, 1H), 7.21-7.29 (m, 2H), 6.82-6.94 (m, 3H), 6.76 (dd, 1H), 4.96 (s, 1H), 4.12 (dd, 1H), 3.90 (s, 3H), 3.85 (t, 1H), 3.41-3.48 (m, 1H), 2.92 (s, 3H). LCMS: <i>m/z</i> 376.2

	Methyl-2-oxoimidazolidine-4-carboxylic acid	$[M+H]^+$
357	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and (<i>R</i>)-5-Oxopyrrolidine-3-carboxylic acid	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.20 (d, 1H), 7.92 (s, 1H), 7.48-7.59 (m, 2H), 6.94-7.05 (m, 2H), 6.89 (d, 1H), 6.79 (dd, 1H), 6.12 (s, 1H), 3.92 (s, 3H), 3.59-3.77 (m, 2H), 3.32-3.45 (m, 1H), 2.75 (dd, 1H), 2.61 (dd, 1H). LCMS: m/z 395.2 $[M+H]^+$
358	 Starting materials: (<i>S</i>)-N-(5-((3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)pyrrolidine-2-carboxamide and Acetic acid	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 9.51 (s, 1H), 8.27 (d, 1H), 8.13-8.19 (m, 1H), 7.64 (dd, 1H), 6.83-6.96 (m, 2H), 4.73-4.80 (m, 1H), 3.92 (s, 3H), 3.54-3.62 (m, 1H), 3.42-3.51 (m, 1H), 2.45-2.54 (m, 1H), 2.14 (s, 3H), 2.08-2.22 (m, 1H), 1.97-2.07 (m, 1H), 1.81-1.93 (m, 1H). LCMS: m/z 442.6 $[M+H]^+$
359	 Starting materials: 5-((3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyaniline and (<i>S</i>)-1,3-Dimethyl-2-oxoimidazolidine-4-carboxylic acid	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.68 (s, 1H), 8.27-8.33 (m, 1H), 8.14-8.19 (m, 1H), 7.67 (dd, 1H), 6.87-6.99 (m, 2H), 3.96 (dd, 1H), 3.92 (s, 3H), 3.76 (t, 1H), 3.30 (dd, 1H), 2.91 (s, 3H), 2.85 (s, 3H). LCMS: m/z 443.3 $[M+H]^+$
360	 Starting materials: 6-((5-(Trifluoromethyl)pyridin-2-yl)oxy)benzo[d]-	$^1\text{H NMR}$ (600 MHz, CDCl_3) δ : 8.44 (s, 1H), 8.03 (s, 1H), 7.89 (dd, 1H), 7.57 (d, 1H), 7.02 (d, 1H), 6.62 (d, 1H), 6.01-6.08 (m, 2H), 3.96 (dd, 1H), 3.77 (t, 1H), 3.30 (dd, 1H), 2.90 (s, 3H), 2.84 (s, 3H). LCMS: m/z

	[1,3]dioxol-4-amine and (S)-1,3-Dimethyl-2-oxoimidazolidine-4-carboxylic acid	439.4 [M+H] ⁺
361	 Starting materials: 2,4-Difluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	¹ H NMR (600 MHz, CDCl ₃) δ: 8.38 (s, 1H), 8.27 (t, 1H), 8.22 (s, 1H), 7.95 (dd, 1H), 7.13 (d, 1H), 7.06 (t, 1H), 5.11 (s, 1H), 4.15 (dd, 1H), 3.87 (t, 1H), 3.46 (t, 1H), 2.91 (s, 3H). LCMS: <i>m/z</i> 417.4 [M+H] ⁺
362	 Starting materials: 3-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)aniline and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	¹ H NMR (600 MHz, CDCl ₃) δ: 8.93 (s, 1H), 8.45 (s, 1H), 7.94 (dd, 1H), 7.42-7.50 (m, 1H), 7.39 (s, 1H), 7.06 (d, 1H), 6.65-6.73 (m, 1H), 5.12 (s, 1H), 4.14 (dd, 1H), 3.83 (t, 1H), 3.42 (t, 1H), 2.86 (s, 3H). LCMS: <i>m/z</i> 399.4 [M+H] ⁺
363	 Starting materials: 2-Fluoro-5-(4-(trifluoromethyl)phenoxy)aniline and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	¹ H NMR (600 MHz, CDCl ₃) δ: 8.10 (d, 1H), 7.77 (s, 1H), 7.55-7.61 (m, 2H), 7.14 (dd, 1H), 7.00-7.06 (m, 2H), 6.80 (ddd, 1H), 4.14 (dd, 1H), 2.93 (s, 3H), 2.54-2.62 (m, 1H), 2.39-2.54 (m, 2H), 2.11-2.19 (m, 1H). LCMS: <i>m/z</i> 397.4 [M+H] ⁺
364	 Starting materials: 5-((5-(Trifluoro-	¹ H NMR (400 MHz, CDCl ₃) δ: 8.40-8.45 (m, 1H), 8.14 (s, 1H), 7.92 (d, 1H), 7.88 (dd, 1H), 7.01 (d, 1H), 6.77-6.83 (m, 1H), 4.61-4.72 (m, 2H), 3.95 (dd, 1H), 3.76 (t, 1H),

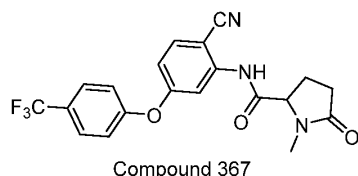
	methylpyridin-2-yl)oxy)-2,3-dihydro-benzofuran-7-amine and (S)-1,3-Di-methyl-2-oxoimidazolidine-4-carboxylic acid	3.23-3.34 (m, 3H), 2.90 (s, 3H), 2.84 (s, 3H). LCMS: m/z 437.4 $[M+H]^+$
365	 Starting materials: 3-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	^1H NMR (400 MHz, CDCl_3) δ : 8.27 (s, 1H), 8.09 (dd, 1H), 7.53-7.63 (m, 2H), 7.14 (t, 1H), 6.99-7.08 (m, 2H), 6.76-6.86 (m, 1H), 5.08 (s, 1H), 4.15 (dd, 1H), 3.87 (t, 1H), 3.42-3.51 (m, 1H), 2.92 (s, 3H). LCMS: m/z 398.3 $[M+H]^+$

Example 15. *N*-(2-Bromo-5-(3-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 366)



- 5 To a cooled (0-5 °C) mixture of 1-methyl-5-oxopyrrolidine-2-carboxylic acid (0.067 g, 0.468 mmol) in dry DCM (1.5 ml) was added 1-chloro-*N,N*,2-trimethyl-1-propenylamine (0.065 ml, 0.488 mmol) and the mixture was stirred at 0-5 °C for 1 h. Then 2-bromo-5-(3-(trifluoromethyl)phenoxy)aniline (0.18 g, 0.390 mmol) dissolved in dry DMF (0.5 ml) and DIPEA (0.34 ml, 1.951 mmol) were added and the mixture was
- 10 stirred at RT overnight. DCM was evaporated and the mixture diluted with EtOAc. Organic phase was washed with water and brine, dried and evaporated. Crude product was purified by reverse phase flash chromatography to afford the title compound. Yield: 0.019 g. ^1H NMR (600 MHz, d_6 -DMSO) δ : 9.88 (s, 1H), 7.72 (d, 1H), 7.65 (t, 1H), 7.51-7.55 (m, 1H), 7.42 (d, 1H), 7.36-7.39 (m, 1H), 7.34 (dd, 1H), 6.93 (dd, 1H), 4.31-
- 15 4.38 (m, 1H), 2.70 (s, 3H), 2.17-2.35 (m, 3H), 1.94-2.02 (m, 1H). LCMS: m/z 457.1 $[M+H]^+$.

Example 16. *N*-(2-Cyano-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 367)

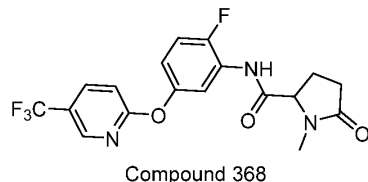


The compound was prepared according to the procedure of the preceding

5 Example starting from 1-methyl-5-oxopyrrolidine-2-carboxylic acid (0.051 g, 0.359 mmol), DCM (1.5 ml), 1-chloro-*N,N*,2-trimethyl-1-propenylamine (0.057 ml, 0.431 mmol), 2-amino-4-(4-(trifluoromethyl)phenoxy)benzonitrile (0.10 g, 0.359 mmol) and DMF (0.75 ml). Yield: 0.022 g. ¹H NMR (600 MHz, d₆-DMSO) δ: 10.5 (s, 1H), 7.90 (d, 1H), 7.81-7.86 (m, 2H), 7.31-7.37 (m, 2H), 7.30 (d, 1H), 7.08 (dd, 1H), 4.30 (dd, 1H),

10 2.70 (s, 3H), 2.19-2.36 (m, 3H), 1.94-2.01 (m, 1H). LCMS: *m/z* 404.4 [M+H]⁺.

Example 17. *N*-(2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 368)

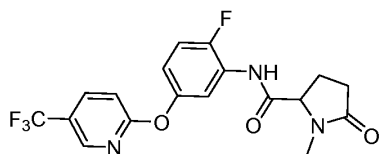


15 The compound was prepared using the procedure of Intermediate 306 starting from *N*-(2-fluoro-5-hydroxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (0.071 g, 0.28 mmol), 2-chloro-5-(trifluoromethyl)pyridine (0.051 g, 0.28 mmol) and K₂CO₃ (0.058 g, 0.42 mmol) in dry DMF (1.0 ml). Crude was purified by reverse phase flash chromatography to afford the title compound. Yield: 0.078 g. ¹H NMR (600 MHz,

20 CDCl₃) δ: 8.40-8.43 (m, 1H), 8.21 (dd, 1H), 7.92 (dd, 1H), 7.79 (s, 1H), 7.18 (dd, 1H), 7.05 (d, 1H), 6.91 (dq, 1H), 4.15 (dd, 1H), 2.93 (s, 3H), 2.54-2.62 (m, 1H), 2.39-2.53 (m, 2H), 2.11-2.18 (m, 1H). LCMS: *m/z* 398.6 [M+H]⁺.

Example 18. *N*-(2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 369)

25

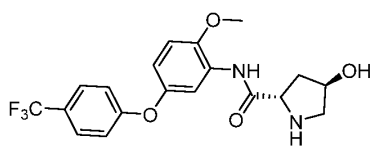


Compound 369

The compound was prepared using the procedure of Intermediate 339 starting from *N*-(2-fluoro-5-hydroxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (0.071 g, 0.28 mmol), 2-chloro-5-(trifluoromethyl)pyridine (0.051 g, 0.28 mmol) and K₂CO₃ (0.058 g, 0.42 mmol) in dry DMF (1.0 ml). Crude was purified by reverse phase flash chromatography to afford the title compound. Yield: 0.078 g. ¹H NMR (600 MHz, CDCl₃): δ 8.40-8.43 (m, 1H), 8.21 (dd, 1H), 7.92 (dd, 1H), 7.79 (s, 1H), 7.18 (dd, 1H), 7.05 (d, 1H), 6.91 (dq, 1H), 4.15 (dd, 1H), 2.93 (s, 3H), 2.54-2.62 (m, 1H), 2.39-2.53 (m, 2H), 2.11-2.18 (m, 1H). LCMS: *m/z* 398.6 [M+H]⁺.

10

Example 19. (2*S*,4*R*)-4-Hydroxy-*N*-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)pyrrolidine-2-carboxamide (Compound 370)

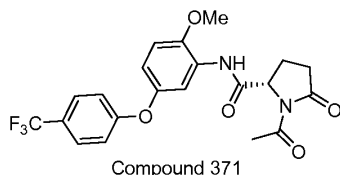


Compound 370

To a mixture of palladium (10 wt-% on carbon, 0.045 g, 0.042 mmol) in methanol (15 ml) was added benzyl (2*S*,4*R*)-4-hydroxy-2-((2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)carbamoyl)pyrrolidine-1-carboxylate (0.111 g, 0.209 mmol) dissolved in methanol (2.0 ml). The mixture was stirred vigorously while ammonium formate (0.132 mg, 2.09 mmol) was added. Stirring was continued at 50 °C until reaction was completed. Cooled mixture was filtered through a short plug of Celite. Celite was washed with methanol. Filtrate was evaporated and re-dissolved in EtOAc. Organic phase was washed with water and brine, dried and evaporated. Crude product was purified by reverse phase flash chromatography to afford the title compound. Yield: 0.041 g. ¹H NMR (600 MHz, d₆-DMSO) δ: 10.3 (s, 1H), 8.13 (d, 1H), 7.68-7.73 (m, 2H), 7.13 (d, 1H), 7.05-7.10 (m, 2H), 6.85 (dd, 1H), 4.71 (d, 1H), 4.16-4.20 (m, 1H), 3.89 (s, 3H), 3.87-3.93 (m, 1H), 3.48 (bs, 1H), 2.88 (d, 1H), 2.74 (d, 1H), 1.99-2.06 (m, 1H), 1.72-1.79 (m, 1H). LCMS: *m/z* 397.6 [M+H]⁺.

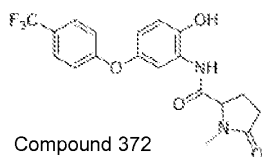
25

Example 20. (*S*)-1-Acetyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)-phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 371)



5 To a cooled (0-5 °C) solution of (*S*)-N-(2-methoxy-5-(4-(trifluoromethyl)-phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (0.086 g, 0.225 mmol) in dry DCM (2.0 ml) was added acetyl chloride (0.018 ml, 0.248 mmol) dissolved in dry DCM (0.25 ml) and triethylamine (0.039 ml, 0.281 mmol) and the mixture was stirred overnight at RT. More acetyl chloride (0.018 ml, 0.248 mmol) and triethylamine (0.039 ml, 0.281
10 mmol) were added and stirring continued until the reaction was completed. The mixture was diluted with DCM and washed with water, saturated NaHCO₃-solution and brine, dried and evaporated. Crude product was purified by reverse phase flash chromatography to afford the title compound. Yield: 0.072 g. ¹H NMR (400 MHz, CDCl₃) δ: 9.44 (s, 1H), 8.18 (s, 1H), 7.43-7.60 (m, 2H), 6.91-7.07 (m, 2H), 6.86 (d, 1H), 6.74 (d, 1H), 4.75 (d, 1H), 3.91 (s, 3H), 3.59 (t, 1H), 3.47 (dd, 1H), 2.41-2.55 (m, 1H), 2.15 (s, 3H), 1.81-2.22. (m, 3H). LCMS: *m/z* 423.6 [M+H]⁺.

