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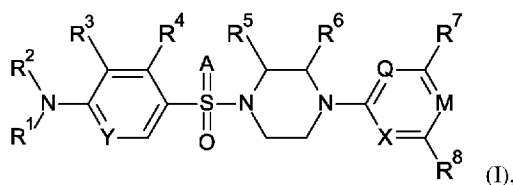
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(54) Title: BENZAMIDE COMPOUNDS FOR TREATMENT OF BACTERIAL INFECTIONS



(I).

(57) Abstract: The present invention relates to compounds of formula (I), wherein R¹ to R⁸, Y, A, Q, X and M are as described herein, and their pharmaceutically acceptable salt thereof, and compositions including the compounds and methods of using the compounds.

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Benzamide compounds for treatment of bacterial infections

The present invention relates to organic compounds useful for the treatment and/or prevention of bacterial infections in a mammal. Specifically these molecules can inhibit the LPS synthesis pathway, in particular to inhibit LpxH, and are useful for treating bacterial infections.

BACKGROUND OF THE INVENTION

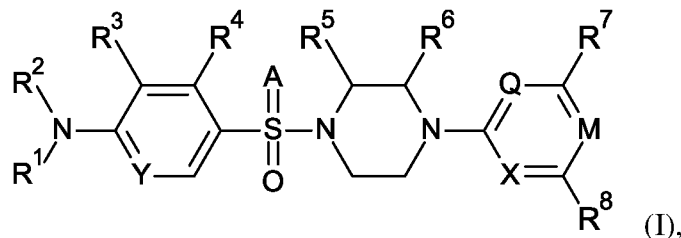
5 The intensive use of antibiotics has exerted a selective evolutionary pressure on microorganisms to produce genetically based resistance mechanisms. Modern medicine and socio-economic behaviour exacerbate the problem of resistance development by creating slow growth situations for pathogenic microbes, e.g. in artificial joints, and by supporting long-term host reservoirs, e.g. in immune-compromised patients. In hospital settings, an increasing number
10 of strains of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus spp.*, *Enterobacteriaceae* such as *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, major sources of infections, are becoming multi-drug resistant and therefore difficult to treat. This is particularly the case for Gram-negative organisms where the situation is getting worrisome since no novel agents with a differentiated mechanism of action have been approved
15 for decades. Therefore, there is an important medical need for new antibacterial compounds addressing Gram-negative resistant bacteria, in particular third generation cephalosporins- and carbapenem-resistant *Enterobacteriaceae* and multi-drug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. One way to tackle the problem of cross-resistance to established classes of antibiotics is to inhibit an essential protein or function not targeted by current
20 antibiotics.

Gram-negative bacteria are unique in that their outer membrane contains Lipopolysaccharide (LPS), which is crucial for maintaining membrane integrity, and is essential for bacterial viability (reviewed in Ann. Rev. Biochem 76: 295-329, 2007). The major lipid component of LPS is Lipid A, and inhibition of Lipid A biosynthesis is lethal to bacteria. Lipid A is
25 synthesized on the cytoplasmic surface of the bacterial inner membrane via a pathway that consists of nine different enzymes. These enzymes are highly conserved in most Gram-negative bacteria. LpxH, a calcineurin-like phosphatase (CLP), catalyzes the hydrolysis of UDP-2,3-diacyl-glucosamine (UDP-DAGn) to yield Lipid X and UMP (22, 24, 25). LpxH has no

mammalian homologue, making it a good target for the development of novel antibiotics targeting Gram-negative bacteria.

SUMMARY OF THE INVENTION

The present invention relates to novel compounds of formula (I),



wherein

R¹ is COR⁹; wherein

R⁹ is ((hydroxyC₁₋₆alkyl)amino)C₁₋₆alkyl,

1-oxa-2,9-diazaspiro[4.5]dec-2-enyl,

4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazinyl,

4,6-dihydropyrrolo[3,4-c]pyrazolyl substituted by C₁₋₆alkyl,

6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl,

indanyl substituted by amino or aminoC₁₋₆alkylamino,

isoindolinyl,

piperazinylC₁₋₆alkyl,

pyrazolo[1,5-a]pyrimidinyl,

pyrazolyl substituted once or twice by the substituents independently selected from

aminoC₁₋₆alkyl, azetidiny, C₁₋₆alkyl and carboxy,

pyridinyl substituted by (aminoC₁₋₆alkylamino)C₁₋₆alkyl, or

phenyl substituted once or twice by the substituents independently selected from

((amino(carboxy)C₁₋₆alkyl)amino)C₁₋₆alkyl, ((aminoC₁₋₆alkyl)-3-

azabicyclo[3.1.0]hexanyl)C₁₋₆alkyl, ((aminoC₁₋₆alkyl)pyrrolidinyl)C₁₋₆alkyl,

((aminoC₃₋₇cycloalkyl)C₁₋₆alkylamino)C₁₋₆alkyl, ((aminoC₃₋

7cycloalkyl)pyrrolidinyl)C₁₋₆alkyl, ((oxooxazolidinyl)C₁₋₆alkylamino)C₁₋₆alkyl,

((oxopyrrolidinyl)C₁₋₆alkylamino)C₁₋₆alkyl, ((piperidinyl)C₁₋₆alkylamino)C₁₋

6alkyl, (3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[3,4-b]pyrrolyl)C₁₋₆alkyl, (3,6-

diazabicyclo[3.1.1]heptanyl)C₁₋₆alkyl, (amino-2-azaspiro[3.3]heptanyl)C₁₋

6alkyl, (amino-5-azaspiro[2.4]heptanyl)C₁₋₆alkyl, (aminoC₁₋₆alkyl)piperazinyl,

(aminoC₁₋₆alkyl)pyrrolidinyl, (aminoC₁₋₆alkylamino)C₁₋₆alkyl,

(aminopyrrolidinyl)C₁₋₆alkyl, (C₁₋₆alkyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-

c]pyrrolyl)C₁₋₆alkyl, (diaminoC₁₋₆alkylcarbonyl)amino, (morpholinylC₁₋₆alkylamino)C₁₋₆alkyl, (piperazinylC₁₋₆alkylamino)C₁₋₆alkyl, (piperidinylC₁₋₆alkylamino)C₁₋₆alkyl, [((C₁₋₆alkyl)₂aminocarbonylC₁₋₆alkyl)amino]C₁₋₆alkyl, [((hydroxyC₁₋₆alkyl)₂amino)C₁₋₆alkylamino]C₁₋₆alkyl, 2,5-diazabicyclo[2.2.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, aminoC₁₋₆alkoxy, aminoC₁₋₆alkyl, aminopyrrolidinyl, azetidinyC₁₋₆alkoxy, azetidinyC₁₋₆alkylamino, C₁₋₆alkylcarbonyloxy, C₁₋₆alkoxy, carboxy, hydroxy and piperazinyl;

R² is H;

10 R³ is H, hydroxy or C₁₋₆alkoxy; or

R² and R³ together with the atoms they are attached to form a pyrrolidinyl;

R⁴ is H, hydroxy or C₁₋₆alkoxy;

R⁵ is H or C₁₋₆alkyl;

R⁶ is H or C₁₋₆alkyl; or

15 R⁵ and R⁶ together with the atoms they are attached to form a C₃₋₇cycloalkyl;

R⁷ is halogen, cyano, haloC₁₋₆alkyl or C₁₋₆alkoxycarbonyl;

R⁸ is H, halogen, cyano, amino, C₃₋₇cycloalkoxy, C₁₋₆alkyl, C₁₋₆alkoxy or haloC₁₋₆alkyl;

Y is CH or N;

A is O, N(CN), or N(C₁₋₆alkyl);

20 Q is CH or N;

X is CH or N;

M is N or CR¹⁰; wherein R¹⁰ is H, halogen, C₁₋₆alkyl or C₃₋₇cycloalkyl;

with the proviso that Q, X and M are not N simultaneously;

or a pharmaceutically acceptable salt thereof.

25 **DETAILED DESCRIPTION OF THE INVENTION**

DEFINITIONS

The term “C₁₋₆alkyl” denotes a saturated, linear or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms, for example methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl and the like. Particular “C₁₋₆alkyl” groups are methyl, ethyl and *n*-propyl.

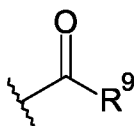
30 The term “C₁₋₆alkylene” denotes a linear or branched saturated divalent hydrocarbon group of 1 to 6 carbon atoms or a divalent branched saturated divalent hydrocarbon group of 3 to 6 carbon atoms. Examples of C₁₋₆alkylene groups include methylene, ethylene, propylene, 2-methylpropylene, butylene, 2-ethylbutylene, pentylene, hexylene.

The term “halogen” and “halo” are used interchangeably herein and denote fluoro, chloro, bromo, or iodo.

The term “haloC₁₋₆alkyl” denotes a C₁₋₆alkyl group wherein at least one of the hydrogen atoms of the C₁₋₆alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloC₁₋₆alkyl include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, trifluoroethyl, fluoromethyl, difluoromethyl, difluoroethyl or trifluoromethyl.

The term “C₃₋₇cycloalkyl” denotes a monovalent saturated monocyclic or bicyclic hydrocarbon group of 3 to 7 ring carbon atoms. Bicyclic means consisting of two saturated carbocycles having one or more carbon atoms in common. Examples for monocyclic cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Examples for bicyclic cycloalkyl are bicyclo[1.1.0]butyl, bicyclo[2.2.1]heptanyl, or bicyclo[2.2.2]octanyl.

The term “C₃₋₇cycloalkoxy” denotes C₃₋₇cycloalkyl-O-.



The term “COR⁹” denotes

The term “oxo” denotes a divalent oxygen atom =O.

The term “phenylene” denotes divalent phenyl group.

The term “pyrazolylen” denotes divalent pyrazolyl group.

The term “pharmaceutically acceptable salts” denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts.

The term “pharmaceutically acceptable acid addition salt” denotes those pharmaceutically acceptable salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, and salicylic acid.

The term “pharmaceutically acceptable base addition salt” denotes those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from pharmaceutically acceptable organic
5 nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine,
10 methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, and polyamine resins.

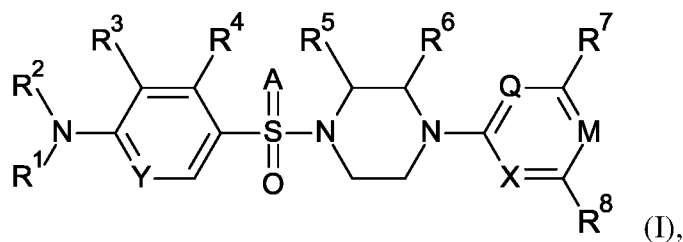
The term “A pharmaceutically active metabolite” denotes a pharmacologically active product produced through metabolism in the body of a specified compound or salt thereof. After entry into the body, most drugs are substrates for chemical reactions that may change their
15 physical properties and biologic effects. These metabolic conversions, which usually affect the polarity of the compounds of the invention, alter the way in which drugs are distributed in and excreted from the body. However, in some cases, metabolism of a drug is required for therapeutic effect.

The term “therapeutically effective amount” denotes an amount of a compound or
20 molecule of the present invention that, when administered to a subject, (i) treats or prevents the particular disease, condition or disorder, (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. The therapeutically effective amount will vary depending on the compound, the disease state being
25 treated, the severity of the disease treated, the age and relative health of the subject, the route and form of administration, the judgement of the attending medical or veterinary practitioner, and other factors.

The term “pharmaceutical composition” denotes a mixture or solution comprising a therapeutically effective amount of an active pharmaceutical ingredient together with
30 pharmaceutically acceptable excipients to be administered to a mammal, e.g., a human in need thereof.

INHIBITOR OF UDP-2,3-DIACYLGLUCOSAMINE HYDROLASE (LpxH)

The present invention relates to (i) a compound of formula (I),



wherein

5 R^1 is COR^9 ; wherein

R^9 is ((hydroxy C_{1-6} alkyl)amino) C_{1-6} alkyl,

1-oxa-2,9-diazaspiro[4.5]dec-2-enyl,

4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazinyl,

4,6-dihydropyrrolo[3,4-c]pyrazolyl substituted by C_{1-6} alkyl,

10 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl,

indanyl substituted by amino or amino C_{1-6} alkylamino,

isoindolinyl,

piperazinyl C_{1-6} alkyl,

pyrazolo[1,5-a]pyrimidinyl,

15 pyrazolyl substituted once or twice by the substituents independently selected from

amino C_{1-6} alkyl, azetidiny, C_{1-6} alkyl and carboxy,

pyridinyl substituted by (amino C_{1-6} alkylamino) C_{1-6} alkyl, or

phenyl substituted once or twice by the substituents independently selected from

((amino(carboxy) C_{1-6} alkyl)amino) C_{1-6} alkyl, ((amino C_{1-6} alkyl)-3-

20 azabicyclo[3.1.0]hexanyl) C_{1-6} alkyl, ((amino C_{1-6} alkyl)pyrrolidinyl) C_{1-6} alkyl,

((amino C_{3-7} cycloalkyl) C_{1-6} alkylamino) C_{1-6} alkyl, ((amino C_{3-7}

7cycloalkyl)pyrrolidinyl) C_{1-6} alkyl, ((oxooxazolidinyl) C_{1-6} alkylamino) C_{1-6} alkyl,

((oxopyrrolidinyl) C_{1-6} alkylamino) C_{1-6} alkyl, ((piperidinyl) C_{1-6} alkylamino) C_{1-6}

6alkyl, (3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[3,4-b]pyrrolyl) C_{1-6} alkyl, (3,6-

25 diazabicyclo[3.1.1]heptanyl) C_{1-6} alkyl, (amino-2-azaspiro[3.3]heptanyl) C_{1-6}

6alkyl, (amino-5-azaspiro[2.4]heptanyl) C_{1-6} alkyl, (amino C_{1-6} alkyl)piperazinyl,

(amino C_{1-6} alkyl)pyrrolidinyl, (amino C_{1-6} alkylamino) C_{1-6} alkyl,

(aminopyrrolidinyl) C_{1-6} alkyl, (C_{1-6} alkyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-

30 c]pyrrolyl) C_{1-6} alkyl, (diamino C_{1-6} alkylcarbonyl)amino, (morpholinyl C_{1-6}

6alkylamino) C_{1-6} alkyl, (piperazinyl C_{1-6} alkylamino) C_{1-6} alkyl, (piperidinyl C_{1-6}

- alkylamino)C₁₋₆alkyl, [((C₁₋₆alkyl)₂aminocarbonylC₁₋₆alkyl)amino]C₁₋₆alkyl, [(hydroxyC₁₋₆alkyl)₂amino]C₁₋₆alkylamino]C₁₋₆alkyl, 2,5-diazabicyclo[2.2.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, aminoC₁₋₆alkoxy, aminoC₁₋₆alkyl, aminopyrrolidinyl, azetidinyC₁₋₆alkoxy, azetidinyC₁₋₆alkylamino, C₁₋₆alkylcarbonyloxy, C₁₋₆alkoxy, carboxy, hydroxy and piperazinyl;
- R² is H;
- R³ is H, hydroxy or C₁₋₆alkoxy; or
- R² and R³ together with the atoms they are attached to form a pyrrolidinyl;
- 10 R⁴ is H, hydroxy or C₁₋₆alkoxy;
- R⁵ is H or C₁₋₆alkyl;
- R⁶ is H or C₁₋₆alkyl; or
- R⁵ and R⁶ together with the atoms they are attached to form a C₃₋₇cycloalkyl;
- R⁷ is halogen, cyano, haloC₁₋₆alkyl or C₁₋₆alkoxycarbonyl;
- 15 R⁸ is H, halogen, cyano, amino, C₃₋₇cycloalkoxy, C₁₋₆alkyl, C₁₋₆alkoxy or haloC₁₋₆alkyl;
- Y is CH or N;
- A is O, N(CN), or N(C₁₋₆alkyl);
- Q is CH or N;
- X is CH or N;
- 20 M is N or CR¹⁰; wherein R¹⁰ is H, halogen, C₁₋₆alkyl or C₃₋₇cycloalkyl;
- with the proviso that Q, X and M are not N simultaneously;
- or a pharmaceutically acceptable salt thereof.

A further embodiment of present invention is (ii) a compound of formula (I), wherein R¹ is COR⁹; wherein

- 25 R⁹ is 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl,
- indanyl substituted by amino or aminoC₁₋₆alkylamino,
- isoindolinyl,
- pyrazolo[1,5-a]pyrimidinyl,
- pyridinyl substituted by (aminoC₁₋₆alkylamino)C₁₋₆alkyl, or
- 30 phenyl substituted once or twice by the substituents independently selected from
- ((aminoC₁₋₆alkyl)-3-azabicyclo[3.1.0]hexanyl)C₁₋₆alkyl, (aminoC₁₋₆alkyl)pyrrolidinyl, (aminoC₁₋₆alkylamino)C₁₋₆alkyl, aminoC₁₋₆alkoxy,

aminoC₁₋₆alkyl, aminopyrrolidinyl, azetidinyC₁₋₆alkoxy, carboxy and piperazinyl.

A further embodiment of present invention is (iii) a compound of formula (I) according to (i) or (ii), or a pharmaceutically acceptable salt thereof, wherein R¹ is COR⁹; wherein R⁹ is 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl, aminoindanyl, (3-aminopropylamino)indanyl, isoindolinyl, pyrazolo[1,5-a]pyrimidinyl, ((3-aminopropylamino)methyl)pyridinyl, ((3-aminopropylamino)methyl)phenyl, ((3-aminopropylamino)ethyl)phenyl, carboxyphenyl, (aminoethoxy)phenyl, (azetidin-3-ylmethoxy)phenyl, (aminopyrrolidin-1-yl)phenyl, (aminoethyl)phenyl, (piperazin-1-yl)phenyl, (3-aminopropoxy)₂phenyl, (1-(3-aminopropyl)pyrrolidin-2-yl)phenyl, (1-(3-aminopropyl)pyrrolidin-3-yl)phenyl or [[1-(aminomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)methyl]phenyl.

A further embodiment of present invention is (iv) a compound of formula (I), according to any one of (i) to (iii), or a pharmaceutically acceptable salt thereof, wherein R² is H; R³ is H; or R² and R³ together with the atoms they are attached to form a pyrrolidinyl.

A further embodiment of present invention is (v) a compound of formula (I), according to any one of (i) to (iv), wherein R⁴ is H; R⁵ is H; and R⁶ is H.

A further embodiment of present invention is (vi) a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (v), wherein R⁷ is halogen or haloC₁₋₆alkyl.

A further embodiment of present invention is (vii) a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (vi), wherein R⁷ is bromo, trifluoromethyl or difluoroethyl.

A further embodiment of present invention is (viii) a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (vii), wherein R⁸ is halogen or C₁₋₆alkyl.

A further embodiment of present invention is (ix) a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (viii), wherein R⁸ is chloro or methyl.

A further embodiment of present invention is (x) a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (ix), wherein Y is CH.

A further embodiment of present invention is (xi) a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (x), wherein A is O.

A further embodiment of present invention is (xii) a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xi), wherein X is N.

A further embodiment of present invention is (xiii) a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of (i) to (xii), wherein M is CH.

5 A further embodiment of present invention is (xiv) a compound of formula (I),
R¹ is COR⁹; wherein

R⁹ is 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl,

indanyl substituted by amino or aminoC₁₋₆alkylamino,

isoindolinyl,

10 pyrazolo[1,5-a]pyrimidinyl,

pyridinyl substituted by (aminoC₁₋₆alkylamino)C₁₋₆alkyl, or

phenyl substituted once or twice by the substituents independently selected from

((aminoC₁₋₆alkyl)-3-azabicyclo[3.1.0]hexanyl)C₁₋₆alkyl, (aminoC₁₋

6alkyl)pyrrolidinyl, (aminoC₁₋₆alkylamino)C₁₋₆alkyl, aminoC₁₋₆alkoxy,

15 aminoC₁₋₆alkyl, aminopyrrolidinyl, azetidinyC₁₋₆alkoxy, carboxy and
piperazinyl;

R² is H;

R³ is H; or

R² and R³ together with the atoms they are attached to form a pyrrolidinyl;

20 R⁴ is H;

R⁵ is H;

R⁶ is H;

R⁷ is halogen or haloC₁₋₆alkyl;

R⁸ is halogen or C₁₋₆alkyl;

25 Y is CH;

A is O;

Q is CH or N;

X is N;

M is CH;

30 or a pharmaceutically acceptable salt thereof.

A further embodiment of present invention is (xv) a compound of formula (I),
R¹ is COR⁹; wherein R⁹ is 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl, aminoindanyl, (3-aminopropylamino)indanyl, isoindolinyl, pyrazolo[1,5-a]pyrimidinyl, ((3-

aminopropylamino)methyl)pyridinyl, ((3-aminopropylamino)methyl)phenyl, ((3-aminopropylamino)ethyl)phenyl, carboxyphenyl, (aminoethoxy)phenyl, (azetidin-3-ylmethoxy)phenyl, (aminopyrrolidin-1-yl)phenyl, (aminoethyl)phenyl, (piperazin-1-yl)phenyl, (3-aminopropoxy)₂phenyl, (1-(3-aminopropyl)pyrrolidin-2-yl)phenyl, (1-(3-aminopropyl)pyrrolidin-3-yl)phenyl or [[1-(aminomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)methyl]phenyl;

R² is H;

R³ is H; or

R² and R³ together with the atoms they are attached to form a pyrrolidinyl;

10 R⁴ is H;

R⁵ is H;

R⁶ is H;

R⁷ is bromo, trifluoromethyl or difluoroethyl;

R⁸ is chloro or methyl;

15 Y is CH;

A is O;

Q is CH or N;

X is N;

M is CH;

20 or a pharmaceutically acceptable salt thereof.

Another embodiment of present invention is a compound of formula (I) or (Ia) selected from the following:

4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

25 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[(3-Aminopropylamino)methyl]-N-[4-[4-[5-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

30 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[3-chloro-5-(trifluoromethyl) phenyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[(3-Aminopropylamino)methyl]-N-[4-[4-[2-chloro-6-(trifluoromethyl)pyrimidin-4-yl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[(3-Aminopropylamino)methyl]-N-[4-[4-[2-amino-6-(trifluoromethyl)pyrimidin-4-yl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[(3-Aminopropylamino)methyl]-N-[4-[4-(4-bromo-6-chloro-2-pyridyl)piperazin-1-yl]sulfonylphenyl]benzamide;

5 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[5-cyclopropyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-(cyclopropoxy)-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

10 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-ethoxy-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-ethyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[(3-Aminopropylamino)methyl]-N-[4-[4-[4-(trifluoromethyl)pyrimidin-2-yl]piperazin-1-yl]sulfonylphenyl]benzamide;

15 4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-[5-methyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-(4,5-dichloro-2-pyridyl)piperazin-1-yl]sulfonylphenyl]benzamide;

20 4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-[4-cyano-6-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-[6-cyano-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-[6-chloro-4-(1,1-difluoroethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

25 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-methyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

Methyl 2-[4-[4-[3-[(3-aminopropylamino)methyl]benzoyl]amino]phenyl]sulfonylpiperazin-1-yl]-6-chloro-pyridine-4-carboxylate;

30 3-[(3-Aminopropylamino)methyl]-N-[4-[4-(6-chloro-4-cyano-2-pyridyl)piperazin-1-yl]sulfonylphenyl]benzamide;

3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-2-methyl-piperazin-1-yl]sulfonylphenyl]benzamide;

3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-3-methyl-piperazin-1-yl]sulfonylphenyl]benzamide;

3-[(3-Aminopropylamino)methyl]-N-[4-[[5-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-2,5-diazabicyclo[4.2.0]octan-2-yl]sulfonyl]phenyl]benzamide;

5 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

3-[2-(3-Aminopropylamino)ethyl]-N-[4-[S-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-N-cyano-sulfonimidoyl]phenyl]benzamide;

10 3-[(3-aminopropylamino)methyl]-N-[4-[S-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-N-methyl-sulfonimidoyl]phenyl]benzamide;

3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-3-methoxy-phenyl]benzamide;

3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-3-hydroxy-phenyl]benzamide;

15 4-[(3-Aminopropylamino)methyl]-N-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-2-pyridyl]benzamide;

3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-2-methoxy-phenyl]benzamide;

20 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-2-hydroxy-phenyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methyl-4,6-dihydropyrrolo[3,4-c]pyrazole-5-carboxamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazole-5-carboxamide;

25 [5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-pyrazolo[1,5-a]pyrimidin-3-yl-methanone;

4-[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]-2-methyl-pyrazole-3-carboxylic acid;

30 [1-(Azetidin-3-yl)pyrazol-4-yl]-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]methanone;

[1-(3-Aminopropyl)pyrazol-4-yl]-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]methanone;

[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)methanone;

[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-(1-oxa-2,9-diazaspiro[4.5]dec-2-en-3-yl)methanone;

5 *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-piperazin-1-yl-acetamide;

1-[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-2-(2-hydroxyethylamino)ethanone;

10 2-[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]benzoic acid;

[2-Acetoxy-4-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]phenyl] acetate;

N-[4-[4-[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]piperazin-1-yl]sulfonylphenyl]-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxamide;

15 *N*-[4-[4-[6-methyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]isoindoline-5-carboxamide;

20 *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-(2,5-diazabicyclo[2.2.1]heptan-2-yl)benzamide;

3-(2-Aminoethoxy)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

3-(Azetidin-3-ylmethylamino)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

25 3-(Azetidin-3-ylmethoxy)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[(3*R*)-3-aminopyrrolidin-1-yl]benzamide;

30 *N*-[4-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[3,6-diazabicyclo[3.2.0]heptan-3-yl]benzamide;

3-(2-Aminoethyl)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-piperazin-1-yl-benzamide;

2-Amino-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]indane-5-carboxamide;

5 5-(Aminomethyl)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-hydroxy-benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-(2,4-diaminobutanoylamino)benzamide;

10 4-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]pyridine-2-carboxamide;

6-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]pyridine-2-carboxamide;

5-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]pyridine-3-carboxamide;

15 2-(3-Aminopropylamino)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]indane-5-carboxamide;

3-(3-Aminopropylamino)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]indane-5-carboxamide;

20 *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methoxy-5-[(5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-*c*]pyrrol-1-yl)methyl]benzamide;

1-(3-Aminopropylamino)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]indane-5-carboxamide;

3,4-Bis(3-Aminopropoxy)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

25 3-[1-(3-Aminopropyl)pyrrolidin-2-yl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

3-[1-(3-Aminopropyl)pyrrolidin-3-yl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

30 3-[4-(3-Aminopropyl)piperazin-1-yl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[2-(3-Aminopyrrolidin-1-yl)ethyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[2-(7-Amino-2-azaspiro[3.3]heptan-2-yl)ethyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-4-[2-(5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-*c*]pyrrol-1-yl)ethyl]benzamide;

5 *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-4-[[2-(2-aminoethyl)pyrrolidin-1-yl]methyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-4-[2-(3-morpholinopropylamino)ethyl]benzamide;

10 4-[2-(2-Amino-5-azaspiro[2.4]heptan-5-yl)ethyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-4-[2-(3,6-diazabicyclo[3.1.1]heptan-6-yl)ethyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[(4-piperidylmethylamino)methyl]benzamide;

15 3-[[3-(3-Aminocyclobutyl)methylamino]methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[(3-piperazin-1-ylpropylamino)methyl]benzamide;

20 3-[[3-(1-Aminocyclopropyl)pyrrolidin-1-yl]methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

3-[[3-[Bis(2-hydroxyethyl)amino]propylamino]methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methoxy-5-[[3-(4-piperidyl)propylamino]methyl]benzamide;

25 3-[[1-(Aminomethyl)-3-azabicyclo[3.1.0]hexan-3-yl]methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

(2*R*)-2-Amino-4-[[3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbonyl]phenyl]methylamino]butanoic acid;

30 *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[[2-oxooxazolidin-4-yl]methylamino]methyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[[5-oxopyrrolidin-3-yl]methylamino]methyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[[[3-(dimethylamino)-3-oxo-propyl]amino]methyl]benzamide;

5-*(3,3a,4,5,6,6a-Hexahydro-2H-pyrrolo[3,4-b]pyrrol-1-ylmethyl)-N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methoxy-benzamide; and

5 2-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;
or a pharmaceutically acceptable salt thereof.

A further embodiment of present invention is (xviii) a compound or pharmaceutically acceptable salt according to any one of (i) to (xvi) for use as therapeutically active substance.

10 A further embodiment of present invention is (xix) a pharmaceutical composition comprising a compound in accordance with any one of claims (i) to (xvi) and a therapeutically inert carrier.

A further embodiment of present invention is (xx) the use of a compound according to any one of (i) to (xvi) for the inhibition of LpxH.

15 A further embodiment of present invention is (xxi) the use of a compound according to any one of (i) to (xvi) for the treatment or prophylaxis of bacterial infection, particularly the bacteria is gram-negative bacteria.

A further embodiment of present invention is (xxii) the use of a compound according to any one of (i) to (xvi) for the preparation of a medicament for the treatment or prophylaxis of
20 bacterial infection, particularly the bacteria is gram-negative bacteria.

A further embodiment of present invention is (xxiii) the use of a compound according to (xxi) or (xxii), wherein the gram-negative bacteria is selected from Enterobacteriaceae, Neisseria gonorrhoeae, Haemophilus influenzae, Helicobacter pylorus, Acinetobacter baumannii and Pseudomonas aeruginosa.

25 A further embodiment of present invention is (xxiv) the use of a compound according to (xxiii), wherein the gram-negative bacteria is Enterobacteriaceae, wherein Enterobacteriaceae is Klebsiella pneumoniae or Escherichia coli.

A further embodiment of present invention is (xxv) a compound or pharmaceutically acceptable salt according to any one of (i) to (xvi) for use in the treatment or prophylaxis of
30 bacterial infection, particularly the bacteria is gram-negative bacteria.

A further embodiment of present invention is (xxvi) a compound according to (xxv), wherein the gram-negative bacteria is selected from Enterobacteriaceae, Neisseria gonorrhoeae,

Haemophilus influenzae, Helicobacter pylorus, Acinetobacter baumannii and Pseudomonas aeruginosa.

A further embodiment of present invention is (xxvii) a compound according to (xxvi), wherein the gram-negative bacteria is Enterobacteriaceae, wherein Enterobacteriaceae is

5 Klebsiella pneumoniae or Escherichia coli.

A further embodiment of present invention is (xxviii) a compound or pharmaceutically acceptable salt according to any one of (i) to (xvi), when manufactured according to a process of (xvii).

A further embodiment of present invention is (xxix) a method for the treatment or
10 prophylaxis of bacterial infection, particularly the bacteria is gram-negative bacteria, which method comprises administering a therapeutically effective amount of a compound as defined in any one of (i) to (xvi), to a patient in need thereof.

PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

15 Another embodiment provides pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. In one example, compounds of formula (I) may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable
20 carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula (I) is formulated in an acetate buffer, at pH 5. In another embodiment, the compounds of formula (I) are sterile. The compound may be stored,
25 for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the
30 cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The “effective amount” of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to reduced bacterial load or improve host survival through the

inhibition of Lipid A biosynthesis by targeting LpxH enzyme. For example, such amount may be below the amount that is toxic to normal cells, or the mammal as a whole.

In one example, the pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.1 to 1000 mg/kg, alternatively about 1 to 100 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. In another embodiment, oral unit dosage forms, such as tablets and capsules, preferably contain from about 5 to about 5000 mg of the compound of the invention.

The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

An example of a suitable oral dosage form is a tablet containing about 10 to 500 mg of the compound of the invention compounded with about 40 to 400mg anhydrous lactose, about 5 to

50 mg sodium croscarmellose, about 5 to 50 mg polyvinylpyrrolidone (PVP) K30, and about 1 to 10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 5 to 1000 mg) of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

An embodiment, therefore, includes a pharmaceutical composition comprising a compound of Formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof. In a further embodiment includes a pharmaceutical composition comprising a compound of Formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

Another embodiment includes a pharmaceutical composition comprising a compound of formula (I) for use in the treatment and/or prevention of bacterial infections.

The following composition A and B illustrate typical compositions of the present invention, but serve merely as representative thereof.

Composition A

A compound of the present invention can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

	<u>Per tablet</u>
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	<u>20 mg</u>
	425 mg

Composition B

A compound of the present invention can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

Per capsule

-20-

Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
5 Magnesium stearate	<u>0.5 mg</u>
	220.0 mg

INDICATIONS AND METHODS OF TREATMENT

10 The compounds of the invention are inhibitors of the LpxH enzyme, a key enzyme of the LPS synthesis pathway that is essential in most gram-negative bacteria. Accordingly, the compounds of the invention can prevent bacterial growth of susceptible organisms and are useful for: preventing or treating a bacterial infection, preferably a Gram-negative bacterial infection (all claimed) e.g. nosocomial pneumonia, urinary tract infections, systemic infections

15 (bacteraemia and sepsis), skin and soft tissue infections, surgical infections, eye infections, intraabdominal infections, lung infections and diabetic foot infections caused by Gram-negative bacteria e.g. third generation cephalosporins- and carbapenem- resistant *Enterobacteriaceae* (e.g. *Klebsiella pneumoniae*, *Escherichia coli*) and multi-drug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* or *Acinetobacter* spp., e.g. *Neisseria gonorrhoeae*,

20 *Haemophilus influenzae*, *Helicobacter pylorus* e.g. *Bacteroides* spp. e.g. *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides distasonis*, *Campylobacter jejuni*, *Campylobacter fetus* or *Campylobacter coli*, *Francisella tularensis* and *Providencia* spp. e.g. *Providencia stuartii*, *Providencia rettgeri* or *Providencia alcalifaciens* and *Pseudomonas* spp.; and for cleaning purposes e.g. to remove pathogenic microbes and bacteria from surgical instruments,

25 catheters and artificial implants or to make a room or an area aseptic.

The products of the invention can be administered, for example, parenterally e.g. by injection, or administered orally, perorally, such as in the form of tablets, coated tablets, dragees, hard and soft gelatin capsules, solutions, emulsions or suspensions, or rectally, such as in the form of suppositories. Pharmaceutical compositions containing these compounds can be

30 prepared using conventional procedures familiar to those skilled in the art, such as by combining the ingredients into a dosage form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, the usual pharmaceutical adjuvants. It is contemplated that the compounds are ultimately embodied into compositions of suitable oral,

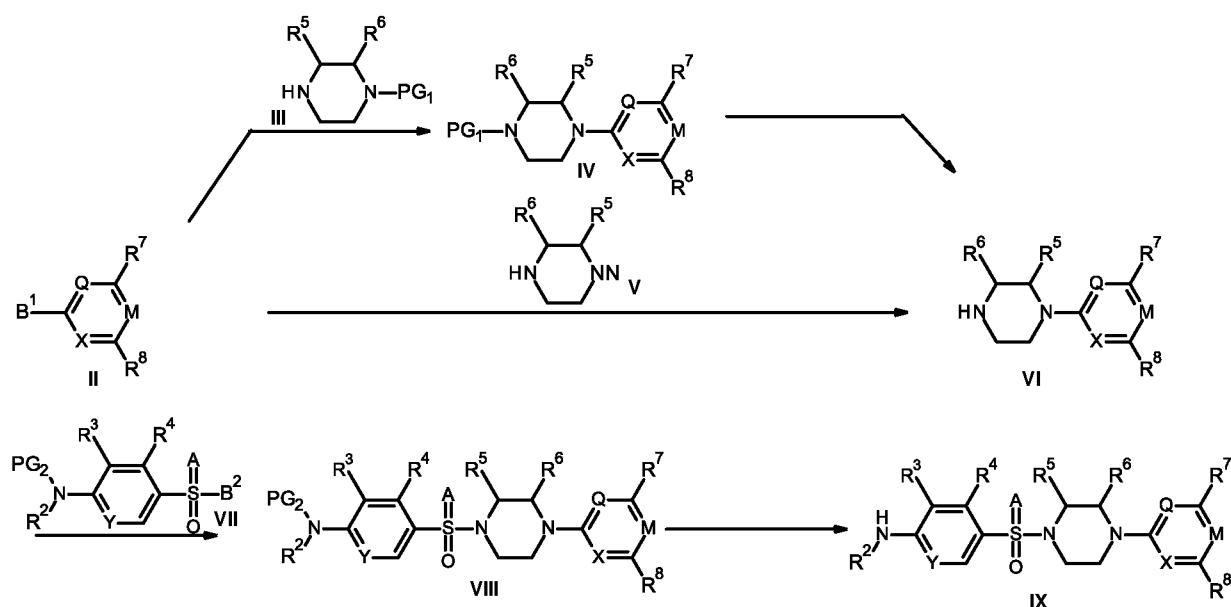
parenteral or topical dosage forms. The compositions of this invention can contain, as optional ingredients, any of the various adjuvants, which are used ordinarily in the production of pharmaceutical preparations. Thus, for example, in formulating the present compositions into the desired oral dosage forms, one may use, as optional ingredients, fillers, such as co-precipitated
5 aluminum hydroxide-calcium carbonate, di-calcium phosphate or lactose; disintegrating agents such as maize starch; and lubricating agents, such as talc, calcium stearate, and the like. It should be fully understood, however, that the optional ingredients herein named are given by way of example only and that the invention is not restricted to the use hereof. Other such adjuvants, which are well known in the art, can be employed in carrying out this invention. Suitable as such
10 carrier materials are not only inorganic, but also organic carrier materials. Thus, for tablets, coated tablets, dragees and hard gelatin capsules there can be used, for example, lactose, maize starch or derivatives thereof, talc, stearic acid or its salts. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active substance; no carriers are, however, required in the case of
15 soft gelatin capsules). Suitable carrier materials for the preparation of solutions and syrups are, for example, water, polyols, saccharose, invert sugar and glucose. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. As pharmaceutical adjuvants there are contemplated the usual preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorings, salts for varying the
20 osmotic pressure, buffers, coating agents and antioxidants.

SYNTHESIS

The compounds of the present invention can be prepared by any conventional means. Suitable processes for synthesizing these compounds as well as their starting materials are provided in the schemes below and in the examples. All substituents, in particular, R^1 , R^2 , R^3 , R^4 ,
25 Y, Q^1 , Q^2 , Q^3 , Q^4 and Q^5 are defined above. Furthermore, and unless explicitly otherwise stated, all reactions, reaction conditions, abbreviations and symbols have the meanings well known to a person of ordinary skill in organic chemistry.

General synthetic routes for preparing the compound of formula (I) are shown below.

Scheme 1:

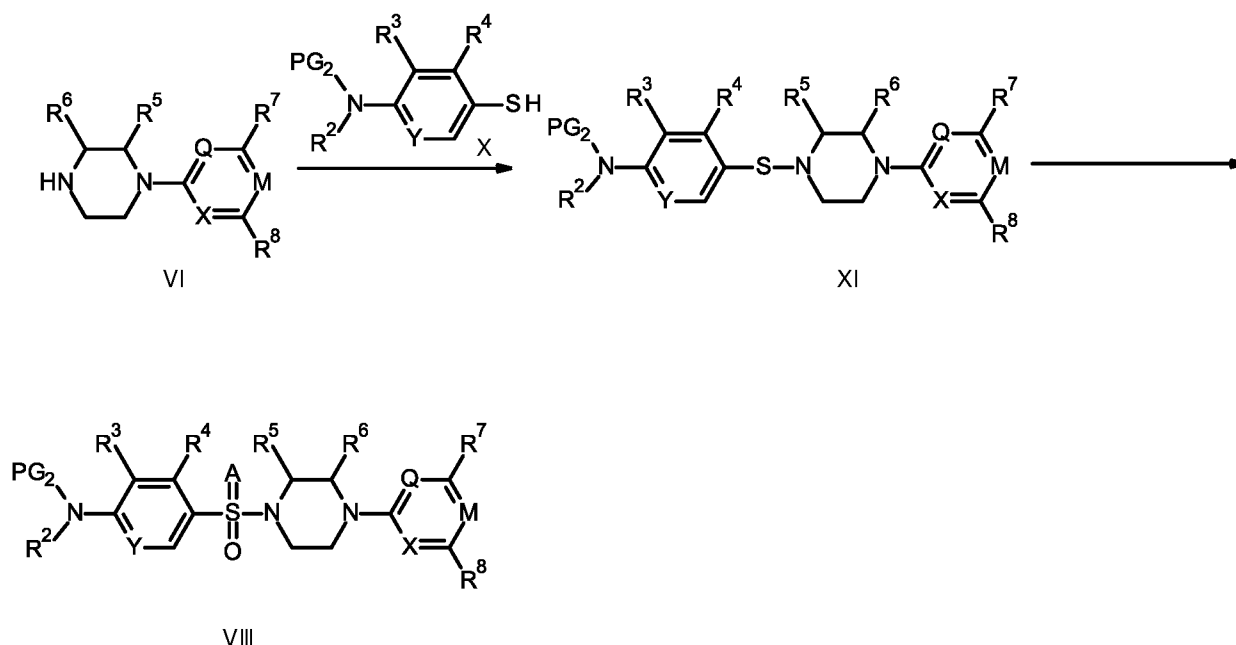


wherein B¹ and B² are halogen; PG¹ is a protecting group, such as *tert*-butoxycarbonyl or benzyloxycarbonyl group; PG² is a protecting group, such as acetyl group.

Nucleophilic substitution reaction between compound of formula **(II)** and compound of formula **(III)** affords compound of formula **(IV)**, which is deprotected with a suitable acid, such as TFA, or reduction reagents, such as palladium on carbon under H₂, to afford compound of formula **(VI)**. Alternatively, compound of formula **(VI)** could be obtained directly using nucleophilic substitution reaction between compound of formula **(II)** and compound of formula **(V)** in the presence a suitable base, such as TEA. Compound of formula **(VIII)** could be obtained from a sulfonating reaction between halogenated phenyl sulfonyl chlorides **(VII)** and compound of formula **(VI)**. The formation of compound **(IX)** can be achieved by treating compound of formula **(VIII)** with a suitable acid, such as HCl, or a base, such as K₂CO₃. .

Scheme 2:

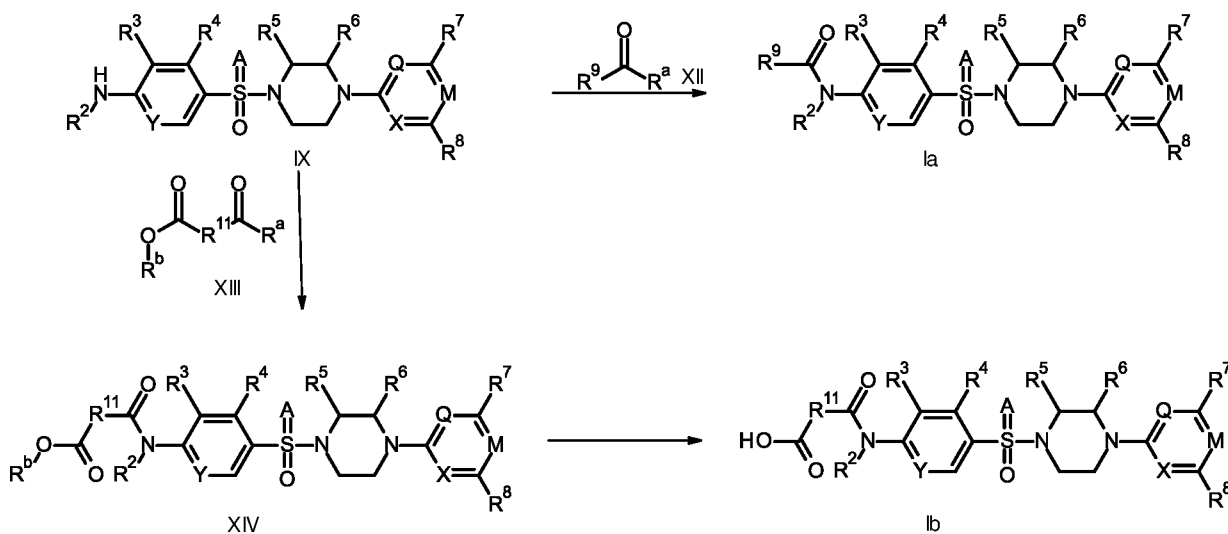
-23-



wherein PG^2 is a protecting group, such as acetyl group.

Alternatively, compound of formula (**VIII**) can also be prepared in the process illustrated in the scheme 2. Compound of formula (**XI**) can be obtained by coupling reaction between compound of formula (**VI**) and compound of formula (**X**) in the presence of catalyst such as CuO. Oxidation of compound of formula (**XI**) will give compound of formula (**VIII**) in the presence of suitable oxidant reagent, such as PIDA.

Scheme 3:

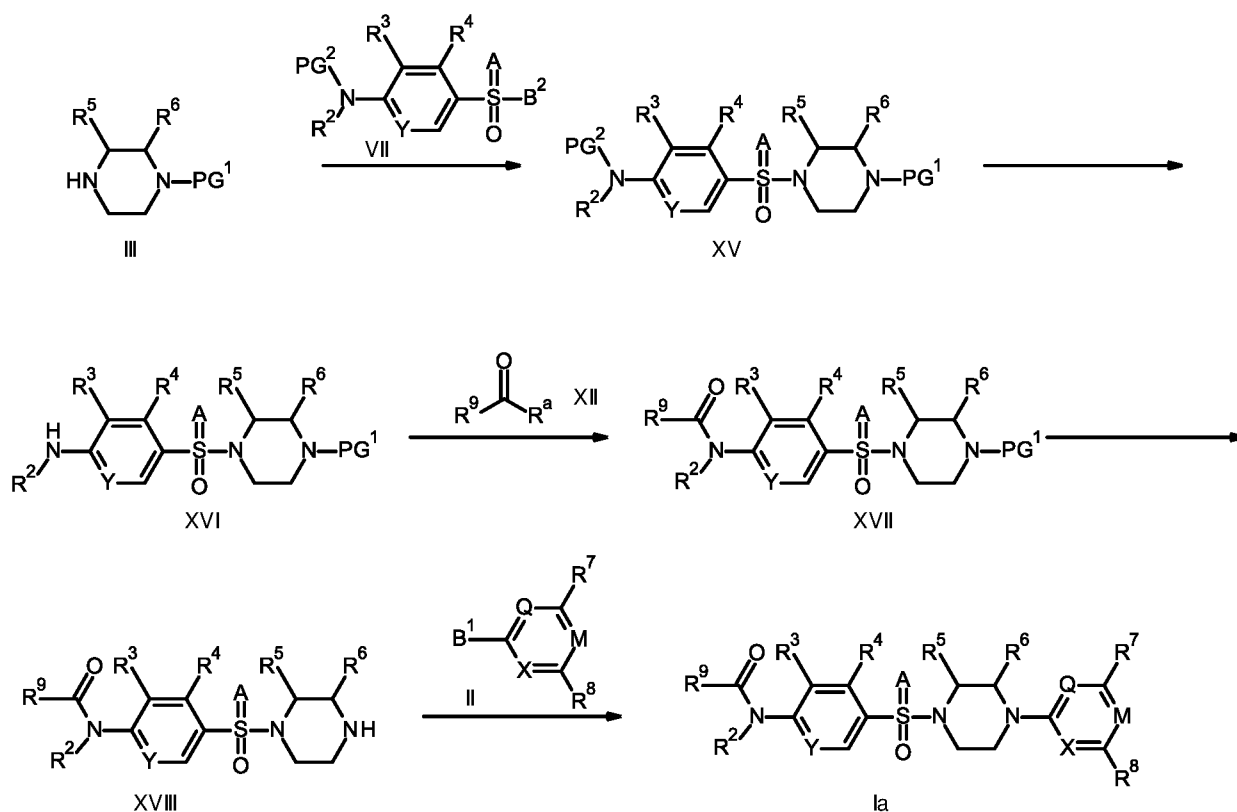


wherein R^a is halogen or OH; R^b is C_{1-6} alkyl, such as methyl or ethyl, R^{11} is pyrazolylen, phenylene or amino C_{1-6} alkylamino C_{1-6} alkylene.

The compound of formula (Ia) can be prepared by coupling reaction between compound of formula (IX) and compound of formula (XII) in the presence of condensation reagent such as TCFH or acylation reaction in the presence of base such as TEA.

The compound of formula (Ib) can be prepared by starting with coupling reaction or
5 acylation reaction between compound of formula (IX) and compound of formula (XIII) to afford compound of formula (XIV). Hydrolysis of compound of formula (XIV) in the presence a suitable base, such as LiOH, affords compound of formula of (Ib).

Scheme 4:



10

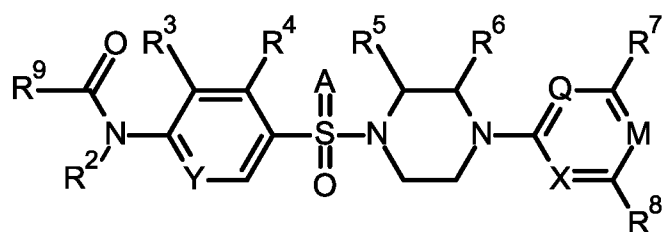
Compound of formula (XV) can be obtained from a nucleophilic substitution reaction between compound of formula (III) and compound of formula (VII) in the presence a suitable base such as DIPEA or TEA. Deprotection of compound of formula (XV) affords compound of formula (XVI) in the presence a suitable acid, such as HCl, or base, such as K_2CO_3 . Compound
15 of formula (XVII) can be obtained by acylation reaction between compound of formula (XVI) and compound of formula (XII) in the presence a suitable base such as TEA. In some cases, compound of formula (XVII) needs to be further protected by another PG^1 . Deprotection of compound of formula (XVII) affords compound of formula (XVIII) using a suitable acid such as TFA or reduction reagents such as palladium on carbon under H_2 atmosphere. The
20 nucleophilic substitution between compound of formula (II) and compound of formula (XVIII)

in the presence of suitable base such as Cs_2CO_3 affords compound of formula (Ia). In some cases, compound of formula (Ia) needs to be further deprotected to remove PG^1 .

Compounds of this invention can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art, e.g. (chiral) HPLC or SFC.

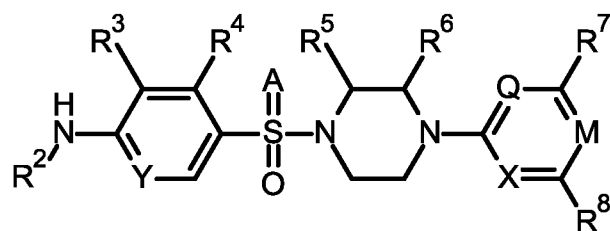
5 This invention also relates to a process for the preparation of a compound of formula (I) comprising any of the following steps:

a) formation of compound of formula (Ia),

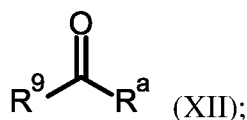


(Ia), via coupling reaction or acylation

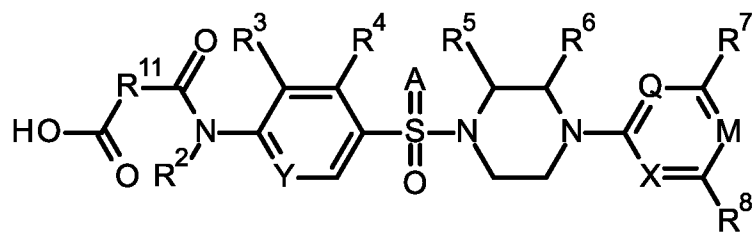
reaction between compound of formula (IX),



10 (IX), and compound of formula (XII),

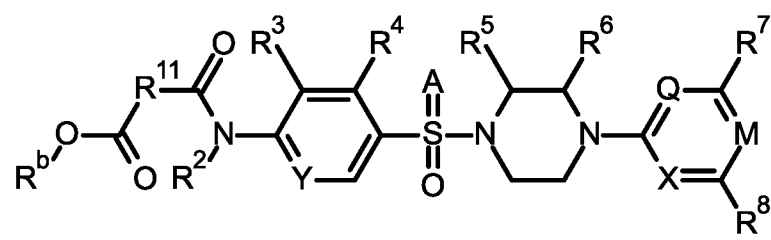


b) formation of compound of formula (Ib),



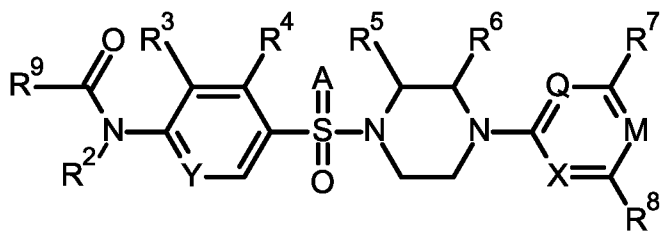
(Ib), via hydrolysis of

compound of formula (XIV),



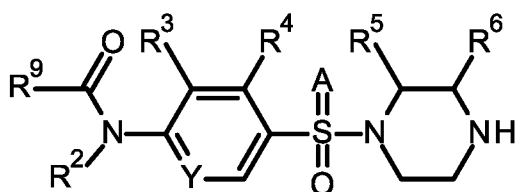
(XIV);

c) formation of compound of formula (Ia),

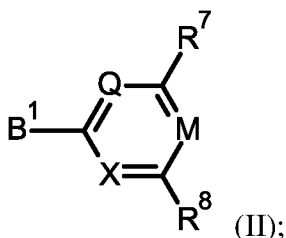


(Ia), via nucleophilic substitution

between compound of formula (XVIII),



(XVIII), and compound of formula (II),



5

wherein B¹ is halogen; PG¹ is a protecting group, such as *tert*-butoxycarbonyl or benzyloxycarbonyl group; PG² is a protecting group, such as acetyl group; R^a is halogen or OH; R^b is C₁₋₆alkyl, such as methyl or ethyl, R¹¹ is pyrazolylene, phenylene or aminoC₁₋₆alkylaminoC₁₋₆alkylene.

10 A compound of formula (I) when manufactured according to the above process is also an object of the invention.

EXAMPLES

15 The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

ABBREVIATIONS

20 The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

Abbreviations used herein are as follows:

aq.: aqueous

	DAST:	diethylaminosulfur trifluoride
	DBU:	1,8-diazabicyclo[5.4.0]undec-7-ene
	DCM:	dichloromethane
	DIPEA:	<i>N,N</i> -Diisopropylethylamine
5	DMAP:	4-dimethylaminopyridine
	DMEDA:	1,2-dimethylethylenediamine
	DMP:	Dess-Martin periodinane
	FA:	formic acid
	FBS:	fetal bovine serum
10	HATU:	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
	IC ₅₀ :	the molar concentration of an inhibitor, which produces 50% of the maximum possible response for that inhibitor.
	HPLC:	high performance liquid chromatography
15	MS (ESI):	mass spectroscopy (electron spray ionization)
	MeCN:	acetonitrile
	MsCl:	methylsulfonyl chloride
	MTBE:	methyl tert-butyl ether
	obsd:	observed
20	PE:	petroleum ether
	PIDA :	phenyliodo(III)diacetate
	TCFH:	Chloro- <i>N,N,N',N'</i> -tetramethylformamidinium hexafluorophosphate
	TFA:	trifluoroacetic acid
	TEA:	triethylamine
25	δ:	chemical shift
	SFC:	supercritical fluid chromatography
	TLC:	thin layer chromatography

GENERAL EXPERIMENTAL CONDITIONS

- 30 Intermediates and final compounds were purified by flash chromatography using one of the following instruments: i) Biotage SP1 system and the Quad 12/25 Cartridge module. ii) ISCO combi-flash chromatography instrument. Silica gel brand and pore size: i) KP-SIL 60 Å, particle

size: 40-60 μm ; ii) CAS registry NO: Silica Gel: 63231-67-4, particle size: 47-60 micron silica gel; iii) ZCX from Qingdao Haiyang Chemical Co., Ltd, pore: 200-300 or 300-400.

Intermediates and final compounds were purified by preparative HPLC on reversed phase column using XBridgeTM Prep-C18 (5 μm , OBDTM 30 $\times$ 100 mm) column, SunFireTM Prep-C18 (5 μm , OBDTM 30 $\times$ 100 mm) column, Phenomenex Synergi-C18 (10 μm , 25 $\times$ 150 mm) or Phenomenex Gemini-C18 (10 μm , 25 $\times$ 150 mm). Waters AutoP purification System (Sample Manager 2767, Pump 2525, Detector: Micromass ZQ and UV 2487, solvent system: acetonitrile and 0.1% ammonium hydroxide in water; acetonitrile and 0.1% FA in water or acetonitrile and 0.1% TFA in water). Or Gilson-281 purification System (Pump 322, Detector: UV 156, solvent system: acetonitrile and 0.05% ammonium hydroxide in water; acetonitrile and 0.225% FA in water; acetonitrile and 0.05% HCl in water; acetonitrile and 0.075% TFA in water; or acetonitrile and water).

For SFC chiral separation, intermediates were separated by chiral column (Daicel chiralpak IC, 5 μm , 30 $\times$ 250 mm), AS (10 μm , 30 $\times$ 250 mm) or AD (10 μm , 30 $\times$ 250 mm) using Mettler Toledo Multigram III system SFC, Waters 80Q preparative SFC or Thar 80 preparative SFC, solvent system: CO₂ and IPA (0.5% TEA in IPA) or CO₂ and MeOH (0.1% NH₃·H₂O in MeOH), back pressure 100bar, detection UV@ 254 or 220 nm.

LC/MS spectra of compounds were obtained using a LC/MS (WatersTM Alliance 2795-Micromass ZQ, Shimadzu Alliance 2020-Micromass ZQ or Agilent Alliance 6110-Micromass ZQ), LC/MS conditions were as follows (running time 3 or 1.5 mins):

Acidic condition I: A: 0.1% TFA in H₂O; B: 0.1% TFA in acetonitrile;

Acidic condition II: A: 0.0375% TFA in H₂O; B: 0.01875% TFA in acetonitrile;

Basic condition I: A: 0.1% NH₃·H₂O in H₂O; B: acetonitrile;

Basic condition II: A: 0.025% NH₃·H₂O in H₂O; B: acetonitrile;

Neutral condition: A: H₂O; B: acetonitrile.

Mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion (MH)⁺.

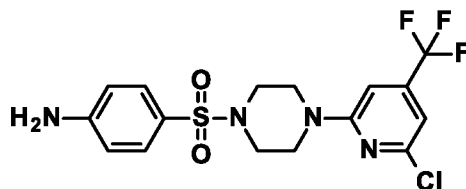
NMR Spectra were obtained using Bruker Avance 400 MHz.

The microwave assisted reactions were carried out in a Biotage Initiator Sixty microwave synthesizer. All reactions involving air-sensitive reagents were performed under an argon or nitrogen atmosphere. Reagents were used as received from commercial suppliers without further purification unless otherwise noted.

PREPARATIVE EXAMPLES

The following examples are intended to illustrate the meaning of the present invention but should by no means represent a limitation within the meaning of the present invention:

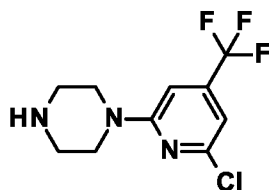
Intermediate 1: 4-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylaniline



5

Int-1

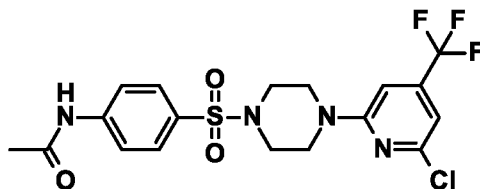
Step 1: 1-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazine



Int-1a

10 To a solution of piperazine (47.86 g, 555.58 mmol) in 1,4-dioxane (150 mL) were added 2,6-dichloro-4-(trifluoromethyl)pyridine (15.0 g, 69.45 mmol) slowly. The mixture was stirred at 60 °C for 1 hour. After completion, the mixture was diluted with water (300 mL) and extracted with EA (200 mL × 3). The combined organic layer was washed with brine (300 mL × 4), dried over anhydrous Na₂SO₄ and concentrated to give compound **Int-1a** (18 g, 67.76 mmol, 97.6%
15 yield) as a white solid. MS obsd.: 265.8 (MH⁺).

Step 2: N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]acetamide



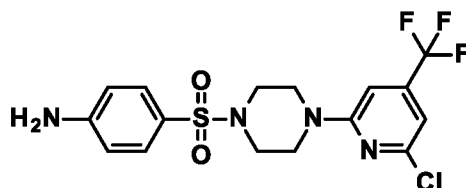
Int-1b

20 To a solution of compound **Int-1a** (500.0 mg, 1.88 mmol) and DIPEA (0.81 mL, 4.63 mmol) in DCM (15 mL) was added 4-acetamidobenzenesulfonyl chloride (468.0 mg, 2.0 mmol) at 0°C. The mixture was slowly warmed up to rt and stirred at rt for 1 hour. After completion, the mixture was poured into water (20 mL) and extracted with DCM (20 mL × 3). The combined organic layer was concentrated under vacuum to give crude product, which was purified by

-30-

silica-gel chromatography (elute with EtOAc:PE = 20%) to afford compound **Int-1b** as a white solid (800 mg, 92% yield). MS obsd. (ESI⁺) [(M+H)⁺]: 463.2.

Step 2: 4-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylaniline



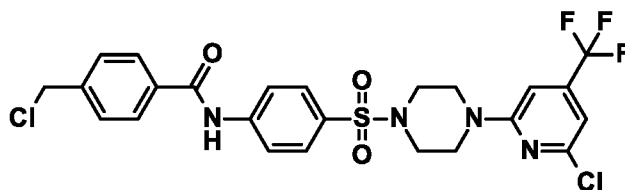
5

Int-1

To a solution of compound **Int-1a** (970.0 mg, 2.1 mmol) in THF (10 mL) was added hydrochloric acid (12 M, 5 mL) at rt. The mixture was heated to 40 °C for 1 hour. After completion, the mixture was concentrate in *vacuo* to give a residue, which was diluted with sat. NaHCO₃ (aq, 30 mL) and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give compound **Int-1** (830 mg, 94.11% yield) as yellow oil. MS obsd. (ESI⁺) [(M+H)⁺]: 421.2.

Intermediate 2: 4-(Chloromethyl)-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

15



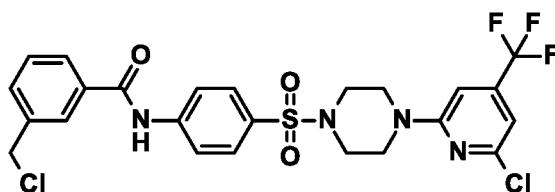
Int-2

To a solution of compound **Int-1** (820.0 mg, 1.95 mmol) and TEA (0.81 mL, 5.85 mmol) in DCM (20 mL) was added 4-(chloromethyl)benzoyl chloride (736.68 mg, 3.9 mmol) at rt and stirred for 1 hour. After completion, the mixture was quenched with water (30 mL) and extracted with DCM (20 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give crude product, which was purified by prep-HPLC (TFA as additive) to give compound **Int-2** (600 mg, 1.05 mmol, 53.7% yield) as yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 573.2.

25

Intermediate 3: 3-(Chloromethyl)-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

-31-

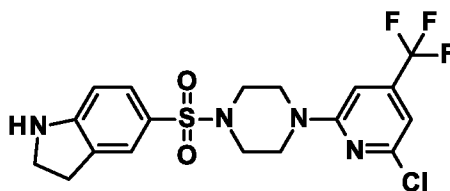
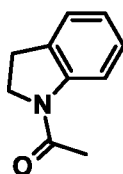
**Int-3**

To a solution of compound **Int-1** (2.0 g, 4.75 mmol) and TEA (1.6 mL, 11.7 mmol) in DCM (40 mL) was added 3-(chloromethyl)benzoyl chloride (1.08 g, 5.7 mmol) at rt and the reaction mixture was stirred for 1 h. After completion, the mixture was quenched with water (50 mL) and extracted with DCM (30 mL $\times$ 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give crude product, which was purified by silica-gel chromatography (elute with EtOAc:PE = 20%) to give **Int-3** (2.0 g, 3.49 mmol, 73.4% yield) as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 573.2.

Intermediate 4:
yl)sulfonylindoline

4:

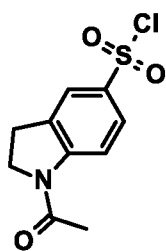
5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-

**Int-4****Step 1: 1-Indolin-1-ylethanone****Int-4a**

A solution of indoline (6.5g, 54.5 mmol) in acetic anhydride (20 mL) was heated at 80 °C for 2 hours. And then, the reaction mixture was concentrated to afford crude **Int-4a** as a yellow gum (8.9 g, 54.6 mmol, 100% yield), which was used in the next step directly. MS obsd. (ESI⁺) [(M+H)⁺]: 162.1.

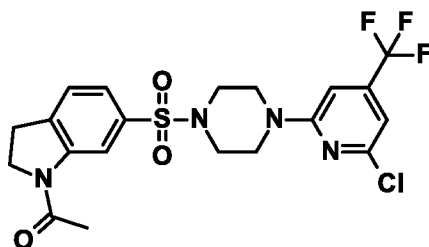
Step 2: 1-Acetyllindoline-5-sulfonyl chloride

-32-

**Int-4b**

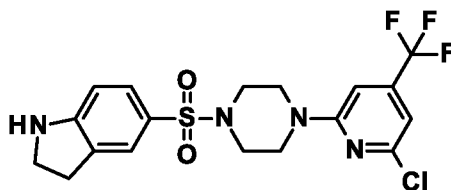
A solution of compound **Int-4a** (8.2g, 50.9 mmol) in sulfurochloridic acid (237 g, 2.03 mol) was stirred at rt for 2 hours. And then, the mixture was poured onto ice, extracted with DCM (100 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated under vacuum to give crude compound **Int-4b** (3.0 g, 22.7 % yield), which was used in the next step directly.

Step 3: 1-[6-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]ethanone

**Int-4c**

To a solution of compound **Int-1a** (1.8 g, 6.78 mmol) and TEA (1.8 g, 17.3 mmol) in DCM (100 mL) was added compound **Int-4b** (1.5 g, 5.8 mmol) portion-wise at 0°C. The mixture was stirred at rt for 2 hours. And then, the mixture was quenched with water (50 mL), extracted with DCM (100 mL × 3). The combined organic layer was concentrated under vacuum to give a crude product, which was purified by silica-gel chromatography (elute with EtOAc:PE = 20%) to afford compound **Int-4c** (2.5 g, 75.3%) as light yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 489.3.

Step 4: 6-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline

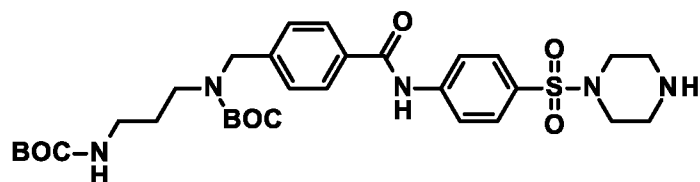
**Int-4**

To a solution of compound **Int-4c** (2.0 g, 4.09 mmol) in THF (20 mL) was added hydrochloric acid (12 M, 5 mL) at rt. The mixture was heated to 70 °C for 1 hour. After

-33-

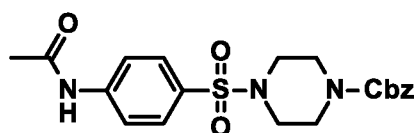
completion, the mixture was concentrate under vacuum to give a residue, which was diluted with sat. NaHCO_3 (30 mL) and extracted with EtOAc (20 mL $\times$ 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give crude compound **Int-4** (1.0 g, 54.7% yield) as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]:
 5 447.2.

Intermediate 5: *Tert*-butyl *N*-[3-(*tert*-butoxycarbonylamino)propyl]-*N*-[[4-[(4-piperazin-1-ylsulfonyl)phenyl]carbamoyl]phenyl]methyl]carbamate



Int-5

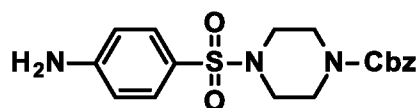
Step 1: Benzyl 4-(4-acetamidophenyl)sulfonylpiperazine-1-carboxylate



Int-5a

To a solution of benzyl piperazine-1-carboxylate (5 g, 22.7 mmol) and 4-acetamidobenzenesulfonyl chloride (5.3 g, 22.7 mmol) in DCM (100 mL) was added TEA (6.88 g, 68.1 mmol) dropwise at rt. The mixture was stirred at rt for 2 hours. And then, the mixture was quenched with NaHCO_3 aq. (100 mL), extracted with DCM (100 mL $\times$ 3). The combined organic layer was concentrated under vacuum to give crude, which was rinsed with hexane to afford desired product **Int-5a** (9.2 g, 97.1 % yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]:
 20 418.2.

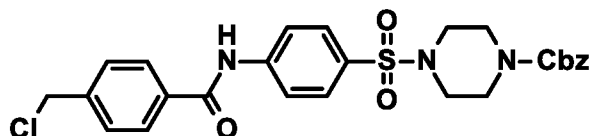
Step 2: Benzyl 4-(4-aminophenyl)sulfonylpiperazine-1-carboxylate



Int-5b

To a mixture of **Int-5a** (9.2 g, 22 mmol) in MeOH (100 mL) was added AcCl (8 mL, 22 mmol) dropwise at rt. The mixture was heated at 60 °C for 4 hours. And then, the reaction mixture was concentrated to afford crude compound **Int-5b** (8.0 g, 96.7 % yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 376.2.

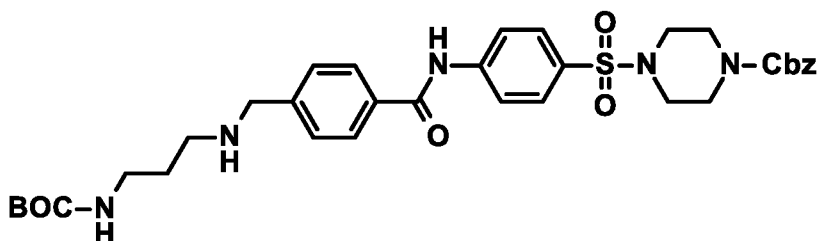
5 **Step 3: Benzyl 4-[4-[[4-(chloromethyl)benzoyl]amino]phenyl]sulfonylpiperazine-1-carboxylate**



Int-5c

10 To a solution of compound **Int-5b** (2.0 g, 5.32 mmol) and TEA (1.6 mL, 11.7 mmol) in DCM (40 mL) was added 4-(chloromethyl)benzoyl chloride (1.08 g, 5.7 mmol) at rt and stirred for 1 hour. After completion, the mixture was quenched with water (50 mL) and extracted with DCM (30 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give crude product, which was purified by
15 silica-gel chromatography (elute with EtOAc:PE = 20%) to give compound **Int-5c** (2.0 g, 73.4% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 528.2.

Step 4: Benzyl 4-[4-[[4-[[3-(tert-butoxycarbonylamino)propylamino]methyl]benzoyl]amino]phenyl]sulfonylpiperazine-1-carboxylate

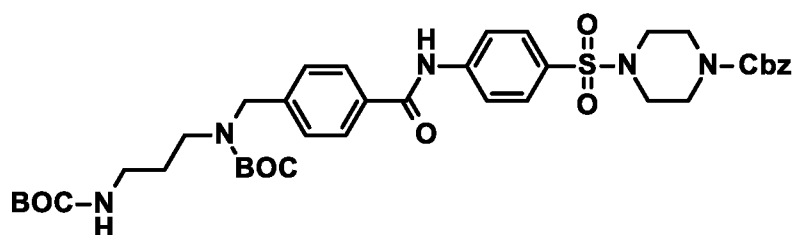


Int-5d

20 A mixture of compound **Int-5c** (2.0 g, 3.78 mmol), DIPEA (2.7 mL, 15.3 mmol) and *tert*-butyl *N*-(3-aminopropyl)carbamate (1.2 mL, 5.6 mmol) in THF (100 mL) was stirred at 70 °C for 16 hours. After completion, the solvent was removed under vacuum and the residue was purified by prep-HPLC (TFA as additive) to afford compound **Int-5d** (1.5 g, 59.5% yield). MS obsd.
25 (ESI⁺) [(M+H)⁺]: 666.3.

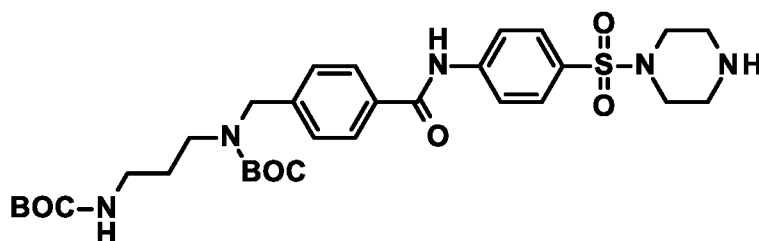
Step 5: Benzyl 4-[4-[[4-[[*tert*-butoxycarbonyl-[3-(*tert*-butoxycarbonylamino)propyl]amino]methyl]benzoyl]amino]phenyl]sulfonylpiperazine-1-carboxylate

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**Int-5e**

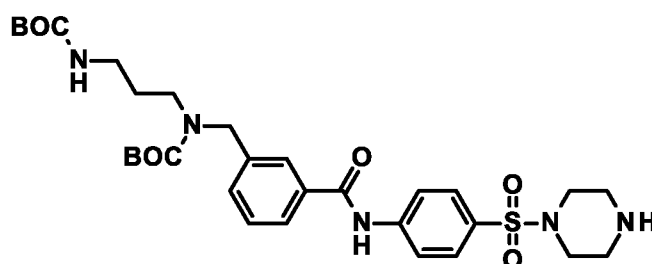
To a mixture of compound **Int-5d** (1.5 g, 2.25 mmol) and DIPEA (1.0 mL, 5.7 mmol) in DCM (40 mL) was added Boc-anhydride (1.0 g, 4.58 mmol) portion-wise at rt and stirred at rt for 1 hour. After completion, the mixture was quenched with saturated NaHCO₃ aq. (40 mL), extracted with DCM (40 mL × 3). The combined organic layer was concentrated under vacuum to give a crude product, which was purified by silica-gel chromatography (elute with MeOH:DCM = 10%) to afford compound **Int-5e** (1.6 g, 2.08 mmol, 92.8% yield). MS obsd. (ESI⁺) [(M+H)⁺]: 766.3.