Example 21. N-(2-Hydroxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 372)

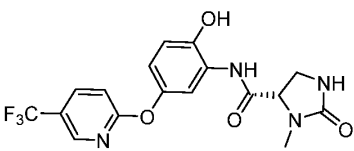


20 To a solution of Compound 48 (100 mg, 245 μmol) in DCM (5 ml) was added tetrabutyl ammonium iodide (90 mg, 245 μmol) at RT. The solution was cooled to -50 °C. Then BCl₃ 1 M in heptane (1.469 ml, 1469 μmol) was added dropwise. The mixture was stirred for 10 min at -78 °C and then 1 h 20 min at RT. The mixture was diluted
25 with DCM (10 ml) and poured into ice cold 1 N HCl (5 ml). Phases were separated. The aqueous phase was extracted twice with DCM. The combined organic phases were concentrated under reduced pressure. The crude product was purified by column

chromatography to afford the title compound (0.055 g). ^1H NMR (400MHz, DMSO) δ : 10.06 (br s 1H), 9.57 (s, 1H), 7.79 (d, 1H), 7.69 (d, 2H), 7.05 (d, 2H), 6.94 (d, 1H), 6.80-6.75 (m, 1H), 4.50-4.42 (m, 1H), 2.65 (s, 3H), 2.31-2.12 (m, 3H), 1.95-1.84 (m, 1H). LCMS: m/z 395.4 $[\text{M}+\text{H}]^+$

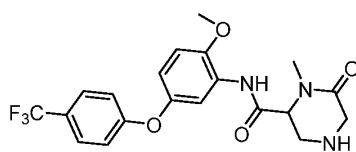
5

The following compound was prepared according to the procedure described for Compound 372. The compound code, structure, starting materials, purification method and characterization data are indicated in the table.

No	Structure and starting material	Purification method and characterization data
373	 Starting materials: (S)-N-(2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide	^1H NMR (400 MHz, DMSO- d_6) δ : 2.64 (3 H, s), 3.14 - 3.20 (1 H, m), 3.55 (1 H, t), 4.33 - 4.40 (1 H, m), 6.49 (1 H, br s), 6.78 - 6.83 (1 H, m), 6.93 (1 H, d), 7.14 - 7.18 (1 H, m), 7.83 (1 H, d), 8.17 - 8.21 (1 H, m), 8.53 - 8.56 (1 H, m), 9.39 (1 H, br s), 10.14 (1 H, br s). LCMS: m/z 397.5 $[\text{M}+\text{H}]^+$

10

Example 22. N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-6-oxopiperazine-2-carboxamide (Compound 374)



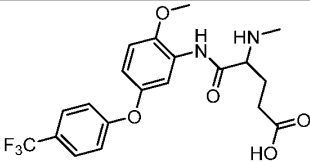
Compound 374

tert-Butyl 3-((2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)carbamoyl)-4-methyl-5-oxopiperazine-1-carboxylate (30.6 mg, 58.5 μmol) was dissolved in HCl (dioxane solution) (2.13 g, 1.43 mL, 10 w-%, 5.85 mmol) and stirred at RT overnight. The mixture was purified by HPLC (Method D) to afford 12.9 mg of the title compound (12.9 mg, 30.5 μmol , 52.1 %, 100 % purity). ^1H NMR (400 MHz, DMSO- d_6) δ : 9.93 (s,

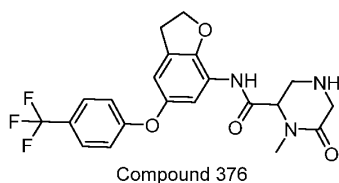
15

1H), 7.92 (d, 1H), 7.71 (d, 2H), 7.10 (dd, 3H), 6.91 (dd, 1H), 4.20 (s, 1H), 3.88 (d, 3H), 3.26 (s, 2H), 3.13 (s, 2H), 2.77 (s, 3H). LCMS: m/z 424.2 $[M+H]^+$.

- The following compounds were prepared according to the procedure described for Compound 374. The compound code, structure, starting materials, purification method and characterization data are indicated in the table.

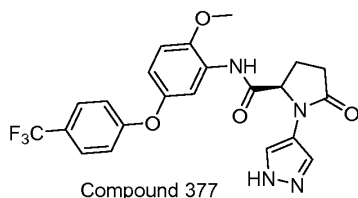
No	Structure and starting material	Purification method and characterization data
375	 Starting materials: tert-Butyl 4-((tert-butoxycarbonyl)amino)-5-((2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)amino)-5-oxopentanoate	Purification method D. ^1H NMR (400 MHz, DMSO-d_6) δ: 8.11–8.01 (m, 1H), 7.71 (d, 2H), 7.13 (d, 1H), 7.09 (d, 2H), 6.91–6.81 (m, 1H), 3.89 (s, 3H), 3.06–2.99 (m, 1H), 2.35–2.30 (m, 3H), 2.27 (s, 3H), 1.90–1.68 (m, 1H). LCMS: m/z 427.2 $[M+H]^+$

- Example 23.** 1-Methyl-6-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydro-benzofuran-7-yl)piperazine-2-carboxamide (Compound 376)



- Tert-butyl 4-methyl-3-oxo-5-((5-(4-(trifluoromethyl)phenoxy)-2,3-dihydro-benzofuran-7-yl)carbamoyl)piperazine-1-carboxylate (0.0416 g, 1 eq., 77.7 μmol) was dissolved in methanol (3 mL). TMS-Cl (42.2 mg, 49.3 μL , 5 eq., 388 μmol) was added dropwise. The mixture was stirred at 25 $^{\circ}\text{C}$ for 16 h and then concentrated under reduced pressure. The obtained mixture was subjected to HPLC (purification method D) to give the title compound (0.01 g, 0.02 mmol, 30 %, 95 % purity). ^1H NMR (400 MHz, DMSO- d_6) δ : 7.70 (d, 2H), 7.60 (s, 1H), 7.07 (d, 2H), 6.86 (s, 1H), 4.65 (t, 2H), 4.20 (t, 1H), 3.29 – 3.20 (m, 4H), 3.18 – 3.02 (m, 2H), 2.74 (s, 3H). LCMS: m/z 436.2 $[M+H]^+$.

Example 24. (R)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-1-(1H-pyrazol-4-yl)pyrrolidine-2-carboxamide (Compound 377)

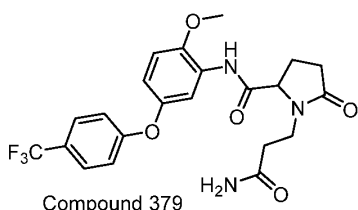


- 5 TFA (335 mg, 226 μ L, 50 eq., 2.94 mmol) was added to (R)-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-(1-(4-methoxybenzyl)-1H-pyrazol-4-yl)-5-oxopyrrolidine-2-carboxamide (0.0341 g, 1 eq., 58.7 μ mol) followed by refluxing the mixture for 16 h. Then the solvent was evaporated and the residue was purified by HPLC (Method G) to give the title compound (0.0057 g, 12 μ mol, 21 %, 100 % purity).
- 10 ^1H NMR (400 MHz, Acetonitrile- d_3) δ : 8.62 (s, 1H), 8.01 (d, 1H), 7.79 (s, 2H), 7.66 (d, 2H), 7.07 (dd, 3H), 6.88 (dd, 1H), 4.75 (dd, 1H), 3.92 (s, 3H), 2.66 – 2.36 (m, 4H), 2.23 – 2.13 (m, 2H). LCMS: m/z 459.1 [M-H].

- The following compounds were prepared according to the procedure described
- 15 for Compound 377. The compound code, structure, starting materials, purification method and characterization data are indicated in the table.

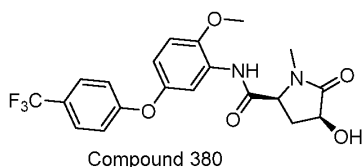
No	Structure and starting material	Purification method and characterization data
378	Starting materials: (R)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-(1-(4-methoxybenzyl)-1H-pyrazol-4-yl)-5-oxopyrrolidine-2-carboxamide	Purification method G. ^1H NMR (500 MHz, Acetonitrile-d_3) δ: 8.58 (s, 1H), 7.99 (d, 1H), 7.77 (s, 2H), 7.65 (d, 2H), 7.06 (dd, 3H), 6.86 (dd, 1H), 4.73 (dd, 1H), 3.90 (s, 3H), 2.64–2.33 (m, 4H). LCMS: m/z 461.0 [M+H]$^+$

Example 25. 1-(3-Amino-3-oxopropyl)-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 379)



To a solution of 1-(2-cyanoethyl)-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (158 mg, 1 eq., 353 μmol) in DMSO (2 mL) potassium carbonate (97.6 mg, 2 eq., 706 μmol) followed by hydrogen peroxide (343 mg, 309 μL , 35 w-%, 10 eq., 3.53 mmol) was added. The mixture was stirred at 40 °C for 36 h. Water (20 mL) was added to the residue and the resulted mixture was extracted with ethyl acetate (2×20 mL). Organic layers were combined, washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by reverse phase HPLC (purification method B) to afford the title compound (13.4 mg, 28.8 μmol , 8.15 %, 100 % purity) ^1H NMR (400 MHz, DMSO-*d*₆) δ : 9.64 (s, 1H), 7.89 (s, 1H), 7.70 (d, 2H), 7.36 (s, 1H), 7.19 – 7.05 (m, 3H), 6.92 (d, 1H), 6.82 (s, 1H), 4.63 – 4.55 (m, 1H), 3.88 (s, 3H), 3.64 – 3.51 (m, 1H), 3.20 – 2.96 (m, 2H), 2.31 – 2.12 (m, 4H), 1.96 – 1.85 (m, 1H). LCMS: *m/z* 466.2 [M+H]⁺.

Example 26. (2S,4S)-4-Hydroxy-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 380)

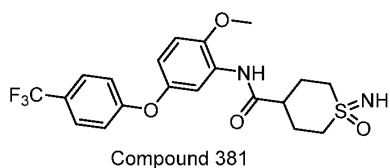


(2S,4S)-4-((tert-Butyldimethylsilyl)oxy)-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (0.185 g, 1 eq., 343 μmol) was dissolved in THF (2 mL). Then TBAF (89.8 mg, 343 μL , 1 molar, 1 eq., 343 μmol) was added to the mixture dropwise at 0 °C. The resulting mixture was stirred for 20 min and slowly heated to 20 °C, stirred at this temperature for 10 h and purified

by HPLC (purification method A) to give the title compound (0.0374 g, 88.1 μmol , 25.7 %, 100 % purity). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ : 9.68 (s, 1H), 7.87 (s, 1H), 7.71 (d, 2H), 7.14 (d, 1H), 7.08 (d, 2H), 6.96 – 6.88 (m, 1H), 4.31 (t, 1H), 4.12 (t, 1H), 3.88 (s, 3H), 2.67 (s, 3H), 2.65 – 2.57 (m, 1H), 1.74 – 1.57 (m, 1H). LCMS: m/z 425.0 $[\text{M}+\text{H}]^+$.

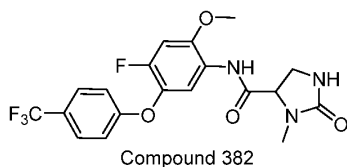
5

Example 27. 1-Imino-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-hexahydro-1 λ^6 -thiopyran-4-carboxamide 1-oxide (Compound 381)



A mixture of N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)tetrahydro-
 10 2H-thiopyran-4-carboxamide 1-oxide (250 mg, 1 eq., 585 μmol), phenyl- λ^3 -iodanediyl diacetate (565 mg, 3 eq., 1.75 mmol) and carbamic acid, ammonia salt (183 mg, 4 eq., 2.34 mmol) in methanol (12 mL) was stirred at 22 °C for 12 h. The mixture was concentrated to provide a mixture of a light yellow sludge and an immiscible colorless liquid. The mixture was washed twice with hexane (2 $\times$ 10 mL) by decantation and dried
 15 under vacuum. The residue was triturated and stirred in ethyl acetate, filtered, and the collected solid was washed with additional ethyl acetate. The filtrate was concentrated to provide a mixture of cis and trans isomers and purified by HPLC (purification method A) to give the title compound (30.5 mg, 65 μmol , 11 %, 95 % purity). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ : 9.34 (d, 1H), 7.87 (t, 1H), 7.70 (d, 2H), 7.09 (dd, 3H), 6.88
 20 (dd, 1H), 3.87 (s, 3H), 3.70 (s, 0H), 3.48 (s, 1H), 3.16 – 2.79 (m, 4H), 2.16 – 1.92 (m, 4H). LCMS: m/z 443.1 $[\text{M}+\text{H}]^+$.

Example 28. N-(4-Fluoro-2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 382)

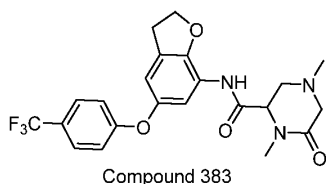


25

N-(5-(2-Chloro-4-(trifluoromethyl)phenoxy)-4-fluoro-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (0.032 g, 1 eq., 69 μmol) was dissolved in

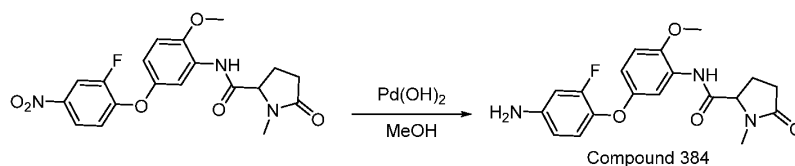
methanol (5 mL). Formic acid, ammonia salt (26 mg, 6 eq., 0.42 mmol) and palladium (7.4 mg, 10 w-%, 0.1 eq., 6.9 μmol) were added. The resulting mixture was stirred at 60 °C for 12 h, cooled to RT and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in DMSO (2 mL) and to the obtained solution metal scavenger (SiliaMetS Dimercaptotriazine, 50 mg) was added. The mixture was stirred at RT for 3 h and filtered. The clear filtrate was purified by HPLC (purification method B) to give the title compound (0.0038 g, 8.4 μmol , 12 %, 95 % purity). ^1H NMR (400 MHz, DMSO-*d*₆) δ : 9.55 (s, 1H), 7.95 (d, 1H), 7.72 (d, 2H), 7.29 (d, 1H), 7.10 (d, 2H), 6.44 (s, 1H), 4.49 – 4.26 (m, 1H), 3.89 (s, 3H), 3.52 (t, 1H), 3.16 (t, 1H), 2.61 (s, 3H). LCMS: m/z 428.0 $[\text{M}+\text{H}]^+$

Example 29. 1,4-Dimethyl-6-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)piperazine-2-carboxamide (Compound 383)



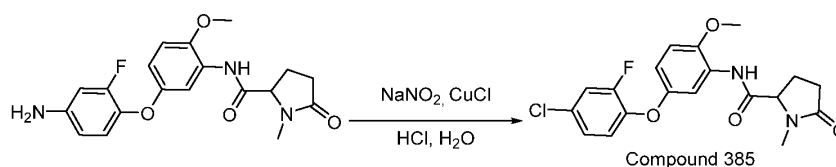
To a solution of 1-methyl-6-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)piperazine-2-carboxamide (0.022 g, 1 eq., 51 μmol) in 1,4-dioxane (2 mL) was added NaCNBH_4 (6.4 mg, 2 eq., 0.10 mmol) and water solution of formaldehyde (8.2 mg, 7.5 μL , 37 w-%, 2 eq., 0.10 mmol). Thereafter HOAc (0.01 mL) was added and the mixture was stirred at 25 °C for 12 h and evaporated. The residue was dissolved in DMSO (2 mL) and the metal scavenger (SiliaMetS Dimercaptotriazine, 10 mg) was added. The obtained mixture was stirred at RT for 3 h, filtered and the clear solution was purified by HPLC (purification method A) to afford the title compound (0.0052 g, 11 μmol , 22 %, 95 % purity). ^1H NMR (500 MHz, DMSO-*d*₆) δ : 9.97 (s, 1H), 7.68 (d, 2H), 7.57 (s, 1H), 7.05 (d, 2H), 6.84 (s, 1H), 4.63 (t, 2H), 4.20 (t, 1H), 3.23 (t, 2H), 3.12 (d, 1H), 2.93 (dd, 1H), 2.82 – 2.64 (m, 5H), 2.17 (s, 3H). LCMS: m/z 450.2 $[\text{M}+\text{H}]^+$