Step 7: Tert-butyl N-[3-(tert-butoxycarbonylamino)propyl]-N-[[4-[(4-piperazin-1-ylsulfonyl)phenyl]carbamoyl]phenyl]methyl]carbamate

**Int-5**

The mixture of compound **Int-5e** (1.6 g, 2.08 mmol) and Pd/C (200 mg, 10% Pd on Carbon) under H₂ balloon was stirred at rt for 8 hours. After completion, the mixture was filtered and the filtrate was concentrated under vacuum to give crude **Int-5** (1.2 g, 91.3%), which was used in the next step directly. MS obsd. (ESI⁺) [(M+H)⁺]: 632.3.

Intermediate 6: Tert-butyl N-[3-(tert-butoxycarbonylamino)propyl]-N-[[3-[(4-piperazin-1-ylsulfonyl)phenyl]carbamoyl]phenyl]methyl]carbamate



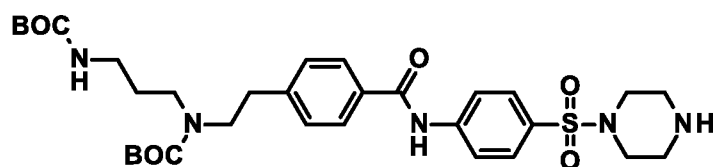
-36-

Int-6

The title compound was prepared in analogy to the preparation of compound **Int-5** by replacing 4-(chloromethyl)benzoyl chloride with 3-(chloromethyl)benzoyl chloride in **Step 3**. Compound **Int-6** (1.0 g) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 623.3.

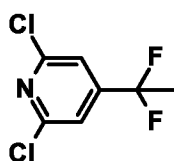
5

Intermediate 7: *Tert*-butyl *N*-[3-(*tert*-butoxycarbonylamino)propyl]-*N*-[2-[4-[(4-piperazin-1-ylsulfonyl)phenyl]carbamoyl]phenyl]ethyl]carbamate

**Int-7**

10 The title compound was prepared in analogy to the preparation of compound **Int-5** by replacing 4-(chloromethyl)benzoyl chloride with 4-(2-bromoethyl)benzoyl chloride in **Step 3**. Compound **Int-7** (1.1 g) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 646.3.

Intermediate 8: 2,6-Dichloro-4-(1,1-difluoroethyl)pyridine



15

Int-8

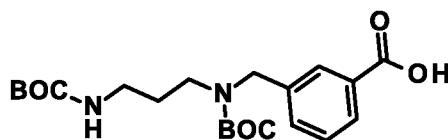
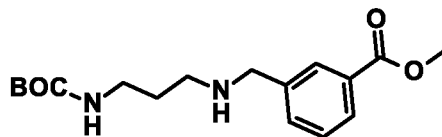
1-(2,6-Dichloro-4-pyridyl)ethanone (300.0 mg, 1.58 mmol, 1 eq) was dissolved in DAST (2.0 mL) and the reaction was stirred at rt for 6 hours. After completion, the mixture was poured into ice-water (40 mL), extracted with EtOAc (20 mL × 3). The combined organic layer was dried over Na₂SO₄, concentrated under vacuum to give residue, which was purified by prep-HPLC (TFA buffer) to afford compound **Int-8** (167 mg, 44.90% yield). MS obsd. (ESI⁺) [(M+H)⁺]: 212.1.

20

Intermediate 9: 3-[[*Tert*-butoxycarbonyl-[3-(*tert*-butoxycarbonylamino)propyl]amino]methyl]benzoic acid

25

-37-

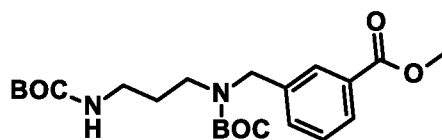
**Int-9****Step 1: Methyl 3-[[3-(*tert*-butoxycarbonylamino)propylamino]methyl]benzoate****Int-9a**

5

A mixture of methyl 3-(bromomethyl)benzoate (2.0 g, 8.73 mmol), *tert*-butyl *N*-(3-aminopropyl)carbamate (2.28 g, 13.1 mmol), K₂CO₃ (12.1 g, 8.73 mmol,) and KI (0.05 mL, 0.870 mmol) in MeCN (20 mL) was heated to 60 °C for 1 hour. After completion, the mixture was concentrated under vacuum to give a crude product, which was diluted with water (20 mL).

10 The aqueous phase was extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine (50 mL), dried with anhydrous Na₂SO₄ and concentrated under vacuum to give compound **Int-9a** (2.8 g, 49.74% yield) as a colorless oil, which was used in the next step directly. MS obsd. (ESI⁺) [(M+H)⁺]: 323.1.

Step 2: Methyl 3-[[*tert*-butoxycarbonyl-[3-(*tert*-
 15 **butoxycarbonylamino)propyl]amino]methyl]benzoate**

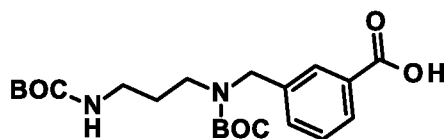
**Int-9b**

To a solution of methyl **Int-9a** (2.8 g, 8.68 mmol) in THF (10 mL) and water (10 mL) were added Na₂CO₃ (1.84 g, 17.37 mmol) and BOC anhydride (1.90 g, 8.68 mmol). The reaction mixture was stirred at 20°C for 1 hour. After completion, the reaction mixture was diluted with water (50 mL), extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄, concentrated under vacuum to give compound **Int-9b** (3.5 g, 47.69% yield) as a colorless oil, which was used directly in the next step. MS obsd. (ESI⁺) [(M+H)⁺]: 423.2.

20

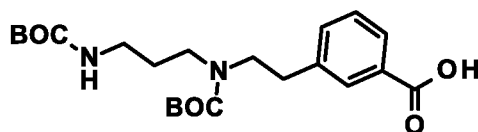
-38-

Step 3: 3-[[*Tert*-butoxycarbonyl-[3-(*tert*-butoxycarbonylamino)propyl]amino]methyl]benzoic acid

**Int-9**

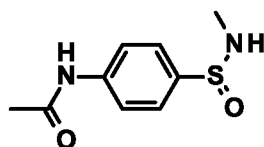
5 To a solution of **Int-9b** (3.5 g, 8.28 mmol) in EtOH (20 mL) and water (10 mL) was added NaOH (1.66 g, 41.42 mmol) in one portion. The reaction mixture was stirred at 20 °C for 2 hours. After completion, the mixture was concentrated under vacuum to remove EtOH. The residue was diluted with water (20 mL) and then adjusted the pH to 5-6 with HCl (aq. 2 mol/L). The aqueous phase was extracted with EtOAc (20 mL × 3). The combined organic layer was dried with
 10 anhydrous Na₂SO₄, concentrated under vacuum to give a crude, which was purified by prep-HPLC (TFA as additive) to give compound **Int-9** (1.4 g, 41.37% yield) as a colorless oil. MS obsd. (ESI⁺) [(M+H)⁺]: 409.2.

Intermediate 10: 3-[2-[*Tert*-butoxycarbonyl-[3-(*tert*-butoxycarbonylamino)propyl]amino]ethyl]benzoic acid

**Int-10**

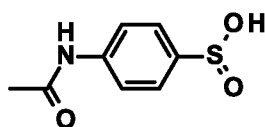
The title compound was prepared in analogy to the preparation of compound **Int-9** by replacing methyl 3-(bromomethyl)benzoate with methyl 3-(2-bromoethyl)benzoate in **step 1**.
 20 Compound **Int-10** (1.2 g) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 423.1.

Intermediate 11: *N*-(4-methylsulfinamoylphenyl)acetamide

**Int-11**

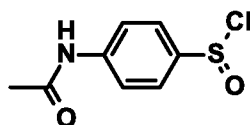
25 **Step 1: 4-Acetamidobenzenesulfinic acid**

-39-

**Int-11a**

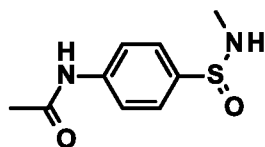
To a solution of sodium sulfite (12.84 g, 101.85 mmol) and NaHCO₃ (10.27 g, 122.22 mmol) in water (55 mL) was added *N*-acetylsulfanilyl chloride (11.9 g, 50.93 mmol) slowly at 70 °C. After the addition, the mixture was stirred at 70 °C for 2 hours. After completion, the mixture was diluted with water (100 mL) and acidified with 60% H₂SO₄ (50 mL) at 0°C and the resulting precipitate was collected by filtration. The filter cake was washed by 20% aq. H₂SO₄ (100 mL) and dried under vacuum to give compound **Int-11a** (8 g, 78.85% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 200.0.

Step 2: 4-Acetamidobenzenesulfinyl chloride

**Int-11b**

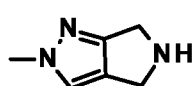
To a solution of compound **Int-11a** (7.0 g, 35.14 mmol) in DCM (30 mL) and THF (30 mL) were added SOCl₂ (16.72 g, 140.54 mmol) in one portion. The mixture was stirred at 15 °C for 4 hours. The mixture was concentrated under vacuum to give crude compound **Int-11b** (7 g, 91.53% yield) as a yellow solid, which was used in the next step directly.

Step 3: *N*-(4-methylsulfinamoylphenyl)acetamide

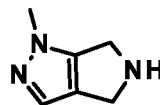
**Int-11**

To a solution of monomethylamine in THF (27.56 mL, 55.13 mmol) in THF (20 mL) was added 4-acetamidobenzenesulfinyl chloride (1.5 g, 6.89 mmol) in DCM (5.0 mL) dropwise. The mixture was stirred at 15 °C for 1 hour. After completion, the mixture was diluted with water (50 mL) and extracted with EtOAc (100 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give compound **Int-11** (1.2 g, 82.04% yield) as a yellow solid, which was used in the next step directly. MS obsd. (ESI⁺) [(M+H)⁺]: 212.8.

Intermediate 12A and 12B: 2-Methyl-5,6-dihydro-4H-pyrrolo[3,4-c]pyrazole (Int-12A) and 1-Methyl-5,6-dihydro-4H-pyrrolo[3,4-c]pyrazole (Int-12B)

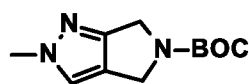


Int-12A

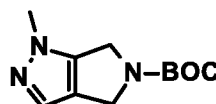


Int-12B

5 Step1: *Tert*-butyl 2-methyl-4,6-dihydropyrrolo[3,4-c]pyrazole-5-carboxylate (Int-11Aa) and *Tert*-butyl 1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazole-5-carboxylate (Int-11Ba)



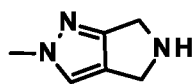
Int-12Aa



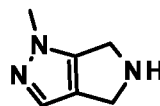
Int-12Ba

To a solution of *tert*-butyl 4,6-dihydro-2*H*-pyrrolo[3,4-c]pyrazole-5-carboxylate (600 mg, 2.87 mmol) in DMF (30 mL) was added NaH (229.4 mg, 5.74 mmol) at 0 °C. The resulting suspension mixture was stirred at rt for 15 minutes. And then, iodomethane (1221 mg, 8.6 mmol) was added to the mixture and the mixture was stirred at 25 °C for 4 hours. After completion, the reaction was quenched with ice-water (30 mL), extracted with EtOAc (30 mL × 2). The combined organic layer was concentrated under vacuum to give a crude product, which was purified by silica-gel chromatography (elute with EtOAc:PE = 50%) to give the mixture of **Int-12Aa&12Ba** (400 mg, 37.48% yield) as a brown oil. MS obsd. (ESI⁺) [(M+H)⁺]: 224.1.

Step 2: 2-Methyl-5,6-dihydro-4*H*-pyrrolo[3,4-c]pyrazole (Int-12A) and 1-Methyl-5,6-dihydro-4*H*-pyrrolo[3,4-c]pyrazole (Int-12B)



Int-12A

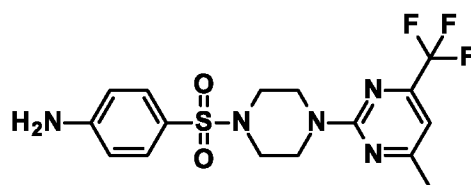


Int-12B

The mixture of compounds **Int-12Aa&12Ba** (400 mg, 1.792 mmol) in DCM (10 mL) and TFA (2 mL) was stirred at rt for 4 hours. After completion, the mixture was concentrated under vacuum to give the TFA salt of **Int-12A&12B** (200 mg, 56.48% yield) as a brown oil. MS obsd. (ESI⁺) [(M+H)⁺]: 124.1.

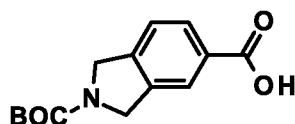
Intermediate 13: 4-[4-[4-Methyl-6-(trifluoromethyl)pyrimidin-2-yl]piperazin-1-yl]sulfonylaniline

-41-

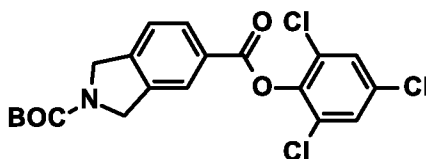
**Int-13**

The title compound was prepared in analogy to the preparation of compound **Int-1** by replacing 2,6-dichloro-4-(trifluoromethyl)pyridine with 2-chloro-4-methyl-6-(trifluoromethyl)pyrimidine in **step1**. Compound **Int-13** (1.2 g) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 402.1.

Intermediate 14: 2-(*Tert*-butoxycarbonyl)isoindoline-5-carboxylic acid

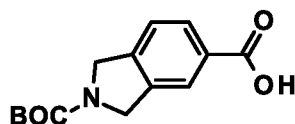
**Int-14**

Step 1: 2-*Tert*-butyl 5-(2,4,6-trichlorophenyl) isoindoline-2,5-dicarboxylate

**Int-14a**

To a solution of *tert*-butyl 5-bromoisindoline-2-carboxylate (238.0 mg, 0.800 mmol) in toluene (4 mL) were added 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (92.37 mg, 0.160 mmol), palladium (II) acetate (17.92 mg, 0.080 mmol), TEA (0.22 mL, 1.6 mmol, 2 eq) and (2,4,6-trichlorophenyl) formate (215.95 mg, 0.960 mmol) in sequence. The reaction mixture was heated to 90 °C for 15 hours under N₂. After completion, the reaction mixture was concentrated to give a residue, which was purified by prep-HPLC (FA as additive) to give compound **Int-14a** (260 mg, 73.58% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 442.0.

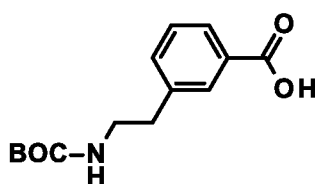
Step 2: 2-(*Tert*-butoxycarbonyl)isoindoline-5-carboxylic acid



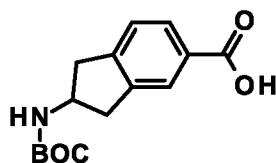
-42-

Int-14

A solution of compound **Int-14a** (240.0 mg, 0.540 mmol) and NaOH (216.84 mg, 5.42 mmol) in THF (1.02 mL) and water (0.102 mL) was stirred for 2 hours at 20 °C. After completion, the mixture was acidified with 1N HCl to pH=6. The solution was extracted with DCM (50 mL × 3). The combined organic layer was washed with brine (100 mL), dried over Na₂SO₄, concentrated under reduced pressure to give compound **Int-14** (130 mg, 91.08% yield) as a yellow oil. MS obsd. (ESI⁺) [(M+H)⁺]: 264.0.

Intermediate 15: 3-[2-(*Tert*-butoxycarbonylamino)ethyl]benzoic acid**Int-15**

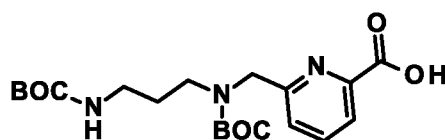
The title compound was prepared in analogy to the preparation of compound **Int-14** by replacing *tert*-butyl 5-bromoisindoline-2-carboxylate with *tert*-butyl *N*-[2-(3-bromophenyl)ethyl]carbamate in **step1**. Compound **Int-15** (1.3 g) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 266.0.

Intermediate 16: 2-(*Tert*-butoxycarbonylamino)indane-5-carboxylic acid**Int-16**

The title compound was prepared in analogy to the preparation of compound **Int-14** by replacing *tert*-butyl 5-bromoisindoline-2-carboxylate with *tert*-butyl *N*-(5-bromoindan-2-yl)carbamate in **step1**. Compound **Int-16** (1.1 g) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 278.1.

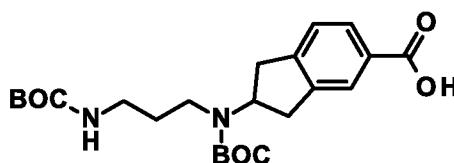
Intermediate 17: 6-[[*Tert*-butoxycarbonyl-[3-(*tert*-butoxycarbonylamino)propyl]amino]methyl]pyridine-2-carboxylic acid

-43-

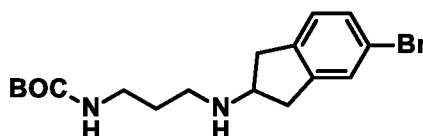
**Int-17**

The title compound was prepared in analogy to the preparation of compound **Int-9** by replacing methyl 3-(bromomethyl)benzoate with methyl 6-(bromomethyl)pyridine-2-carboxylate in **step 1**. Compound **Int-17** (1.0 g) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 410.2

Intermediate 18: 2-[*Tert*-butoxycarbonyl-[3-(*tert*-butoxycarbonylamino)propyl]amino]indane-5-carboxylic acid

**Int-18**

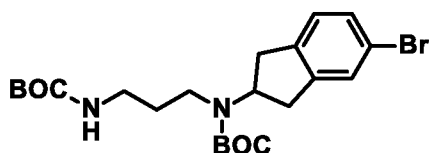
Step 1: *Tert*-butyl *N*-[3-[(5-bromoindan-2-yl)amino]propyl]carbamate

**Int-18a**

A mixture of 5-bromoindan-2-one (600.0 mg, 2.84 mmol), *tert*-butyl *N*-(3-aminopropyl)carbamate (0.99 g, 5.69 mmol) and anhydrous Na₂SO₄ (400 mg, 2.84 mmol) in MeOH (5 mL) and THF (5 mL) was stirred at 25 °C for 3 hours. Then sodium cyanoborohydride (893.21 mg, 14.21 mmol) was added to the mixture and stirred at 25 °C for another 12 hours. After completion, the mixture was poured into ice-water (100 mL) and extracted with EtOAc (150 mL × 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give crude compound **Int-18a** (800 mg, 76.2% yield) as a light yellow oil, which was used in next step directly. MS obsd. (ESI⁺) [(M+H)⁺]: 369.1.

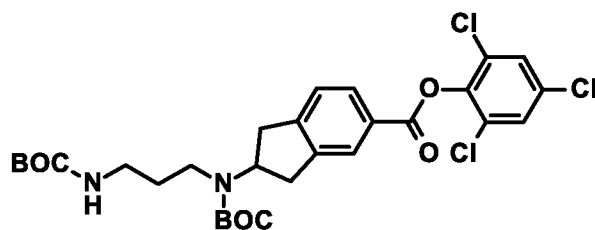
Step 2: *Tert*-butyl *N*-(5-bromoindan-2-yl)-*N*-[3-(*tert*-butoxycarbonylamino)propyl]carbamate

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**Int-18b**

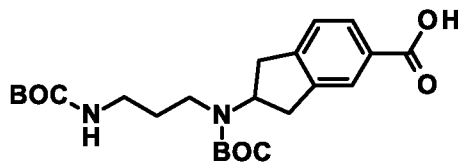
To a solution of compound **Int-18a** (800.0 mg, 2.17 mmol) and Boc anhydride (0.57 g, 2.6 mmol) in THF (20 mL) was added TEA (0.3 mL, 2.17 mmol) dropwise. The mixture was stirred at 15 °C for 12 hours. After completion, the mixture was poured into water (50 mL) and extracted with EtOAc (50mL × 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give residue, which was purified by silica-gel chromatography (elute with EtOAc:PE = 20%) to give compound **Int-18b** (900 mg, 88.51% yield) as a yellow oil. MS obsd. (ESI⁺) [(M+H)⁺]: 469.3.

Step 3: (2,4,6-Trichlorophenyl) 2-[tert-butoxycarbonyl-[3-(tert-butoxycarbonylamino)propyl]amino]indane-5-carboxylate

**Int-18c**

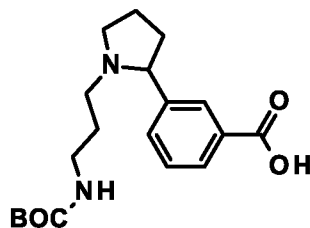
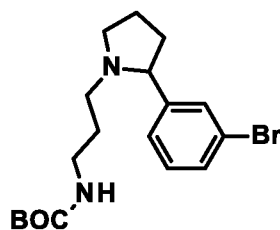
The title compound was prepared in analogy to the preparation of compound **Int-14a** by replacing *tert*-butyl 5-bromoisindoline-2-carboxylate with compound **18b** in **step1**. Compound **Int-18c** (800 mg) was obtained as yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 613.0.

Step 4: 2-[Tert-butoxycarbonyl-[3-(tert-butoxycarbonylamino)propyl]amino]indane-5-carboxylic acid

**Int-18**

The title compound was prepared in analogy to the preparation of compound **Int-14** by replacing compound **Int-14a** with compound **Int-18c** in **step 2**. Compound **Int-18** (300 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 435.2.

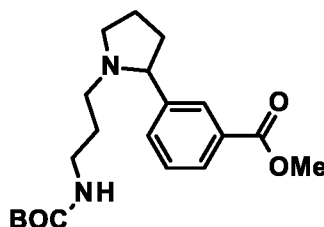
-45-

Intermediate 19: 3-[1-[3-(*Tert*-butoxycarbonylamino)propyl]pyrrolidin-2-yl]benzoic acid**Int-19****Step 1: *Tert*-butyl *N*-[3-[2-(3-bromophenyl)pyrrolidin-1-yl]propyl]carbamate****Int-19a**

5

The mixture of 2-(3-bromophenyl) pyrrolidine (2.0 g, 8.85 mmol), K₂CO₃ (2.44 g, 17.69 mmol), KI (0.23 mL, 4.42 mmol) and *tert*-butyl *N*-(3-chloropropyl) carbamate (2.56 g, 13.27 mmol) in MeCN (10 mL) was stirred at 65 °C for 2 hours. After completion, the mixture was poured into water (100mL) and extracted with EtOAc (100 mL × 3). The combined organic layer was washed by brine, dried over Na₂SO₄ and concentrated under vacuum to give crude product, which was purified by and prep-HPLC (FA as additive) to afford compound **Int-18a** (2.5 g, 73.73% yield) as yellow oil. MS obsd. (ESI⁺) [(M+H)⁺]: 383.2.

10

Step 2: Methyl 3-[1-[3-(*tert*-butoxycarbonylamino)propyl]pyrrolidin-2-yl]benzoate**Int-19b**

15

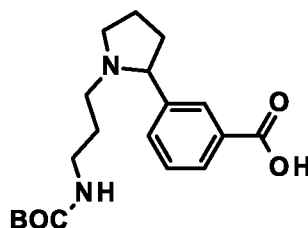
The mixture of **Int-19a** (1000.0 mg, 2.61 mmol), TEA (0.65 mL, 4.7 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (114.53 mg, 0.160 mmol) was purged with carbon oxide and heated to 80 °C for 16 hours under CO atmosphere. After completion, the mixture was concentrated under vacuum to give a residue, which was purified by silica-gel

20

-46-

chromatography (elute with EtOAc:PE = 10%) to give compound **int-19b** (500 mg, 1.38 mmol) as yellow oil. MS obsd. (ESI⁺) [(M+H)⁺]: 363.3.

Step 3: 3-[1-[3-(*Tert*-butoxycarbonylamino)propyl]pyrrolidin-2-yl] benzoic acid

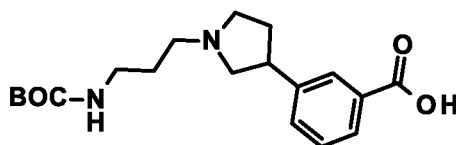


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Int-19

The mixture of compound **Int-19b** (400.0 mg, 1.1 mmol) and LiOH (264.31 mg, 11.04 mmol) in THF (9.35 mL) and water (9.35 mL) was stirred at 60 °C for 2 hours. After completion, the mixture was acidified to PH=5~6 using 1N HCl solution. The mixture was extracted with EA: MeOH=10:1(100 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated under vacuum to give crude product which was further purified by silica-gel chromatography (elute with MeOH:DCM = 20%) to provide compound **Int-19** (100 mg, 26.01% yield) as yellow oil. MS obsd. (ESI⁺) [(M+H)⁺]: 349.1.

Intermediate 20: 3-[1-[3-(*Tert*-butoxycarbonylamino)propyl]pyrrolidin-3-yl]benzoic acid



15

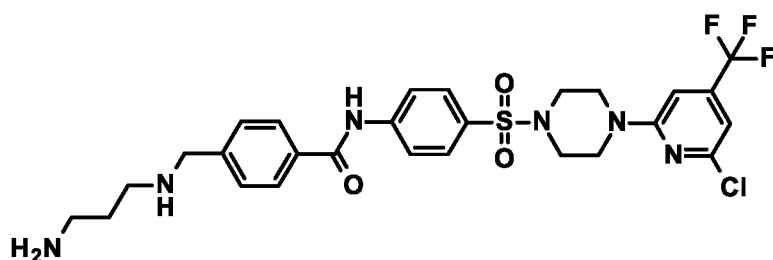
Int-20

The title compound was prepared in analogy to the preparation of compound **Int-19** by replacing 2-(3-bromophenyl) pyrrolidine with 3-(3-bromophenyl) pyrrolidine in **step 1**. Compound **Int-20** (300 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 349.1.

20

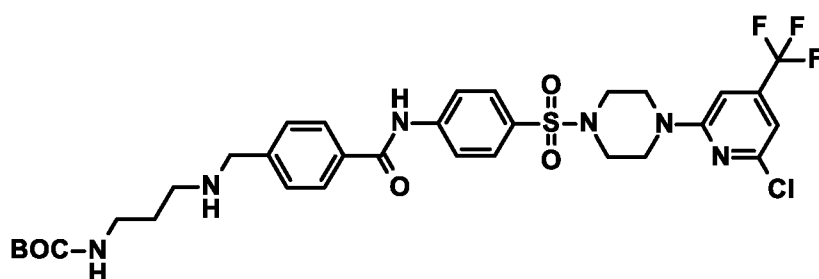
Example 001: 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

-47-



001

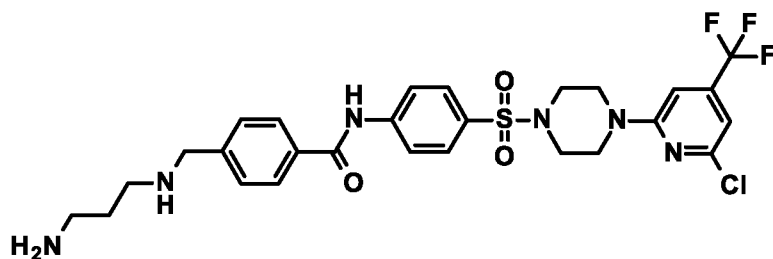
Step 1: *Tert*-butyl *N*-[3-[[4-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]methylamino]propyl]carbamate



001a

To a solution of compound **Int-2** (60.0 mg, 0.100 mmol) in MeCN (10 mL) were added *tert*-butyl *N*-(3-aminopropyl)carbamate (36.46 mg, 0.210 mmol), K₂CO₃ (28.92 mg, 0.210 mmol) and KI (8.3 mg, 0.050 mmol) in one portion. The mixture was heated to 60 °C for 2 hours. After completion, the mixture was concentrated in *vacuo* to give a residue, which was diluted with water (20 mL). The aqueous phase was extracted with DCM (10 mL × 3). The combined organic layer was washed with brine (20 mL), dried with anhydrous Na₂SO₄ and concentrated under vacuum to give crude product, which was purified by prep-TLC (DCM/MeOH=10/1) to afford compound **001a** (55 mg, 73.91% yield) as a yellow solid. MS obsd. (ESI⁺) [(M+H)]⁺: 711.3.

Step 2: 4-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



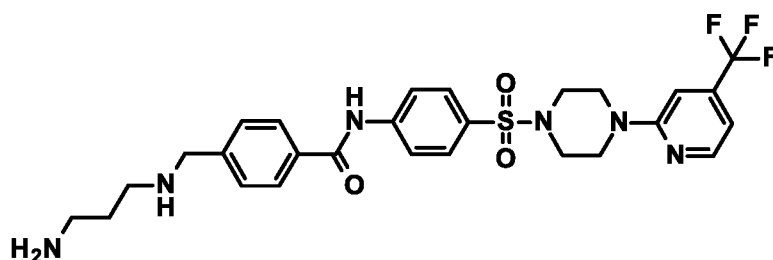
001

To a solution of compound **001a** (55.0 mg, 0.080 mmol) in DCM (1 mL) was added TFA (0.6 mL, 7.73 mmol) in one portion. The mixture was stirred at 25 °C for 1 hour. After

completion, the mixture was concentrated under vacuum to give a residue, which was purified by prep-HPLC (HCl as additive) to afford **Example 001** (25 mg, 48.07% yield) was obtained as white solid. MS obsd. (ESI⁺) [(M+H)]⁺: 611.3.

Example 001: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.78 (s, 1H), 9.68 - 9.53 (m, 2H), 8.15 - 8.01 (m, 7H), 7.80 - 7.73 (m, 4H), 7.13 - 7.06 (m, 1H), 6.96 (s, 1H), 4.26 - 4.18 (m, 2H), 3.76 - 3.68 (m, 4H), 3.06 - 2.95 (m, 6H), 2.94 - 2.85 (m, 2H), 2.08 - 1.99 (m, 2H).

Example 002: 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

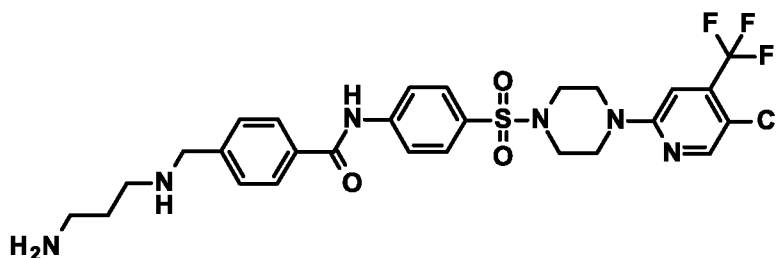


002

The title compound was prepared in analogy to the preparation of **Example 001**, replacing compound 2,6-dichloro-4-(trifluoromethyl)pyridine with 2-chloro-4-(trifluoromethyl)pyridine in **Step 1** of preparing **Int-1**. **Example 002** (100 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)]⁺: 577.2.

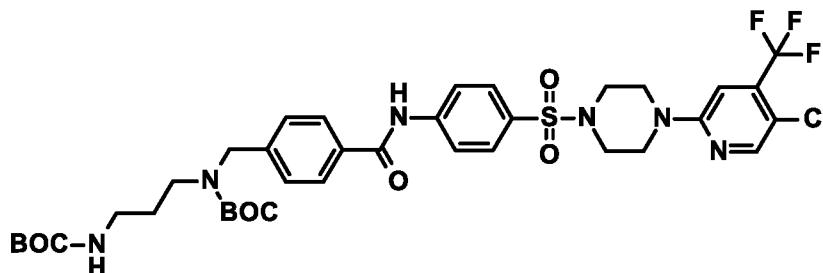
Example 002: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.71 (s, 1H), 8.30 (d, *J* = 4.9 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 2H), 7.94 (d, *J* = 7.3 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 7.1 Hz, 2H), 7.09 (s, 1H), 6.89 (d, *J* = 5.0 Hz, 1H), 3.82 (s, 2H), 3.71 (s, 4H), 2.97 (s, 4H), 2.86 (s, 2H), 2.62 (s, 2H), 1.74 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -63.57 (s, 3F).

Example 003: 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[5-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



003

Step 1: *Tert*-butyl *N*-[3-(*tert*-butoxycarbonylamino)propyl]-*N*-[[4-[4-[5-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]methyl] carbamate

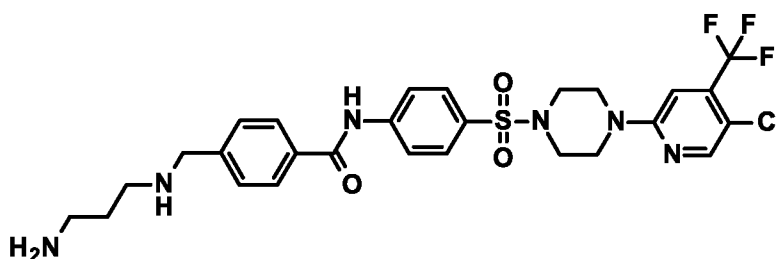


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003a

A mixture of 2,5-dichloro-4-(trifluoromethyl)pyridine (38.83 mg, 0.180 mmol), compound **Int-5** (80.0 mg, 0.180 mmol) and Cs₂CO₃ (mg, 0.180 mmol) in NMP (5 mL) was heated at 100 °C for 1 hour. After completion, the mixture was poured into 50 mL water and extracted with EtOAc (25 mL × 2). The combined organic layer was washed with brine (25 mL × 2), dried over Na₂SO₄ and concentrated to give a residue, which was purified by silica-gel chromatography (elute with EtOAc:PE = 30%) to afford the desired product compound **003a** (65 mg, 40.11% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 811.2.

Step 2: 4-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[5-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



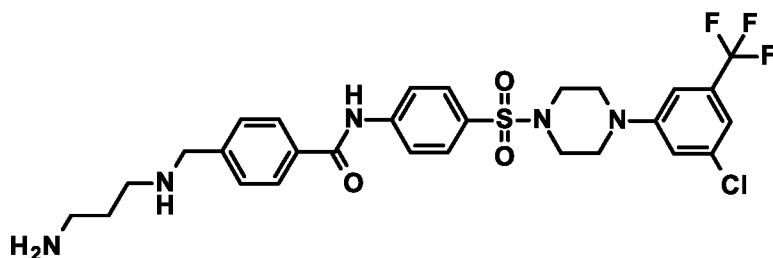
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003

A solution of compound **003a** (55.0 mg, 0.070 mmol) in TFA/dioxane (4 M, 5 mL) was stirred at rt for 4 hours. After completion, the solvent was removed under vacuum to give the crude product which was purified by prep-HPLC (TFA as additive) to afford **Example 003** (35 mg, 78.2% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 611.2.

Example 003: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.70 (s, 1H), 8.31 (s, 1H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.18 (s, 1H), 3.80 (s, 2H), 3.71 (s, 4H), 2.98 (s, 4H), 2.85 (t, *J* = 6.9 Hz, 2H), 2.60 (t, *J* = 6.3 Hz, 2H), 1.65 – 1.79 (m, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -63.43 (s, 3F).

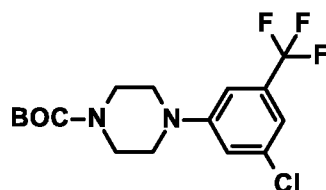
Example 004: 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[3-chloro-5-(trifluoromethyl)phenyl]piperazin-1-yl]sulfonylphenyl]benzamide



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004

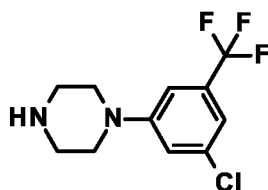
Step 1: *Tert*-butyl 4-[3-chloro-5-(trifluoromethyl)phenyl]piperazine-1-carboxylate



004a

A mixture of 1-chloro-3-iodo-5-(trifluoromethyl)benzene (2.0 g, 6.53 mmol), *tert*-butyl piperazine-1-carboxylate (1.82 g, 9.79 mmol), copper(I) iodide (1.24 g, 6.53 mmol), K₂CO₃ (1.8 g, 13.1 mmol), proline (225 mg, 1.96 mmol) in DMF (30 mL) was stirred for 3 hours at 130 °C in a microwave reactor. After completion, the mixture was diluted with EtOAc (150 mL), and washed with water (50 mL × 3). The organic layer was dried over Na₂SO₄ and concentrated under vacuum to give a residue, which was purified by silica-gel chromatography (elute with EtOAc:PE = 20%) to afford compound **004a** (1.0 g, 42.0% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 365.1.

Step 2: 1-[3-Chloro-5-(trifluoromethyl)phenyl]piperazine

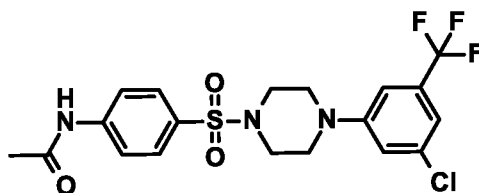


004b

A mixture of compound **004a** (800 mg, 2.19 mmol) and TFA (2.5 g, 21.9 mmol) in DCM (15 mL) was stirred for 2 hours at rt. And then, the reaction mixture was concentrated to afford crude compound **004b** (580 mg, 100% yield) as yellow gum, which was used in the next step directly. MS obsd. (ESI⁺) [(M+H)⁺]: 265.1.

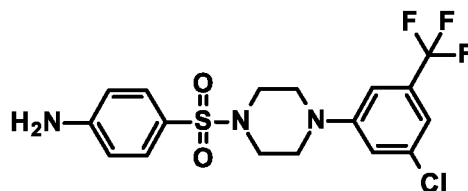
-51-

Step 3: *N*-[4-[4-[3-chloro-5-(trifluoromethyl)phenyl]piperazin-1-yl]sulfonylphenyl]acetamide

**004c**

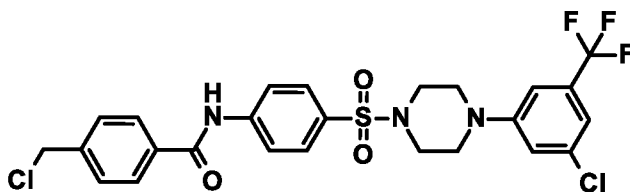
5 A mixture of compound **004b** (580 mg, 2.18 mmol), 4-acetamidobenzenesulfonyl chloride (510 mg, 2.18 mmol) and DIPEA (500 mg, 3.87 mmol) in DCM (20 mL) was stirred for 1 hour at rt. Then the mixture was washed with saturated NaHCO₃ aqueous solution (20 mL × 3). The organic layer was dried over Na₂SO₄ and concentrated under vacuum to give a crude residue, which was purified by silica-gel chromatography (elute with EtOAc:PE = 15%) to afford
10 compound **004c** (1.0 g, 42.0% yield) as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 462.1.

Step 4: 4-[4-[3-Chloro-5-(trifluoromethyl)phenyl]piperazin-1-yl]sulfonylaniline

**004d**

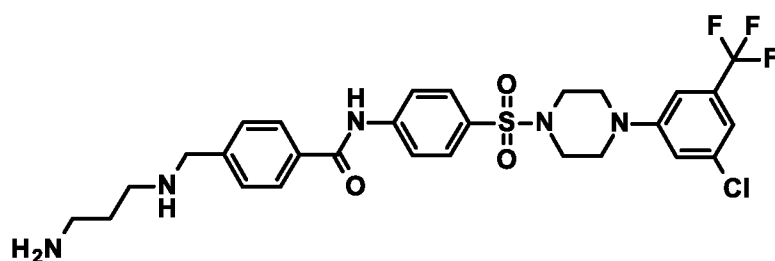
A mixture of compound **004c** (400 mg, 866 μmol), HCl aqueous solution (1 mL, 866 μmol)
15 in MeOH (3 mL) was heated for 10 minutes at 100 °C in a microwave reactor. After removal of solvent, the residue was dissolved in DCM (20 mL), washed with saturated NaHCO₃ solution (20 mL × 2) and brine (20 mL × 2). The organic layer was dried over Na₂SO₄, concentrated under vacuum to give crude compound **004d** (363.6 mg, 100%) as a white solid, which was used in next step directly. MS obsd. (ESI⁺) [(M+H)⁺]: 419.9.

20 Step 5: 4-(Chloromethyl)-*N*-[4-[4-[3-chloro-5-(trifluoromethyl)phenyl]piperazin-1-yl]sulfonylphenyl]benzamide

**004e**

A mixture of compound **004d** (190 mg, 453 μ mol), 4-(chloromethyl)benzoyl chloride (128 mg, 679 μ mol) and pyridine (107 mg, 1.36 mmol) in DCM (3 mL) was stirred for 4 hours at rt. After completion, the reaction mixture was concentrated to afford residue, which was purified by silica-gel chromatography (elute with EtOAc:PE = 20%) to afford compound **004e** (36.1 mg, 30.0% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 572.1.

Step 6: 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[3-chloro-5-(trifluoromethyl)phenyl]piperazin-1-yl]sulfonylphenyl]benzamide

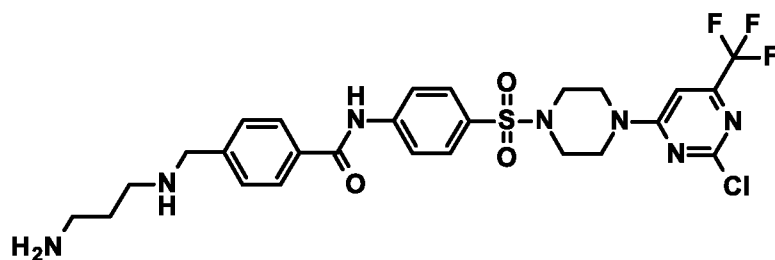


004

A mixture of compound **004d** (80 mg, 140 μ mol), propane-1,3-diamine (51.8 mg, 699 μ mol) in DMF (5 mL) was stirred at 100 °C for 3 h. After completion, the reaction mixture was concentrated and residue was purified by prep-HPLC (TFA as additive) to afford **Example 004** (29.1 mg, 32.94%). MS obsd. (ESI⁺) [(M+H)⁺]: 610.3.

Example 004: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.35 (s, 1H), 8.08 (d, 2H, *J* = 8.8 Hz), 7.93 (d, 2H, *J* = 8.3 Hz), 7.77 (d, 2H, *J* = 8.9 Hz), 7.49 (d, 2H, *J* = 8.2 Hz), 7.23 (s, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 3.76 (s, 2H), 3.3-3.4 (m, 4H), 3.0-3.0 (m, 4H), 2.8-2.9 (m, 2H), 2.56 (s, 2H), 1.6-1.7 (m, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -61.38 (s, 3F).

Example 005: 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[2-chloro-6-(trifluoromethyl)pyrimidin-4-yl]piperazin-1-yl]sulfonylphenyl]benzamide



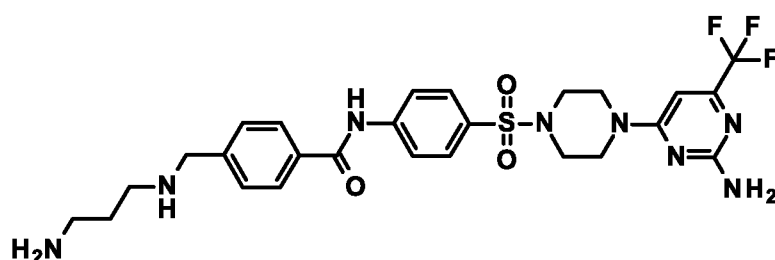
005

The title compound was prepared in analogy to the preparation of **Example 003** by replacing compound 2,5-dichloro-4-(trifluoromethyl)pyridine with compound 2,4-dichloro-6-

(trifluoromethyl)pyrimidine in **step 1** and the reaction was run at rt. **Example 005** (32 mg) was obtained as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 612.1.

Example 005: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.70 (s, 1H), 8.67 (s, 1H), 8.07 (d, *J* = 8.1 Hz, 2H), 7.94 (s, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.51 (s, 2H), 3.88 (s, 4H), 3.80 (s, 2H), 2.99 (s, 4H), 2.86 (s, 2H), 2.57 (d, *J* = 20.2 Hz, 2H), 1.73 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -69.48 (s, 3F).

Example 006: 4-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[2-amino-6-(trifluoromethyl)pyrimidin-4-yl]piperazin-1-yl]sulfonylphenyl]benzamide

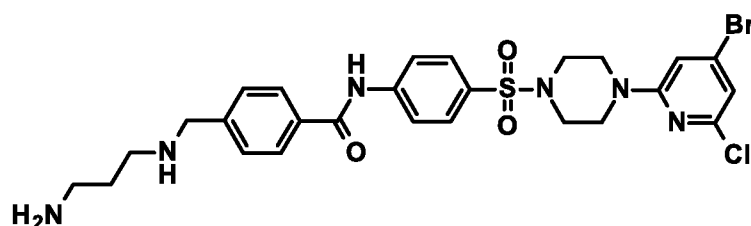


006

The title compound was prepared in analogy to the preparation of **Example 003** by replacing compound 2,5-dichloro-4-(trifluoromethyl)pyridine with compound 2-chloro-6-(trifluoromethyl)pyrimidin-4-amine in **Step 1** and the reaction was heated at 160°C for 1 hour in a microwave reactor. **Example 006** (10 mg) was obtained as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 593.2.

Example 006: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.70 (s, 1H), 8.09 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.12 (s, 2H), 6.10 (s, 1H), 3.84 (s, 2H), 3.78 (s, 4H), 2.80 – 2.97 (m, 6H), 2.65 (s, 2H), 1.77 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -63.43 (s, 3F).

Example 007: 4-[(3-Aminopropylamino)methyl]-*N*-[4-[4-(4-bromo-6-chloro-2-pyridyl)piperazin-1-yl]sulfonylphenyl]benzamide

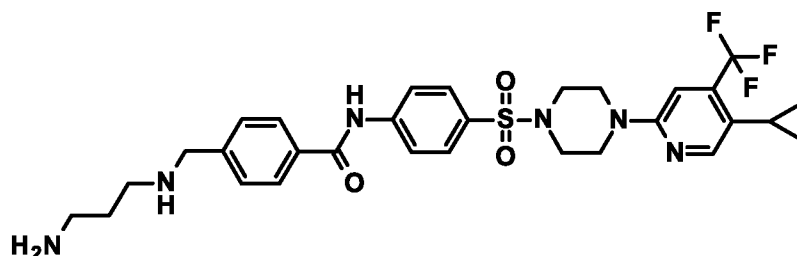


007

The title compound was prepared in analogy to the preparation of **Example 003** by replacing compound 2,5-dichloro-4-(trifluoromethyl)pyridine with 4-bromo-2,6-dichloro-pyridine in **Step 1**. **Example 007** (8 mg) was obtained as an off-white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 621.1.

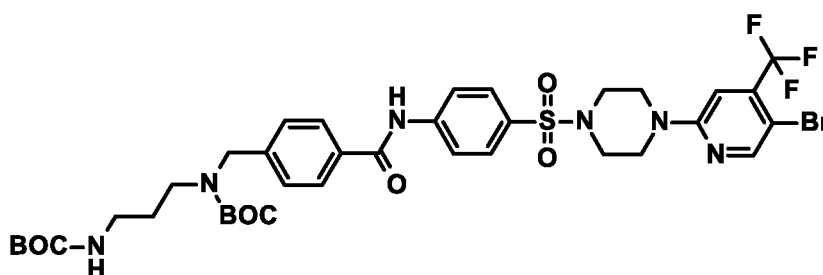
5 **Example 007:** ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.65 (s, 1H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.04 (s, 1H), 6.93 (s, 1H), 3.77 (s, 2H), 3.63 (s, 4H), 2.96 (d, *J* = 4.3 Hz, 4H), 2.85 (s, 2H), 2.56 (d, *J* = 6.3 Hz, 2H), 1.70 (s, 2H).

10 **Example 008:** 4-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[5-cyclopropyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



008

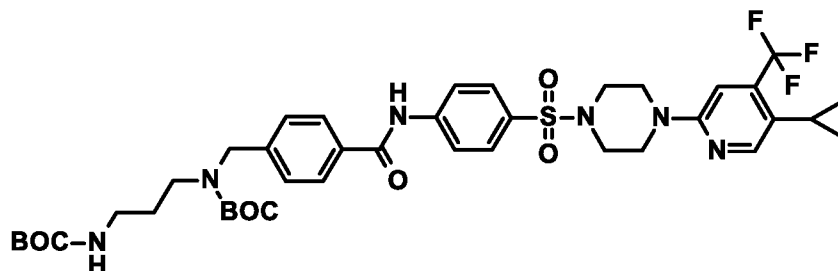
15 **Step 1:** *Tert*-butyl *N*-[[4-[4-[4-[5-bromo-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]methyl]-*N*-[3-(*tert*-butoxycarbonylamino)propyl]carbamate



008a

20 Compound **008a** was prepared in analogy to the preparation of compound **003a** by replacing 2,5-dichloro-4-(trifluoromethyl)pyridine with 5-bromo-2-chloro-4-(trifluoromethyl)pyridine in **step 1**. Compound **008a** (48 mg) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 855.1.

Step 2: *Tert*-butyl *N*-[3-(*tert*-butoxycarbonylamino)propyl]-*N*-[[4-[[4-[4-[5-cyclopropyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]methyl]carbamate

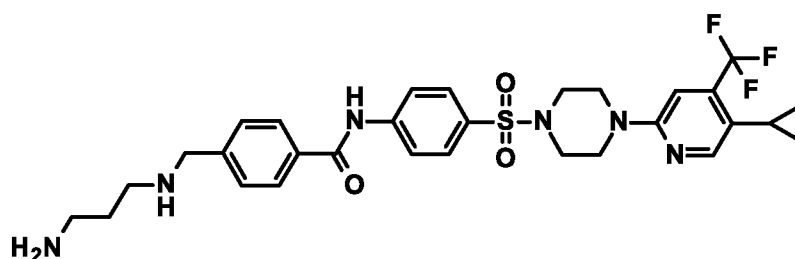


5

008b

A mixture of Pd(OAc)₂ (4.72 mg, 0.020 mmol), compound **008a** (72.0 mg, 0.080 mmol), potassium cyclopropyltrifluoroborate (3.11 mg, 0.020 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.86 mg) in toluene (8.17 mL) and water (0.817 mL) was bubbled with N₂ and stirred at 90 °C for 12 hours. After completion, the reaction was filtrated with Buchner
10 funnel and the filtrate was concentrated under vacuum to give residue, which was purified by prep-HPLC (FA as additive) to give compound **008b** (32 mg, 41.9% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 817.1.

Step 3: 4-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[5-cyclopropyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



15

008

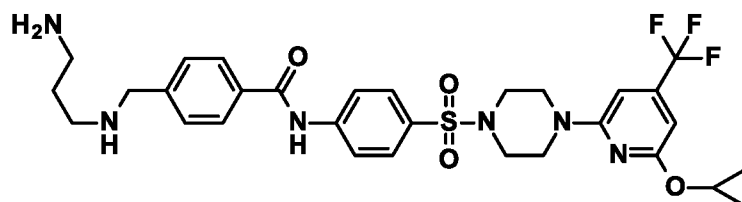
Compound **008b** (30.0 mg, 0.040 mmol) in 4M TFA/dioxane (5 mL) was stirred at rt for 4 hours. After completion, the solvent was removed under vacuum to give the crude product, which was purified by prep-HPLC to afford **Example 008** (8 mg, 23.53% yield). MS obsd. (ESI⁺)
20 [(M+H)⁺]: 617.1.

Example 008: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.69 (s, 1H), 8.39 (s, 2H), 8.07 (d, *J* = 8.5 Hz, 2H), 8.01 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 7.4 Hz, 2H), 7.01 (s, 1H), 3.78 (s, 2H), 3.71 (s, 1H), 3.64 (s, 4H), 2.97 (s, 4H), 2.85 (s, 2H), 2.58 (s, 2H), 1.85

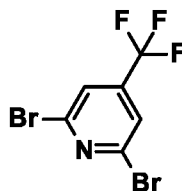
-56-

(s, 1H), 1.71 (s, 2H), 0.87 (d, $J = 7.6$ Hz, 2H), 0.69 (d, $J = 4.7$ Hz, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -61.59 (s, 3F).

Example 009: 4-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[6-(cyclopropoxy)-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

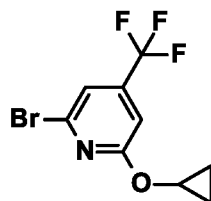
**009**

Step 1: 2,6-Dibromo-4-(trifluoromethyl)pyridine

**009a**

Into the flask charged with 2,6-dichloro-4-(trifluoromethyl)pyridine (2.65 mL, 18.1 mmol) was added HBr in AcOH (30 mL, 166 mmol). The reaction was heated at 85 °C and stirred overnight. After completion, the reaction was extracted with EtOAc (100 mL $\times$ 3). The combined organic layer was washed with brine (150 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum to give crude compound **009a** (4.31 g, 78% yield) as yellow oil, which was used directly in the next step.

Step 2: 2-Bromo-6-(cyclopropoxy)-4-(trifluoromethyl)pyridine

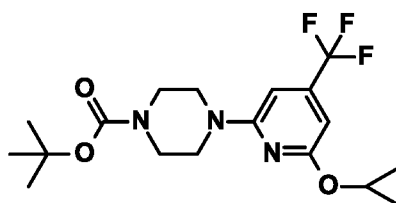
**009b**

-57-

Compound **009a** (0.4 g, 1.31 mmol) was dissolved in THF (5 mL), followed by adding cyclopropanol (100 mg, 1.72 mmol) and then NaH (78.7 mg, 1.97 mmol) in the sealed tube. The reaction was heated at 90 °C and kept stirring at the same temperature overnight. After completion, the reaction was cooled to room temperature and quenched by adding water (50 mL).

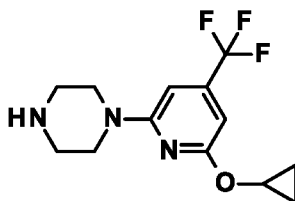
- 5 The resulting residue was extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to afford compound **009b** (366 mg, 100% yield) as yellow oil. MS obsd. (ESI+) [(M+H)⁺]: 282.0.

10 **Step 3: *Tert*-butyl 4-[6-(cyclopropoxy)-4-(trifluoromethyl)-2-pyridyl]piperazine-1-carboxylate**

**009c**

- Compound **009b** (800 mg, 2.84 mmol), *tert*-butyl piperazine-1-carboxylate (1.06 g, 5.67 mmol) and K₂CO₃ (1.18 g, 8.51 mmol) were dissolved in DMSO (20 mL). The reaction was heated at 100 °C and stirred overnight. After the starting material was consumed, the reaction was cooled to rt and quenched by adding water (50 mL). The reaction mixture was extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to afford compound **009c** (1.0 g, 91% yield) as yellow oil. MS obsd. (ESI+) [(M+H)⁺]: 388.4.

20 **Step 4: 1-[6-(Cyclopropoxy)-4-(trifluoromethyl)-2-pyridyl]piperazine**

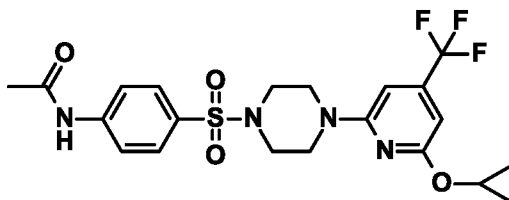
**009d**

Compound **009c** (1.0 g, 2.58 mmol) was dissolved in the DCM (2.5 mL), followed by adding TFA (2.5 mL, 1.86 mmol). The reaction was stirred at rt and went completed after 1 hour.

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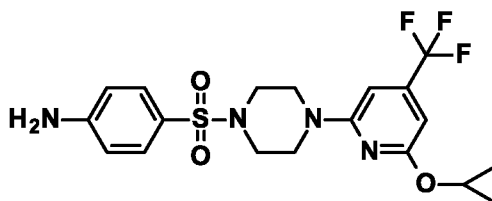
Then the reaction mixture was concentrated *in vacuo* and the residue formed an azeotrope with toluene 2 times to afford compound **009d** (0.6 g, 80 % yield) as a yellow solid. MS obsd. (ESI+) [(M+H)⁺]: 288.4.

Step 5: *N*-[4-[4-[6-(cyclopropoxy)-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]acetamide

**009e**

A mixture of compound **009d** (74 mg, 258 μ mol), pyridine (249 μ L, 3.09 mmol) and 4-acetamidobenzenesulfonyl chloride (300 mg, 1.28 mmol) in DCM (12.5 mL) was stirred at 0 °C for 30 minutes, then allowed to warm to rt. After competition, the reaction was extracted with EtOAc (10 mL $\times$ 3). The combined organic layer was washed with brine (15 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to give crude compound **009e** (100 mg, 80.6 % yield) as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 485.2.

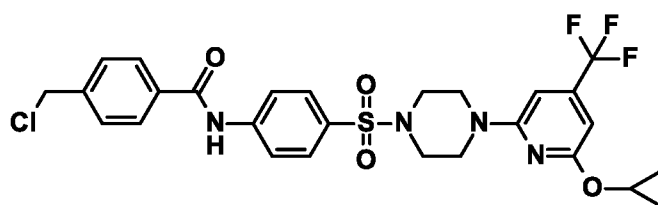
Step 5: 4-[4-[6-(Cyclopropoxy)-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylaniline

**009f**

Compound **009e** (100 mg, 206 μ mol) was dissolved in the MeOH (5 mL). Into the stirring solution was added HCl (2 mL, 8 mmol) dropwise. The mixture was then heated at 70 °C and kept stirring overnight. After competition, the reaction was extracted with EtOAc (10 mL $\times$ 3). The combined organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give crude compound **009f** (90 mg, 98.6 % yield) as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 443.2.

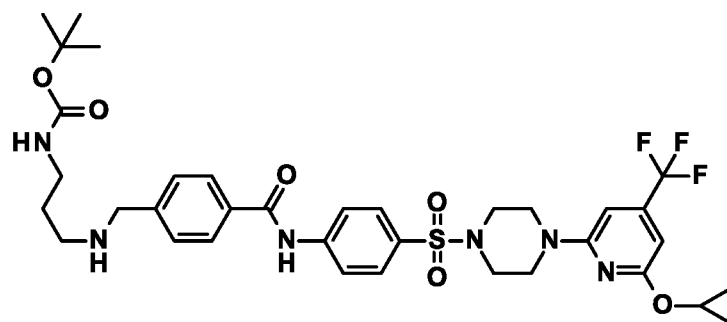
Step 6: 4-(Chloromethyl)-*N*-[4-[4-[6-(cyclopropoxy)-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

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**009g**

Compound **009f** (100 mg, 226 μmol), 4-(chloromethyl)benzoyl chloride (128 mg, 678 μmol) and TEA (94.5 μL , 678 μmol) were stirred at rt overnight. After completion, the mixture was quenched with water (50 mL), diluted with DCM (30 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give curde product, which was purified by silica-gel chromatography (eluent with EtOAc : PE = 25%) to afford compound **009g** (120 mg, 89.2 % yield) as a white solid. MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 595.0.

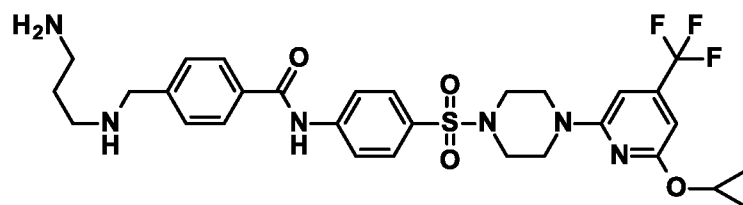
10 **Step 7:** *Tert*-butyl *N*-[3-[[4-[[4-[4-[6-(cyclopropoxy)-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]methylamino]propyl]carbamate

**009h**

Compound **009g** (0.1 g, 168 μmol) and *tert*-butyl (3-aminopropyl)carbamate (58.6 mg, 336 μmol) were dissolved in the MeCN (1.68 mL), followed by adding potassium carbonate (69.7 mg, 504 μmol). The reaction was stirred at 70 $^{\circ}\text{C}$ for 3 hours. After completion, the reaction was cooled to rt and extracted with EtOAc (10 mL $\times$ 3). The combined organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give crude compound **009h** (105 mg, 85.7 % yield) as yellow oil. MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 733.3.

Step 8: 4-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[6-(cyclopropoxy)-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

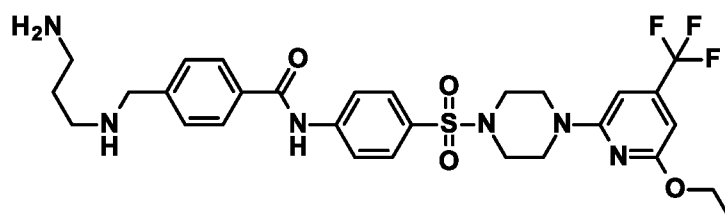
-60-

**009**

Compound **009h** (0.2 g, 273 μ mol) was dissolved in the DCM (10 mL), followed by adding TFA (2.5 mL, 1.86 mmol). The reaction mixture was stirred at rt for 1 hour. The reaction mixture was concentrated under vacuum and purified by prep-HPLC (TFA as additive) to afford **Example 009** (20 mg, 7.3 % yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 633.1.

Example 009: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.91 - 9.08 (m, 1 H), 8.00 - 8.15 (m, 3 H), 7.73 - 7.79 (m, 3 H), 7.56 - 7.69 (m, 2 H), 6.54 - 6.71 (m, 1 H), 6.22 - 6.37 (m, 1 H), 4.04 - 4.32 (m, 3 H), 3.60 - 3.83 (m, 4 H), 2.92 - 3.07 (m, 6 H), 2.75 - 2.92 (m, 2 H), 2.02 - 2.15 (m, 1 H), 1.80 - 2.00 (m, 2 H), 0.70 - 0.82 (m, 2 H), 0.55 - 0.70 (m, 2 H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -63.48 (m, 3F).

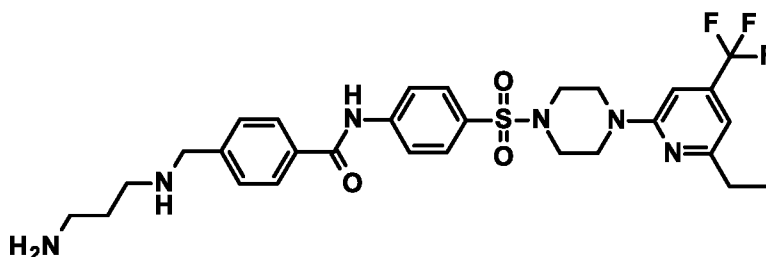
Example 010: 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-ethoxy-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

**010**

The title compound was prepared in analogy to the preparation of **Example 009** by using ethanol instead of cyclopropanol in **Step 2**. **Example 010** (15 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 621.1.

Example 010: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.98 - 8.17 (m, 3 H), 7.73 - 7.87 (m, 4 H), 7.59 - 7.70 (m, 2 H), 6.48 - 6.61 (m, 1 H), 6.17 - 6.31 (m, 1 H), 4.15 - 4.36 (m, 4 H), 3.62 - 3.76 (m, 4 H), 2.93 - 3.09 (m, 6 H), 2.79 - 2.93 (m, 2 H), 1.78 - 1.98 (m, 2 H), 1.18 - 1.34 (m, 3 H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -63.55 (m, 3F).

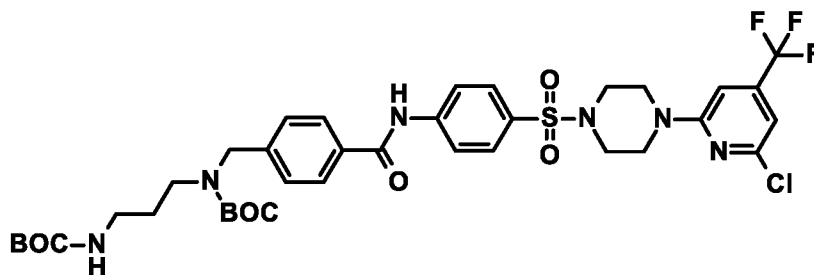
Example 011: 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-ethyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



5

011

Step 1: *Tert*-butyl N-[3-(*tert*-butoxycarbonylamino)propyl]-N-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]methyl]carbamate

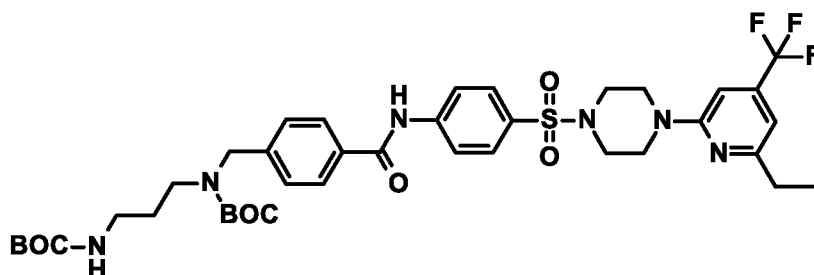


10

011a

The title compound was prepared in analogy to **step 1** of the preparation of compound **003a** by replacing compound 2,5-dichloro-4-(trifluoromethyl)pyridine with compound 2,6-dichloro-4-(trifluoromethyl)pyridine. Compound **011a** (1.0 g) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 811.3.

Step 2: *Tert*-butyl N-[3-(*tert*-butoxycarbonylamino)propyl]-N-[[4-[4-[6-ethyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]methyl]carbamate

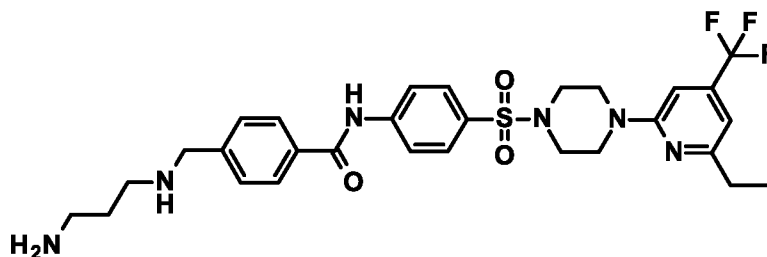


011b

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Compound **011a** (40.0 mg, 0.050 mmol) and bis(tri-*tert*-butylphosphine)palladium(0) (50.0 mg) was dissolved in DCM (5 mL). Then Al(Et)₃ (11.26 mg, 0.10 mmol) was added and the reaction was stirred at rt for 12 hours. The solid was filtered and the filtrate was concentrated under vacuum to give crude, which was purified by silica-gel chromatography (elute with EtOAc:PE = 40%) to afford compound **011b** (35 mg, 79.38% yield). MS obsd. (ESI⁺) [(M+H)⁺]: 805.3.

Step 3: 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-ethyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



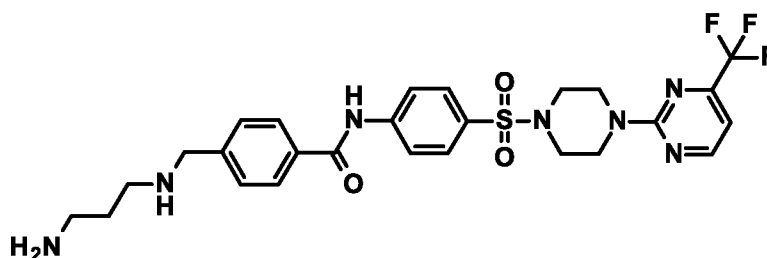
10

011

The title compound was prepared in analogy to the preparation of **Example 003** by replacing compound **003a** with compound **011b** in **step 2**. **Example 011** (14 mg) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 605.2.

Example 011: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.68 (s, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 7.2 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 6.3 Hz, 2H), 6.88 (s, 1H), 6.77 (s, 1H), 3.81 (d, J = 17.2 Hz, 2H), 3.70 (s, 4H), 2.98 (s, 4H), 2.85 (s, 2H), 2.70 – 2.54 (m, 4H), 1.72 (s, 2H), 1.17 (t, J = 7.5 Hz, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -63.43 (s, 3F).

Example 012: 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[4-(trifluoromethyl)pyrimidin-2-yl]piperazin-1-yl]sulfonylphenyl]benzamide

**012**

The title compound was prepared in analogy to the preparation of **Example 003** by replacing 2,5-dichloro-4-(trifluoromethyl)pyridine with 2-chloro-4-(trifluoromethyl)pyrimidine in **step 1**. **Example 012** (14 mg) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 578.3.

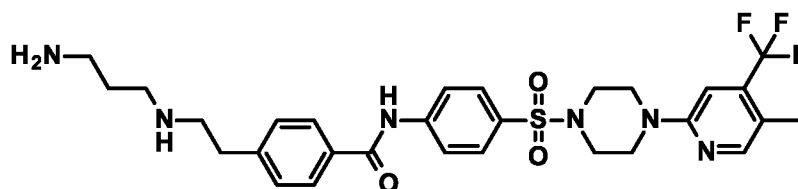
25

-63-

Example 012: ^1H NMR (400 MHz, DMSO- d_6) δ ppm 10.70 (s, 1H), 8.67 (d, $J = 4.6$ Hz, 1H), 8.07 (d, $J = 8.1$ Hz, 2H), 7.94 (s, 2H), 7.74 (d, $J = 8.2$ Hz, 2H), 7.51 (s, 2H), 7.04 (d, $J = 4.7$ Hz, 1H), 3.88 (s, 4H), 3.80 (s, 2H), 2.99 (s, 4H), 2.86 (s, 2H), 2.57 (d, $J = 20.2$ Hz, 2H), 1.73 (s, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ ppm -69.48 (s, 3F).

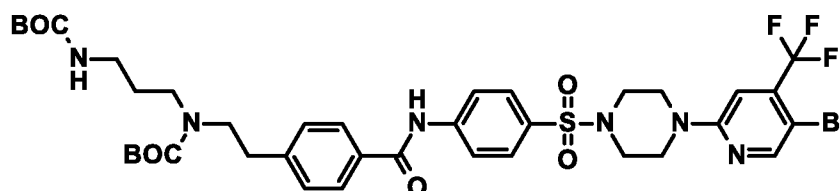
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Example 013: 4-[2-(3-Aminopropylamino)ethyl]-*N*-[4-[4-[5-methyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



013

10 **Step 1:** *Tert*-butyl *N*-[2-[4-[[4-[4-[5-bromo-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]ethyl]-*N*-[3-(*tert*-butoxycarbonylamino)propyl]carbamate

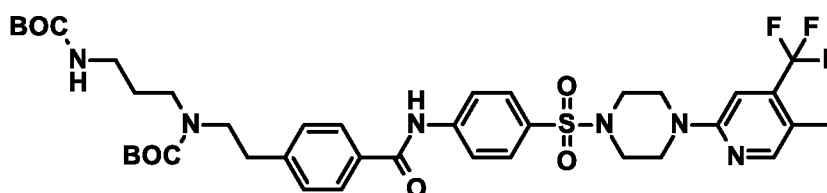


013a

15 The title compound was prepared in analogy to the preparation of compound **003a** in **step 1** by replacing 2,5-dichloro-4-(trifluoromethyl)pyridine with 5-bromo-2-chloro-4-(trifluoromethyl)pyridine and compound **Int-5** with compound **Int-7**. Compound **013a** (31 mg) was obtained. MS obsd. (ESI $^+$) [(M+H) $^+$]: 869.3.

Step 2: *Tert*-butyl *N*-[3-(*tert*-butoxycarbonylamino)propyl]-*N*-[2-[4-[[4-[4-[5-methyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]ethyl]carbamate

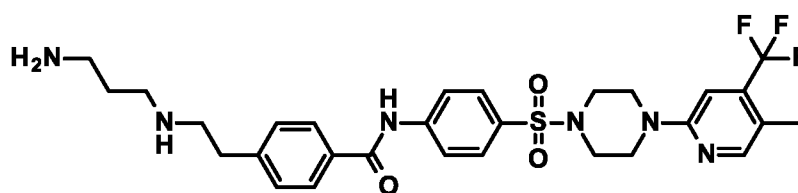
20



013b

A mixture of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (52.16 mg, 0.070 mmol), compound **013a** (31.0 mg, 0.040 mmol) and 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (0.1 mmol) in 1,4-dioxane (2.31 mL) was bubbled with N₂ and then heated at 110 °C for 1 hour in a microwave reactor. The mixture was poured into water (10 mL), extracted with EtOAc (10 mL × 3). The combined organic layer were dried over Na₂SO₄ and concentrated under vacuum to give crude product, which was purified by silica-gel chromatography (elute with EtOAc:PE = 50%) to give compound **013b** as a white solid (21 mg, 65.88% yield). MS obsd. (ESI⁺) [(M+H)⁺]: 805.1.