Example 30. N-(5-(4-Amino-2-fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 384)



N-(5-(2-Fluoro-4-nitrophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (0.080 g, 1 eq., 0.20 mmol) was dissolved in MeOH and dihydroxy-palladium (28 mg, 10 w-%, 0.1 eq., 20 μ mol) was added. The resulting mixture was stirred under hydrogen atmosphere for 16 h, filtered and concentrated to give the title compound (0.065 g, 0.16 mmol, 79 %, 90 % purity). LCMS: m/z 393.0 $[M+H]^+$

Example 31. N-(5-(4-Chloro-2-fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 385)

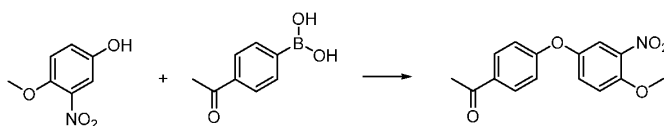


To a solution of N-(5-(4-amino-2-fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (0.056 g, 1 eq., 0.15 mmol) in hydrochloric acid, 22 % (0.5 mL) solution of sodium nitrite (12 mg, 1.2 eq., 0.18 mmol) in water (0.1 mL) was added at 0 °C. The resulting mixture was stirred at the same temperature for 15 min, then the mixture was poured into solution of copper(I) chloride (21 mg, 1.4 eq., 0.21 mmol) in 37 % hydrochloric acid (2 mL) at 0 °C. The resulting mixture was stirred at 22 °C for 10 h. The mixture was concentrated under reduced pressure and purified by HPLC (purification method A) to give the title compound (0.0181 g, 46.1 μ mol, 31 %, 100 % purity). 1H NMR (400 MHz, DMSO- d_6) δ : 9.61 (s, 1H), 7.83 (d, 1H), 7.69 – 7.53 (m, 1H), 7.26 (d, 1H), 7.06 (t, 2H), 6.88 – 6.70 (m, 1H), 4.55 – 4.39 (m, 1H), 3.85 (s, 3H), 2.64 (s, 3H), 2.41 – 2.11 (m, 3H), 1.95 – 1.74 (m, 1H). LCMS: m/z 393.0 $[M+H]^+$.

Example 32. N-(5-(3-Acetylphenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 386)

a) 1-(4-(4-Methoxy-3-nitrophenoxy)phenyl)ethan-1-one

250



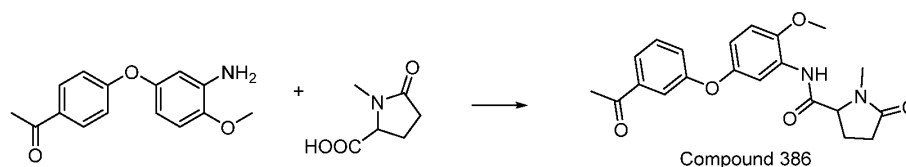
4-Acetylphenylboronic acid (0.33 g, 1.99 mmol), 4-methoxy-3-nitrophenol (0.28 g, 1.66 mmol), $\text{Cu}(\text{OAc})_2$ (0.451 mg, 2.48 mmol) and freshly activated powdered 4 Å molecular sieves were added to dry DCM (20 mL). Et_3N (1.15 mL, 8.28 mmol) was then added to the mixture. The mixture was stirred under air atmosphere. Reaction progress was monitored by LCMS. After 24 h, the resulting slurry was filtered through celite and concentrated. The crude product was purified by flash column chromatography (heptane: EtOAc) to yield 0.3 g of the title compound. LCMS: m/z 288.21 $[\text{M}+\text{H}]^+$.

b) 1-(4-(3-Amino-4-methoxyphenoxy)phenyl)ethan-1-one



A mixture of 1-(4-(4-methoxy-3-nitrophenoxy)phenyl)ethan-1-one (300 mg, 1.04 mmol), zinc (0.68 g, 10 eq., 10.44 mmol), ammonium chloride (0.56 g, 10 eq., 10.44 mmol) in THF (5 ml), MeOH (3 ml) and water (3 ml) was stirred at RT for 4 h. The mixture was filtered through celite. The filtrate was washed with water (2×30 mL), dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography to afford (0.19 g) of the title compound. LCMS: m/z 258.65 $[\text{M}+\text{H}]^+$.

c) N-(5-(4-Acetylphenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 386)

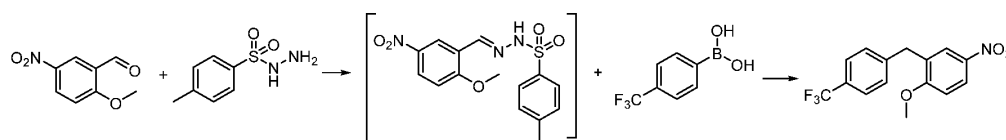


To a solution of 1-methyl-5-oxopyrrolidine-2-carboxylic acid (22.25 mg, 0.15 mmol), 1-(4-(3-amino-4-methoxyphenoxy)phenyl)ethan-1-one (40 mg, 0.16 mmol) and TEA (0.11, 0.78 mmol) in dry DMF (2 ml) at 0°C , was added 1-propanephosphonic acid cyclic anhydride (0.73 ml, 1.24 mmol). The mixture was stirred at RT overnight. The reaction mixture was quenched with water (10 ml) then extracted with ethyl acetate

(2 x 10 ml). The combined organic layers were washed with 2 M NaHCO₃, then with water, dried over sodium sulfate, evaporated and then purified by reverse phase chromatography to yield (40.5 mg) of the title compound. ¹H NMR (600 MHz, DMSO-*d*₆): δ: 1.86 - 1.92 (m, 1H), 2.16 - 2.30 (m, 3H), 2.52 - 2.54 (m, 3H), 2.61 - 2.65 (m, 3H), 3.89 (s, 3H), 4.47 (dd, 1H), 6.91 (dd, 1H), 6.98 - 7.01 (m, 2H), 7.14 (d, 1H), 7.87 (d, 1H), 7.94 - 8.02 (m, 2H), 9.65 (s, 1H). LCMS: m/z 383.28 [M+H]⁺.

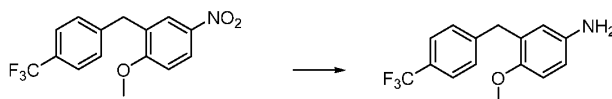
Example 33. N-(5-(3-Acetylphenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 387)

10 a) 1-Methoxy-4-nitro-2-(4-(trifluoromethyl)benzyl)benzene



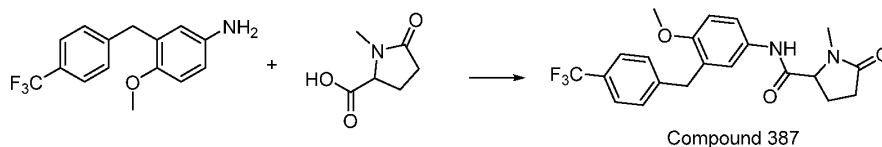
A mixture of 2-methoxy-5-nitro benzaldehyde (0.5 g, 2.8 mmol) and toluene-sulfon hydrazide (0.51 g, 2.8 mmol) in 1,4-dioxane (5 ml) was heated at 60 °C for 90 min. To the crude (E)-N'-(2-methoxy-5-nitrobenzylidene)-4-methylbenzenesulfonylhydrazide was added K₂CO₃ (0.53 g, 3.86 mmol) and 4-(trifluoromethyl)phenylboronic acid (0.49 g, 2.6 mmol). The mixture was heated under nitrogen atmosphere at 110 °C for 4 h. After cooling at RT the mixture was quenched with 2 M NaHCO₃ (5 ml). The mixture was extracted with ethyl acetate (2 x 10 ml). The combined organic layers were washed with water, dried, evaporated and then purified by flash chromatography to yield (0.35 g) of the title compound. LCMS: m/z 312.2 [M+H]⁺.

b) 4-Methoxy-3-(4-(trifluoromethyl)benzyl)aniline



A mixture of 1-methoxy-4-nitro-2-(4-(trifluoromethyl)benzyl)benzene (100 mg, 0.32 mmol), zinc (0.21 g, 10 eq., 3.21 mmol) and ammonium chloride (0.17 g, 10 eq. 3.21 mmol) in THF (10 ml), MeOH (3 ml) and water (3 ml) was stirred at RT for 4 h. The mixture was filtered through celite. The filtrate was washed with water (2 x 30 mL), dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography to afford (0.12 g) of the title compound. LCMS: m/z 282.05 [M+H]⁺.

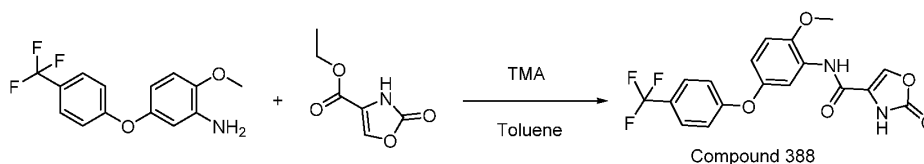
c) N-(4-Methoxy-3-(4-(trifluoromethyl)benzyl)phenyl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide (Compound 387)



To a solution of 1-methyl-5-oxopyrrolidine-2-carboxylic acid (45.8 mg, 0.32 mmol), 4-methoxy-3-(4-(trifluoromethyl)benzyl)aniline (90 mg, 0.32 mmol) and TEA (0.22, 1.60 mmol) in dry DMF (2 ml) at 0 °C was added 1-propanephosphonic acid cyclic anhydride (1.51 ml, 2.56 mmol). The mixture was stirred at RT overnight. The reaction mixture was quenched with water (10 ml) then extracted with ethyl acetate (2 x 10 ml). The combined organic layers were washed with 2 M NaHCO₃, then with water, dried over sodium sulfate, evaporated and then purified by reverse phase chromatography to yield (5 mg) of the title compound. ¹H NMR (400 MHz, Chloroform-*d*) δ: 1.75 - 2.02 (m, 1H), 2.06 - 2.22 (m, 1H), 2.31 - 2.59 (m, 3H), 2.81 - 2.91 (m, 3H), 3.79 - 3.93 (m, 3H), 3.96 - 4.10 (m, 3H), 6.85 (d, 1H), 7.25 - 7.33 (m, 4H), 7.44 - 7.57 (m, 3H), 7.84 (br s, 1H). LCMS: *m/z* 282.05 [M+H]⁺.

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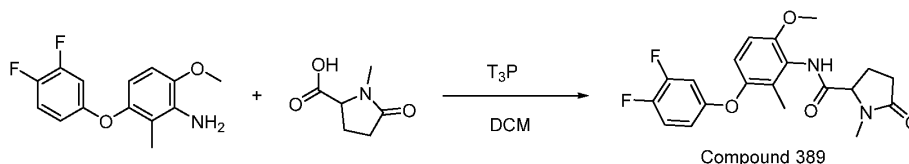
Example 34. N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-2-oxo-2,3-dihydrooxazole-4-carboxamide (Compound 388)



TMA (2 M in Chlorobenzene, 397 μL, 0.794 mmol) was added to a mixture of 2-methoxy-5-(4-(trifluoromethyl)phenoxy)aniline (0.075 g, 0.265 mmol) and ethyl-2-oxo-2,3-dihydrooxazole-4-carboxylate (0.064 g, 0.397 mmol) in toluene (2 ml) followed by heating the mixture at 90 °C for 3 h. The reaction mixture was quenched with ice cold water. The aqueous layer was extracted with EtOAc (2 x 5 ml). The combined organic layers were evaporated and then purified by reverse phase chromatography to yield 0.029 g of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.87 (3H, s), 7.00 (1H, m), 7.11 (2H, d), 7.17 (1H, d), 7.59 (1H, d), 7.72 (2H, d), 7.98 (1H, s), 9.46 (1H, s), 11.44 (1H, br s). LCMS: *m/z* 395.2 [M+H]⁺

25

Example 35. N-(3-(3,4-Difluorophenoxy)-6-methoxy-2-methylphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 389)

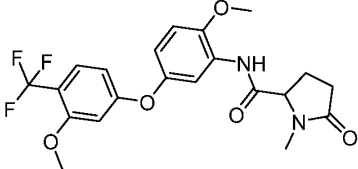
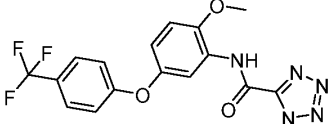
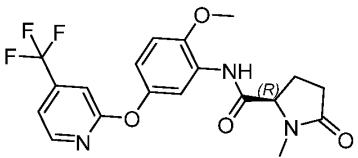
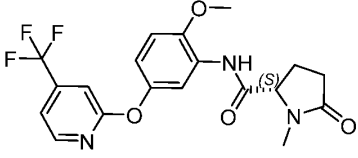


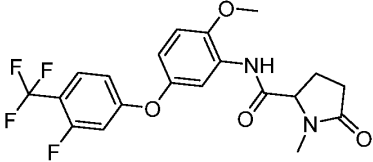
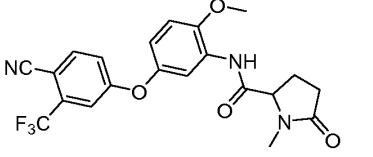
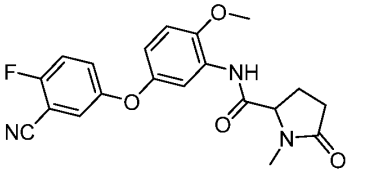
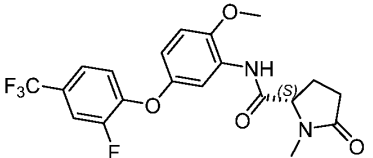
- 5 To a solution of 1-methyl-5-oxopyrrolidine-2-carboxylic acid (15 mg, 0.10 mmol), 3-(3,4-difluorophenoxy)-6-methoxy-2-methylaniline (24 mg, 0.09 mmol), T₃P (50 % in EtOAc, 80 μ l, 0.14 mmol) and DCM (2 ml) was added DIPEA (47 μ l, 0.27 mmol). After refluxing for 3 h, additional starting material and reagents were added (1-methyl-5-oxopyrrolidine-2-carboxylic acid 1.15 eq., T₃P 1.5 eq., DIPEA 3.0 eq.)
- 10 followed by stirring in a closed vessel at 80 °C for 7 h. The reaction mixture was quenched with 2N NaOH (2 ml). The organic layer was separated and the aqueous layer was extracted with EtOAc (1 x 4 ml). The combined organic layers were evaporated and then purified by reverse phase chromatography to yield 0.016 g of the title compound.
- ¹H NMR (400 MHz, DMSO-*d*₆) δ : 1.94 (3H, s), 1.94 - 2.03 (1H, m), 2.19 - 2.37 (3H, m), 2.71 (3H, s), 3.79 (3H, s), 4.26 - 4.33 (1H, m), 6.61 (1H, m), 6.90 - 7.02 (3H, m), 7.36 - 7.45 (1H, m), 9.66 (1H, s). LCMS: *m/z* 391.1 [M+H]⁺
- 15

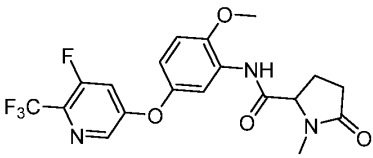
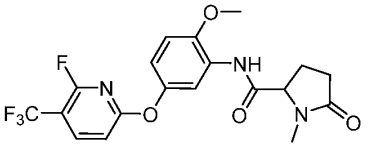
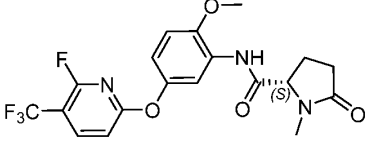
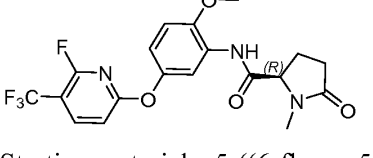
The following compounds were prepared according to the procedure described for Compound 389. The compound code, structure, starting materials, purification

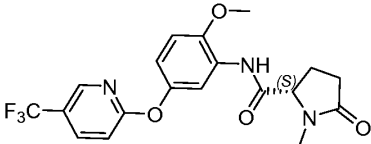
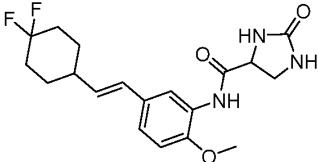
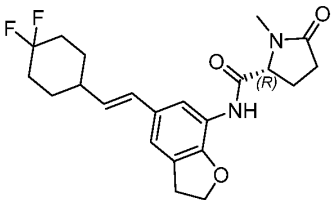
20 method and characterization data are indicated in the table.