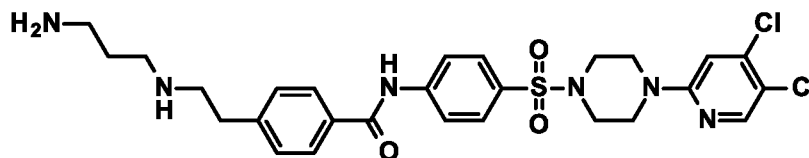
Step 3: 4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-[5-methyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

**013**

The title compound was prepared in analogy to the preparation of Example **003** in **step 2** by replacing compound **003a** with compound **013b**. **Example 013** (6 mg) was obtained as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 605.3.

Example 013: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.71 (s, 1H), 8.14 (s, 1H), 8.07 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 7.5 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 7.4 Hz, 2H), 7.02 (s, 1H), 3.64 (s, 4H), 2.97 (s, 4H), 2.82 (s, 6H), 2.67 (s, 2H), 2.22 (s, 3H), 1.68 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -62.89 (s, 3F).

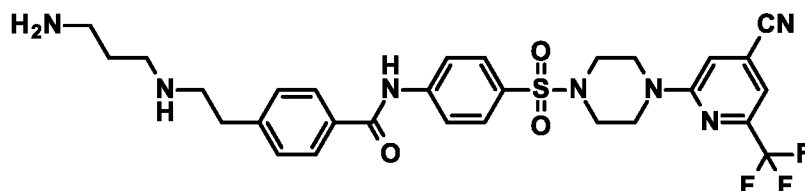
Example 014: 4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-(4,5-dichloro-2-pyridyl)piperazin-1-yl]sulfonylphenyl]benzamide

**014**

The title compound was prepared in analogy to the preparation of **Example 003** by replacing compound 2,5-dichloro-4-(trifluoromethyl)pyridine with 2,4,5-trichloropyridine and compound **Int-5** with compound **Int-7** in **step 1**. **Example 014** (31 mg) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 591.2.

Example 014: ^1H NMR (400 MHz, CD_3OD) δ ppm 8.04 (s, 1H), 7.92 (d, $J = 8.2$ Hz, 2H), 7.85 (d, $J = 7.6$ Hz, 2H), 7.71 (d, $J = 8.1$ Hz, 2H), 7.36 (d, $J = 7.7$ Hz, 2H), 6.97 (s, 1H), 3.23 (d, $J = 4.0$ Hz, 4H), 3.10 (d, $J = 15.0$ Hz, 6H), 2.98 (s, 6H), 1.93 (s, 2H).

5 **Example 015:** 4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-[4-cyano-6-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



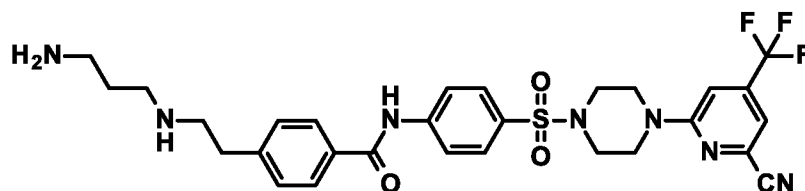
015

The title compound was prepared in analogy to the preparation of **Example 003** by replacing compound 2,5-dichloro-4-(trifluoromethyl)pyridine with 2-chloro-6-(trifluoromethyl)pyridine-4-carbonitrile and compound **Int-5** with compound **Int-7** in **step 1**.

Example 015 (10 mg) was obtained as a white solid. MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 616.3.

Example 015: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 10.68 (s, 1H), 8.06 (d, $J = 8.7$ Hz, 2H), 7.90 (d, $J = 8.0$ Hz, 2H), 7.75 (d, $J = 8.7$ Hz, 2H), 7.67 (s, 1H), 7.44 (s, 1H), 7.39 (d, $J = 7.9$ Hz, 2H), 3.76 (s, 5H), 3.00 (s, 4H), 2.81 (s, 6H), 2.66 (s, 2H), 1.67 (s, 2H). ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ ppm -67.72 (s, 3F).

Example 016: 4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-[6-cyano-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



016

The title compound was prepared in analogy to the preparation of **Example 003** by replacing compound 2,5-dichloro-4-(trifluoromethyl)pyridine with 6-chloro-4-(trifluoromethyl)pyridine-2-carbonitrile and compound **Int-5** with compound **Int-7** in **step 1**.

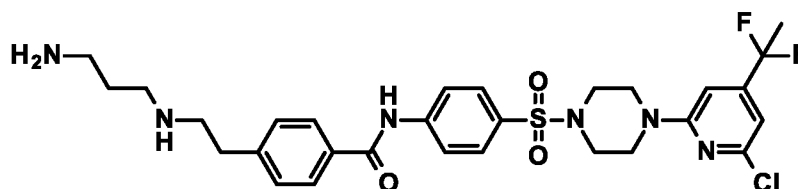
25 **Example 016** (10 mg) was obtained as a white solid. MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 616.2.

Example 016: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 10.68 (s, 1H), 8.36 (s, 2H), 8.04 (d, $J = 8.7$ Hz, 2H), 7.87 (d, $J = 7.9$ Hz, 2H), 7.72 (d, $J = 8.7$ Hz, 2H), 7.56 (s, 1H), 7.45 (s, 1H), 7.37 (d,

-66-

$J = 7.8$ Hz, 2H), 3.74 (s, 4H), 2.97 (s, 4H), 2.79 (s, 6H), 2.64 (s, 2H), 1.65 (s, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ ppm -63.71 (s, 3F).

Example 017: 4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-[6-chloro-4-(1,1-difluoroethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

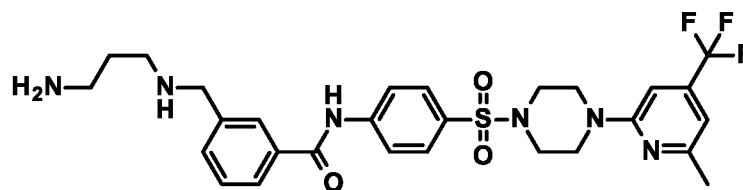


017

The title compound was prepared in analogy to the preparation of **Example 003** by replacing compound 2,5-dichloro-4-(trifluoromethyl)pyridine with compound **Int-8** and compound **Int-5** with compound **Int-7** in **step 1**. **Example 015** (8 mg) was obtained as a white solid. MS obsd. (ESI $^+$) [(M+H) $^+$]: 621.1.

Example 017: ^1H NMR (400 MHz, DMSO- d_6) δ ppm 10.70 (s, 1H), 8.37 (s, 2H), 8.08 (d, $J = 8.6$ Hz, 2H), 7.91 (d, $J = 7.6$ Hz, 2H), 7.75 (d, $J = 8.6$ Hz, 2H), 7.39 (d, $J = 7.6$ Hz, 2H), 6.87 (s, 1H), 6.79 (s, 1H), 3.67 (s, 4H), 2.98 (s, 4H), 2.83 (s, 6H), 2.69 (s, 2H), 1.91 (t, $J = 19.2$ Hz, 3H), 1.70 (s, 2H). ^{19}F NMR (376 MHz, DMSO) δ ppm -87.87 (s, 2F).

Example 018: 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-methyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



018

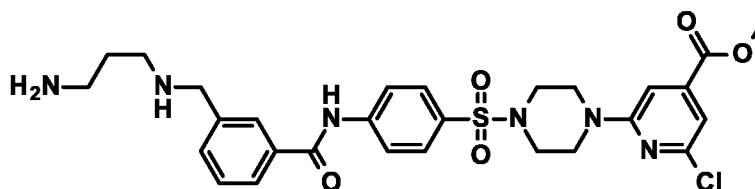
The title compound was prepared in analogy to the preparation of **Example 003** by replacing 2,5-dichloro-4-(trifluoromethyl)pyridine with 2-chloro-6-methyl-4-(trifluoromethyl)pyridine and compound **Int-5** with compound **Int-6** in **step 1**. **Example 018** (8 mg) was obtained as a white solid. MS obsd. (ESI $^+$) [(M+H) $^+$]: 591.1.

Example 018: ^1H NMR (CD $_3$ OD, 400 MHz) δ ppm 7.99 (s, 1H), 7.9-8.0 (m, 3H), 7.7-7.7 (m, 2H), 7.6-7.7 (m, 1H), 7.5-7.6 (m, 1H), 6.67 (s, 1H), 6.62 (s, 1H), 4.2-4.3 (m, 2H), 3.6-3.6 (m,

-67-

4H), 3.1-3.1 (m, 2H), 2.9-3.0 (m, 6H), 2.3-2.3 (s, 3H), 2.0-2.1 (m, 2H). ^{19}F NMR (376 MHz, DMSO-*d*₆) δ ppm -66.52 (s, 3F).

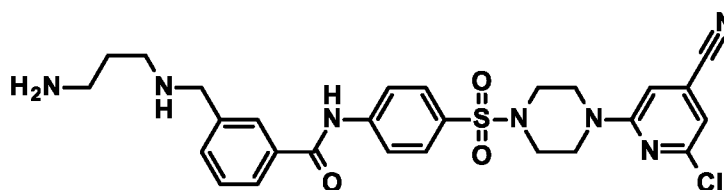
Example 019: Methyl 2-[4-[4-[[3-[(3-aminopropylamino)methyl]benzoyl]amino]phenyl]sulfonylpiperazin-1-yl]-6-chloro-pyridine-4-carboxylate

**019**

The title compound was prepared in analogy to the preparation of **Example 003** by replacing 2,5-dichloro-4-(trifluoromethyl)pyridine with methyl 2,6-dichloropyridine-4-carboxylate and compound **Int-5** with compound **Int-6** in **step 1**. **Example 019** (12 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 601.1.

Example 019: ^1H NMR (CD₃OD, 400 MHz) δ ppm 7.98 (s, 1H), 7.9-8.0 (m, 3H), 7.7-7.7 (m, 2H), 7.62 (d, 1H, $J = 7.6$ Hz), 7.5-7.6 (m, 1H), 7.09 (d, 1H, $J = 0.7$ Hz), 6.96 (d, 1H, $J = 0.7$ Hz), 4.19 (s, 2H), 3.79 (s, 3H), 3.6-3.6 (m, 4H), 2.9-3.1 (m, 8H), 1.98 (quin, 2H, $J = 7.7$ Hz).

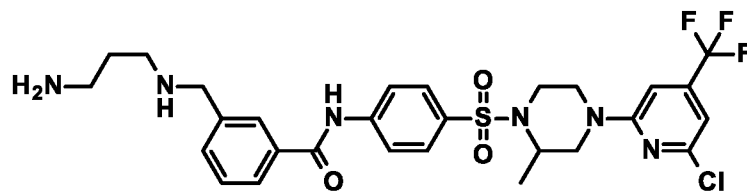
Example 020: 3-[(3-Aminopropylamino)methyl]-N-[4-[4-(6-chloro-4-cyano-2-pyridyl)piperazin-1-yl]sulfonylphenyl]benzamide

**020**

The title compound was prepared in analogy to the preparation of **Example 003** by replacing 2,5-dichloro-4-(trifluoromethyl)pyridine with 2,6-dichloropyridine-4-carbonitrile and compound **Int-5** with compound **Int-6** in **step 1**. **Example 020** (15 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 568.2.

Example 020: ^1H NMR (CD₃OD, 400 MHz) δ ppm 8.0 (s, 1H), 7.91 (d, 3H, $J = 8.8$ Hz), 7.70 (d, 2H, $J = 8.8$ Hz), 7.6-7.7 (m, 1H), 7.5-7.6 (m, 1H), 6.94 (s, 1H), 6.77 (s, 1H), 4.23 (s, 2H), 3.6-3.7 (m, 4H), 3.1-3.1 (m, 2H), 2.9-3.0 (m, 6H), 2.01 (t, 2H, $J = 7.7$ Hz).

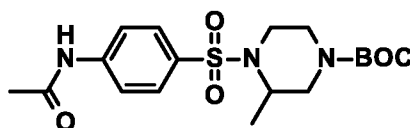
Example 021: 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-2-methyl-piperazin-1-yl]sulfonylphenyl]benzamide



5

021

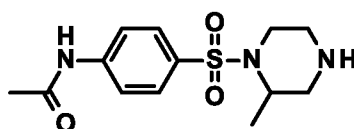
Step 1: *Tert*-butyl 4-(4-acetamidophenyl)sulfonyl-3-methyl-piperazine-1-carboxylate



021a

To a solution of 4-*N*-BOC-2-methylpiperazine (857.11 mg, 4.28 mmol), TEA (1.19 mL, 8.56 mmol) in DCM (10 mL) was added *N*-acetylsulfanilyl chloride (1.0 g, 4.28 mmol) in one portion and the reaction was at 25 °C for 1 hour. After completion, the mixture was diluted with DCM (20 mL), washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na₂SO₄, concentrated under vacuum to afford compound **021a** (1.5 g, 88.18% yield) as yellow solid, which was used in the next step directly. MS obsd. (ESI⁺) [(M+Na)⁺]: 420.3.

Step 2: *N*-[4-(2-methylpiperazin-1-yl)sulfonylphenyl]acetamide

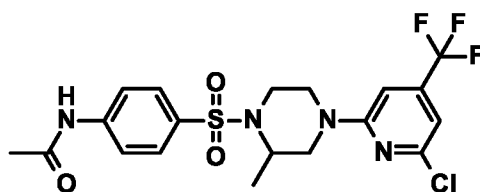


021b

A mixture of compound **021a** (1.5 g, 3.77 mmol) in DCM (15 mL) and TFA (14.54 mL, 188.68 mmol) was stirred at 20 °C for 1 hour. After completion, the mixture was concentrated under vacuum to give compound **021b** (1.5 g, 96.62% yield) as a yellow oil, which was used in the next step directly. MS obsd. (ESI⁺) [(M+H)⁺]: 297.9.

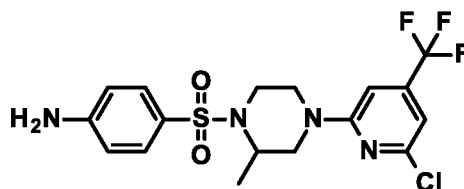
Step 3: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-2-methyl-piperazin-1-yl]sulfonylphenyl]acetamide

-69-

**021c**

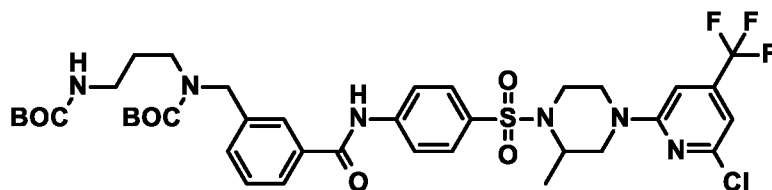
The mixture of compound **021b** (1.5 g, 3.65 mmol), DIPEA (1.27 mL, 7.29 mmol), 2,6-dichloro-4-(trifluoromethyl)pyridine (787.52 mg, 3.65 mmol) in DMSO (20 mL) was heated at 90 °C for 24 hours. After completion, the reaction mixture was diluted with water (50 mL), extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄, concentrated under vacuum to give crude product, which was purified by prep-HPLC (TFA as additive) to give compound **021c** (400 mg, 23% yield) as a yellow oil. MS obsd. (ESI⁺) [(M+H)⁺]: 477.1.

Step 4: 4-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]-2-methyl-piperazin-1-yl]sulfonylaniline

**021d**

Compound **021d** was prepared in analogy to the preparation of compound **004d** by replacing compound **004c** with compound **021c**. Compound **021d** (180 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+Na)⁺]: 435.2.

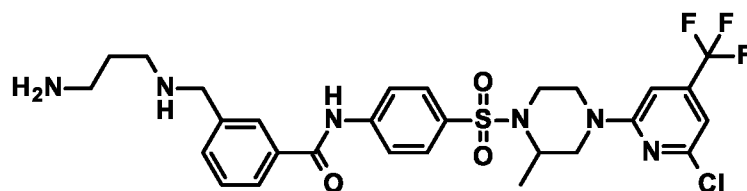
Step 5: *Tert*-butyl *N*-[3-(*tert*-butoxycarbonylamino)propyl]-*N*-[[3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-2-methyl-piperazin-1-yl]sulfonyl]phenyl]carbonyl]phenyl]methyl]carbamate

**021e**

To a solution of compound **Int-9** (100.0 mg, 0.240 mmol) in MeCN (2 mL) was added 3-methylpyridine (45.6 mg, 0.490 mmol), methanesulfonyl chloride (0.03 mL, 0.370 mmol) in one

portion and the mixture was stirred at rt for 1 hour. And then, compound **021d** (117.1 mg, 0.270 mmol) was added to the mixture and the reaction was stirred at rt for 2 hours. After completion, the mixture was concentrated under vacuum to give a residue, which was purified by prep-HPLC (TFA as additive) to give compound **021e** (78 mg, 37.96% yield) as a yellow oil. MS obsd. (ESI⁺) [(M+H)⁺]: 825.3.

Step 6: 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-2-methyl-piperazin-1-yl]sulfonylphenyl]benzamide

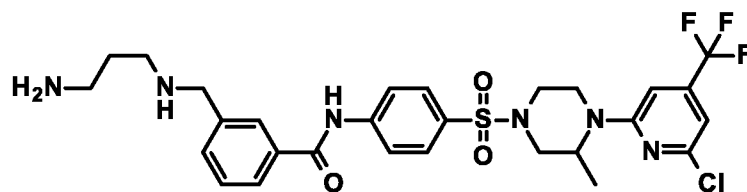


021

The mixture of compound **021e** (78.0 mg, 0.090 mmol) in DCM (1 mL) and TFA (0.36 mL) was stirred at 20°C for 1 hour. After completion, the mixture was concentrated under vacuum to give a residue, which was purified by prep-HPLC (NH₄HCO₃ as additive) to afford **Example 021** (28 mg, 47.03% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 625.5.

Example 021: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.10 - 7.97 (m, 2H), 7.93 - 7.88 (m, 1H), 7.86 - 7.76 (m, 3H), 7.63 - 7.54 (m, 1H), 7.51 - 7.44 (m, 1H), 7.03 (s, 1H), 6.92 (s, 1H), 4.17 - 4.07 (m, 2H), 4.06 - 3.98 (m, 1H), 3.77 (s, 2H), 3.71 - 3.63 (m, 1H), 3.20 - 3.13 (m, 2H), 3.03 - 2.92 (m, 2H), 1.57 - 1.45 (m, 2H), 1.02 (d, 3H).

Example 022: 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-3-methyl-piperazin-1-yl]sulfonylphenyl]benzamide



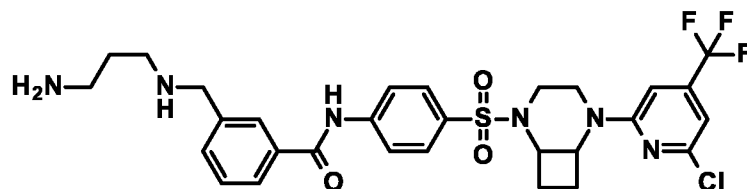
022

The title compound was prepared in analogy to the preparation of **Example 021** by replacing 4-*N*-BOC-3-methylpiperazine with 4-*N*-BOC-2-methylpiperazine in **step 1**. **Example 022** (18 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 625.1.

Example 022: ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.12 - 8.04 (m, 2H), 7.95 - 7.89 (m, 1H), 7.86 - 7.79 (m, 1H), 7.77 - 7.71 (m, 2H), 7.60 - 7.52 (m, 1H), 7.52 - 7.43 (m, 1H), 7.04 (s, 1H),

7.00 - 6.94 (m, 1H), 4.74 - 4.63 (m, 1H), 4.28 - 4.16 (m, 1H), 3.76 (s, 2H), 3.72 - 3.66 (m, 1H), 3.54 - 3.47 (m, 2H), 3.27 - 3.16 (m, 2H), 2.91 - 2.72 (m, 2H), 2.46 - 2.29 (m, 2H), 1.70 - 1.50 (m, 2H), 1.19 (d, 3H).

5 **Example 023:** 3-[(3-Aminopropylamino)methyl]-N-[4-[[5-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-2,5-diazabicyclo[4.2.0]octan-2-yl]sulfonyl]phenyl]benzamide

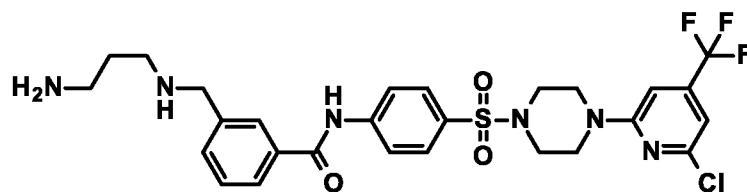


023

The title compound was prepared in analogy to the preparation of **Example 021** by replacing 4-N-BOC-2-methylpiperazine with tert-butyl 2,5-diazabicyclo[4.2.0]octane-2-carboxylate in **step 1**. **Example 023** (10 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 637.2.

Example 023: ¹H NMR (400MHz, DMSO-*d*₆) δ 11.01 - 10.70 (m, 1H), 9.75 - 9.44 (m, 2H), 8.33 - 8.26 (m, 1H), 8.20 - 8.08 (m, 5H), 8.05 - 7.96 (m, 1H), 7.86 - 7.75 (m, 3H), 7.65 - 7.54 (m, 1H), 7.07 - 6.98 (m, 1H), 6.85 - 6.73 (m, 1H), 4.52 - 4.40 (m, 1H), 4.32 - 4.18 (m, 2H), 4.10 - 3.98 (m, 1H), 3.85 - 3.73 (m, 1H), 3.65 - 3.51 (m, 2H), 3.10 - 2.99 (m, 2H), 2.98 - 2.87 (m, 3H), 2.22 - 2.10 (m, 2H), 2.07 - 1.92 (m, 4H).

20 **Example 024:** 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



024

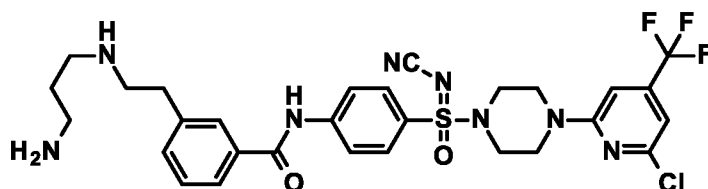
The title compound was prepared in analogy to the preparation of **Example 003** by replacing compound **Int-5** with compound **Int-6** in **step 1**. **Example 024** (10 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 611.1.

Example 024: ¹H NMR (CD₃OD, 400 MHz) δ ppm 8.01 (s, 1H), 7.96 (d, 3H, *J* = 8.7 Hz), 7.8-7.8 (m, 2H), 7.65 (d, 1H, *J* = 7.8 Hz), 7.5-7.6 (m, 1H), 6.83 (s, 1H), 6.70 (s, 1H), 4.41 (d, 2H, *J* =

-72-

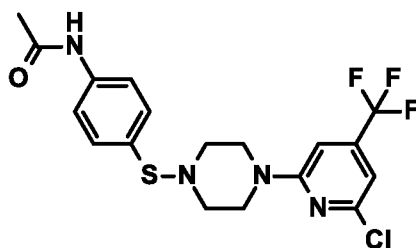
13.7 Hz), 4.24 (s, 2H), 3.1-3.1 (m, 2H), 2.9-3.0 (m, 2H), 2.8-2.9 (m, 2H), 1.9-2.1 (m, 4H), 1.57 (dq, 2H, $J=4.3, 12.5$ Hz).

Example 025: 3-[2-(3-Aminopropylamino)ethyl]-*N*-[4-[S-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-*N*-cyano-sulfonimidoyl]phenyl]benzamide



025

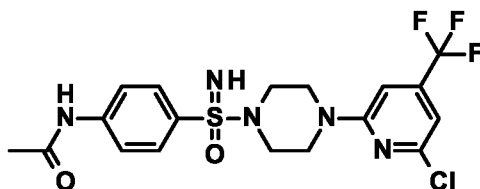
Step 1: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfanylphenyl]acetamide



025a

The mixture of 4-acetamidothiophenol (2.64 g, 15.81 mmol), compound **Int-1a** (3.5 g, 13.17 mmol), 1,10-Phenanthroline (474.84 mg, 2.63 mmol) and copper oxide (210.8 mg, 2.63 mmol) in DMSO (25 mL) was stirred at 60 °C for 24 hours under oxygen (1.5 L, 0.750 mmol) (15 Psi, one balloon). After completion, the mixture was diluted with water (100 mL) and extracted with EtOAc (200 mL × 3). The combined organic layer was washed with brine (200 mL), dried over anhydrous Na₂SO₄, concentrated under vacuum to give residue, which was purified by silica-gel column chromatography (elute with EtOAc:PE = 20%) to give compound **025a** (3 g, 52.85% yield) as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 430.9.

Step 2: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonimidoyl]phenyl]acetamide

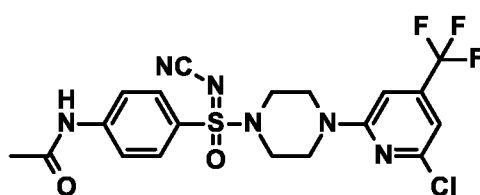


025b

-73-

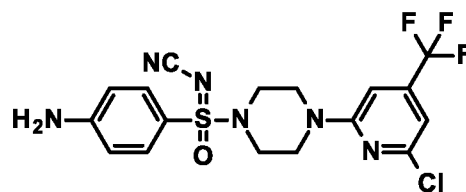
To a solution of compound **025a** (800.0 mg, 1.86 mmol) and ammonia in THF (2.79 mL, 2.79 mmol) in methanol (15 mL) were added PIDA (1.79 g, 5.57 mmol) portion-wise at rt. The reaction mixture was stirred at 15 °C for 12 hours. After completion, the mixture was diluted with water (100 mL), extracted with EtOAc (100 mL × 3). The combined organic layer was washed with brine (100 mL × 3), dried over anhydrous Na₂SO₄, concentrated under vacuum to give residue, which was purified by silica-gel chromatography (elute with EtOAc:PE = 10%) to give compound **025b** (600 mg, 69.96% yield) as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 461.9.

Step 3: N-[4-[S-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-N-cyano-sulfonimidoyl]phenyl]acetamide

**025c**

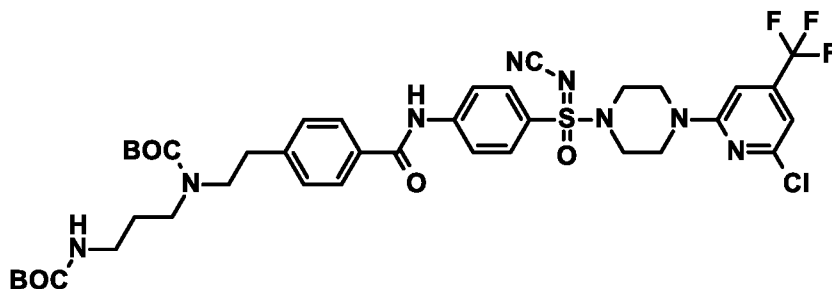
To a solution of compound **025b** (550.0 mg, 1.19 mmol) in MeCN (20 mL) were added 2,2'-azobis(2-methylpropionitrile) (293.3 mg, 1.79 mmol), potassium carbonate (329.14 mg, 2.38 mmol) and copper iodide (45.36 mg, 0.240 mmol). The reaction mixture was stirred at 75 °C for 12 hours under oxygen (1.5 L, 1.19 mmol, 1 eq) (one balloon pressure). After completion, the mixture was diluted with EA (200 mL) and filtered. The filtrate was concentrated to give residue, which was purified by silica-gel chromatography (15% EA in PE) to give compound **025c** (300 mg, 50.32% yield) as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 487.0.

Step 4: [(4-Aminophenyl)-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-oxo-λ⁶-sulfanylidene]cyanamide

**025d**

To a solution of compound **025c** (120.0 mg, 0.250 mmol) in isopropyl alcohol (4 mL) were added concentrated hydrochloric acid (1.0 mL, 12 mmol) in one portion. The mixture was stirred at 25 °C for 12 hours. After completion, the mixture was concentrated under vacuum to give residue, which was purified by prep-TLC (elute with EtOAc:PE = 50%) to afford compound **025d** (70 mg, 63.85% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 444.9.

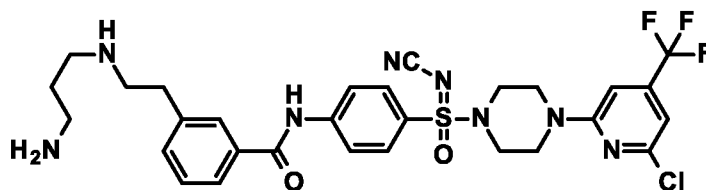
Step 5: *Tert*-butyl *N*-[3-(*tert*-butoxycarbonylamino)propyl]-*N*-[2-[3-[[4-[*S*-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-*N*-cyano-sulfonimidoyl]phenyl]carbamoyl]phenyl]ethyl]carbamate



5 **025d**

To a solution of compound **Int-9** (79.78 mg, 0.190 mmol) and 3-methylpyridine (43.96 mg, 0.470 mmol, 3 eq) in MeCN (1.5 mL) was added MsCl (0.02 mL, 0.240 mmol) and the mixture was stirred at 15 °C for 3 h. And then, compound **025c** (70.0 mg, 0.160 mmol) was added to the mixture and the mixture was stirred at 30°C for 12 h. After completion, the mixture was concentrated under vacuum and the residue was purified by prep-HPLC (FA as additive) to give compound **025d** (80 mg, 59.86% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 849.3.

Step 6: 3-[2-(3-Aminopropylamino)ethyl]-*N*-[4-[*S*-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-*N*-cyano-sulfonimidoyl]phenyl]benzamide

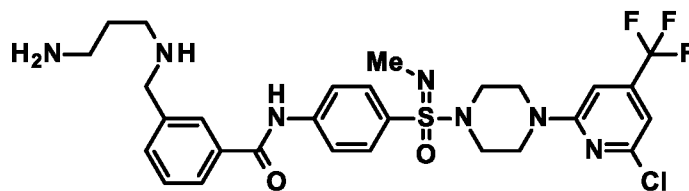


15 **025**

The mixture of compound **025d** (70.0 mg, 0.080 mmol) in DCM (2 mL) and TFA (0.3 mL, 0.080 mmol) was stirred at 15 °C for 2 hours. After completion, the mixture was concentrated under vacuum to give a residue, which was purified by prep-HPLC (TFA as additive) to give example **025** (20.5 mg, 29.92% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 649.3.

Example 025: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.33 - 8.43 (m, 1 H), 8.15 - 8.24 (m, 2 H), 7.97 - 8.07 (m, 2 H), 7.83 - 7.91 (m, 2 H), 7.49 - 7.58 (m, 2 H), 7.15 - 7.18 (m, 1 H), 7.01 - 7.06 (m, 1 H), 3.80 - 3.84 (m, 4 H), 3.23 - 3.32 (m, 4 H), 2.86 - 2.95 (m, 6 H), 2.73 - 2.81 (m, 2 H), 1.70 - 1.81 (m, 2 H).

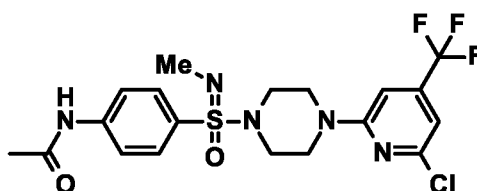
Example 026: 3-[(3-aminopropylamino)methyl]-*N*-[4-[*S*-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-*N*-methyl-sulfonimidoyl]phenyl]benzamide



5

026

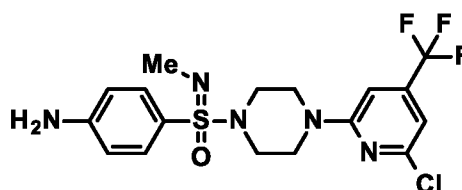
Step 1: *N*-[4-[*S*-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-*N*-methyl-sulfonimidoyl]phenyl]acetamide



026a

10 To a solution of compound **Int-1a** (1.0 g, 3.77 mmol) in THF (40 mL) was added NCS (1.11 g, 8.29 mmol) in one portion. The mixture was stirred at 45 °C for 1 h. Then triethylamine (1.58 mL, 11.31 mmol) and compound **Int-11** (800.0 mg, 3.77 mmol) was added successively into the reaction mixture and stirred at 45 °C for 3 hours. After completion, the mixture was diluted with water (100 mL) and extracted with EtOAc (150 mL × 3). The combined organic
15 layer was washed with brine (100 mL × 2), dried over Na₂SO₄ and concentrated under vacuum to give residue, which was purified by silica-gel chromatography (20% EA in PE) to give compound **026a** (800 mg, 40.79% yield) as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 476.0.

Step 2: 4-[*S*-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-*N*-methyl-sulfonimidoyl]aniline



20

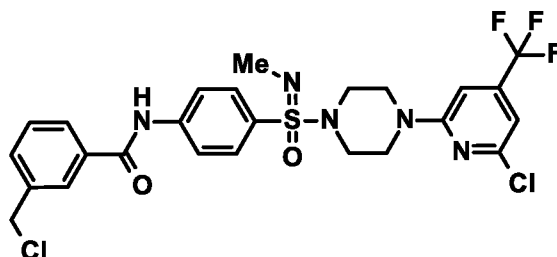
026b

The mixture of compound **026a** (700.0 mg, 1.47 mmol) in THF (15 mL) and concentrated hydrochloric acid (4.0 mL, 48 mmol) was stirred at 50 °C for 2 hours. After completion, the mixture was concentrated under vacuum to give residue, which was purified by prep-HPLC

-76-

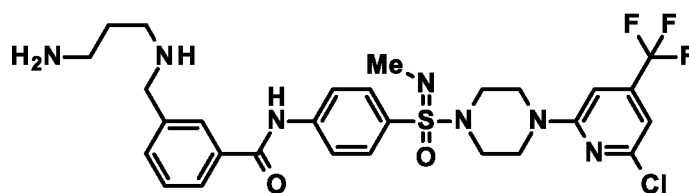
(NH₃•H₂O as additive) to give compound **026b** (500 mg, 77.1% yield) as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 433.9.

Step 3: 3-(Chloromethyl)-N-[4-[S-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-N-methyl-sulfonimidoyl]phenyl]benzamide

**026c**

To a mixture of compound **026b** (150.0 mg, 0.350 mmol) and 3-(chloromethyl)benzoyl chloride (78.43 mg, 0.410 mmol) in DCM (4 mL) was added TEA (0.14 mL, 1.04 mmol) dropwise. The mixture was stirred at 20 °C for 2 hours. After completion, the mixture was diluted with water (50 mL) and extracted with EtOAc (100 mL × 3). The combined organic layer was washed with brine (50 mL × 2), dried with anhydrous Na₂SO₄ and concentrated under vacuum to give residue, which was purified by prep-HPLC (FA as additive) to afford compound **026c** (150 mg, 73.25% yield) as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 586.3.

Step 4: 3-[2-(3-Aminopropylamino)ethyl]-N-[4-[S-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-N-cyano-sulfonimidoyl]phenyl]benzamide

**026**

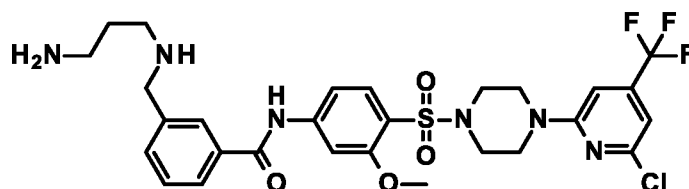
The mixture of compound **026c** (100.0 mg, 0.170 mmol), 1,3-diaminopropane (101.11 mg, 1.36 mmol), K₂CO₃ (70.7 mg, 0.510 mmol) and KI (0.01 mL, 0.170 mmol) was stirred at 60 °C for 1 hour. After completion, the mixture was concentrated under vacuum to give residue, which was purified by prep-HPLC (HCl as additive) to give **Example 026** (68.4 mg, 64.19% yield) as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 624.3.

Example 026: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.95 - 11.12 (m, 1 H), 9.63 - 9.87 (m, 2 H), 8.31 - 8.40 (m, 1 H), 8.15 - 8.27 (m, 4 H), 7.98 - 8.08 (m, 1 H), 7.87 - 7.94 (m, 2 H), 7.76 - 7.87 (m, 1 H), 7.54 - 7.64 (m, 1 H), 7.07 - 7.19 (m, 1 H), 6.92 - 7.01 (m, 1 H), 4.15 - 4.30 (m, 2

-77-

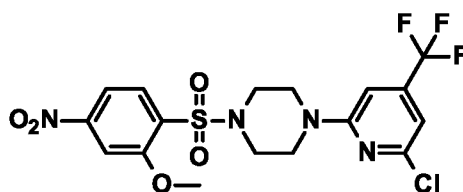
H), 3.65 - 3.83 (m, 4 H), 2.99 - 3.20 (m, 6 H), 2.88 - 2.98 (m, 2 H), 2.74 - 2.84 (m, 3 H), 1.98 - 2.16 (m, 2 H).

Example 027: 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-3-methoxy-phenyl]benzamide



027

Step 1: 1-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]-4-(2-methoxy-4-nitro-phenyl)sulfonyl-piperazine

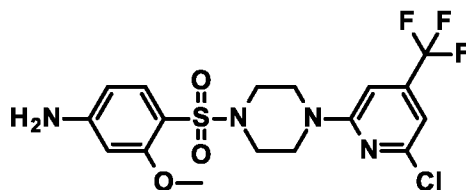


027a

The title compound was prepared in analogy to the preparation of compound **Int-1b** by replacing 4-acetamidobenzenesulfonyl chloride with 2-methoxy-4-nitrobenzenesulfonyl chloride. Compound **027a** (400 mg) was obtained as a light yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]:

483.0.

Step 2: 4-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-3-methoxy-aniline

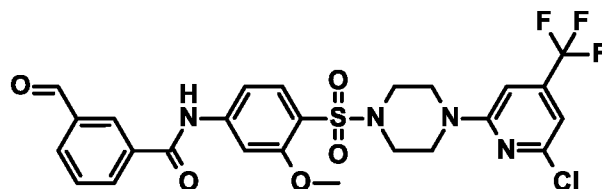


027b

A mixture of compound **027a** (400.0 mg, 0.830 mmol) and Fe (465.84 mg, 8.32 mmol) in methanol (15 mL) and NH₄Cl (sat., 3 mL) was heated at 65 °C for 1 hour. After completion, the mixture was filtered, the filtrate was poured into water (25 mL) and extracted by EtOAc (20 mL × 2). The combined organic layer was washed with brine (20 mL × 2), dried over Na₂SO₄ and

concentrated under vacuum to give crude compound **027b** (320 mg, 81.91% yield), which was used in the next step directly. MS obsd. (ESI⁺) [(M+H)⁺]: 451.1.

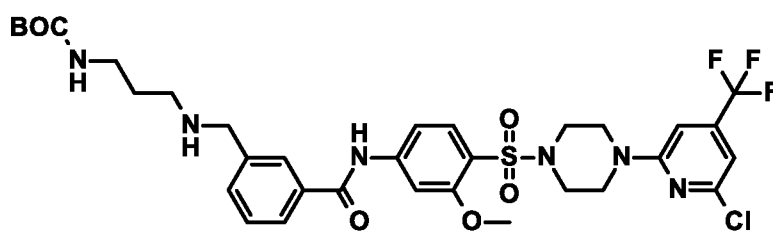
Step 3 : *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-3-methoxy-phenyl]-4-formyl-benzamide



027c

To a mixture of 4-formylbenzoic acid (49.95 mg, 0.330 mmol) in DCM (12.86 mL) was added oxalyl chloride (42.23 mg, 0.330 mmol, 1 eq) and a drop of DMF. The resulted mixture was stirred at rt. After completion, the solvent was removed under vacuum to give a residue, which was added to a mixture of compound **027b** (150.0 mg, 0.330 mmol) and TEA (0.2 mL), DMAP (25 mg) in DCM (12.86 mL). The mixture was stirred at rt for 1 hour. After completion, the solvent was removed under vacuum to give residue which was purified by silica-gel chromatography (elute with EtOAc:PE = 50%) to give the desired product compound **027c** (180 mg, 33.81% yield) as a colorless oil. MS obsd. (ESI⁺) [(M+H)⁺]: 583.0.

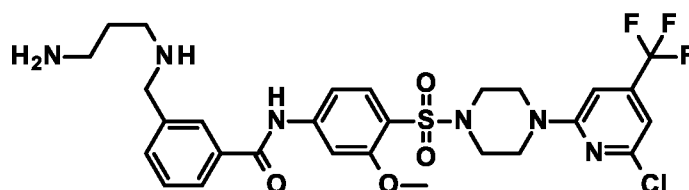
Step 4 : *Tert*-butyl *N*-[3-[[3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-3-methoxy-phenyl]carbamoyl]phenyl]methylamino]propyl]carbamate



027d

A mixture of *N*-BOC-1,3-diaminopropane (89.66 mg, 0.510 mmol), compound **027c** (150.0 mg, 0.260 mmol) and Ti(OEt)₄ (58.69 mg, 0.260 mmol) in THF (15 mL) was stirred at 25 °C for 2 hours. And then, sodium cyanoborohydride (32.34 mg, 0.510 mmol, 2 eq) was added to this mixture and the resulted mixture was stirred at rt for another 1 hour. After completion, brine (20 mL) was added to this mixture. The mixture was extracted by EtOAc (25 mL × 2), washed with brine (25 mL), dried over Na₂SO₄ and purified by silica-gel chromatography (elute with EtOAc:PE = 50%) to afford the desired product compound **027d** (40 mg, 19.3% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 741.2.

Step 4 : 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-3-methoxy-phenyl]benzamide

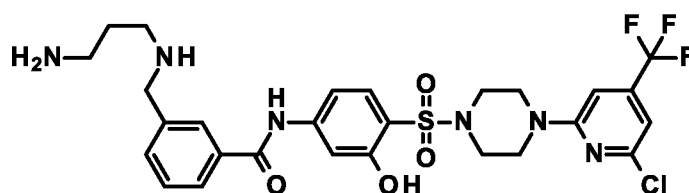


027

- 5 A mixture of compound **027d** (60.0 mg, 0.080 mmol) in HCl-dioxane (5 mL, 4 M) was stirred at 25 °C for 1 hour. After completion, the solvent was removed under vacuum to give a residue, which was purified by prep-HPLC (ACN/water = 35-45%) to give the desired product **Example 027** (TFA as additive) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 641.2.

- Example 027:** ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.68 (s, 1H), 8.23 (s, 1H), 7.99 (s, 1H),
 10 7.85 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 1.6 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.54 – 7.64 (m, 2H),
 7.48 (t, *J* = 7.7 Hz, 1H), 7.07 (s, 1H), 6.96 (s, 1H), 3.85 (s, 3H), 3.81 (s, 2H), 3.66 – 3.62 (m, 4H),
 3.11 – 3.18 (m, 4H), 2.84 (t, *J* = 7.3 Hz, 2H), 2.62 (t, *J* = 6.7 Hz, 2H), 1.74 (dd, *J* = 14.0, 6.9 Hz,
 2H). ¹⁹F NMR (376 MHz, CDCl₃) δ ppm -58.72 (s, 3F).

- 15 **Example 028: 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-3-hydroxy-phenyl]benzamide**



028

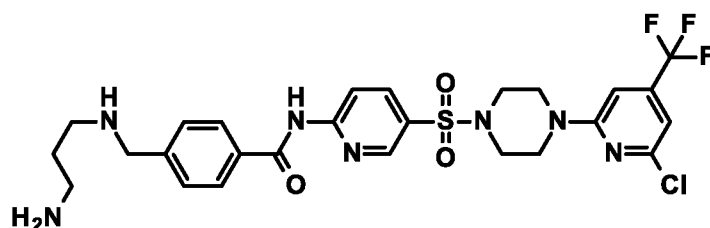
- To a mixture of **Example 027** (40.0 mg, 0.060 mmol) in DCM (10 mL) was added BBr₃
 20 (156.31 mg, 0.620 mmol) dropwise. The mixture was stirred at rt for 2 hours. After completion, the mixture was poured into 20 mL ice water, extracted with DCM (10 mL × 2). The combined organic layer was washed with NaHCO₃ aq. (15 mL), dried over Na₂SO₄ and concentrated under vacuum to give residue, which was purified by prep-HPLC (TFA as additive) to afford **Example 028** (2.6 mg, 6.03% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 627.2.

- 25 **Example 028:** ¹H NMR (400 MHz, CD₃OD) δ ppm 8.06 (s, 1H), 8.00 (d, *J* = 7.4 Hz, 1H), 7.58 –
 7.77 (m, 4H), 7.24 (d, *J* = 8.4 Hz, 1H), 6.93 (s, 1H), 6.83 (s, 1H), 4.32 (s, 2H), 3.71 (s, 4H),

-80-

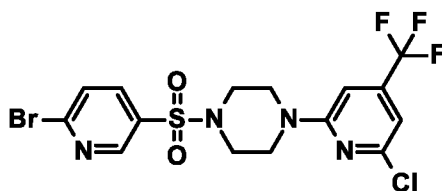
3.26 – 3.29 (m, 4H), 3.19 (s, 2H), 3.05 (s, 2H), 2.10 (s, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ ppm -66.50 (s, 3F).

Example 029: 4-[(3-Aminopropylamino)methyl]-N-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-2-pyridyl]benzamide



029

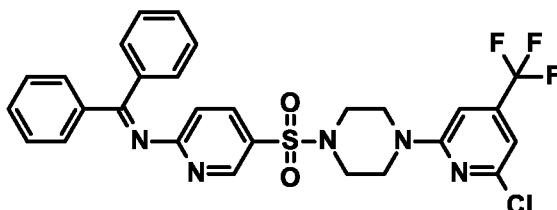
Step 1: 1-[(6-Bromo-3-pyridyl)sulfonyl]-4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazine



029a

The title compound was prepared in analogy to the preparation of compound **Int-1b** by replacing 4-acetamidobenzenesulfonyl chloride with bromo-pyridine-3-sulfonyl chloride. Compound **029a** (350 mg) was obtained as a white solid. MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 484.9.

Step 2: N-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-2-pyridyl]-1,1-diphenyl-methanimine

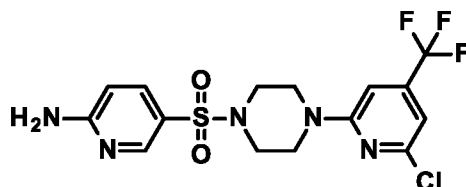


029b

A mixture of compound **029a** (350.0 mg, 0.720 mmol), benzenemethanimine (200 mg, 1.10 mmol), tris(dibenzylideneacetone)dipalladium (0) (65.99 mg, 0.070 mmol), (R)-BINAP (44.87 mg, 0.070 mmol) and Cs_2CO_3 (352.18 mg, 1.08 mmol) in 1,4-dioxane (15 mL) was heated at 90 °C under N_2 for 16 hours. After being cooled to rt, the mixture was filtered and the filtrate was concentrated under vacuum to give a residue, which was purified by silica-gel chromatography

(elute with EtOAc:PE = 20%) to afford the desired product compound **029b** (300 mg, 39.07% yield) as a light yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 586.1.

Step 3: 5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylpyridin-2-amine



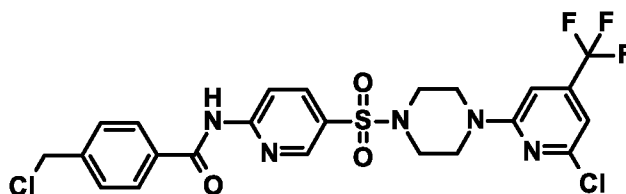
5

029c

To a mixture of compound **029b** (200.0 mg, 0.340 mmol) in THF (10 mL) was added hydrochloric acid (0.5 mL, 6 mmol). The mixture was stirred at 25 °C for 1 hour. After completion, the solvent was removed under vacuum and purified by silica-gel chromatography (elute with EtOAc:PE = 70%) to afford the desired product compound **029c** (120 mg, 80.02% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 422.1.

10

Step 4: 4-(Chloromethyl)-N-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-2-pyridyl]benzamide



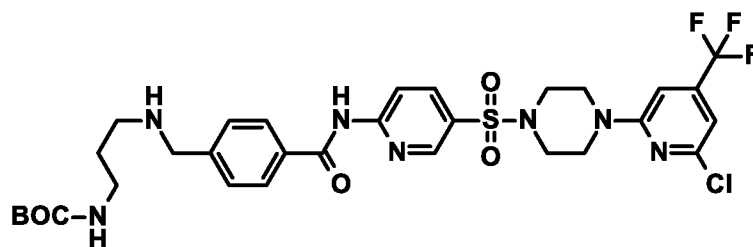
15

029d

Compound **029d** was prepared in analogy to the preparation of compound **Int-2** by replacing compound **Int-1** with compound **029c**. Compound **029d** (17 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 574.0.

Step 5 : *Tert*-butyl N-[3-[[4-[[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-2-pyridyl]carbamoyl]phenyl]methylamino]propyl]carbamate

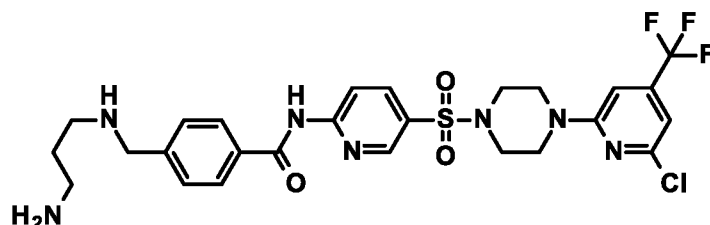
20



029e

Compound **029e** was prepared in analogy to the preparation of compound **001a** by replacing compound **Int-2** with compound **029d** in **step 1**. Compound **029e** (40 mg) was obtained as a colorless oil. MS obsd. (ESI⁺) [(M+H)⁺]: 712.1.

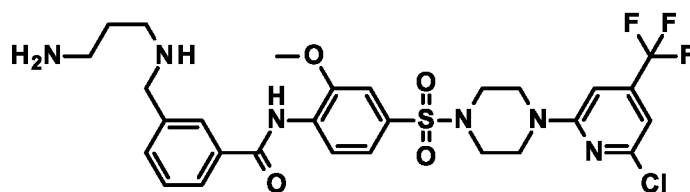
Step 6 : 4-[(3-Aminopropylamino)methyl]-N-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-2-pyridyl]benzamide

**029**

The title compound was prepared in analogy to the preparation of **Example 001** by replacing compound **001a** with compound **029e** in **step 2**. **Example 029** (4 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 612.2.

Example 029: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.71 (d, *J* = 2.3 Hz, 1H), 8.44 (d, *J* = 8.9 Hz, 1H), 8.35 (s, 2H), 8.21 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.10 (s, 1H), 6.97 (s, 1H), 3.76 (s, 6H), 3.07 (s, 4H), 2.84 (s, 2H), 2.56 (d, *J* = 6.2 Hz, 2H), 1.69 (s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -63.45 (s, 3F).

Example 030: 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-2-methoxy-phenyl]benzamide

**030**

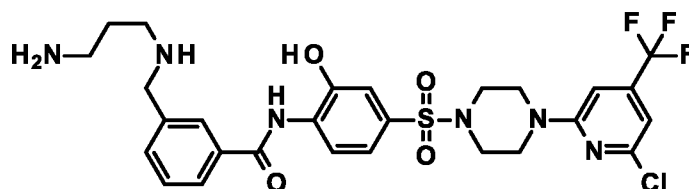
The title compound was prepared in analogy to the preparation of **Example 027** by replacing 2-methoxy-4-nitrobenzenesulfonyl chloride with 3-methoxy-4-nitrobenzenesulfonyl chloride in **step 1**. **Example 030** (4 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 641.2.

Example 030: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.61 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.92 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 7.1 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.41 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.32 (d, *J* = 1.5 Hz, 1H), 7.10 (s, 1H), 6.97 (s, 1H), 3.97 (s, 3H), 3.75 (d, *J* =

-83-

19.4 Hz, 6H), 3.05 (s, 4H), 2.84 (s, 2H), 2.60 (s, 2H), 1.71 (s, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ ppm -63.46 (s, 3F).

Example 031: 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-2-hydroxy-phenyl]benzamide



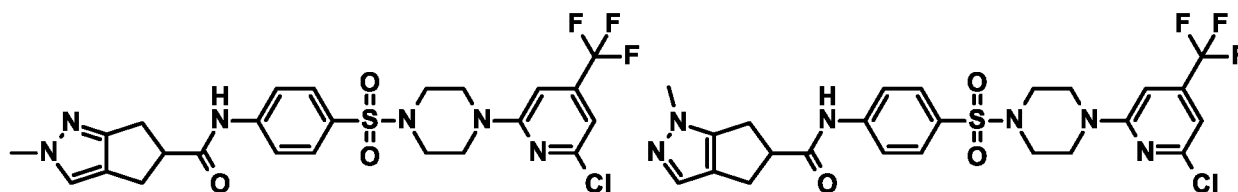
031

The title compound was prepared in analogy to the preparation of **Example 028** by replacing **Example 027** with **Example 030**. Example **031** (6 mg) was obtained as a white solid.

MS obsd. (ESI $^+$) [(M+H) $^+$]: 627.2.

Example 031: ^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.27 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.56 (d, J = 7.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.16 (s, 1H), 7.07 (s, 1H), 6.98 (d, J = 8.7 Hz, 2H), 3.80 (s, 2H), 3.66 (s, 4H), 2.87 (dd, J = 19.4, 12.4 Hz, 6H), 2.61 (t, J = 6.3 Hz, 2H), 1.65 – 1.81 (m, 2H). ^{19}F NMR (376 MHz, DMSO- d_6) δ ppm -63.50 (s, 3F).

Example 032 and 033: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methyl-4,6-dihydropyrrolo[3,4-*c*]pyrazole-5-carboxamide (**Example 032**) and *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-1-methyl-4,6-dihydropyrrolo[3,4-*c*]pyrazole-5-carboxamide (**Example 033**)



032

033

To a mixture solution of compound **Int-1** (130 mg, 0.309 mmol) in DCM (5 mL) was added DIEA (0.204 mL, 1.24 mmol), triphosgene (45.83 mg, 0.154 mmol) and stirred at 0 °C for 15 minutes. And then, mixture of compound **Int-12A&12B** (80.6, mg, 0.340 mmol) was added to the mixture and stirred at 0 °C for another 2 hours. After completion, the mixture was quenched with water (20 mL), extracted with DCM (10 mL $\times$ 2). The combined organic layer was dried over anhydrous Na_2SO_4 , concentrated under vacuum to give a residue, which was purified by

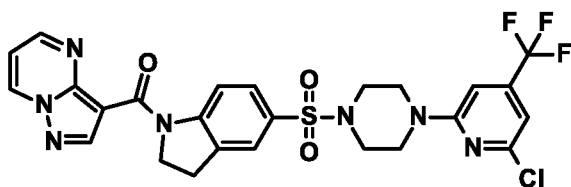
prep-HPLC (NH₄HCO₃ as additive) to give 110 mg mixture of desired products. The further SFC purification to give pure **Example 032** (19.2 mg, 10.73% yield) as a white solid and **Example 033** (19.2 mg, 10.73% yield) as a white solid.

Example 032: ¹H NMR (400 MHz, CDCl₃) δ ppm 7.55-7.61 (m, 4H), 6.70 (s, 1H), 6.59 (s, 1H), 6.53 (s, 1H), 4.59 (s, 2H), 4.52 (s, 2H), 3.78 (s, 3H), 3.65 (s, 4H), 3.01 (s, 4H). ¹⁹F NMR (376 MHz, CDCl₃) -65.03. MS obsd. (ESI⁺) [(M+H)⁺]: 570.1.

Example 033: ¹H NMR (400 MHz, CDCl₃) δ ppm 7.64 -7.69 (m, 4H), 7.18 (s, 1H), 6.77 (s, 1H), 6.60 (s, 1H), 4.62 (d, *J* = 6.9 Hz, 4H), 3.93 (s, 3H), 3.72 (s, 4H), 3.09 (s, 4H). ¹⁹F NMR (376 MHz, CDCl₃) -65.03. MS obsd. (ESI⁺) [(M+H)⁺]: 570.1.

10

Example 034: [5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-pyrazolo[1,5-a]pyrimidin-3-yl-methanone



034

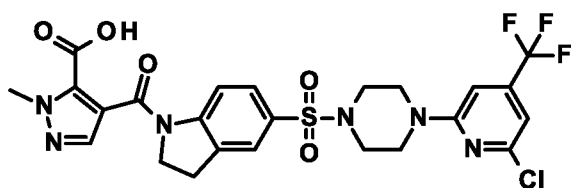
To a solution of pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (84.44 mg, 0.520 mmol) in DCM (6 mL) was added oxalyl chloride (0.3 mL) and the reaction was stirred at rt for 3 hours. The reaction mixture was concentrated under vacuum to give crude residue, which was re-dissolved in 4 mL DCM. To a solution of compound **Int-4** (50.0 mg, 0.110 mmol) and DIPEA (129 mg, 1.0 mmol) in DCM (4 mL) was added above solution dropwise. The reaction was stirred at rt for 4 hours. And then, the mixture was concentrated under vacuum and purified by silica-gel chromatography (elute with EtOAc:PE = 50%) to give **Example 034** (9 mg, 13.54% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 592.1.

Example 034: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.28 (dd, *J* = 7.0, 1.7 Hz, 1H), 8.70 – 8.77 (m, 1H), 8.60 (d, *J* = 4.5 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.63 (s, 1H), 7.48 (dd, *J* = 39.6, 7.9 Hz, 1H), 7.23 – 7.29 (m, 1H), 7.10 (s, 1H), 6.97 (s, 1H), 4.37 (dd, *J* = 10.3, 6.5 Hz, 2H), 3.73 (s, 4H), 3.21 (t, *J* = 7.0 Hz, 2H), 2.99 (s, 4H). ¹⁹F NMR (376 MHz, DMSO-*d*₆): δ ppm -63.46 (s, 3F).

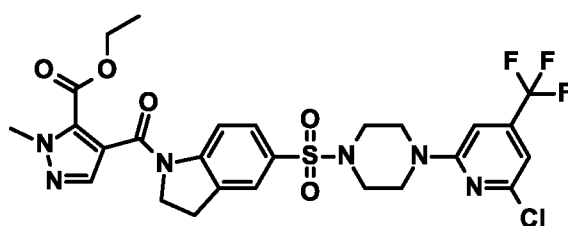
25

-85-

Example 035: 4-[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]-2-methyl-pyrazole-3-carboxylic acid

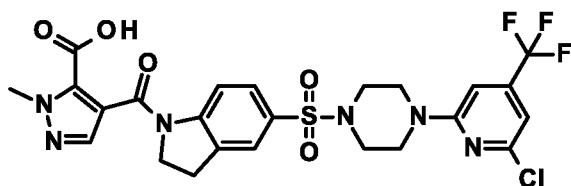
**035**

5 Step 1: Ethyl 4-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]-2-methyl-pyrazole-3-carboxylate

**035a**

Compound 035a was prepared in analogy to the preparation of **Example 034** by replacing
 10 pyrazolo[1,5-a]pyrimidine-3-carboxylic acid with 5-ethoxycarbonyl-1-methyl-pyrazole-4-carboxylic acid. Compound **035a** (50 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 627.2.

Step 2: 4-[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]-2-methyl-pyrazole-3-carboxylic acid

**035**

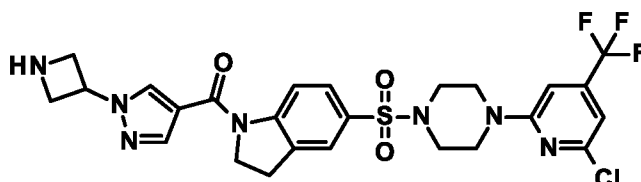
15 A solution of ethyl compound **035a** (20 mg, 0.032 mmol) and LiOH (2.93 mg, 0.128 mmol) in THF/MeOH/water (4/4/1 mL). The resulting mixture was stirred at rt for 16 hours. To the mixture was added 0.1 mL 2 M HCl aq. The resulting mixture was concentrated under
 20 vacuum to give a residue, which was purified by prep-HPLC to give **Example 035** (3.5 mg, 18.21% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 599.1.

Example 035: ¹H NMR (400 MHz, CD₃OD) δ ppm 8.41 (d, *J* = 8.4 Hz, 1H), 7.83 (s, 1H), 7.75 - 7.65 (m, 2H), 6.93 (s, 1H), 6.83 (s, 1H), 4.04 (s, 2H), 3.86 (s, 3H), 3.74 (dd, *J* = 12.5, 7.6 Hz,

-86-

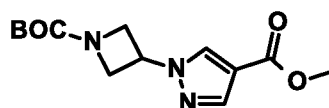
4H), 3.24 (t, $J = 7.7$ Hz, 2H), 3.07 (dd, $J = 16.9, 12.0$ Hz, 4H). ^{19}F NMR (376 MHz, CD_3OD) δ ppm -66.46 (s, 3F).

Example 036: [1-(Azetidin-3-yl)pyrazol-4-yl]-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]methanone



036

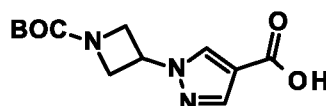
Step 1: Methyl 1-(1-tert-butoxycarbonylazetidin-3-yl)pyrazole-4-carboxylate



036a

To a solution of methyl 1*H*-pyrazole-4-carboxylate (63 mg, 0.500 mmol) in MeCN (10 mL) were added Cs_2CO_3 (325.56 mg, 0.999 mmol) and *tert*-butyl 3-bromoazetidine-1-carboxylate (129.75 mg, 0.999 mmol). The resulting suspension mixture was stirred at 90 °C for 16 hours. After completion, the mixture was concentrated under vacuum to give a residue, which was purified by silica-gel chromatography (elute with EtOAc:PE = 50%) to give the desired crude compound **036a** (50 mg, 71.32% yield) as a white solid. MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 281.0.

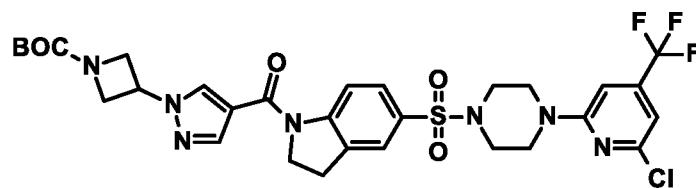
Step 2: 1-(1-*Tert*-butoxycarbonylazetidin-3-yl)pyrazole-4-carboxylic acid



036b

A solution of compound **036a** (50 mg, 0.178 mmol) and LiOH (8.18 mg, 0.355 mmol) in THF/MeOH/water (5/5/0.5 mL) was stirred at rt for 16 hours. After completion, the mixture was concentrated under vacuum to give a residue, which was purified by silica-gel chromatography (elute with EtOAc:PE = 50%) to give the desired crude compound **036b** (30 mg, 63.05% yield) as a white solid. MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 267.1.

Step 3: *Tert*-butyl 3-[4-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]pyrazol-1-yl]azetidine-1-carboxylate



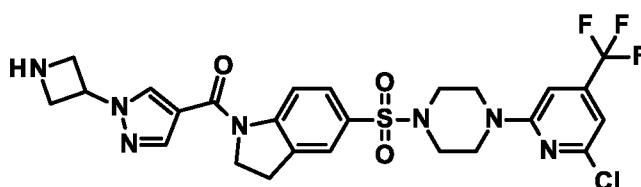
036c

5

To a solution of compound **036b** (30 mg, 0.112 mmol) in MeCN (45 mL) was added 1-methylimidazole (27.61 mg, 0.337 mmol), TCFH (62.86 mg, 0.224 mmol). The resulting mixture was stirred at rt for 15 minutes. Then a solution of compound **Int-4** was added to the mixture and the mixture was stirred at 25 °C for 16 hours. After completion, the reaction was quenched with 10 mL water, extracted with DCM (10 mL × 2). The combined organic layer was dried over anhydrous Na₂SO₄, concentrated under vacuum to give a residue, which was purified by prep-TLC (EtOAc:PE = 50%) to give compound **036c** (30 mg, 19.2% yield) as a colorless oil. MS obsd. (ESI⁺) [(M+H)⁺]: 696.1.

Step 4: [1-(Azetidin-3-yl)pyrazol-4-yl]-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]methanone

15



036

To a solution of compound **036** (30 mg, 0.034 mmol) in DCM (10 mL) was added TFA (2 mL). The mixture was stirred at 25 °C for 3 hours. Then the mixture was concentrated under vacuum to give a residue, which was purified by prep-HPLC to give **Example 036** (5 mg, 11.08% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 596.1.

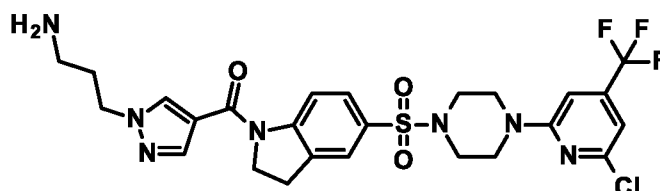
20

Example 036: ¹H NMR (400 MHz, CD₃OD) δ ppm 8.28 (d, *J* = 7.2 Hz, 2H), 8.14 (s, 1H), 7.60 (dd, *J* = 40.0, 31.3 Hz, 2H), 6.91 (s, 1H), 6.82 (s, 1H), 5.54-5.42 (m, 1H), 4.52 (d, *J* = 6.8 Hz,

-88-

4H), 4.43 (t, $J = 8.4$ Hz, 2H), 3.77-3.68 (m, 4H), 3.34 (d, $J = 8.4$ Hz, 2H), 3.12-3.02 (m, 4H). ^{19}F NMR (376 MHz, CD_3OD) δ ppm -63.46 (s, 3F).

Example 037: [1-(3-Aminopropyl)pyrazol-4-yl]-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]methanone

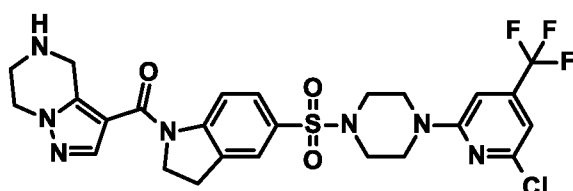


037

The title compound was prepared in analogy to the preparation of **Example 036** by replacing *tert*-butyl 3-bromoazetidine-1-carboxylate with *tert*-butyl *N*-(3-aminopropyl)carbamate in **step 1**. Compound **037a** (50 mg) was obtained as a white solid. MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 597.2.

Example 037: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.44 (d, $J = 22.7$ Hz, 2H), 8.26 (d, $J = 8.5$ Hz, 1H), 7.97 (s, 1H), 7.60 (d, $J = 11.2$ Hz, 1H), 7.46 (dd, $J = 40.1, 7.7$ Hz, 1H), 7.09 (s, 1H), 6.96 (s, 1H), 4.40 (s, 2H), 4.26 (s, 2H), 3.72 (s, 4H), 3.28 (d, $J = 6.2$ Hz, 2H), 2.97 (s, 4H), 2.67 (s, 2H), 2.03 (s, 2H). ^{19}F NMR (376 MHz, DMSO) δ ppm -63.47 (s, 3F).

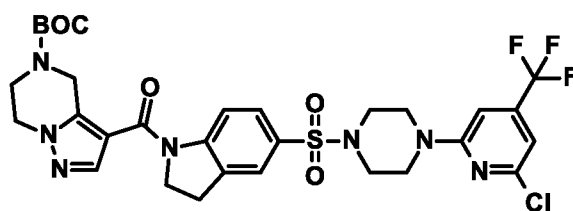
Example 038: [5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)methanone



038

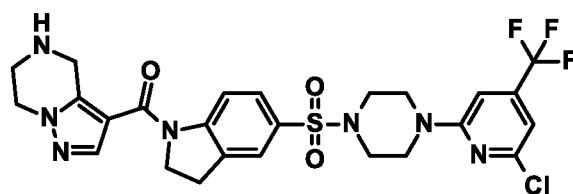
Step 1: *Tert*-butyl 3-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]-6,7-dihydro-4*H*-pyrazolo[1,5-a]pyrazine-5-carboxylate

-89-

**038a**

The title compound was prepared in analogy to the preparation of **Example 034** by replacing pyrazolo[1,5-a]pyrimidine-3-carboxylic acid with 5-*tert*-butoxycarbonyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-3-carboxylic acid. Compound **038a** (95 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 696.2.

Step 2: [5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)methanone

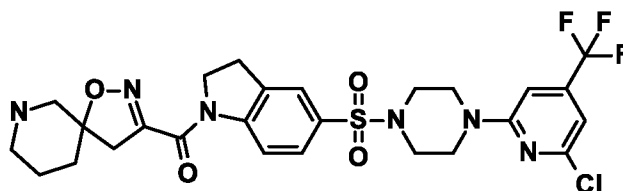
**038**

Compound **038a** (95.0 mg, 0.140 mmol) in 2 M HCl/EA(10mL) was stirred at rt for 4 hours. After completion, the solvent was removed under vacuum to give the crude product, which was purified by prep-HPLC (TFA as additive) to afford **Example 038** (40 mg, 46.11% yield). MS obsd. (ESI⁺) [(M+H)⁺]: 596.2.

Example 038: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.20 (d, *J* = 8.5 Hz, 1H), 7.94 (s, 1H), 7.63 – 7.54 (m, 2H), 7.09 (s, 1H), 6.97 (s, 1H), 4.40 (t, *J* = 8.4 Hz, 2H), 4.09 (d, *J* = 11.5 Hz, 2H), 4.02 (s, 2H), 3.72 (s, 4H), 3.24 (t, *J* = 8.3 Hz, 2H), 3.12 (s, 2H), 2.97 (d, *J* = 4.2 Hz, 4H). ¹⁹F NMR (376 MHz, DMSO) δ ppm -63.47 (s, 3F).

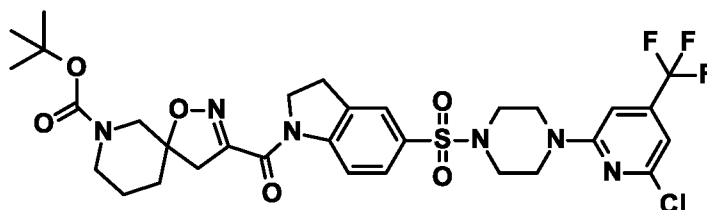
Example 039: [5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-(1-oxa-2,9-diazaspiro[4.5]dec-2-en-3-yl)methanone

-90-



039

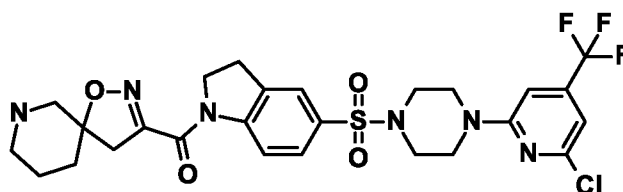
Step 1: *Tert*-butyl 3-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]-1-oxa-2,9-diazaspiro[4.5]dec-2-ene-9-carboxylate



039a

To a solution of 7-(*tert*-butoxycarbonyl)-1-oxa-2,7-diazaspiro[4.5]dec-2-ene-3-carboxylic acid (35 mg, 123 μ mol) in MeCN (2.5 mL) was added 1-methylimidazole (30.3 mg, 369 μ mol) and HATU (69.1 mg, 246 μ mol). The resulting mixture was stirred at rt for 15 minutes. Then a solution of compound **Int-4** (59 mg, 132 μ mol) in MeCN was added. The mixture was stirred at 25 °C for 5 hours. After completion, the reaction was quenched with water (10 mL). The reaction mixture was extracted with EtOAc (10 mL $\times$ 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to afford crude compound **039a** (80 mg, 91 % yield) as yellow oil. MS obsd. (ESI⁺) [(M+Na)⁺]: 735.60.

Step 2: [5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-(1-oxa-2,9-diazaspiro[4.5]dec-2-en-3-yl)methanone



039

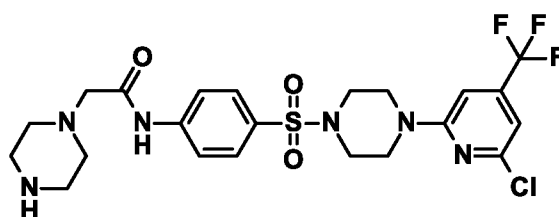
Compound **039a** (70 mg, 98.2 μ mol) was dissolved in the DCM (7.5 mL), followed by adding TFA (2mL, 98.2 μ mol). The reaction was stirred at rt and went completed for 2 hours.

-91-

After completion, the reaction was concentrated *in vacuo* to give crude product, which was purified by prep-HPLC to afford **Example 039** (34.87 mg, 46.4 % yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 613.3.

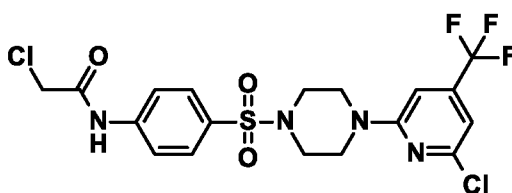
Example 039: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.8-9.1 (m, 1H), 8.6-8.8 (m, 1H), 8.24 (br d, 1H, *J* = 7.6 Hz), 7.5-7.8 (m, 2H), 7.09 (s, 1H), 6.98 (s, 1H), 4.42 (s, 2H), 3.7-3.8 (m, 4H), 3.1-3.3 (m, 6H), 2.9-3.0 (m, 5H), 1.7-2.1 (m, 4H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -63.46 (m, 3F).