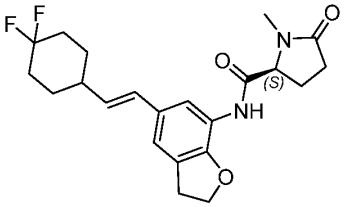
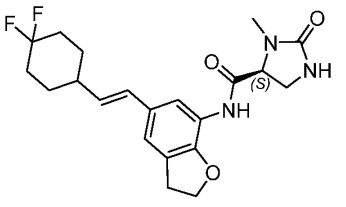
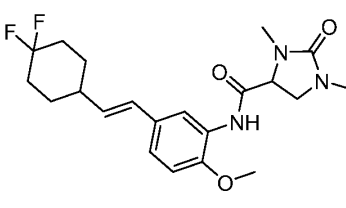
No	Structure and starting material	Purification method and characterization data
390	Starting materials: 3-(3-Amino-4-methoxyphenoxy)benzonitrile and 1-Methyl-5-oxopyrrolidine-2-	Purification method Column chromatography. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.86 - 1.92 (1H, m), 2.15 - 2.30 (3H, m), 2.64 (3H, s), 3.88 (3H, s), 4.47 (1H, m), 6.88 (1H, m), 7.12 (1H, d), 7.26 (1H, m), 7.38 (1H, m), 7.51 - 7.57 (2H, m), 7.85 (1H, d), 9.64 (1H,

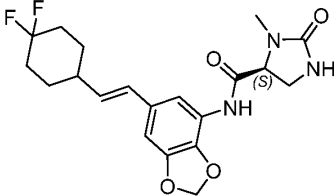
	carboxylic acid	s). LCMS: m/z 366.3 [M+H] ⁺
391	 Starting materials: 2-Methoxy-5-(3-methoxy-4-(trifluoromethyl)phenoxy)aniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.83 - 1.96 (1H, m), 2.13 - 2.34 (3H, m), 2.65 (3H, s), 3.85 (3H, s), 3.88 (3H, s), 4.43 - 4.50 (1H, m), 6.44 (1H, m), 6.88 - 6.95 (2H, m), 7.13 (1H, d), 7.54 (1H, d), 7.88 (1H, d), 9.65 (1H, s). LCMS: m/z 439.4 [M+H]⁺
392	 Starting materials: 2-Methoxy-5-(4-(trifluoromethyl)phenoxy)aniline and 1H-Tetrazole-5-carboxylic acid	Purification method Column chromatography. ¹H NMR (400 MHz, CDCl₃) δ: 3.98 (3H, s), 6.86 - 6.91 (1H, m), 6.96 (1H, d), 7.01 (2H, d), 7.54 (2H, d), 8.22 (1H, d), 9.72 (1H, s). LCMS: m/z 379.9 [M+H]⁺
393	 Starting materials: 2-Methoxy-5-((4-(trifluoromethyl)pyridin-2-yl)oxy)aniline and (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.83 - 1.96 (1H, m), 2.11 - 2.35 (3H, m), 2.65 (3H, s), 3.89 (3H, s), 4.43 - 4.51 (1H, m), 6.95 (1H, d), 7.12 (1H, d), 7.41 (1H, br s), 7.46 (1H, d), 7.87 (1H, d), 8.38 (1H, d), 9.62 (1H, s). LCMS: m/z 410.4 [M+H]⁺
394	 Starting materials: 2-Methoxy-5-((4-(trifluoromethyl)pyridin-2-yl)oxy)aniline and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.83 - 1.96 (1H, m), 2.11 - 2.35 (3H, m), 2.65 (3H, s), 3.89 (3H, s), 4.43 - 4.51 (1H, m), 6.95 (1H, m), 7.12 (1H, d), 7.41 (1H, s), 7.46 (1H, d), 7.87 (1H, d), 8.38 (1H, d), 9.62 (1H, s). LCMS: m/z 410.5 [M+H]⁺

395	 Starting material: 5-(3-Fluoro-4-(trifluoromethyl)phenoxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method: Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.85 - 1.95 (1H, m), 2.14 - 2.32 (3H, m), 2.65 (3H, s), 3.89 (4H, s), 4.44 - 4.52 (1H, m), 6.85 (1H, m), 6.97 (1H, m), 7.07 (1H, m), 7.16 (1H, d), 7.74 (1H, t), 7.90 (1H, d), 9.68 (1H, s). LCMS: m/z 427.0 [M+H]⁺
396	 Starting material: 4-(3-Amino-4-methoxyphenoxy)-2-(trifluoromethyl)benzonitrile and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method: Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.83 - 1.96 (1H, m), 2.14 - 2.36 (3H, m), 2.65 (3H, s), 3.90 (3H, s), 4.44 - 4.52 (1H, m), 7.01 (1H, m), 7.18 (1H, d), 7.26 (1H, m), 7.52 (1H, d), 7.92 (1H, d), 8.12 (1H, d), 9.71 (1H, s). LCMS: m/z 434.2 [M+H]⁺
397	 Starting material: 5-(3-Amino-4-methoxyphenoxy)-2-fluorobenzonitrile and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method: Column chromatography. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.86 - 1.92 (1H, m), 2.15 - 2.30 (3H, m), 2.64 (3H, s), 3.87 (3H, s), 4.47 (1H, m), 6.85 (1H, m), 7.11 (1H, d), 7.35 (1H, m), 7.50 (1H, d), 7.53 (1H, m), 7.84 (1H, d), 9.64 (1H, s). LCMS: m/z 384.2 [M+H]⁺
398	 Starting materials: 5-(2-Fluoro-4-(trifluoromethyl)phenoxy)-2-methoxyaniline and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method: Column chromatography. ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ: 1.86 - 1.92 (1H, m), 2.16 - 2.30 (3H, m), 2.64 (3H, s), 3.88 (3H, s), 4.47 (1H, m), 6.93 (1H, m), 7.08 (1H, t), 7.13 (1H, d), 7.54 (1H, d), 7.86 (1H, m), 7.90 (1H, d), 9.66 (1H, s). LCMS: m/z 427.4 [M+H]⁺

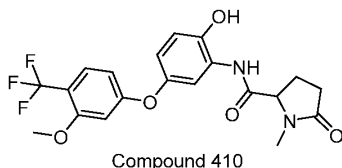
399	 Starting material: 5-(((5-Fluoro-6-(trifluoromethyl)pyridin-3-yl)oxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method: Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.83 - 1.95 (1H, m), 2.15 - 2.34 (3H, m), 2.65 (3H, s), 3.90 (3H, s), 4.45 - 4.53 (1H, m), 7.03 (1H, m), 7.17 (1H, d), 7.58 (1H, m), 7.96 (1H, d), 8.33 (1H, d), 9.71 (1H, s). LCMS: m/z 428.3 [M+H]⁺
400	 Starting material: 5-(((6-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyaniline and 1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method: Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.83 - 1.97 (1H, m), 2.15 - 2.33 (3H, m), 2.65 (3H, s), 3.90 (3H, s), 4.41 - 4.54 (1H, m), 6.98-7.03 (1H, m), 7.06 (1H, d), 7.15 (1H, d), 7.91 (1H, d), 8.36 (1H, t), 9.68 (1H, s). LCMS: m/z 428.4 [M+H]⁺
401	 Starting materials: 5-(((6-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyaniline and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method: Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.84 - 1.96 (1H, m), 2.15 - 2.35 (3H, m), 2.66 (3H, s), 3.90 (3H, s), 4.44 - 4.53 (1H, m), 6.98-7.04 (1H, m), 7.07 (1H, d), 7.16 (1H, d), 7.92 (1H, d), 8.37 (1H, t), 9.69 (1H, s). LCMS: m/z 428.4 [M+H]⁺
402	 Starting materials: 5-(((6-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyaniline, (2R)-1-methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method: Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.83 - 1.96 (1H, m), 2.14 - 2.34 (3H, m), 2.65 (3H, s), 3.90 (3H, s), 4.44 - 4.51 (1H, m), 6.99 - 7.03 (1H, m), 7.07 (1H, d), 7.15 (1H, d), 7.91 (1H, d), 8.36 (1H, t), 9.68 (1H, s). LCMS: m/z 428.4 [M+H]⁺

403	 Starting materials: 2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-aniline and (S)-1-Methyl-5-oxo-pyrrolidine-2-carboxylic acid	Purification method: Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.82 - 1.95 (1H, m), 2.13 - 2.34 (3H, m), 2.65 (3H, s), 3.89 (3H, s), 4.43 - 4.50 (1H, m), 6.93 - 6.98 (1H, m), 7.12 (1H, d), 7.19 (1H, d), 7.88 (1H, d), 8.18 - 8.23 (1H, m), 8.54 (1H, s), 9.63 (1H, s). LCMS: m/z 410.5 [M+H]⁺
404	 Starting materials: (E)-5-(2-(4,4-difluorocyclohexyl)vinyl)-2-methoxy-aniline and 2-Oxoimidazolidine-4-carboxylic acid	Purification method: Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.36 - 1.50 (2H, m), 1.77 - 1.97 (4H, m), 1.97 - 2.09 (2H, m), 2.22 - 2.34 (1H, m), 3.24 - 3.31 (1H, m), 3.65 (1H, t), 3.85 (3H, s), 4.30 - 4.37 (1H, m), 6.02 - 6.09 (1H, range), 6.35 (1H, d), 6.48 (1H, s), 6.79 (1H, s), 7.01 (1H, d), 7.09 - 7.16 (1H, m), 8.15 (1H, d), 9.12 (1H, s). LCMS: m/z 380.4 [M+H]⁺
405	 Starting materials: (E)-5-(2-(4,4-Difluorocyclohexyl)vinyl)-2,3-dihydro-benzofuran-7-amine and (2R)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method: Column chromatography. ¹H NMR (400 MHz, CDCl₃) δ: 1.48 - 1.60 (2H, m), 1.63 - 1.89 (4H, m), 2.05 - 2.27 (4H, m), 2.34 - 2.66 (3H, m), 2.93 (3H, s), 3.24 (2H, t), 4.07 - 4.13 (1H, m), 4.62 (2H, t), 5.98 - 6.05 (1H, m), 6.34 (1H, d), 7.01 (1H, s), 7.49 (1H, s), 8.05 (1H, s). LCMS: m/z 405.4 [M+H]⁺

406	 Starting materials: (E)-5-(2-(4,4-Difluorocyclohexyl)vinyl)-2,3-dihydrobenzofuran-7-amine and (S)-1-Methyl-5-oxopyrrolidine-2-carboxylic acid	Purification method: Column chromatography. ¹H NMR (400 MHz, CDCl₃) δ: 1.47 - 1.60 (2H, m), 1.67 - 1.89 (4H, m), 2.05 - 2.26 (4H, m), 2.35 - 2.53 (2H, m), 2.54 - 2.66 (1H, m), 2.93 (3H, s), 3.24 (2H, t), 4.08 - 4.13 (1H, m), 4.62 (2H, t), 5.98 - 6.05 (1H, m), 6.34 (1H, d), 7.01 (1H, s), 7.49 (1H, s), 8.05 (1H, s). LCMS: m/z 405.4 [M+H]⁺
407	 Starting materials: (E)-5-(2-(4,4-Difluorocyclohexyl)vinyl)-2,3-dihydrobenzofuran-7-amine and (S)-3-Methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method: Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.36 - 1.48 (2H, m), 1.77 - 1.97 (4H, m), 1.97 - 2.10 (2H, m), 2.27 (1H, br s), 2.63 (3H, s), 3.12 - 3.27 (3H, m), 3.52 (1H, br t), 4.31 (1H, br t), 4.59 (2H, br t), 6.00 - 6.08 (1H, m), 6.32 (1H, br d), 6.42 (1H, br s), 7.11 (1H, br s), 7.66 (1H, br s), 9.62 (1H, br s). LCMS: m/z 406.3 [M+H]⁺
408	 Starting materials: (E)-5-(2-(4,4-Difluorocyclohexyl)vinyl)-2-methoxyaniline and 1,3-Dimethyl-2-oxoimidazolidine-4-carboxylic acid	Purification method: Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.37 - 1.49 (2H, m), 1.78 - 1.96 (4H, m), 1.98 - 2.09 (2H, m), 2.22 - 2.39 (1H, m), 2.66 (3H, s), 2.68 (3H, s), 3.17 - 3.25 (1H, m), 3.56 (1H, t), 3.83 (3H, s), 4.26 - 4.33 (1H, m), 6.02 - 6.10 (1H, m), 6.35 (1H, d), 7.00 (1H, d), 7.11 - 7.16 (1H, m), 8.02 (1H, d), 9.41 (1H, s). LCMS: m/z 397.5 [M+H]⁺

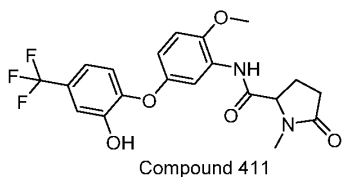
409	 Starting materials: (E)-6-(2-(4,4-difluorocyclohexyl)vinyl)benzo[d][1,3]dioxol-4-amine, (S)-3-methyl-2-oxoimidazolidine-4-carboxylic acid	Purification method: Column chromatography. ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ: 1.36 - 1.48 (2H, m), 1.77 - 1.96 (4H, m), 1.98 - 2.08 (2H, m), 2.23 - 2.32 (1H, m), 2.63 (3H, s), 3.16 - 3.21 (1H, m), 3.53 (1H, t), 4.25 - 4.31 (1H, m), 6.04 (2H, s), 6.08 - 6.15 (1H, m), 6.31 (1H, d), 6.44 (1H, s), 6.91 (1H, d), 7.23 (1H, br d), 9.93 (1H, s). LCMS: m/z 408.3 [M+H]⁺
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Example 36. N-(2-Hydroxy-5-(3-methoxy-4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 410)