Example 040: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-piperazin-1-yl-acetamide



040

Step 1: 2-Chloro-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]acetamide

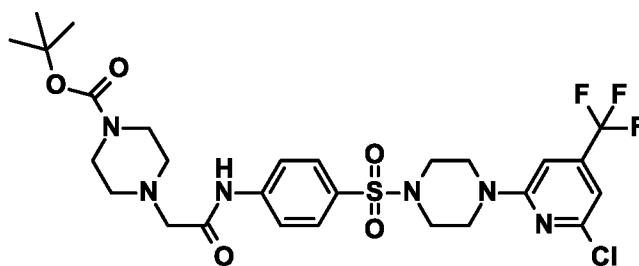


040a

Compound **Int-1** (100 mg, 238 μmol), chloroacetyl chloride (67.1 mg, 594 μmol) and DIPEA (468 mg, 3.62 mmol) was stirred at rt for 4 hours. After completion, the reaction mixture was extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum to afford crude product **040a** (118 mg, 100 % yield) as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 496.8.

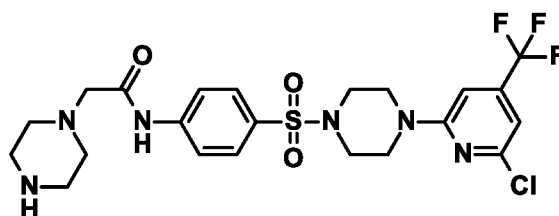
Step 2: *Tert*-butyl 4-[2-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylanilino]-2-oxo-ethyl]piperazine-1-carboxylate

-92-

**040b**

Compound **040b** (60 mg, 121 μ mol) and *tert*-butyl piperazine-1-carboxylate (44.9 mg, 241 μ mol) were dissolved in the DCM (10 mL), followed by adding DIPEA (46.8 mg, 63.2 μ L, 362 μ mol). The reaction was stirred at rt for 1 hour. After completion, the reaction mixture was extracted with EtOAc (50 mL $\times$ 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford crude product **040b** (75 mg, 96.1 % yield) as yellow oil. MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 647.8.

Step 3: N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-piperazin-1-yl-acetamide

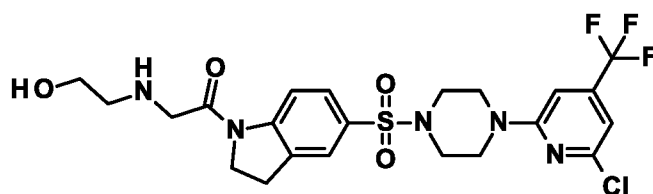
**040**

Compound **040b** (70 mg, 108 μ mol) in the DCM (5 mL) and TFA (2 mL, 108 μ mol) was stirred at rt for 2 hours. After completion, the reaction mixture was concentrated under vacuum to give crude product, which was purified by prep-HPLC (TFA as additive) to afford **Example 040** (29 mg, 38.5 % yield) as a white solid. MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 547.5.

Example 040: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.4-8.7 (m, 2H), 7.82 (d, 2H, $J = 8.7$ Hz), 7.66 (d, 2H, $J = 8.8$ Hz), 7.01 (s, 1H), 6.8-6.9 (m, 1H), 3.64 (br d, 4H, $J = 4.6$ Hz), 3.10 (s, 6H), 2.89 (d, 4H, $J = 4.4$ Hz), 2.7-2.8 (m, 4H). ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ ppm -63.46 (m, 3F).

Example 041: **1-[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-2-(2-hydroxyethylamino)ethanone**

-93-

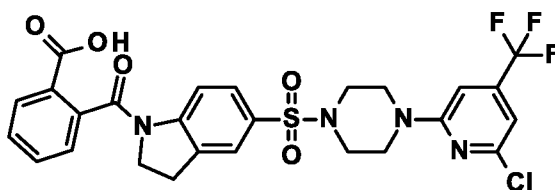
**041**

The title compound was prepared in analogy to the preparation of compound **040** by replacing compound **Int-1** with compound **Int-4** in **Step 1** and *tert*-butyl piperazine-1-carboxylate with 2-aminoethanol in **step 2**. **Example 041** (20 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 548.5.

Example 041: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.8-9.1 (m, 2H), 8.21 (d, 1H, *J* = 8.3 Hz), 7.5-7.8 (m, 2H), 7.09 (s, 1H), 6.9-7.0 (m, 1H), 4.0-4.3 (m, 4H), 3.72 (br s, 6H), 3.08 (s, 2H), 2.97 (s, 4H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -63.45 (m, 3F).

10

Example 042: 2-[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]benzoic acid

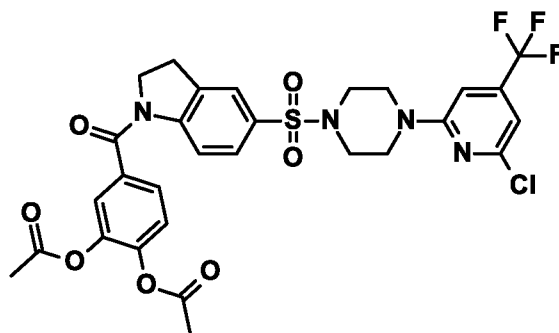
**042**

The title compound was prepared in analogy to the preparation of **Example 035** by replacing 5-ethoxycarbonyl-1-methyl-pyrazole-4-carboxylic acid with 2-methoxycarbonylbenzoic acid in **step 1**. **Example 042** (15.1 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 595.2.

Example 042: ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 8.30 (br d, *J* = 8.4 Hz, 1H), 8.08 - 7.93 (m, 1H), 7.79 - 7.55 (m, 4H), 7.53 - 7.43 (m, 1H), 7.09 (s, 1H), 6.97 (s, 1H), 3.76 - 3.63 (m, 6H), 3.14 (br s, 1H), 3.06 - 2.82 (m, 5H).

Example 043: [2-Acetoxy-4-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]phenyl] acetate

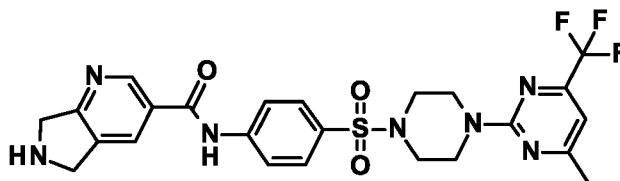
-94-

**043**

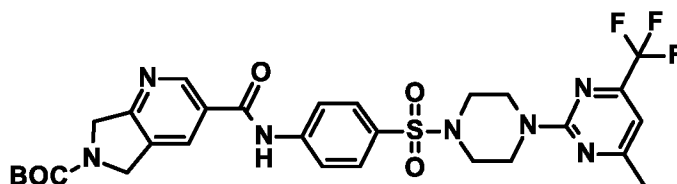
The title compound was prepared in analogy to the step of preparation of compound **039a** by replacing (*tert*-butoxycarbonyl)-1-oxa-2,7-diazaspiro[4.5]dec-2-ene-3-carboxylic acid with 7-3,4-diacetoxybenzoic acid. **Example 043** (9 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 667.6.

Example 043: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.5-7.8 (m, 4H), 7.42 (s, 1H), 7.10 (s, 1H), 6.97 (s, 1H), 5.75 (s, 1H), 3.9-4.2 (m, 2H), 3.6-3.8 (m, 4H), 3.1-3.3 (m, 2H), 2.97 (br t, 4H, J=4.8 Hz), 2.30 (d, 6H, J=8.8 Hz). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -63.46 (m, 3F).

Example 044: *N*-[4-[4-[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]piperazin-1-yl]sulfonylphenyl]-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxamide

**044**

Step 1: *Tert*-butyl 3-[[4-[4-[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]piperazin-1-yl]sulfonylphenyl]carbamoyl]-5,7-dihydropyrrolo[3,4-*b*]pyridine-6-carboxylate

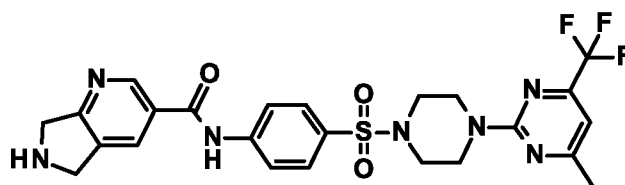
**044a**

To a solution of 6-*tert*-butoxycarbonyl-5,7-dihydropyrrolo[3,4-*b*]pyridine-3-carboxylic acid (80.0 mg, 0.300 mmol) in ACN (1 mL) were added 3-methylpyridine (56.38 mg, 0.610 mmol),

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methanesulfonyl chloride (0.04 mL, 0.450 mmol, 1.5 eq) in one portion. The reaction was heated at 50 °C for 1 hour and then compound **Int-13** (133.66 mg, 0.330 mmol) was added to the mixture. The reaction was stirred at 50°C for another 3 hours. After completion, the mixture was diluted with water (20 mL), extracted with DCM (20 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄, concentrated under vacuum to afford the crude product, which was purified by prep-HPLC (TFA as additive) to give **Example 044a** (85 mg, 43.36% yield) as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 648.2.

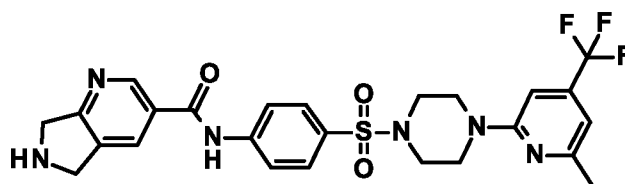
Step 2: N-[4-[4-[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]piperazin-1-yl]sulfonylphenyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxamide hydrochloride

**044**

A mixture of compound **044a** (85.0 mg, 0.130 mmol) in DCM (1.0 mL) and TFA (0.5 mL) was stirred at 25 °C for 1 hour. After completion, the reaction solution was concentrated under vacuum to give a residue, which was purified by prep-HPLC (HCl as additive) to give **Example 044** (74 mg, 95.99% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 548.2.

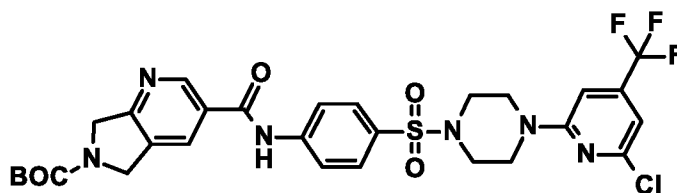
Example 044: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.03 - 10.97 (m, 1H), 10.30 - 10.09 (m, 2H), 9.11 - 9.05 (m, 1H), 8.41 - 8.32 (m, 1H), 8.11 - 8.01 (m, 2H), 7.79 - 7.71 (m, 2H), 6.96 (s, 1H), 4.68 - 4.62 (m, 2H), 4.59 - 4.53 (m, 2H), 3.90 - 3.79 (m, 4H), 3.03 - 2.92 (m, 4H), 2.37 (s, 3H).

Example 045: N-[4-[4-[6-methyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxamide

**045**

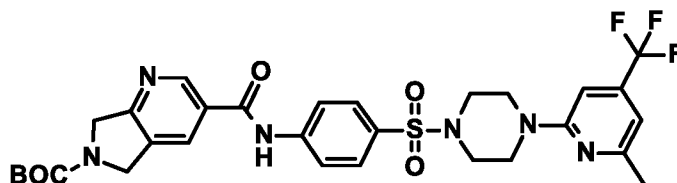
Step 1: Tert-butyl 3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbonyl]-5,7-dihydropyrrolo[3,4-b]pyridine-6-carboxylate

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**045a**

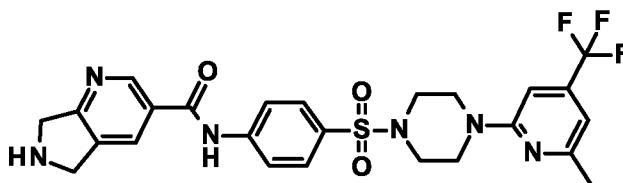
Compound **045a** was prepared in analogy to the step of preparation compound **044a** by replacing compound **Int-13** with compound **Int-1**. Compound **045a** (34 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 667.2.

Step 2: *N*-[4-[4-[6-methyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxamide

**045b**

A mixture of trimethylboroxine (33.95 mg, 0.270 mmol), compound **045b** (150.0 mg, 0.220 mmol), K₃PO₄ (67.9 mg, 0.320 mmol) and chloro[(di(1-adamantyl)-N-butylphosphine)-2-(2-aminobiphenyl)]palladium(II) (15.03 mg, 0.020 mmol) in THF (8 mL) and water (0.800 mL) was stirred at 70 °C for 3 h under Ar. After completion, the mixture was poured into water (100 mL), extracted with EA (100 mL × 2). The combined organic layer was washed with brine (100 mL × 2), dried over Na₂SO₄ and concentrated under vacuum to give residue, which was purified by prep-HPLC (FA as additive) to give compound **045b** (105 mg, 85.44% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 647.2.

Step 3: *N*-[4-[4-[6-methyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxamide

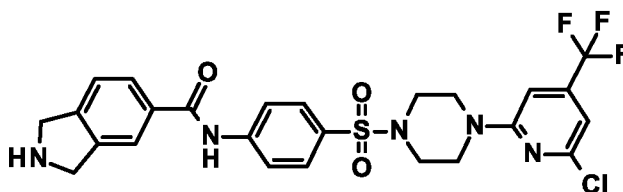
**045**

-97-

A solution of compound **045b** (100.0 mg, 0.150 mmol) in DCM (2 mL) and TFA (1.0 mL) was stirred at 25 °C for 1 hour. After completion, the mixture was concentrated under vacuum to give a residue, which was purified by prep-HPLC (HCl as additive) to give **Example 045** (48.3 mg, 53.55% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 547.3.

5 **Example 045:** ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.09 - 11.24 (m, 1 H), 10.38 - 10.62 (m, 2 H), 9.06 - 9.14 (m, 1 H), 8.36 - 8.42 (m, 1 H), 8.04 - 8.16 (m, 2 H), 7.67 - 7.86 (m, 2 H), 6.90 - 6.98 (m, 1 H), 6.76 - 6.85 (m, 1 H), 4.57 (br t, *J* = 5.50 Hz, 4 H), 3.68 - 3.79 (m, 4 H), 2.90 - 3.04 (m, 4 H), 2.35 - 2.43 (m, 3 H).

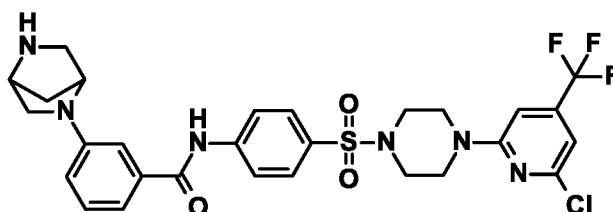
10 **Example 046:** *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]isoindoline-5-carboxamide

**046**

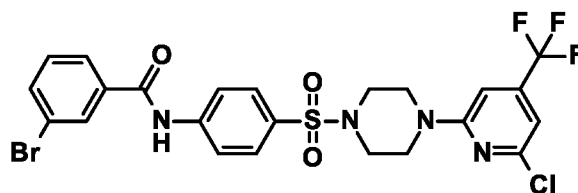
The title compound was prepared in analogy to the preparation of **Example 044** by replacing
15 6-*tert*-butoxycarbonyl-5,7-dihydropyrrolo[3,4-*b*]pyridine-3-carboxylic acid with compound **Int-14** and compound **Int-13** with compound **Int-1** in **step1**. **Example 045** (22.85 mg) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 566.1.

Example 046: ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 10.87 - 10.64 (m, 1H), 10.11 - 9.70 (m, 2H), 8.12 - 8.03 (m, 2H), 8.01 - 7.93 (m, 2H), 7.82 - 7.68 (m, 2H), 7.61 - 7.52 (m, 1H), 7.13 -
20 7.02 (m, 1H), 6.95 (s, 1H), 4.75 - 4.42 (m, 4H), 3.78 - 3.64 (m, 4H), 2.98 (br t, *J* = 4.6 Hz, 4H).

Example 047: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-(2,5-diazabicyclo[2.2.1]heptan-2-yl)benzamide

**047**

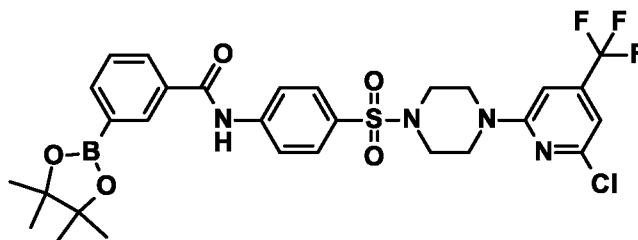
Step 1: 3-Bromo-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



047a

5 A mixture of compound **Int-1** (0.5 g, 1.19 mmol), 3-bromobenzoyl chloride (0.3 g, 1.36 mmol) and TEA (331 μ L, 2.38 mmol) in DCM (12 mL) was stirred at rt overnight. After completion, the mixture was quenched with water (20 mL), diluted with DCM (30 mL). The organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give crude compound **047a** (700 mg, 95.7 % yield) as a light yellow solid. MS
10 obsd. (ESI⁺) [(M+H)⁺]: 604.8.

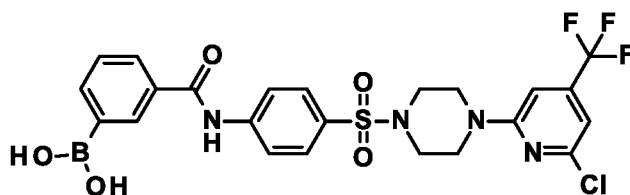
Step 2: N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



047b

15 A mixture of compound **047a** (1.0 g, 1.66 mmol), bis(pinacolato)diboron (463 mg, 1.82 mmol) and potassium acetate (406 mg, 4.14 mmol) in 1,4-dioxane (5 mL) was degassed for 5 minutes, then 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (67.6 mg, 82.8 μ mol) was added. The reaction mixture was stirred in a sealed tube at 90°C for 2 hours. After completion, the reaction was cooled to rt and quenched with water (100
20 mL) and extracted with EtOAc (50 mL $\times$ 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford crude product, which was purified by silica gel chromatography (elute with EtOAc:PE = 30%) to afford compound **047b** (0.6 g, 55.4 % yield) as orange oil. MS obsd. (ESI⁺) [(M+H)⁺]: 651.3.

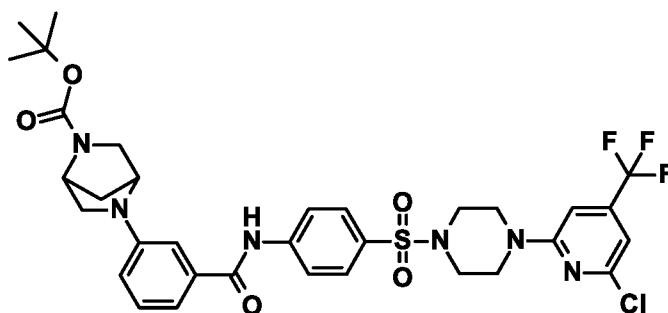
Step 3: [3-[[4-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]boronic acid



047c

5 Compound **047b** (0.5 g, 768 μ mol) was dissolved in the 1,4-dioxane (10 mL), followed by adding 6 N HCl (2 mL, 12 mmol). The reaction was heated at 90 °C for 4 hours. After completion, the reaction was concentrated under vacuum to give crude **047c** (0.4 g, 91.6%) as a brown oil, which was used directly in the next step.

Step 4: *Tert*-butyl 5-[3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

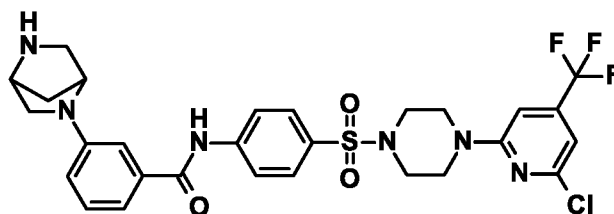


047d

A mixture of compound **047c** (130 mg, 229 μ mol), *tert*-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (45.3 mg, 229 μ mol), copper (I) chloride (22.6 mg, 229 μ mol), TEA (100 μ L, 686 μ mol) and molecular sieve 4Å (0.2 g, 229 μ mol) in MeCN (5 mL) was stirred for 12 h in air. Then the mixture was filtered and the filtrate was concentrated under vacuum to give a crude green residue, which was purified by silica gel chromatography (eluent with EtOAc : PE = 40%) to afford compound **047d** (90 mg, 54.6 % yield) as yellow oil. MS obsd. (ESI+) [(M+H)⁺]: 721.2.

20 Step 5: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[2,5-diazabicyclo[2.2.1]heptan-2-yl]benzamide

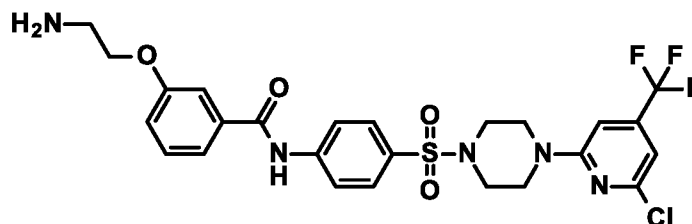
-100-

**047**

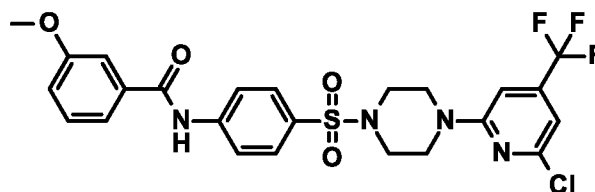
Compound **047d** (100 mg, 139 μ mol) was dissolved in the DCM (5 mL), followed by adding TFA (2 mL, 139 μ mol). The reaction was stirred at rt for 1 hour. After completion, the reaction was concentrated under vacuum and purified by prep-HPLC (TFA as additive) to give **Example 047** (1.5 mg, 1.4 % yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 621.2.

Example 047: ¹H NMR (400 MHz, CD₃OD) δ ppm 8.00 (d, 2H, J = 8.8 Hz), 7.82 (d, 2H, J = 8.8 Hz), 7.3-7.5 (m, 2H), 7.23 (s, 1H), 6.95 (s, 2H), 6.85 (s, 1H), 4.78 (s, 1H), 4.53 (s, 1H), 3.82 (dd, 1H, J = 2.4, 10.6 Hz), 3.7-3.8 (m, 4H), 3.41 (br s, 3H), 3.1-3.2 (m, 5H), 2.35 (br d, 1H, J = 11.4 Hz), 2.0-2.2 (m, 1H). ¹⁹F NMR (376 MHz, CD₃OD) δ ppm -66.49 (m, 3F).

Example 048: 3-(2-Aminoethoxy)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

**048**

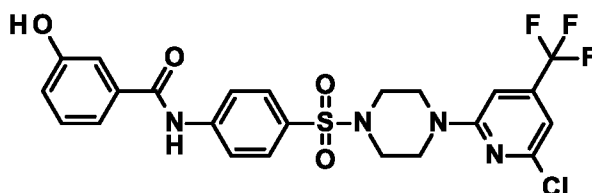
Step 1: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-methoxy-benzamide

**048a**

-101-

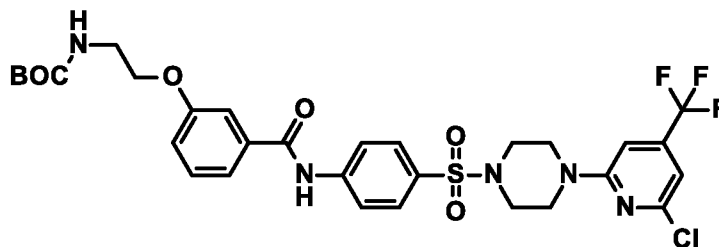
To a solution of compound **Int-1** (800.0 mg, 1.9 mmol, 1 eq) in DCM (8 mL) was added TEA (0.79 mL, 5.7 mmol, 3 eq), 3-methoxybenzoyl chloride (0.53 mL, 3.8 mmol, 2 eq) in sequence. The reaction was stirred at 20 °C for 1 hour. After completion, the mixture was diluted with DCM (100 mL), washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under vacuum to give a residue, which was purified by prep-HPLC (TFA as additive) to give compound **048a** (1000 mg, 94.79% yield) as a red solid. MS obsd. (ESI⁺) [(M+H)⁺]: 555.2.

Step 2 : N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-hydroxy-benzamide

**048b**

A solution of compound **048a** (980.0 mg, 1.77 mmol, 1 eq), BBr₃ (0.01 mL, 2.65 mmol) in DCM (20 mL) was stirred at 20 °C for 2 hours. After completion, the mixture was quenched with MeOH (10 mL) and water (20 mL). The mixture was extracted with EtOAc (20 mL × 3). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated under vacuum to give crude product, which was purified by silica-gel chromatography (elute with EtOAc:PE = 20%) to give compound **048b** (810 mg, 84.8% yield) as a red solid. MS obsd. (ESI⁺) [(M+H)⁺]: 563.2.

Step 3 : Tert-butyl N-[2-[3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenoxy]ethyl]carbamate

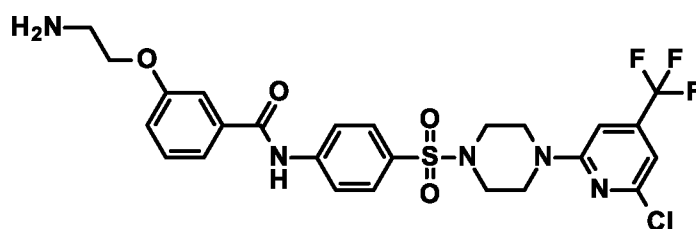


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048c

A mixture of compound **048b** (150.0 mg, 0.280 mmol), *tert*-butyl *N*-(2-bromoethyl)carbamate (124.28 mg, 0.550 mmol) and K₂CO₃ (114.97 mg, 0.830 mmol) in DMF (1.25 mL) was stirred at 90 °C for 2 hours. After completion, the mixture was diluted with water (20 mL) and then extracted with EtOAc (20 mL × 3). The combined organic layer was washed with water (50 mL), dried over anhydrous Na₂SO₄ and concentrated in *vacuo* to give a residue, which was purified by prep-HPLC (TFA as additive) to give compound **048c** (110 mg, 57.98% yield) as a white solid. MS obsd. (ESI+) [(M+H)⁺]: 684.2.

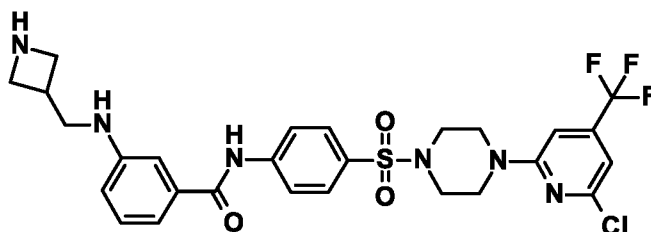
Step 4 : 3-(2-Aminoethoxy)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

**048**

A mixture of compound **048c** (110.0 mg, 0.160 mmol) in DCM (1 mL) and TFA (0.5 mL) was stirred at 20 °C for 1 hour. After completion, the mixture was concentrated in *vacuo* to give a residue, which was purified by prep-HPLC (HCl as additive) to afford **Example 048** (45 mg, 45.1% yield) as a white solid. MS obsd. (ESI+) [(M+H)⁺]: 584.1.

Example 048: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 10.73 (s, 1H), 8.21 - 8.13 (m, 3H), 8.11 - 8.05 (m, 2H), 7.78 - 7.73 (m, 2H), 7.64 - 7.60 (m, 1H), 7.57 - 7.54 (m, 1H), 7.52 - 7.46 (m, 1H), 7.26 - 7.21 (m, 1H), 7.09 (s, 1H), 6.99 - 6.94 (m, 1H), 4.31 - 4.24 (m, 2H), 3.75 - 3.66 (m, 4H), 3.27 - 3.21 (m, 2H), 3.02 - 2.94 (m, 4H).

Example 049: 3-(Azetidin-3-ylmethylamino)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



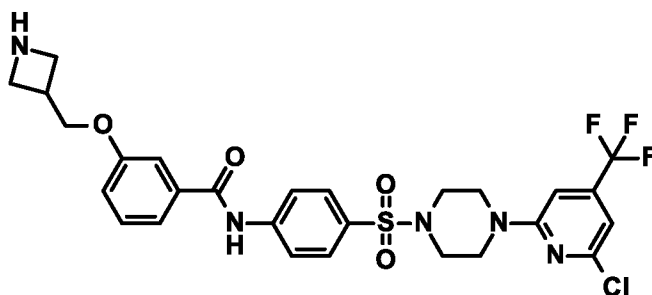
-103-

049

The title compound was prepared in analogy to the preparation of **Example 047** by replacing *tert*-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate with *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate in **step 4**. **Example 049** (1 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 609.4.

Example 049: ¹H NMR (400 MHz, CD₃OD) δ ppm 7.8-7.9 (m, 2H), 7.69 (d, 2H, *J* = 8.8 Hz), 7.3-7.5 (m, 1H), 7.0-7.2 (m, 3H), 6.7-6.9 (m, 3H), 5.25 (br, 2H, *J* = 4.6 Hz), 4.06 (dd, 1H, *J* = 9.4, 10.7 Hz), 3.82 (dd, 1H, *J* = 7.2, 10.9 Hz), 3.6-3.7 (m, 4H), 3.34 (d, 2H, *J* = 6.8 Hz), 2.9-3.1 (m, 4H), 2.10 (t, 2H, *J* = 7.5 Hz). ¹⁹F NMR (376 MHz, CD₃OD) δ ppm -66.48 (m, 3F).

Example 050: 3-(Azetidin-3-ylmethoxy)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

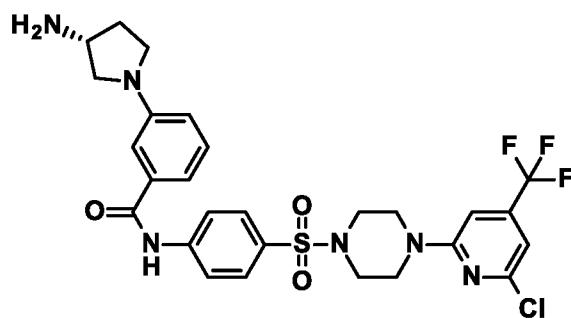
**050**

The title compound was prepared in analogy to the preparation of **Example 048** by replacing *tert*-butyl *N*-(2-bromoethyl)carbamate with *tert*-butyl 3-(bromomethyl)azetidine-1-carboxylate in **step 3**. **Example 050** (56 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 610.4.

Example 050: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.74 - 10.69 (m, 1H), 9.12 - 8.98 (m, 2H), 8.08 (d, *J* = 8.9 Hz, 2H), 7.78 - 7.73 (m, 2H), 7.62 - 7.55 (m, 2H), 7.52 - 7.46 (m, 1H), 7.26 - 7.22 (m, 1H), 7.10 - 7.07 (m, 1H), 6.98 - 6.95 (m, 1H), 4.27 - 4.22 (m, 2H), 4.13 - 4.04 (m, 2H), 3.90 - 3.81 (m, 2H), 3.75 - 3.66 (m, 4H), 3.26 - 3.15 (m, 1H), 2.98 (br t, *J* = 4.6 Hz, 4H).

Example 051: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[(3*R*)-3-aminopyrrolidin-1-yl]benzamide

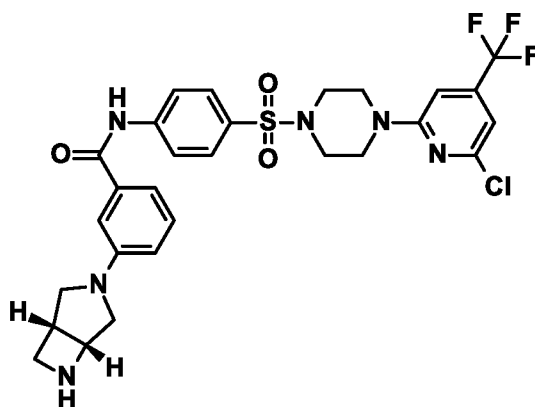
-104-

**051**

The title compound was prepared in analogy to the preparation of **Example 052** by replacing *tert*-butyl-3,6-diazabicyclo[3.2.0]heptane-6-carboxylate with *tert*-butyl (*R*)-pyrrolidin-3-ylcarbamate hydrochloride in **step 2**. **Example 051** (18 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 609.9.

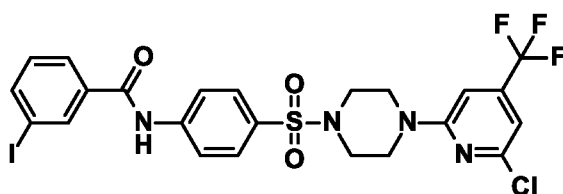
Example 051: ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.56 (s, 1H), 8.0-8.2 (m, 5H), 7.75 (d, 2H, J=8.8 Hz), 7.3-7.4 (m, 1H), 7.28 (s, 1H), 7.0-7.2 (m, 2H), 6.97 (s, 1H), 6.82 (dd, 1H, J = 1.9, 8.1 Hz), 3.99 (br s, 1H), 3.7-3.8 (m, 4H), 3.5-3.6 (m, 3H), 3.0-3.1 (m, 4H), 2.3-2.4 (m, 1H), 2.0-2.2 (m, 1H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm -63.46 (m, 3F).

Example 052: *N*-[4-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[3,6-diazabicyclo[3.2.0]heptan-3-yl]benzamide

**052**

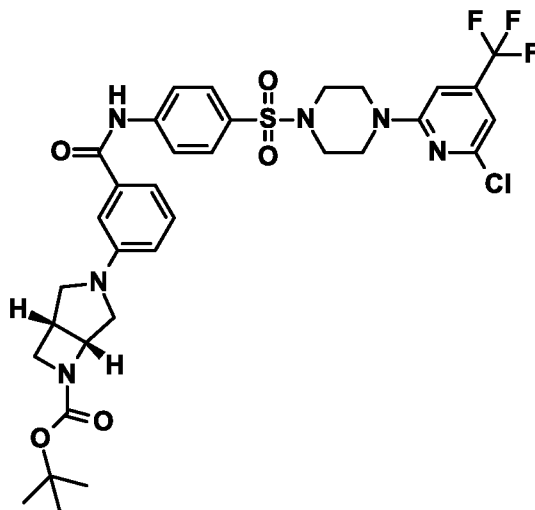
Step 1: *N*-[4-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-iodo-benzamide

-105-

**052a**

Compound **Int-1** (0.15 g, 356 μ mol), 3-iodobenzoyl chloride (190 mg, 713 μ mol) and TEA (100 μ L, 713 μ mol) was stirred at rt overnight. After completion, the mixture was quenched with water (10 mL), diluted with DCM (30 mL). The organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product, which was purified by silica-gel chromatography (eluent with EtOAc : PE = 20%) to afford compound **052a** (180 mg, 77.6 % yield) as yellow oil. MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 651.2.

Step 2: *Tert*-butyl-3-[3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]-3,6-diazabicyclo[3.2.0]heptane-6-carboxylate

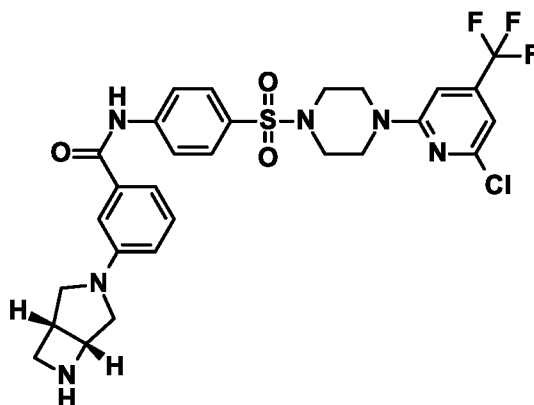
**052b**

A degassed mixture of Cs_2CO_3 (150 mg, 461 μ mol), chloro[(di(1-adamantyl)-N-butylphosphine)-2-(2-aminobiphenyl)]palladium(II) (15.4 mg, 23 μ mol), *tert*-butyl-3,6-diazabicyclo[3.2.0]heptane-6-carboxylate (45.7 mg, 230 μ mol), *N*-(4-((4-(6-chloro-4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonylphenyl)-3-iodobenzamide (75 mg, 115 μ mol) in 1,4-dioxane (2.5 mL) was heated at 75 $^\circ\text{C}$ in a microwave reactor for 1 hour. After completion, the mixture was poured into ice water (20 mL), extracted with DCM (10 mL $\times$ 3), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product, which

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was purified by silica-gel chromatography (eluent with EtOAc : PE = 40%) to afford compound **052b** (50 mg, 60.2 % yield) as yellow oil. MS obsd. (ESI⁺) [(M+H)⁺]: 721.2.