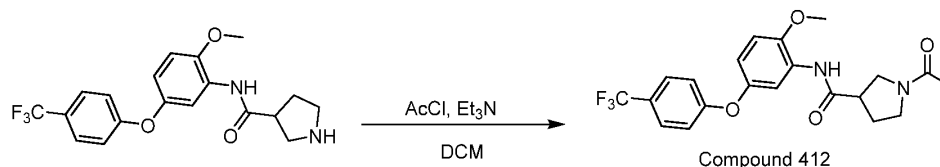
- 5 BCl₃ (1M in heptane, 798 μL, 0.798 mmol) was added dropwise to a cooled solution of N-(2-methoxy-5-(3-methoxy-4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (0.100 g, 0.228 mmol) in DCM (9 ml) at -50 °C followed by stirring at RT for 50 min. The reaction mixture was quenched with 1 N HCl (5 ml). The organic layer was separated and evaporated. The residue was purified by
- 10 reverse phase chromatography to yield 0.066 g of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.85 - 1.95 (1H, m), 2.13 - 2.35 (3H, m), 2.65 (3H, s), 3.84 (3H, s), 4.43 - 4.50 (1H, m), 6.42 (1H, m), 6.78 (1H, m), 6.86 (1H, d), 6.94 (1H, d), 7.53 (1H, d), 7.79 (1H, d), 9.57 (1H, s), 10.07 (1H, s). LCMS: m/z 425.2 [M+H]⁺

- 15 **Example 37.** N-(5-(2-Hydroxy-4-(trifluoromethyl)phenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 411)



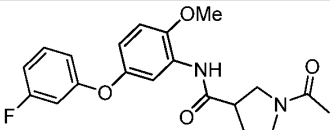
NaH (60 % in oil, 0.028 g, 0.704 mmol) was added to a cooled solution of N-(5-(2-fluoro-4-(trifluoromethyl)phenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (0.100 g, 0.235 mmol) in DMF (2 ml) at 0 °C followed by stirring for 15 min at RT. Then 2-(Methylsulfonyl)ethanol was added and the mixture was heated at 50 °C for 2.5 h. Additional NaH (60 % in oil, 5 eq.) and 2-(Methylsulfonyl)ethanol were then added twice and heated at 80 °C for 5 h and at 100 °C for 5.5 h, respectively. The reaction mixture was quenched with 2 N HCl (2 ml) and extracted with EtOAc (3 x 3 ml). The organic layer was separated and evaporated. The residue was purified by reverse phase chromatography to yield 0.012 g of the title compound. ¹H NMR (600 MHz, DMSO-*d*₆) δ: 1.85 - 1.92 (1H, m), 2.16 - 2.31 (3H, m), 2.64 (3H, s), 3.85 (3H, s), 4.46 (1H, m), 6.76 (1H, m), 6.92 (1H, d), 7.07 (1H, d), 7.11 (1H, m), 7.20 (1H, d), 7.80 (1H, d), 9.58 (1H, s), 10.17 (1H, s). LCMS: *m/z* 425.2 [M+H]⁺

Example 38. 1-Acetyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)pyrrolidine-3-carboxamide (Compound 412)



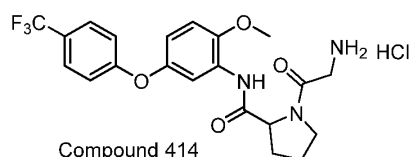
N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)pyrrolidine-3-carboxamide (74 mg, 1 Eq., 1.321 mmol) and Et₃N (271 μL, 10 eq., 1.945 mmol) were dissolved in DCM (5 mL) under nitrogen. Acetyl chloride was added dropwise at 0 °C and the mixture was stirred and gradually raised to RT. After completion the reaction, the mixture was diluted with EtOAc (20 ml) and washed with brine (2×10 ml). The organic phase was dried over sodium sulfate, filtered and concentrated. The crude residue was purified further with reverse phase chromatography to obtain 36 mg of the title compound. ¹H NMR (400 MHz, CDCl₃ mixture of rotamers in ~ 1.0:1.2 ratio) δ: 8.19 (m, 1H), 7.93 (br s, 0.45H), 7.88 (br s, 0.52H), 7.57-7.50 (m, 2.1H), 7.02-6.94 (m, 2.1H), 6.90 (m, 1.1H), 6.78 (m, 1H), 3.93 (s, 1.54H), 3.92 (s, 1.72H), 3.91-3.84 (m, 0.59H), 3.81-3.65 (m, 2.7H), 3.55-3.42 (m, 1.12H), 3.16 (m, 0.5H), 3.06 (quin, 0.58H), 2.45-2.34 (m, 0.67H), 2.31-2.16 (m, 1.8H), 2.08 (s, 1.44H), 2.07 (s, 1.63H). LCMS: *m/z* 423.2 [M+H]⁺

The following compounds were prepared according to the procedure described for Compound 412. The compound code, structure, starting materials, purification method and characterization data are indicated in the table.

No	Structure and starting material	Purification method and characterization data
413	 Starting materials: N-(5-(3-fluorophenoxy)-2-methoxyphenyl)pyrrolidine-3-carboxamide and Acetyl chloride	Purification method A. ^1H NMR (CDCl_3, 600 MHz, mixture of rotamers) δ: 8.14 (d, 1H), 7.97 (br s, 1H), 7.22 (dt, 1H), 6.86 (d, 1H), 6.76 (dd, 1H), 6.74-6.69 (m, 2H), 6.60 (dt, 1H), 3.90 (s, 3H), 3.66 (dd, 1H), 3.59 (dd, 1H), 3.50 (ddd, 2H), 3.43 (m, 1H), 3.21-3.07 (m, 1H), 2.90 (s, 3H), 2.36-2.22 (m, 2H). LCMS: m/z 373.231 ($\text{M}+\text{H}$)$^+$

5

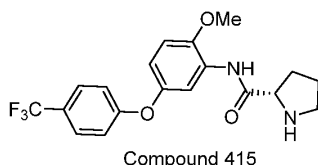
Example 39. 1-Glycyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide, HCl (Compound 414)



In a Büchner flask benzyl (2-(2-((2-methoxy-5-(4-(trifluoromethyl)phenoxy)-phenyl)carbamoyl)-5-oxopyrrolidin-1-yl)-2-oxoethyl)carbamate (168 mg, 0.287 mmol, 1 eq.) was dissolved in EtOH (10 ml) and palladium (24.4 mg, 0.023 mmol, 0.08 eq.) and HCl (37 %, 0.120 ml, 1.435 mmol, 5 eq.) was added. The flask was connected to a H_2/N_2 /vacuum line and after replacement of air with nitrogen, the mixture was stirred under hydrogen for 2.5 h. The mixture was filtered through a pad of Celite® and washed with a 1:1 mixture of acetonitrile/ H_2O . The product was frozen at -78°C and solvents removed on freeze dryer to obtain the title compound. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 9.91 (s, 1H), 8.17 (br.s, 1H), 7.85 (d, 1H), 7.70 (d, 2H), 7.15 (d, 1H), 7.06 (d, 2H), 6.93 (dd, 1H), 5.15 (m, 1H), 4.20 (d, 1H), 4.17 (d, 1H), 3.91 (s, 3H), 2.71-2.30 (m, 3H), 2.04 (m, 1H). LCMS: m/z 452.598 [$\text{M}+\text{H}$] $^+$.

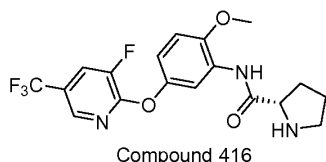
20

Example 40. (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-pyrrolidine-2-carboxamide (Compound 415)



The compound was prepared according to the procedure described for
 5 Intermediate 364 starting from *tert*-butyl (S)-2-((2-methoxy-5-(4-(trifluoromethyl)-phenoxy)phenyl)carbamoyl)-5-oxopyrrolidine-1-carboxylate. The crude end product was treated with saturated Na₂CO₃ solution and then extracted with DCM. The organic phase was dried and evaporated to obtain the title compound. ¹H NMR (400 MHz, CDCl₃) δ: 10.2 (s, 1H), 8.27 (d, 1H), 7.48-7.56 (m, 2H), 6.96-7.03 (m, 2H), 6.87 (d,
 10 1H), 6.74 (dd, 1H), 3.91 (s, 3H), 3.85-3.92 (m, 1H), 2.98-3.15 (m, 2H), 2.14-2.26 (m, 1H), 1.97-2.08 (m, 1H), 1.68-1.85 (m, 2H). LCMS: m/z 381.7 [M+H]⁺

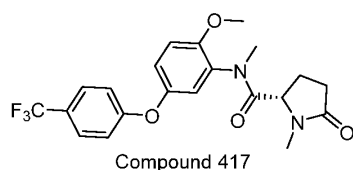
Example 41. (S)-N-(5-((3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)pyrrolidine-2-carboxamide (Compound 416)



15 The compound was prepared according to the procedure described for Intermediate 364 starting from *tert*-butyl (2S)-2-((5-((3-fluoro-5-(trifluoromethyl)-pyridin-2-yl)oxy)-2-methoxyphenyl)carbamoyl)-1H-pyrrolidine-1-carboxylate. The crude end product was treated with saturated Na₂CO₃ solution and then extracted with
 20 DCM. The organic phase was dried and evaporated to obtain the title compound. ¹H NMR (400 MHz, CDCl₃) δ: 10.2 (s, 1H), 8.37 (d, 1H), 8.14-8.19 (m, 1H), 7.64 (dd, 1H), 6.91 (d, 1H), 6.86 (dd, 1H), 3.92 (s, 3H), 3.86 (dd, 1H), 2.96-3.14 (m, 2H), 2.13 (br, 1H), 2.12-2.24 (m, 1H), 1.96-2.07 (m, 1H), 1.67-1.84 (m, 2H). LCMS: m/z 400.6 [M+H]⁺

25

Example 42. (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-N,1-dimethyl-5-oxopyrrolidine-2-carboxamide (Compound 417)



To a cooled (0-5 °C) solution of (*S*)-*N*-(2-methoxy-5-(4-(trifluoromethyl)-phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (0.204 g, 0.50 mmol) in dry DMF (2.0 mmol) was added sodium hydride, 60 wt-% in oil (0.025 g, 0.625 mmol) followed by stirring the mixture at 0-5 °C for 15 min. Iodomethane (0.062 ml, 1.00 mmol) was added and stirring was continued at RT until reaction was completed. The mixture was diluted with water and extracted with EtOAc. Organic phase was washed with water and brine, dried and evaporated. Crude product was purified by reverse phase flash chromatography to afford the title compound. Yield: 0.152 g. ¹H NMR (400 MHz, CDCl₃), mixture of rotamers. Chemical shifts for the main rotamer: δ: 7.56-7.64 (m, 2H), 7.07-7.14 (m, 1H), 6.98-7.06 (m, 3H), 6.96 (dd, 1H), 3.93 (dd, 1H), 3.90 (s, 3H), 3.21 (s, 3H), 2.76 (s, 3H), 2.43-2.62 (m, 1H), 2.18-2.31 (m, 1H), 1.77-2.08 (m, 2H). LCMS: *m/z* 423.4 [M+H]⁺.

15

Abbreviations

- DCM – Dichloromethane
DEAD – Diethyl azodicarboxylate
DIPEA – N,N-diisopropylethylamine
DMA – Dimethylacetamide
DMAP – 4-Dimethylaminopyridine
DMF – N,N-Dimethylformamide
DMSO – Dimethylsulfoxide
ee – Enantiomeric excess
eq. – Molar equivalent
GCMS – Gas chromatography–mass spectrometry
HATU – 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC – High-performance liquid chromatography
LCMS – Liquid chromatography–mass spectrometry

- LiHMDS – Lithium bis(trimethylsilyl)amide
MTBE – Methyl tert-butyl ether
Pd₂(dba)₃ – Tris(dibenzylideneacetone)dipalladium
PdCl₂(dppf) – [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
- 5 RT – Room temperature
rt – Retention time
SPhos Pd G2 – Chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)
T₃P – 1-propanephosphonic acid cyclic anhydride
- 10 TBAF – Tetra-n-butylammonium fluoride
TEA – Triethylamine
TFA – Trifluoroacetic acid
THF – Tetrahydrofuran
TMA – trimethylaluminium
- 15 TMS-Cl – Trimethylsilyl chloride
XantPhos – 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

EXPERIMENTS

20

Experiment 1. TEAD inhibition

TEAD inhibition was assayed using Hippo Pathway TEAD Reporter – MCF-7 cell line (BPS Bioscience, Catalog #: 60618) which contains firefly luciferase gene under the control of TEAD responsive elements. In the cell line, YAP1 remains in the nucleus inducing constitutive expression of luciferase reporter. Amount of expressed luciferase was detected using ONE-Glo Luciferase Assay System (Promega) and measuring plates with Enspire Multimode Plate Reader (PerkinElmer).

30 Hippo Pathway TEAD Reporter – MCF-7 cells were plated on white/clear Poly-D-Lysine coated 384 plates (Corning # 356660) at the density of 8500 cells/well. Next day test compounds (11 concentrations with 4 replicates) and DMSO control (0.1 %) were added to the plate. After 24 h cells were lysed and luciferase activity was

measured. The half maximal inhibitory concentration (IC_{50}) of the test compounds on YAP-TEAD inhibition was determined.

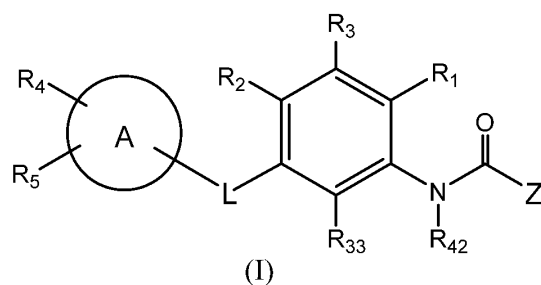
- The compounds of the invention were screened in the above mentioned assay
- 5 and the IC_{50} values of the compounds are set forth in Table 1 below wherein “A” refers to a group of compounds having IC_{50} value of less than 50 nM, “B” refers to a group of compounds having IC_{50} value in range of 50 to 300 nM and “C” refers to a group of compounds having IC_{50} value in range of 301 nM to 2000 nM.

Table 1.

Group	Compound No.
A	1, 21, 22, 23, 28, 33, 45, 47, 48, 59, 66, 67, 68, 69, 70, 75, 76, 81, 87, 88, 91, 92, 93, 97, 99, 100, 101, 102, 103, 105, 107, 109, 110, 114, 117, 118, 119, 128, 129, 130, 131, 133, 134, 136, 139, 141, 143, 149, 150, 151, 152, 153, 154, 156, 157, 159, 162, 163, 164, 165, 166, 167, 168, 170, 171, 175, 176, 177, 178, 179, 180, 182, 184, 185, 186, 187, 189, 192, 196, 206, 208, 209, 210, 213, 214, 215, 216, 217, 222, 223, 226, 227, 229, 230, 231, 234, 237, 239, 240, 248, 253, 255, 264, 265, 276, 278, 279, 282, 283, 290, 292, 294, 296, 297, 298, 299, 300, 304, 305, 307, 308, 312, 313, 316, 317, 318, 319, 320, 322, 335, 338, 339, 340, 345, 348, 349, 351, 352, 355, 356, 361, 362, 363, 365, 375, 377, 382, 385, 391, 395, 398, 399, 400, 401, 402, 403, 405, 406, 407, 409 and 414.
B	8, 10, 11, 17, 18, 19, 24, 25, 27, 29, 30, 32, 34, 36, 37, 39, 42, 43, 49, 52, 53, 55, 56, 57, 60, 62, 63, 71, 73, 74, 77, 78, 80, 82, 83, 86, 89, 90, 94, 95, 96, 98, 104, 108, 111, 112, 115, 116, 125, 126, 127, 135, 138, 140, 144, 147, 148, 155, 160, 161, 169, 172, 173, 174, 194, 197, 198, 200, 207, 211, 212, 218, 232, 233, 235, 238, 241, 242, 244, 245, 247, 249, 254, 256, 257, 258, 259, 260, 261, 263, 266, 267, 268, 269, 270, 271, 273, 274, 275, 277, 281, 284, 285, 286, 288, 291, 293, 295, 309, 310, 315, 321, 325, 328, 331, 334, 336, 337, 342, 346, 350, 357, 359, 360, 364, 368, 369, 371, 376, 379, 379, 380, 381, 383, 396, 404, 408 and 417.
C	2, 3, 4, 5, 6, 7, 9, 12, 13, 14, 15, 16, 20, 26, 31, 35, 38, 40, 41, 44, 46, 50, 51, 54, 58, 61, 64, 65, 72, 79, 84, 85, 106, 113, 120, 121, 122, 123, 124, 132, 137, 142, 145, 146, 181, 183, 188, 190, 191, 193, 199, 201, 202, 203, 205, 224, 225, 228, 236, 243, 246, 251, 252, 262, 272, 287, 289, 301, 302, 303, 306, 311, 317, 323, 324, 326, 327, 329, 330, 332, 333, 341, 343, 344, 347, 353, 354, 358, 366, 367, 370, 372, 373, 374, 378, 386, 387, 388, 389, 390, 392, 393, 394, 397, 410, 411, 412 and 413.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof



wherein

A is pyridyl, tetrahydropyranyl, a 4-10 membered carbocyclic ring;

L is -O-, -S-, -NH-, -C₁₋₇ alkyl-, -C₂₋₇ alkenyl-, -C₁₋₇ alkyl-O-, -O-C₁₋₇ alkyl- or -NH-C₁₋₇ alkyl-;

R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxyl, cyano, -C(O)NR₃₆R₃₇, or an optionally substituted 5-6 membered heterocyclic ring having 1-3 heteroatoms as ring atoms independently selected from O, S and N;

R₂ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy or halogen;

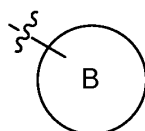
R₃ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, halogen C₁₋₇ alkyl or cyano, or

R₁ and R₃ together with the carbon atoms to which they are attached form an optionally substituted 5-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

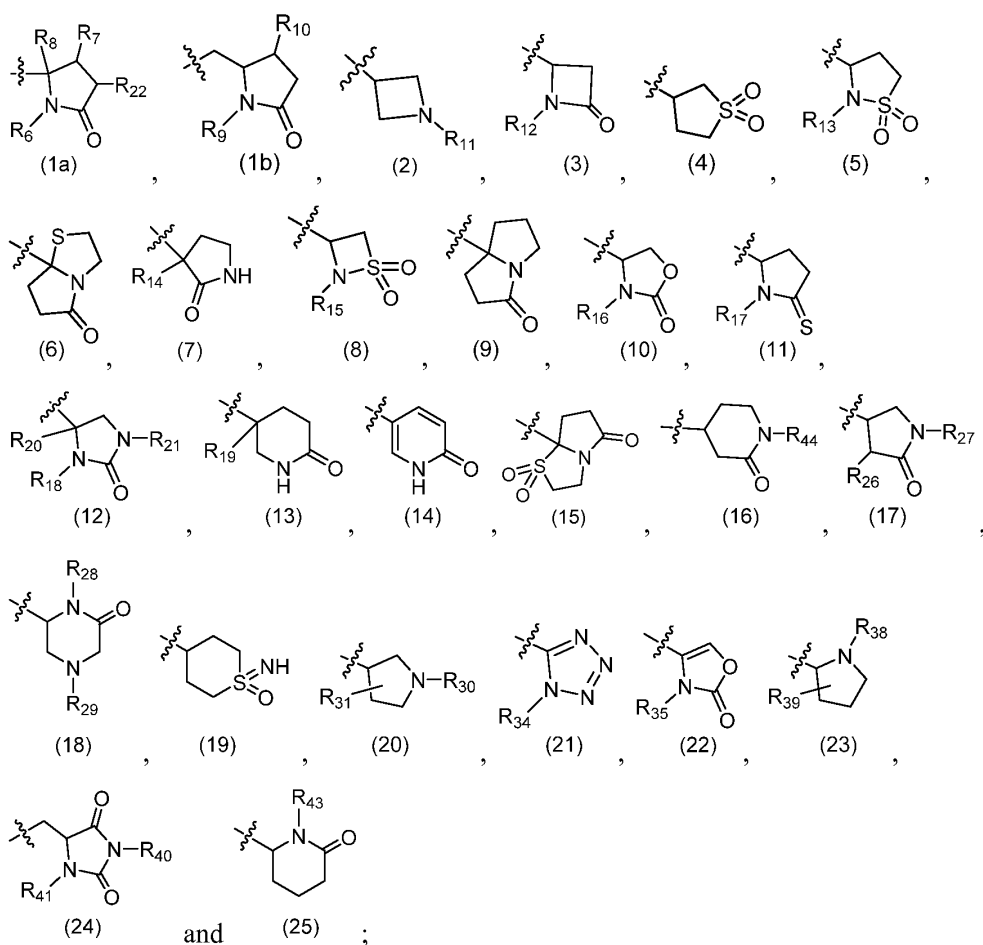
R₄ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, halogen C₁₋₇ alkyl, halogen C₁₋₇ alkoxy, cyano or C₁₋₇ alkylcarbonyl;

R₅ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, nitro, amino, hydroxyl, halogen C₁₋₇ alkyl, halogen C₁₋₇ alkoxy, or R₄ and R₅ together with the carbon atoms to which they are attached form an optionally substituted 5-6 membered ring having 1-3 heteroatoms as ring atoms independently selected from O, S and N;

Z is -CH(NHR₂₅)-(CH₂)₂-COOH or a group of formula



wherein B is any one of the following groups



provided that

when B is ring (2), then L is -O- or -O-C₁₋₇ alkyl-, and R₁ is C₁₋₇ alkoxy;

when B is ring (3), then L is -O-;

when B is ring (4), then L is -O- and R₁ is C₁₋₇ alkoxy;

when B is ring (20), (21), (23), (25) or (26), then L is -O- and R₁ is C₁₋₇ alkoxy;

when L is -C₁₋₇ alkyl-O-, then R₁ is C₁₋₇ alkoxy or R₁ and R₃ together with the carbon atoms to which they are attached form an optionally substituted 5-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

when A is a 4-, 5-, 7-, 8-, 9- or 10-membered carbocyclic ring, then R₁ is C₁₋₇ alkoxy;

R₆ and R₉ are, independently, hydrogen, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₇ alkyl, -C(O)-R_X, C₁₋₇ alkoxy C₁₋₇ alkyl, C₁₋₇ alkoxycarbonyl C₁₋₇ alkyl, -SO₂C₁₋₇ alkyl, -C₁₋₇ alkyl-C(O)-NR₂₃R₂₄ or an optionally substituted 4-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

- 5 R_X is C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₁₋₇ alkoxy C₁₋₇ alkyl, C₁₋₇ alkyl-NR₃₆R₃₇, or an optionally substituted 4-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

- R₇, R₈, R₁₀, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂ and R₂₆ are, independently, hydrogen, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, hydroxyl, C₁₋₇ alkoxy or C₁₋₇ alkylcarbonyl;

R₁₁ is hydrogen, C₁₋₇ alkyl, halogen C₁₋₇ alkyl or C₁₋₇ alkylcarbonyl;

R₂₃, R₂₄, R₂₇, R₂₈, R₂₉, R₃₁, R₃₂, R₃₃, R₃₄, R₃₅, R₃₆, R₃₇, R₄₀, R₄₁, R₄₂, R₄₃, R₄₄, and R₄₅ are, independently, hydrogen, or C₁₋₇ alkyl;

R₂₅ is C₁₋₇ alkyl;

- 15 R₃₀ is C₁₋₇ alkyl, C₁₋₇ alkylcarbonyl or -SO₂C₁₋₇ alkyl;

R₃₈ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkylcarbonyl, C₁₋₇ alkoxy C₁₋₇ alkylcarbonyl or -C₁₋₇ alkyl-C(O)-NR₂₃R₂₄;

R₃₉ is hydrogen, C₁₋₇ alkyl or hydroxyl;

wherein optional substitution, in each occurrence, is 1-2 substituents

- 20 independently selected from C₁₋₇ alkyl, halogen, halogen C₁₋₇ alkyl, C₁₋₇ alkoxy and oxo; with the proviso that compound of formula (I) is not

N-[2-Methyl-3-(phenoxy)methyl]phenyl]-5-oxo-2-pyrrolidinecarboxamide;

N-[5-[(3-Fluorophenoxy)methyl]-2-methoxyphenyl]-1-methyl-5-oxo-2-pyrrolidinecarboxamide;

- 25 N-[3-[(4-Chlorophenyl)methyl]phenyl]-5-oxo-2-pyrrolidinecarboxamide;

N-[3-[(Cyclohexyloxy)methyl]phenyl]-1-methyl-5-oxo-2-pyrrolidinecarboxamide;

N-[4-Methyl-3-[(4-methyl-2-pyridinyl)oxy]phenyl]-5-oxo-2-pyrrolidinecarboxamide;

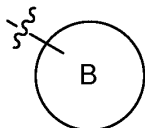
- 30 N-[3-(Cyclopentylamino)phenyl]-1-methyl-5-oxo-2-pyrrolidinecarboxamide;

N-[3-[(3-Methylcyclohexyl)oxy]methyl]phenyl]-6-oxo-3-piperidinecarboxamide;

1-Ethyl-5-oxo-N-(3-phenoxyphenyl)-3-pyrrolidinecarboxamide;

- N*-[5-[(3-Fluorophenoxy)methyl]-2-methoxyphenyl]-2-pyrrolidinecarboxamide;
 1-(1-Ethylpropyl)-*N*-[5-[(3-fluorophenoxy)methyl]-2-methoxyphenyl]-5-oxo-3-pyrrolidinecarboxamide;
N-[3-[(4-Chlorophenyl)methyl]phenyl]-1,6-dihydro-6-oxo-3-pyridine-
 5 carboxamide;
 1,6-Dihydro-*N*-[4-methoxy-3-(phenylmethyl)phenyl]-6-oxo-3-pyridine-
 carboxamide;
 1,6-Dihydro-6-oxo-*N*-[3-[2-(2-pyridinyl)ethenyl]phenyl]-3-pyridinecarboxamide;
 10 *N*-[3-[(3-Fluorophenoxy)methyl]phenyl]-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxamide;
 1-Methyl-*N*-[2-methyl-3-(phenoxyethyl)phenyl]-5-oxo-3-pyrrolidinecarboxamide;
N-[3-[(1,3-Benzodioxol-5-yloxy)methyl]phenyl]-1-(2-methylpropyl)-5-oxo-3-pyrrolidinecarboxamide;
 15 1,6-Dihydro-*N*-[3-[(3-methylcyclohexyl)oxy]methyl]phenyl]-6-oxo-3-pyridinecarboxamide;
N-[3-[(Cyclohexyloxy)methyl]phenyl]-1-ethyl-5-oxo-3-pyrrolidinecarboxamide;
 1-Methyl-*N*-[3-[(3-methylcyclohexyl)oxy]methyl]phenyl]-5-oxo-3-pyrrolidinecarboxamide;
 20 2,3-Dihydro-3-methyl-*N*-[3-[(3-methylcyclohexyl)oxy]methyl]phenyl]-2-oxo-1*H*-imidazole-4-carboxamide;
 2,3-Dihydro-1,3-dimethyl-*N*-[3-[(3-methylcyclohexyl)oxy]methyl]phenyl]-2-oxo-1*H*-imidazole-4-carboxamide;
 1-Ethyl-*N*-[4-methoxy-3-(4-pyridinylmethoxy)phenyl]-5-oxo-3-pyrrolidinecarboxamide;
N-[4-Methoxy-3-(4-methoxyphenoxy)phenyl]-1-(2-methylpropyl)-5-oxo-3-pyrrolidinecarboxamide or
 6-Oxo-*N*-(3-phenoxyphenyl)-2-piperazinecarboxamide.
 30
2. A compound according to claim 1, wherein A is phenyl, pyridyl or cyclohexyl.

3. A compound according to claim 1 or 2, wherein Z is a group of formula



4. A compound according to claim 3, wherein B is ring (1a), (3), (4), (6), (8), (9), (10), (11), (12), (13), (16), (17) or (18).

5

5. A compound according to claim 4, wherein B is ring (1a), (4), (10), (11), (12), (13), (16) or (17).

10

6. A compound according to claim 5, wherein B is ring (1a), (10), (11) or (12).

7. A compound according to claim 6, wherein B is ring (1a) or (12).

15

8. A compound according to any one of the preceding claims, wherein R₇ and R₈ are hydrogen.

9. A compound according to any one of the preceding claims, wherein R₆ is hydrogen, C₁₋₇ alkyl or C₃₋₇ cycloalkyl.

10. A compound according to any one of the preceding claims, wherein R₆ is -C(O)-R_X, wherein R_X is C₁₋₇ alkyl or an optionally substituted 4-6 membered ring having 1-3 heteroatoms as ring atoms independently selected from O, S and N.

11. A compound according to any one of the preceding claims, wherein R₂₀ is hydrogen and R₁₈ is C₁₋₇ alkyl or C₃₋₇ cycloalkyl.

25

12. A compound according to any one of the preceding claims, wherein R₂₁ is hydrogen or C₁₋₇ alkyl.

13. A compound according to any one of the preceding claims, wherein L is -O-, -S-, -NH-, -C₁₋₇ alkyl-, -C₂₋₇ alkenyl-, -C₁₋₇ alkyl-O-, or -O-C₁₋₇ alkyl-.

30

14. A compound according to any one of the preceding claims, wherein L is -O-, -C₂₋₇ alkenyl-, -C₁₋₇ alkyl-O-, or -O-C₁₋₇ alkyl-.

5 15. A compound according to any one of the preceding claims, wherein L is -O-, -C₂₋₇ alkenyl- or -O-C₁₋₇ alkyl-.

16. A compound according to any one of the preceding claims, wherein L is -O- or -C₂₋₇ alkenyl-.

10

17. A compound according to any one of the preceding claims, wherein L is -O-.

18. A compound according to any one of the preceding claims, wherein R₁ is hydrogen, C₁₋₇ alkoxy or halogen.

15

19. A compound according to any one of the preceding claims, wherein R₁ is C₁₋₇ alkoxy or halogen.

20. A compound according to any one of the preceding claims, wherein R₁ is C₁₋₇ alkoxy.

20

21. A compound according to any one of the preceding claims, wherein R₂ is hydrogen, C₁₋₇ alkoxy or halogen.

22. A compound according to any one of the preceding claims, wherein R₂ is hydrogen or halogen.

25

23. A compound according to any one of the preceding claims, wherein R₂ is hydrogen.

30

24. A compound according to any one of the preceding claims, wherein R₃ is hydrogen, halogen or C₁₋₇ alkoxy.

25. A compound according to any one of the preceding claims, wherein R₃ is hydrogen or C₁₋₇ alkoxy.

26. A compound according to any one of the preceding claims, wherein R₃ is
5 hydrogen.

27. A compound according to any one of the preceding claims, wherein R₁ and R₃ together with the carbon atoms to which they are attached form an optionally substituted 5-6 membered ring having 0-3 heteroatoms as ring atoms independently
10 selected from O, S and N.

28. A compound according to any one of the preceding claims, wherein R₁ and R₃ together with the carbon atoms to which they are attached form a 5-6 membered ring having 1-2 heteroatoms as ring atoms independently selected from O and N.
15

29. A compound according to any one of the preceding claims, wherein R₁ and R₃ together with the carbon atoms to which they are attached form a 5-6 membered ring having 1-2 heteroatoms wherein the heteroatom is O.

20 30. A compound according to any one of the preceding claims, wherein R₄ is hydrogen, halogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen C₁₋₇ alkyl or halogen C₁₋₇ alkoxy, and R₅ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, cyano, amino or halogen.

31. A compound according to any one of the preceding claims, wherein
25 A is phenyl or pyridyl; L is -O-; R₁ is C₁₋₇ alkoxy; R₂, R₃, R₅, R₃₃ and R₄₂ are hydrogen; Z is ring (1a) or (12); and R₄ is halogen C₁₋₇ alkyl.

32. A compound according to any one of the preceding claims, wherein the compound is

30 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 1);

(E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 21);

- (E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 22);
- (E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide, enantiomer 1 (Compound 23);
- 5 1-Methyl-5-oxo-N-(5-(3-(trifluoromethyl)phenoxy)benzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 28);
- 5-Oxo-N-(6-(3-(trifluoromethyl)phenoxy)benzo[d][1,3]dioxol-4-yl)pyrrolidine-2-carboxamide (Compound 33);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 45);
- 10 1-Acetyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 47);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 48);
- 15 N-(5-(3,4-Difluorophenoxy)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 59);
- 5-Oxo-N-(7-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)pyrrolidine-2-carboxamide (Compound 66);
- 1-Methyl-5-oxo-N-(7-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo-
- 20 [b][1,4]dioxin-5-yl)pyrrolidine-2-carboxamide (Compound 67);
- 1-Ethyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 68);
- (R)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 69);
- 25 (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 70);
- N-(2-Fluoro-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 75);
- N-(2-Fluoro-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 76);
- 30 1-Isopropyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 81);

- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxo-oxazolidine-4-carboxamide (Compound 87);
- N-(5-(3,4-Difluorophenoxy)-2-methoxyphenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 88);
- 5 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-thioxo-pyrrolidine-2-carboxamide (Compound 91);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-thioxopyrrolidine-2-carboxamide (Compound 92);
- (R)-N-(5-(3,4-Difluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 93);
- 10 (R)-N-(7-(3,4-Difluorophenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 97);
- (R)-1-Methyl-5-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 99);
- 15 (S)-N-(5-(3,4-Difluorophenoxy)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 100);
- (R)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 101);
- (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 102);
- 20 (R)-N-(2-Methoxy-5-(((trans)-4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 103);
- (S)-N-(2-Methoxy-5-(((trans)-4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 105);
- 25 (S)-1-Methyl-5-oxo-N-(5-(((cis)-4-(trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 107);
- 1-Cyclopropyl-5-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 109);
- 1-Cyclopropyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 110);
- 30 1-Cyclopropyl-5-oxo-N-(7-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)pyrrolidine-2-carboxamide (Compound 114);

N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 117);

N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 118);

5 (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-6-oxopiperidine-3-carboxamide (Compound 119);

(R)-1-Cyclopropyl-N-(2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 128);

10 (S)-1-Cyclopropyl-N-(2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 129);

(S)-N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 130);

3-Cyclopropyl-N-(2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-2-oxoimidazolidine-4-carboxamide (Compound 131);

15 1-(Cyclopropylmethyl)-N-(2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-5-oxopyrrolidine-2-carboxamide, enantiomer 2 (Compound 133);

(R)-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1,2-dimethyl-5-oxopyrrolidine-2-carboxamide (Compound 134);

20 1-(2-Amino-2-oxoethyl)-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 136);

N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1,3-dimethyl-2-oxoimidazolidine-4-carboxamide (Compound 139);

(S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 141);

25 (2S)-4-Methoxy-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 143);

N-(5-(4-(Difluoromethyl)phenoxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 149);

30 (S)-1-Methyl-5-oxo-N-(5-(((trans)-4-(trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 150);

(R)-1-Methyl-5-oxo-N-(5-(((trans)-4-(trifluoromethyl)cyclohexyl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 151);

- N-(4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 152);
- N-(4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 153);
- 5 (R)-N-(4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)-oxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 154);
- (S)-N-(4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 156);
- (S)-N-(4-Fluoro-2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxooxazolidine-4-carboxamide (Compound 157);
- 10 3-Methyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)imidazolidine-4-carboxamide (Compound 159);
- (R)-1-Methyl-5-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 162);
- 15 (S)-1-Methyl-5-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 163);
- 3-Cyclopropyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)imidazolidine-4-carboxamide (Compound 164);
- (S)-1-Cyclopropyl-5-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 165);
- 20 (R)-1-Cyclopropyl-5-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 166);
- 3-Ethyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)imidazolidine-4-carboxamide (Compound 167);
- 25 (S)-3-Methyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)imidazolidine-4-carboxamide (Compound 168);
- (R)-1-Ethyl-5-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 170);
- (S)-1-Ethyl-5-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 171);
- 30 (R)-1-Methyl-5-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)chroman-8-yl)pyrrolidine-2-carboxamide (Compound 175);

- 3-Methyl-2-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)chroman-8-yl)-imidazolidine-4-carboxamide (Compound 176);
- 1-Methyl-5-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)chroman-8-yl)-pyrrolidine-2-carboxamide (Compound 177);
- 5 3-Methyl-2-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzo[d]-[1,3]dioxol-4-yl)imidazolidine-4-carboxamide (Compound 178);
- 1-Cyclopropyl-5-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzo[d]-[1,3]dioxol-4-yl)pyrrolidine-2-carboxamide (Compound 179);
- (S)-3-Methyl-2-oxo-N-(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzo-
- 10 [d][1,3]dioxol-4-yl)imidazolidine-4-carboxamide (Compound 180);
- 3-Methyl-2-oxo-N-(7-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzo-[b][1,4]dioxin-5-yl)imidazolidine-4-carboxamide (Compound 182);
- 3-Methyl-2-oxo-N-(7-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2,3-dihydrobenzo-[b][1,4]dioxin-5-yl)imidazolidine-4-carboxamide, enantiomer 2 (Compound 184);
- 15 1-Methyl-5-oxo-N-(5-(4-(trifluoromethyl)phenoxy)benzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 185);
- 3-Methyl-2-oxo-N-(6-(4-(trifluoromethyl)phenoxy)benzo[d][1,3]dioxol-4-yl)-imidazolidine-4-carboxamide (Compound 186);
- 2-Oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)-
- 20 piperidine-4-carboxamide (Compound 187);
- 1-(2-Amino-2-oxoethyl)-5-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 189);
- 3-Methyl-2-oxo-N-(7-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]-dioxin-5-yl)imidazolidine-4-carboxamide (Compound 192);
- 25 (R)-N-(2-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 196);
- N-(5-((4,4-Difluorocyclohexyl)methoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 206);
- (R)-N-(2-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-3-methyl-2-
- 30 oxooxazolidine-4-carboxamide (Compound 208);
- (R)-N-(2-Methoxy-5-(((cis)-4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 209);

- (S)-N-(2-Methoxy-5-(((cis)-4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 210);
- N-(5-(4-(Difluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 213);
- 5 (S)-N-(5-(4-(Difluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 214);
- (R)-N-(5-(4-(Difluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 215);
- (S)-3-Methyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzofuran-7-yl)imidazolidine-4-carboxamide (Compound 216);
- 10 (R)-3-Methyl-2-oxo-N-(5-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzofuran-7-yl)imidazolidine-4-carboxamide (Compound 217);
- N-(5-(3,4-Dichlorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 222);
- 15 N-(5-(3-Chloro-4-fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 223);
- (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1,3-dimethyl-2-oxoimidazolidine-4-carboxamide (Compound 226);
- (R)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1,3-dimethyl-2-oxoimidazolidine-4-carboxamide (Compound 227);
- 20 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-1-(5-oxopyrrolidine-2-carbonyl)pyrrolidine-2-carboxamide (Compound 229);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-(1-methyl-5-oxopyrrolidine-2-carbonyl)-5-oxopyrrolidine-2-carboxamide (Compound 230);
- 25 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-1-(4-oxoazetidine-2-carbonyl)pyrrolidine-2-carboxamide (Compound 231);
- 1-Methyl-5-oxo-N-(7-(3-(trifluoromethyl)phenoxy)-2,3-dihydrobenzo[b][1,4]-dioxin-5-yl)pyrrolidine-2-carboxamide, enantiomer 1 (Compound 234);
- 1-Methyl-5-oxo-N-(5-(4-(trifluoromethyl)phenoxy)-2,3-dihydrobenzofuran-7-yl)pyrrolidine-2-carboxamide (Compound 237);
- 30 N-(5-(3,4-Difluorophenoxy)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 239);

- N-(7-(3,4-Difluorophenoxy)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 240);
- N-(5-((3,4-Difluorobenzyl)oxy)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 248);
- 5 N-(3-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 253);
- N-(2-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 255);
- N-(2-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 264);
- 10 (R)-N-(2-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 265);
- N-(2-methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 276);
- 15 (R)-N-(3-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 278);
- N-(3-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 279);
- (R)-N-(3-Methoxy-5-((4-(trifluoromethyl)cyclohexyl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 282);
- 20 (R)-N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 283);
- (R)-N-(2-Methoxy-5-(4-(trifluoromethoxy)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 290);
- 25 N-(5-(4-(Difluoromethyl)phenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 292);
- N-(5-(Cyclohexylmethoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 294);
- N-(5-((4,4-Dimethylcyclohexyl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 296);
- 30 N-(5-((3,4-Difluorophenyl)thio)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 297);

N-(5-((3,4-Difluorophenyl)thio)-2-methoxyphenyl)-5-oxopyrrolidine-2-carboxamide (Compound 298);

N-(5-(3-Bromophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 299);

5 N-(2-Methoxy-5-(4-(trifluoromethoxy)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide (Compound 300);

N-(5-(4-Chlorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 304);

10 N-(5-(4-Chloro-3-fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 305);

(S)-N-(5-(4-Chlorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 307);

(R)-N-(5-(4-Chlorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 308);

15 (S)-N-(5-(4-Chloro-3-fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 312);

(S)-N-(5-(4-(Difluoromethyl)phenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 313);

20 N-(5-(3-Chlorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 316);

N-(5-(4-Cyano-3-methylphenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 317);

N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-(2-methoxyethyl)-5-oxopyrrolidine-2-carboxamide (Compound 318);

25 (R)-N-(5-(4-(Difluoromethyl)phenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 319);

N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-6-oxopiperidine-2-carboxamide (Compound 320);

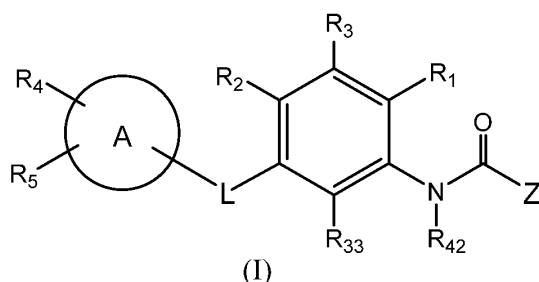
30 N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-2-oxopiperidine-4-carboxamide (Compound 322);

N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-3-carboxamide (Compound 335);

- (S)-N-(5-(4-Chloro-3-fluorophenoxy)-2-methoxyphenyl)-3-methyl-2-oxo-imidazolidine-4-carboxamide (Compound 338);
- (S)-N-(5-((3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 339);
- 5 (S)-N-(5-(4-(Difluoromethyl)phenoxy)-2-methoxyphenyl)-3-methyl-2-oxo-imidazolidine-4-carboxamide (Compound 340);
- (S)-N-(5-((3-Chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 345);
- (S)-N-(5-(3-Chlorophenoxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-
10 carboxamide (Compound 348);
- N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxo-pyrrolidine-3-carboxamide (Compound 349);
- (S)-N-(3-Chloro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 351);
- 15 N-(3-Chloro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 352);
- (S)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-3-carboxamide (Compound 355);
- (S)-N-(5-(4-Chlorophenoxy)-2-methoxyphenyl)-3-methyl-2-oxoimidazolidine-4-
20 carboxamide (Compound 356);
- (S)-N-(2,4-Difluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 361);
- (S)-N-(3-Fluoro-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 362);
- 25 (S)-N-(2-Fluoro-5-(4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxo-pyrrolidine-2-carboxamide (Compound 363);
- (S)-N-(2-Fluoro-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxo-imidazolidine-4-carboxamide (Compound 365);
- 4-Amino-5-((2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)amino)-5-
30 oxopentanoic acid (Compound 375);
- (R)-N-(2-Methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxo-1-(1H-pyrazol-4-yl)pyrrolidine-2-carboxamide (Compound 377);

- N-(4-Fluoro-2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 382);
- N-(5-(4-Chloro-2-fluorophenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 385);
- 5 N-(2-Methoxy-5-(3-methoxy-4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 391);
- N-(2-Methoxy-5-(3-methoxy-4-(trifluoromethyl)phenoxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 395);
- (S)-N-(5-(2-Fluoro-4-(trifluoromethyl)phenoxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 398);
- 10 (N-(5-((6-Fluoro-6-(trifluoromethyl)pyridin-3-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 399);
- N-(5-((6-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 400);
- 15 (S)-N-(5-((6-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 401);
- (R)-N-(5-((6-Fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-methoxyphenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 402);
- (S)-N-(2-Methoxy-5-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 403);
- 20 (R,E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 405);
- (S,E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2,3-dihydrobenzofuran-7-yl)-1-methyl-5-oxopyrrolidine-2-carboxamide (Compound 406);
- 25 (S,E)-N-(5-(2-(4,4-Difluorocyclohexyl)vinyl)-2,3-dihydrobenzofuran-7-yl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 407);
- ((S,E)-N-(6-(2-(4,4-Difluorocyclohexyl)vinyl)benzo[d][1,3]dioxol-4-yl)-3-methyl-2-oxoimidazolidine-4-carboxamide (Compound 409);
- 1-Glycyl-N-(2-methoxy-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-oxopyrrolidine-2-carboxamide, HCl (Compound 414);
- 30 or a tautomer or a pharmaceutically acceptable salt thereof.

33. A compound of formula (I) or a pharmaceutically acceptable salt thereof



wherein

A is pyridyl, tetrahydropyranyl, a 4-10 membered carbocyclic ring;

L is -O-, -S-, -NH-, -C₁₋₇ alkyl-, -C₂₋₇ alkenyl-, -C₁₋₇ alkyl-O-, -O-C₁₋₇ alkyl- or
 5 -NH-C₁₋₇ alkyl-;

R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxyl, cyano, -C(O)NR₃₆R₃₇,
 or an optionally substituted 5-6 membered heterocyclic ring having 1-3 heteroatoms as
 ring atoms independently selected from O, S and N;

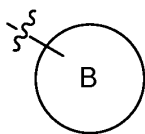
R₂ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy or halogen;

10 R₃ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, halogen C₁₋₇ alkyl or cyano, or
 R₁ and R₃ together with the carbon atoms to which they are attached form an optionally
 substituted 5-6 membered ring having 0-3 heteroatoms as ring atoms independently
 selected from O, S and N;

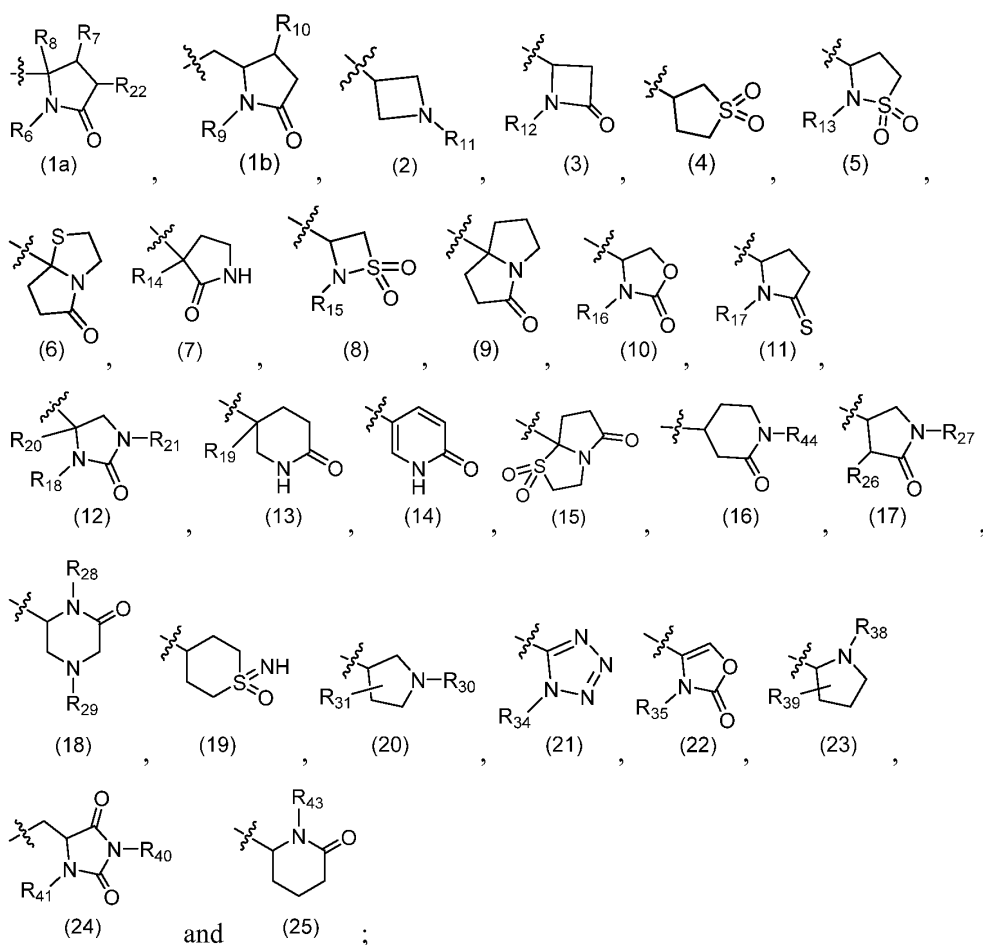
R₄ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, halogen C₁₋₇ alkyl,
 15 halogen C₁₋₇ alkoxy, cyano or C₁₋₇ alkylcarbonyl;

R₅ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, nitro, amino, hydroxyl, halogen
 C₁₋₇ alkyl, halogen C₁₋₇ alkoxy, or R₄ and R₅ together with the carbon atoms to which
 they are attached form an optionally substituted 5-6 membered ring having 1-3
 heteroatoms as ring atoms independently selected from O, S and N;

20 Z is -CH(NHR₂₅)-(CH₂)₂-COOH or a group of formula



wherein B is any one of the following groups



provided that

when B is ring (2), then L is -O- or -O-C₁₋₇ alkyl-, and R₁ is C₁₋₇ alkoxy;

when B is ring (3), then L is -O-;

when B is ring (4), then L is -O- and R₁ is C₁₋₇ alkoxy;

when B is ring (20), (21), (23), (25) or (26), then L is -O- and R₁ is C₁₋₇ alkoxy;

when L is -C₁₋₇ alkyl-O-, then R₁ is C₁₋₇ alkoxy or R₁ and R₃ together with the carbon atoms to which they are attached form an optionally substituted 5-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

when A is a 4-, 5-, 7-, 8-, 9- or 10-membered carbocyclic ring, then R₁ is C₁₋₇ alkoxy;

R₆ and R₉ are, independently, hydrogen, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₇ alkyl, -C(O)-R_X, C₁₋₇ alkoxy C₁₋₇ alkyl, C₁₋₇ alkoxycarbonyl C₁₋₇ alkyl, -SO₂C₁₋₇ alkyl, -C₁₋₇ alkyl-C(O)-NR₂₃R₂₄ or an optionally substituted 4-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

- 5 R_X is C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₁₋₇ alkoxy C₁₋₇ alkyl, C₁₋₇ alkyl-NR₃₆R₃₇, or an optionally substituted 4-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

- R₇, R₈, R₁₀, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂ and R₂₆ are, independently, hydrogen, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, hydroxyl, C₁₋₇ alkoxy or C₁₋₇ alkylcarbonyl;
- 10

 R₁₁ is hydrogen, C₁₋₇ alkyl, halogen C₁₋₇ alkyl or C₁₋₇ alkylcarbonyl;

 R₂₃, R₂₄, R₂₇, R₂₈, R₂₉, R₃₁, R₃₂, R₃₃, R₃₄, R₃₅, R₃₆, R₃₇, R₄₀, R₄₁, R₄₂, R₄₃, R₄₄, and R₄₅ are, independently, hydrogen, or C₁₋₇ alkyl;

 R₂₅ is C₁₋₇ alkyl;

- 15 R₃₀ is C₁₋₇ alkyl, C₁₋₇ alkylcarbonyl or -SO₂C₁₋₇ alkyl;

 R₃₈ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkylcarbonyl, C₁₋₇ alkoxy C₁₋₇ alkylcarbonyl or -C₁₋₇ alkyl-C(O)-NR₂₃R₂₄;

 R₃₉ is hydrogen, C₁₋₇ alkyl or hydroxyl;

- wherein optional substitution, in each occurrence, is 1-2 substituents independently selected from C₁₋₇ alkyl, halogen, halogen C₁₋₇ alkyl, C₁₋₇ alkoxy and oxo; for use as a medicament.
- 20

34. A compound for use according to claim 33, for use in the treatment of a disease or condition wherein inhibition of TEAD is desired.

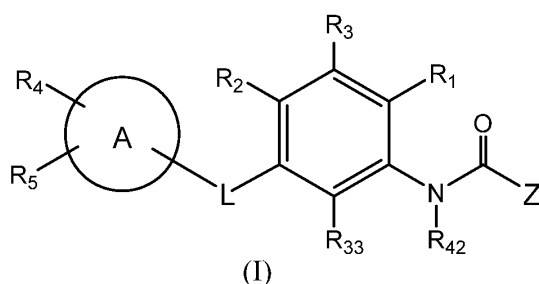
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35. A compound for use according to claim 34, wherein the disease is cancer or chronic pain.

36. A compound for use according to claim 35, wherein the cancer is mesothelioma, squamous cell carcinoma, a gynaecological cancer, bladder cancer, gastric cancer, liver cancer, lung cancer and colon cancer.
- 30

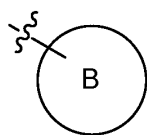
37. A compound for use according to claim 36, wherein the chronic pain is chronic neuropathic pain or chronic musculoskeletal pain.

38. A method for the treatment of a disease or condition wherein inhibition of
 5 TEAD is desired comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof

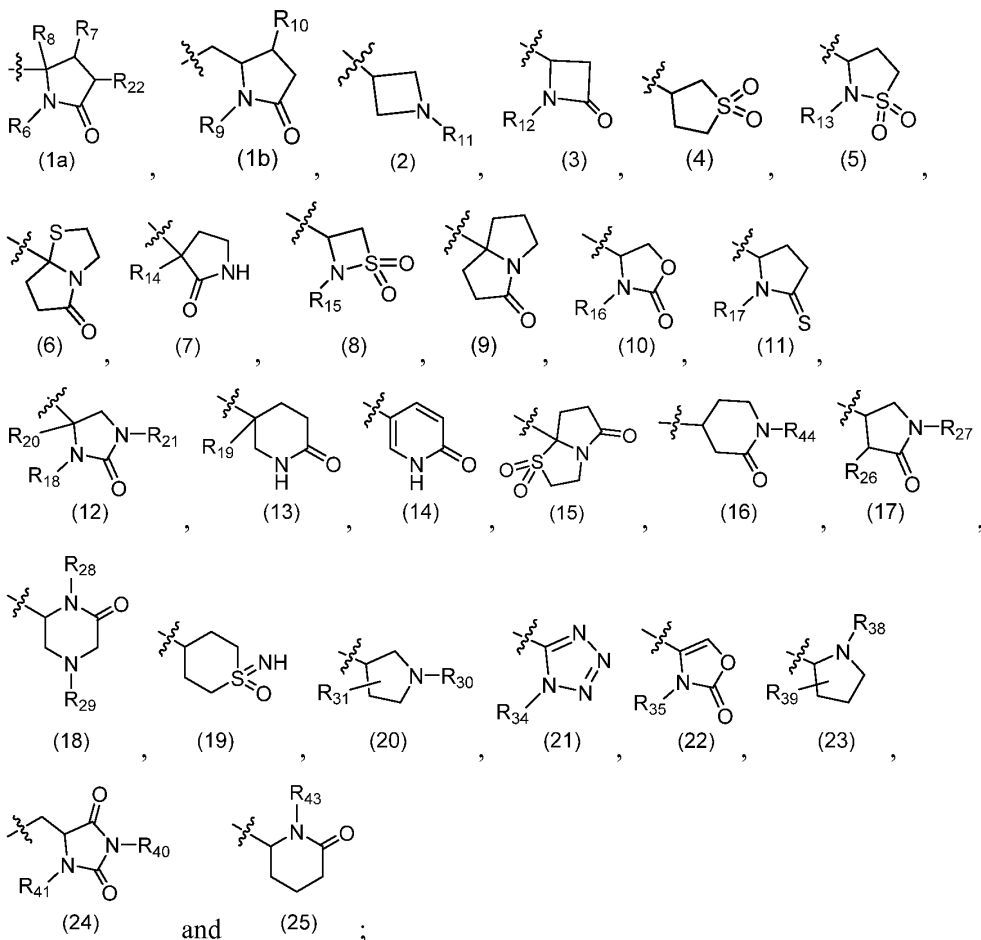


wherein

- 10 A is pyridyl, tetrahydropyranyl, a 4-10 membered carbocyclic ring;
 L is -O-, -S-, -NH-, -C₁₋₇ alkyl-, -C₂₋₇ alkenyl-, -C₁₋₇ alkyl-O-, -O-C₁₋₇ alkyl- or -NH-C₁₋₇ alkyl-;
 R₁ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, hydroxyl, cyano, -C(O)NR₃₆R₃₇, or an optionally substituted 5-6 membered heterocyclic ring having 1-3 heteroatoms as
 15 ring atoms independently selected from O, S and N;
 R₂ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy or halogen;
 R₃ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, halogen C₁₋₇ alkyl or cyano, or
 R₁ and R₃ together with the carbon atoms to which they are attached form an optionally substituted 5-6 membered ring having 0-3 heteroatoms as ring atoms independently
 20 selected from O, S and N;
 R₄ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, halogen C₁₋₇ alkyl, halogen C₁₋₇ alkoxy, cyano or C₁₋₇ alkylcarbonyl;
 R₅ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halogen, nitro, amino, hydroxyl, halogen C₁₋₇ alkyl, halogen C₁₋₇ alkoxy, or R₄ and R₅ together with the carbon atoms to which
 25 they are attached form an optionally substituted 5-6 membered ring having 1-3 heteroatoms as ring atoms independently selected from O, S and N;
 Z is -CH(NHR₂₅)-(CH₂)₂-COOH or a group of formula



wherein B is any one of the following groups



provided that

when B is ring (2), then L is -O- or -O-C₁₋₇ alkyl-, and R₁ is C₁₋₇ alkoxy;

when B is ring (3), then L is -O-;

when B is ring (4), then L is -O- and R₁ is C₁₋₇ alkoxy;

when B is ring (20), (21), (23), (25) or (26), then L is -O- and R₁ is C₁₋₇ alkoxy;

when L is -C₁₋₇ alkyl-O-, then R₁ is C₁₋₇ alkoxy or R₁ and R₃ together with the carbon atoms to which they are attached form an optionally substituted

5-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

when A is a 4-, 5-, 7-, 8-, 9- or 10-membered carbocyclic ring, then R₁ is C₁₋₇ alkoxy;

5 R₆ and R₉ are, independently, hydrogen, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₇ alkyl, -C(O)-R_X, C₁₋₇ alkoxy C₁₋₇ alkyl, C₁₋₇ alkoxycarbonyl C₁₋₇ alkyl, -SO₂C₁₋₇ alkyl, -C₁₋₇ alkyl-C(O)-NR₂₃R₂₄ or an optionally substituted 4-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

R_X is C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₁₋₇ alkoxy C₁₋₇ alkyl, C₁₋₇ alkyl-NR₃₆R₃₇, or an
10 optionally substituted 4-6 membered ring having 0-3 heteroatoms as ring atoms independently selected from O, S and N;

R₇, R₈, R₁₀, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂ and R₂₆ are, independently, hydrogen, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, hydroxyl, C₁₋₇ alkoxy or C₁₋₇ alkylcarbonyl;

15 R₁₁ is hydrogen, C₁₋₇ alkyl, halogen C₁₋₇ alkyl or C₁₋₇ alkylcarbonyl;

R₂₃, R₂₄, R₂₇, R₂₈, R₂₉, R₃₁, R₃₂, R₃₃, R₃₄, R₃₅, R₃₆, R₃₇, R₄₀, R₄₁, R₄₂, R₄₃, R₄₄, and R₄₅ are, independently, hydrogen, or C₁₋₇ alkyl;

R₂₅ is C₁₋₇ alkyl;

R₃₀ is C₁₋₇ alkyl, C₁₋₇ alkylcarbonyl or -SO₂C₁₋₇ alkyl;

20 R₃₈ is hydrogen, C₁₋₇ alkyl, C₁₋₇ alkylcarbonyl, C₁₋₇ alkoxy C₁₋₇ alkylcarbonyl or -C₁₋₇ alkyl-C(O)-NR₂₃R₂₄;

R₃₉ is hydrogen, C₁₋₇ alkyl or hydroxyl;

wherein optional substitution, in each occurrence, is 1-2 substituents independently selected from C₁₋₇ alkyl, halogen, halogen C₁₋₇ alkyl, C₁₋₇ alkoxy and oxo.

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39. A method according to claim 38 wherein the disease is cancer or chronic pain.

40. A method according to claim 39 wherein the cancer is mesothelioma,
30 squamous cell carcinoma, a gynaecological cancer, bladder cancer, gastric cancer, liver cancer, lung cancer or colon cancer.

41. A method according to claim 39 wherein the chronic pain is chronic neuropathic pain or chronic musculoskeletal pain.

42. A pharmaceutical composition comprising a compound according to any of
5 claims 1 to 32 together with a pharmaceutically acceptable carrier.