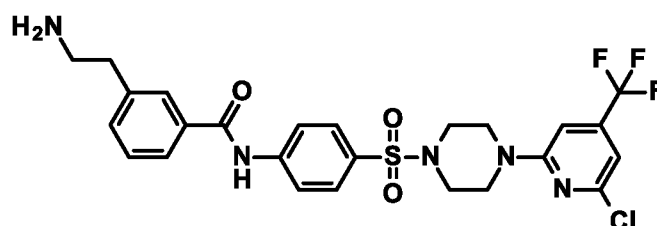
Step 3: N-[4-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[3,6-diazabicyclo[3.2.0]heptan-3-yl]benzamide

**052**

Compound **052b** (50 mg, 69.3 μ mol) was dissolved in the DCM (5 mL), followed by adding TFA (2 mL, 69.3 μ mol). The reaction was stirred at rt and went complete after 1 hour. After completion, the reaction was concentrated under vacuum and purified by prep-HPLC (TFA as additive) to afford **Example 052** (2.7 mg, 5.2 % yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 621.2.

Example 052: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.01 (d, 2H, *J* = 8.9 Hz), 7.82 (d, 2H, *J* = 8.9 Hz), 7.46 (d, 3H, *J* = 5.0 Hz), 7.1-7.3 (m, 1H), 6.95 (s, 1H), 6.85 (s, 1H), 4.60 (s, 3H), 4.19 (d, 1H, *J* = 12.6 Hz), 3.98 (d, 1H, *J* = 10.6 Hz), 3.7-3.8 (m, 4H), 3.5-3.6 (m, 2H), 3.1-3.2 (m, 4H), 3.0-3.1 (m, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -66.49 (m, 3F).

Example 053: 3-(2-Aminoethyl)-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

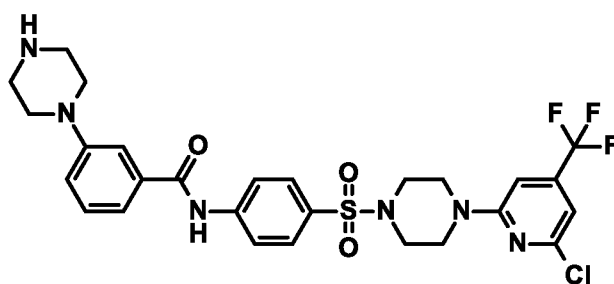


The title compound was prepared in analogy to the preparation of **Example 044** by replacing 6-*tert*-butoxycarbonyl-5,7-dihydropyrrolo[3,4-*b*]pyridine-3-carboxylic acid with compound **Int-**

15 and compound **Int-13** with compound **Int-1** in **step1**. **Example 053** (93.9 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 568.3.

Example 053: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.51 - 10.84 (m, 1 H), 8.03 - 8.11 (m, 2 H), 7.72 - 7.83 (m, 4 H), 7.41 - 7.47 (m, 2 H), 7.07 - 7.12 (m, 1 H), 6.94 - 6.99 (m, 1 H), 3.65 -
 5 3.80 (m, 4 H), 2.99 (br t, *J* = 4.77 Hz, 4 H), 2.70 - 2.87 (m, 4 H).

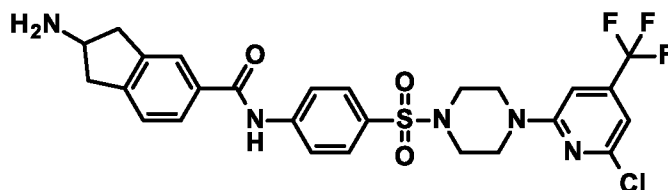
Example 054: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-piperazin-1-yl-benzamide

**054**

The title compound was prepared in analogy to the preparation of **Example 044** by replacing 6-*tert*-butoxycarbonyl-5,7-dihydropyrrolo[3,4-*b*]pyridine-3-carboxylic acid with 3-(4-*tert*-butoxycarbonylpiperazin-1-yl)benzoic acid and compound **Int-13** with compound **Int-1** in **step1**. **Example 054** (100.2 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 609.3.

Example 054: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.46 - 10.70 (m, 1 H), 7.98 - 8.14 (m, 2 H), 7.69 - 7.84 (m, 2 H), 7.29 - 7.51 (m, 3 H), 7.08 - 7.20 (m, 2 H), 6.94 - 7.01 (m, 1 H), 3.64 - 3.83 (m, 4 H), 3.08 - 3.16 (m, 4 H), 2.98 (br t, *J* = 4.63 Hz, 4 H), 2.86 (br d, *J* = 4.50 Hz, 4 H).

Example 055: 2-Amino-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]indane-5-carboxamide

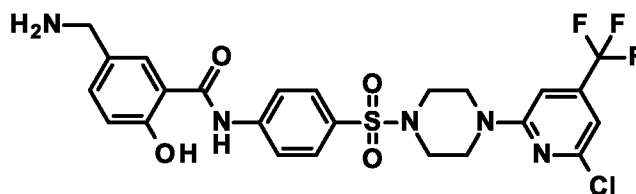


The title compound was prepared in analogy to the preparation of **Example 044** by replacing 6-*tert*-butoxycarbonyl-5,7-dihydropyrrolo[3,4-*b*]pyridine-3-carboxylic acid with compound **Int-16** and compound **Int-13** with compound **Int-1** in **step1**. **Example 055** (49.6 mg) was obtained
 25 as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 580.3.

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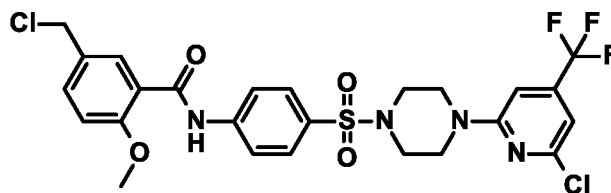
Example 055: ^1H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.47 - 10.64 (m, 1 H), 8.04 - 8.14 (m, 2 H), 7.70 - 7.87 (m, 4 H), 7.30 - 7.40 (m, 1 H), 7.08 - 7.15 (m, 1 H), 6.93 - 6.99 (m, 1 H), 3.65 - 3.83 (m, 5 H), 3.09 - 3.15 (m, 2 H), 2.99 (br d, *J*=4.16 Hz, 4 H), 2.60 - 2.70 (m, 2 H).

Example 056: 5-(Aminomethyl)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-hydroxy-benzamide



056

Step 1: *N*-(4-((4-(6-chloro-4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)-5-(chloromethyl)-2-methoxybenzamide



056a

10

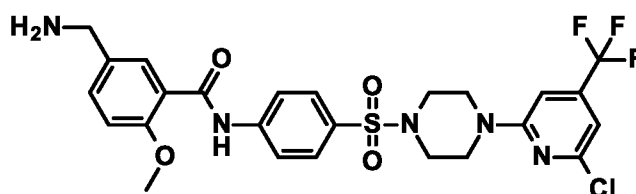
To a solution of 5-(chloromethyl)-2-methoxy-benzoic acid (100.0 mg, 0.500 mmol) in DCM (1 mL) was added SOCl₂ (92.84 mg, 1 mmol) dropwise. The mixture was stirred at 20 °C for 30 minutes. And then, the reaction mixture was concentrated and the residue was re-dissolved in dry DCM (5 mL). Then compound **Int-1** (0.21 g, 0.500 mmol) and TEA (0.10 g, 1.0 mmol) were added to the above solution. The mixture was stirred at 20 °C for 3 hours. After completion, the reaction mixture was concentrated under vacuum to give compound **056a** (280 mg, 93.09% yield) as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 603.2.

15

Step 2: 5-(Aminomethyl)-*N*-(4-((4-(6-chloro-4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)-2-methoxybenzamide

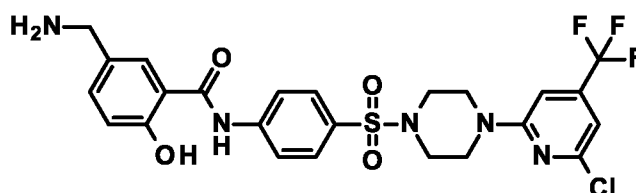
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**056b**

To a solution of compound **056a** (200.0 mg, 0.330 mmol) in MeCN (5 mL) were added NH₃.H₂O (1.0 mL, 0.430 mmol) in one portion. The mixture was stirred in a sealed tube at 50 °C for 4 hours. After completion, the solution was poured into water (15 mL), extracted with DCM (20 mL × 3). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give crude compound **056b** (185 mg, 95.58% yield) as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 584.1.

Step 3: 5-(Aminomethyl)-N-(4-((4-(6-chloro-4-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)-2-hydroxybenzamide

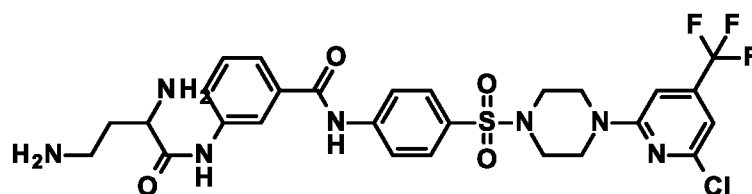
**056**

To a mixture of compound **056b** (100.0 mg, 0.170 mmol, 1 eq) in DCM (5 mL) was added AlCl₃ (112.92 mg, 0.860 mmol), the mixture was stirred at 20 °C for 15 hours. After completion, solvent was concentrated under vacuum to give a residue which was purified by prep-HPLC (HCl as additive) to afford **Example 056** (6.1 mg, 6.13% yield) as a blue solid. MS obsd. (ESI⁺) [(M+H)⁺]: 570.0.

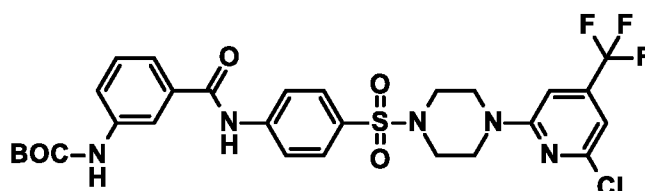
Example 056: ¹H NMR (400MHz, DMSO-*d*₆) δ ppm 11.65 - 11.45 (m, 1H), 10.77 (s, 1H), 8.34 - 8.17 (m, 3H), 8.07 - 7.98 (m, 3H), 7.80 - 7.70 (m, 2H), 7.56 - 7.48 (m, 1H), 7.11 - 7.04 (m, 2H), 6.96 (s, 1H), 4.07 - 3.94 (m, 2H), 3.76 - 3.66 (m, 4H), 3.06 - 2.94 (m, 4H).

Example 057: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-(2,4-diaminobutanoylamino)benzamide

-110-

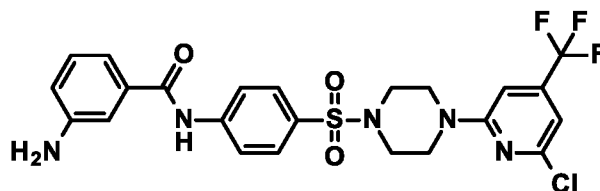
**057**

Step 1: *Tert*-butyl *N*-[3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]carbamate

**057a**

5
A mixture of 3-(*tert*-butoxycarbonylamino)benzoic acid (563.75 mg, 2.38 mmol) and SOCl₂ (2.83 g, 23.76 mmol) in dry DCM (10.0 mL) and THF (10.0 mL) was stirred at 25 °C for 6 hours. And then, the mixture was concentrated under vacuum to give residue, which was re-dissolved in dry DCM (10.0 mL) and added to the mixture of compound **Int-1** (500.0 mg, 1.19 mmol) and TEA (0.5 mL, 3.56 mmol) in DCM (10 mL). The mixture was stirred at 15 °C for 2 hours. After completion, the mixture was diluted with EtOAc (200 mL), washed with brine (50 mL × 3). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under vacuum to give crude product, which was purified by prep-HPLC (FA as additive) to give compound **057a** (620 mg, 15
81.53% yield) as light yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 640.1.

Step 2: 3-Amino-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

**057b**

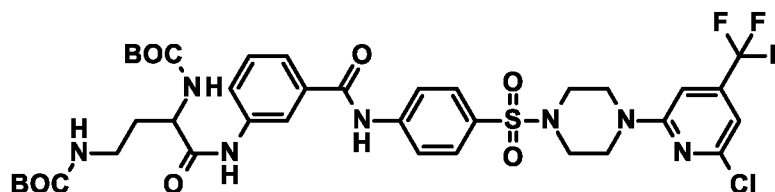
20

A mixture of compound **057a** (620.0 mg, 0.970 mmol), hydrochloric acid in dioxane (20.0 mL, 80 mmol) was stirred at 25 °C for 2 hours. After completion, the mixture concentrated under vacuum to give residue, which was re-dissolved in EtOAc (300 mL) and basified with aq.K₂CO₃ to pH 8.0. The organic layer was washed with brine (50 mL × 2) and dried over anhydrous

-111-

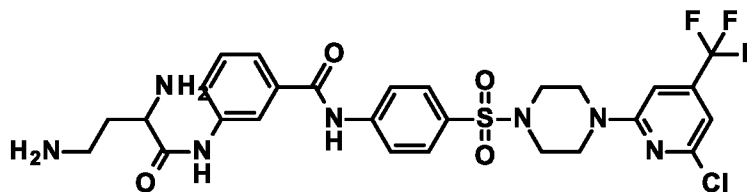
Na₂SO₄ and concentrated *in vacuo* to give compound **057b** (500 mg, 95.6% yield) as a light yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 540.1.

Step 3: *Tert-butyl N-[3-(tert-butoxycarbonylamino)-4-[3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]anilino]-4-oxo-butyl]carbamate*

**057c**

To a solution of 2,4-bis(*tert*-butoxycarbonylamino)butanoic acid (176.89 mg, 0.560 mmol) and 3-methylpyridine (137.98 mg, 1.48 mmol) in MeCN (3.03 mL) was added MsCl (0.05 mL, 0.590 mmol) and stirred at 15 °C for 4 hours. And then, compound **057b** (200.0 mg, 0.370 mmol) was added to the above mixture which was stirred at 50 °C for 2 hours. After completion, the mixture was concentrated *in vacuo* to give crude compound **057c** (200 mg, 64.26% yield) as a yellow oil, which was used in the next step directly. MS obsd. (ESI⁺) [(M+H)⁺]: 840.3.

Step 4: *N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-(2,4-diaminobutanoylamino)benzamide*

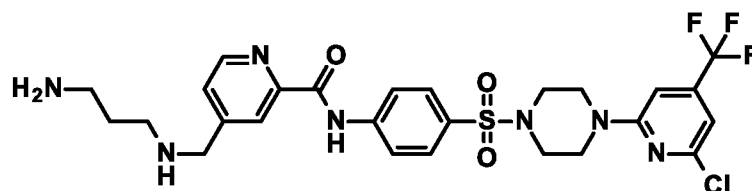
**057**

A mixture of compound **057c** (200.0 mg, 0.240 mmol) in HCl in dioxane (5.0 mL, 20 mmol) was stirred at 25 °C for 2 hours. After completion, the mixture was concentrated under vacuum to give a residue, which was purified by prep-HPLC (NH₄HCO₃ as additive) to afford **Example 057** (32.8 mg, 21.27% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 640.2.

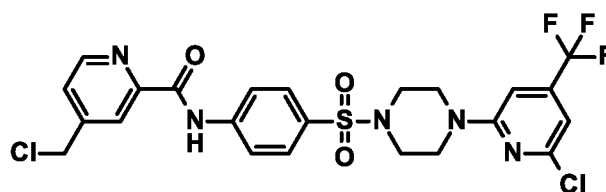
Example 057: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.27 - 10.96 (m, 1 H), 8.17 - 8.30 (m, 1 H), 8.04 - 8.11 (m, 2 H), 7.90 - 7.96 (m, 1 H), 7.73 - 7.81 (m, 2 H), 7.60 - 7.69 (m, 1 H), 7.44 - 7.53 (m, 1 H), 7.07 - 7.11 (m, 1 H), 6.94 - 6.99 (m, 1 H), 3.70 - 3.80 (m, 4 H), 3.29 - 3.44 (m, 5 H), 2.99 (br t, J=4.52 Hz, 4 H).

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Example 058: 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]pyridine-2-carboxamide

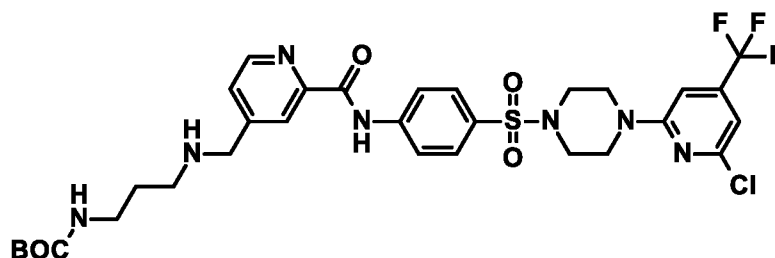
**058**

5 **Step 1:** 4-(Chloromethyl)-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]pyridine-2-carboxamide

**058a**

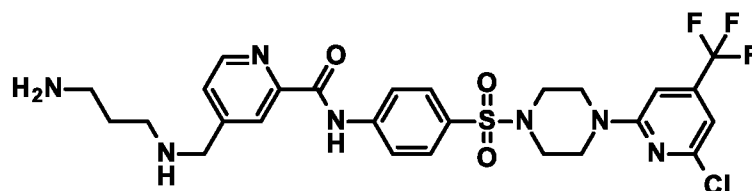
Compound **058a** was prepared in analogy to the step of preparation compound **057a** by
 10 replacing 3-(*tert*-butoxycarbonylamino)benzoic acid with 4-(chloromethyl)pyridine-2-carboxylic acid. Compound **058a** (200 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 574.2.

Step 2: *Tert*-butyl N-[3-[[2-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl] piperazin-1-yl]sulfonylphenyl]carbamoyl]-4-pyridyl]methylamino]propyl]carbamate

**058b**

A mixture of compound **058a** (200.0 mg, 0.350 mmol), K₂CO₃ (144.37 mg, 1.04 mmol), KI (0.01 mL, 0.170 mmol) and *tert*-butyl N-(3-aminopropyl)carbamate (121.34 mg, 0.700 mmol) in MeCN (5 mL) was stirred at 70 °C for 2 hours. After completion, the mixture was concentrated
 20 *in vacuo* to give a crude compound **058b** (200 mg, 80.65% yield) as yellow oil, which was used in the next step directly. MS obsd. (ESI⁺) [(M+H)⁺]: 712.2.

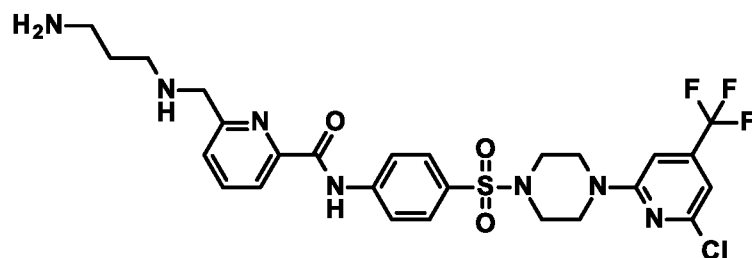
Step 3: 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]pyridine-2-carboxamide

**058**

A mixture of compound **058b** (200.0 mg, 0.280 mmol) in DCM (4 mL) and TFA (3.2 g, 28.08 mmol) was stirred at 25 °C for 1 hour. After completion, the mixture was concentrated under vacuum to give crude, which was purified by prep-HPLC (NH₄HCO₃ as additive) to afford **Example 058** (97.5 mg, 56.3% yield) as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 612.3.

Example 058: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.25 - 10.84 (m, 1H), 8.66 (d, *J* = 4.9 Hz, 1H), 8.30 - 8.08 (m, 3H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.64 (br d, *J* = 4.6 Hz, 1H), 7.08 (s, 1H), 6.95 (s, 1H), 4.61 - 3.83 (s, 2H), 3.75 - 3.65 (m, 4H), 3.07 - 2.95 (m, 4H), 2.95 - 2.85 (m, 2H), 2.58 - 2.51 (m, 2H), 1.69 - 1.40 (m, 2H).

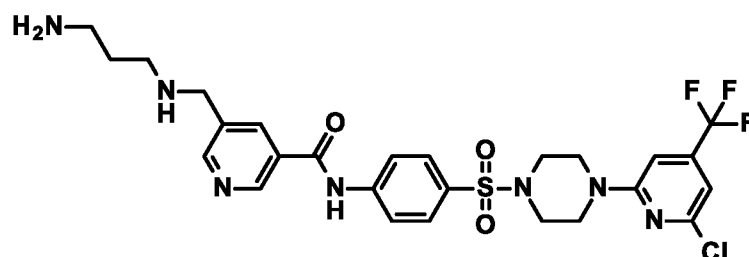
Example 059: 6-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]pyridine-2-carboxamide

**059**

The title compound was prepared in analogy to the preparation of **Example 044** by replacing 6-*tert*-butoxycarbonyl-5,7-dihydropyrrolo[3,4-*b*]pyridine-3-carboxylic acid with compound **Int-17** and compound **Int-13** with compound **Int-1** in **step1**. **Example 059** (51.3 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 612.3.

Example 059: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.20 (d, *J* = 7.9 Hz, 2H), 8.02 (d, *J* = 4.8 Hz, 2H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.69 (t, *J* = 4.5 Hz, 1H), 7.09 (s, 1H), 6.97 (s, 1H), 3.92 (s, 2H), 3.80 - 3.69 (m, 5H), 3.01 (t, *J* = 4.8 Hz, 5H), 2.62 - 2.57 (m, 2H), 1.55 (t, *J* = 6.8 Hz, 2H).

Example 060: 5-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]pyridine-3-carboxamide

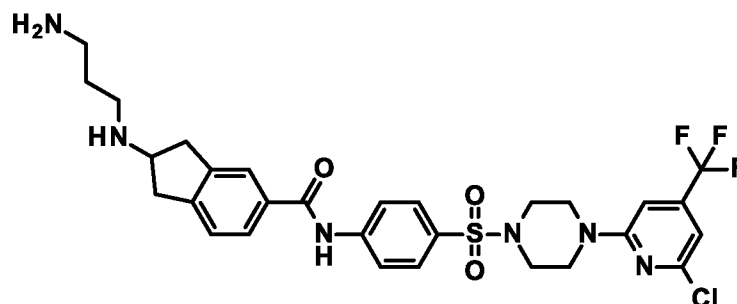


060

5 The title compound was prepared in analogy to the preparation of **Example 058** by replacing 4-(chloromethyl)pyridine-2-carboxylic acid with 5-(bromomethyl)pyridine-3-carboxylic acid in **step 1**. **Example 060** (38 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 612.0.

Example 060: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.95 (s, 1H), 8.75 - 8.64 (m, 1H), 8.31 - 8.17 (m, 1H), 8.10 - 8.03 (m, 2H), 7.80 - 7.74 (m, 2H), 7.09 (s, 1H), 6.98 - 6.91 (m, 1H), 3.77 (s, 10 2H), 3.74 - 3.68 (m, 4H), 2.99 (br s, 4H), 2.66 - 2.52 (m, 4H), 1.51 (s, 2H).

Example 061: 2-(3-Aminopropylamino)-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]indane-5-carboxamide

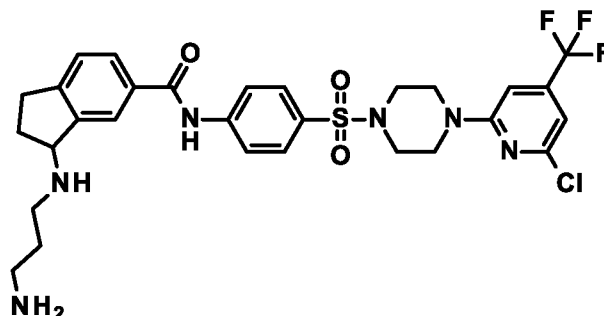


061

15 The title compound was prepared in analogy to the preparation of **Example 044** by replacing 6-*tert*-butoxycarbonyl-5,7-dihydropyrrolo[3,4-*b*]pyridine-3-carboxylic acid with compound **Int-18** and compound **Int-13** with compound **Int-1** in **step1**. **Example 061** (87.9 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 637.2.

20 **Example 061:** ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.66 - 10.82 (m, 1 H), 9.71 - 9.97 (m, 2 H), 8.07 - 8.37 (m, 5 H), 7.82 - 7.96 (m, 2 H), 7.70 - 7.78 (m, 2 H), 7.40 - 7.51 (m, 1 H), 7.05 - 7.15 (m, 1 H), 6.87 - 7.00 (m, 1 H), 3.98 - 4.15 (m, 1 H), 3.63 - 3.79 (m, 4 H), 3.22 - 3.37 (m, 4 H), 3.08 - 3.18 (m, 2 H), 2.91 - 3.02 (m, 6 H), 2.00 - 2.10 (m, 2 H).

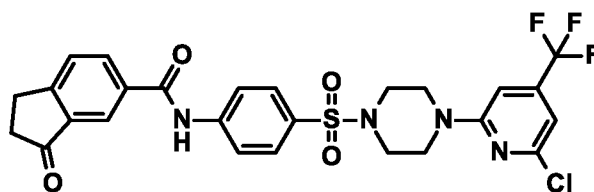
Example 062: 3-(3-Aminopropylamino)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]indane-5-carboxamide



5

062

Step 1: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-1-oxo-indane-5-carboxamide

**062a**

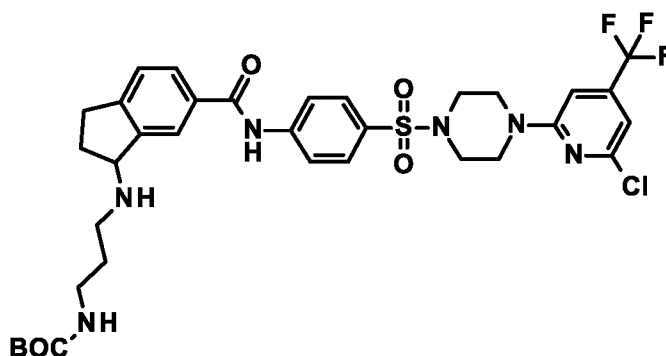
10

To a mixture of 3-oxoindane-5-carboxylic acid (200.0 mg, 1.14 mmol), compound **Int-1** (477.77 mg, 1.14 mmol) and 3-methylpyridine (0.43 mL, 4.54 mmol) in MeCN (5 mL) was added MsCl (520.18 mg, 4.54 mmol) dropwise at rt. The mixture was heated to 45 °C and stirred for 2 hours. After completion, the mixture was poured in to water (20mL), extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated under vacuum to give crude product, which was purified by prep-HPLC (FA as additive) to give compound **062a** (180 mg, 27.38% yield) as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 579.2.

Step 2: *Tert*-butyl *N*-[3-[[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbonyl]indan-1-yl]amino]propyl]carbamate

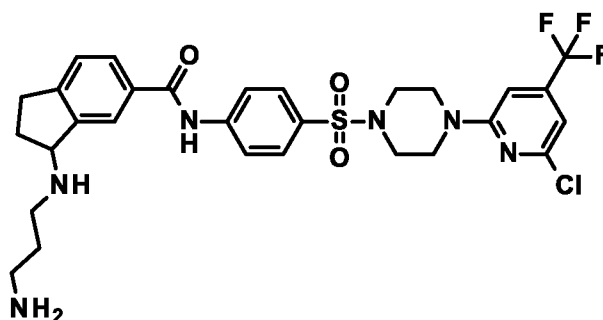
20

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**062b**

The mixture of compound **062a** (100.0 mg, 0.170 mmol), *tert*-butyl *N*-(3-aminopropyl)carbamate (60.19 mg, 0.350 mmol), and titanium(IV)isopropoxide (98.18 mg, 0.350 mmol) in toluene (10 mL) was stirred at 50 °C for 15 hours. And then, the mixture was concentrated under vacuum to give a residue. Sodium cyanoborohydride (43.41 mg, 0.690 mmol) in MeOH was added to the above residue and the mixture was stirred for 4 hours at 50°C. After completion, the mixture was concentrated *in vacuo* to give a crude compound **062b** (100 mg, 78.54% yield) as a yellow oil, which was used in the next step directly. MS obsd. (ESI⁺) [(M+H)⁺]: 737.4.

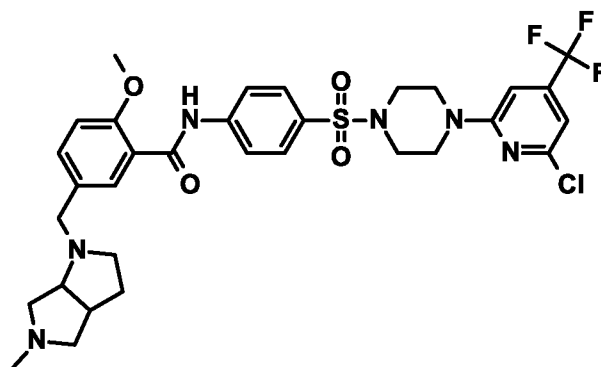
Step 3: 3-(3-Aminopropylamino)-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]indane-5-carboxamide

**062**

The mixture of compound **062b** (100.0 mg, 0.140 mmol) in DCM (5 mL) and TFA (10.0 mL) was stirred at 25 °C for 2 hours. Solvent was evaporated and the residue was concentrated under vacuum to give crude product which was purified by and prep-HPLC (HCl as additive) to afford **Example 062** (1.9 mg, 2.16% yield) as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 637.3.

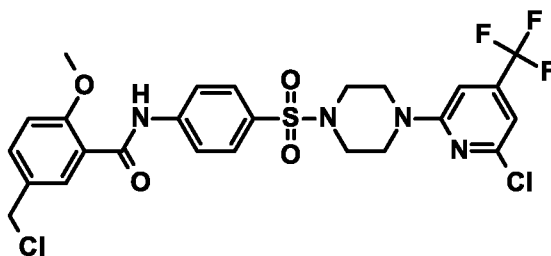
Example 062: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.85 (s, 1H), 9.66 - 9.23 (m, 2H), 8.37 (s, 1H), 8.20 - 8.05 (m, 4H), 8.00 (dd, *J* = 1.2, 7.9 Hz, 3H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.09 (s, 1H), 6.97 (s, 1H), 4.80 (br d, *J* = 1.8 Hz, 1H), 3.82 - 3.65 (m, 4H), 3.31 - 3.23 (m, 2H), 3.23 - 3.09 (m, 2H), 3.04 - 2.89 (m, 7H), 2.47 - 2.42 (m, 1H), 2.13 - 1.96 (m, 2H).

Example 063: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methoxy-5-[(5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-1-yl)methyl]benzamide



063

Step 1: 5-(Chloromethyl)-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methoxy-benzamide

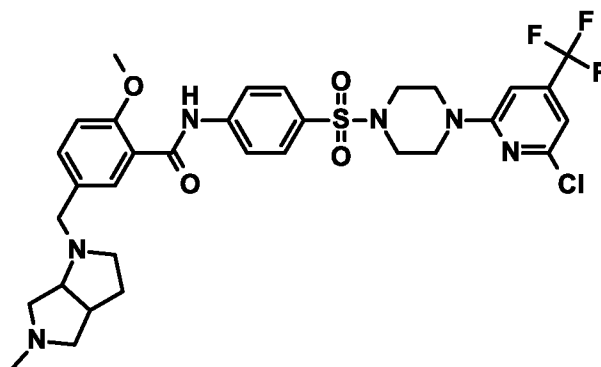


063a

A mixture of 5-(chloromethyl)-2-methoxybenzoyl chloride (687 mg, 3.14 mmol), compound **Int-1** (0.660 g, 1.57 mmol) and TEA (794 mg, 7.84 mmol) in DCM (10 mL) was stirred at rt for 16 hours. After completion, the mixture was quenched with water (20 mL), extracted with DCM (10 mL $\times$ 3). The combined organic layer was dried over anhydrous Na₂SO₄, and concentrated under vacuum to give crude compound **063a** (946 mg, 100%), which was used in the next step directly. MS obsd. (ESI⁺) [(M+H)]⁺: 603.1

Step 2: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methoxy-5-[(5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl)methyl]benzamide

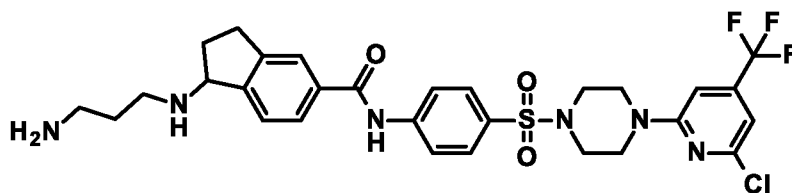
-118-

**063**

A mixture of compound **063a** (0.060 g, 99.4 μ mol), DIPEA (38.6 mg, 298 μ mol) and 5-methyloctahydropyrrolo[3,4-b]pyrrole (25.1 mg, 199 μ mol) in DMF (10 mL) was stirred at 80 °C overnight. After completion, the mixture was diluted with EtOAc (20 mL), washed with water (20 mL). The organic layer was dried over Na₂SO₄, concentrated under vacuum to give a residue, which was purified by prep-HPLC (TFA as additive) to give product (1 mg, 1.41%) as a white solid. MS obsd. (ESI⁺) [(M+H)]⁺: 693.1

Example 063: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.53 (s, 1H), 8.00 - 7.96 (m, 2H), 7.76 - 7.71 (m, 2H), 7.60 (br s, 1H), 7.48 (br d, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 7.09 (s, 1H), 6.97 (s, 1H), 3.93 - 3.90 (m, 1H), 3.88 - 3.86 (m, 3H), 3.80 - 3.75 (m, 1H), 3.73 - 3.70 (m, 4H), 3.43 - 3.37 (m, 3H), 3.00 - 2.95 (m, 6H), 2.80 - 2.72 (m, 4H), 2.64 - 2.58 (m, 1H), 2.20 - 2.09 (m, 1H), 2.06 - 1.96 (m, 1H), 1.56 - 1.46 (m, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -68.55 (s, 3F).

Example 064: 1-(3-Aminopropylamino)-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]indane-5-carboxamide

**064**

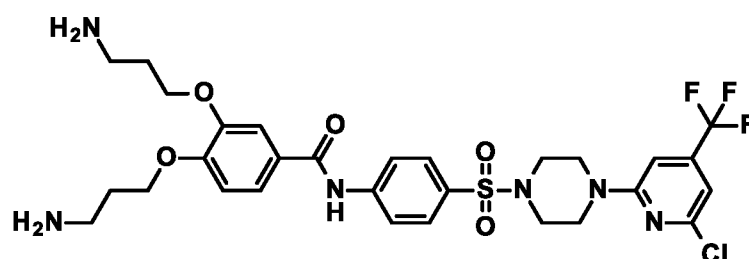
The title compound was prepared in analogy to the preparation of **Example 062** by replacing 3-oxoindane-5-carboxylic acid with 1-oxoindane-5-carboxylic acid in **step1**. **Example 064** (87.9 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)]⁺: 637.3.

Example 064: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.79 (s, 1H), 10.03 - 9.45 (m, 2H), 8.15 (br d, *J* = 8.9 Hz, 4H), 8.04 - 7.92 (m, 3H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.12 (s, 1H), 6.97 (s, 1H),

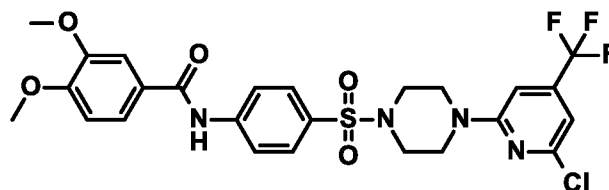
-119-

5.92 - 5.67 (m, 1H), 4.87 (br s, 1H), 3.86 - 3.73 (m, 4H), 3.70 - 3.60 (m, 2H), 3.12 (br s, 2H), 3.07 - 2.93 (m, 7H), 2.18 - 2.06 (m, 1H), 1.86 - 1.73 (m, 2H).

Example 065: 3,4-Bis(3-Aminopropoxy)-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

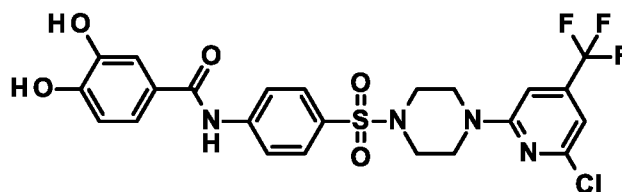
**065**

Step 1: N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3,4-dimethoxy-benzamide

**065a**

SOCl₂ (4.0 mL, 0.750 mmol, 1 eq) was added to a solution of 3,4-dimethoxybenzoic acid (274.44 mg, 1.51 mmol) in toluene (4 mL) at rt. And then, the mixture was heated to 100 °C for 3 hours. And then, the reaction mixture was concentrated and the residue was re-dissolved in 4 mL DCM, which was added dropwise to a mixture of compound **Int-1** (317 mg, 0.8 mmol) and DIPEA (0.3 mL) in 10 mL DCM at rt. After completion, the mixture was concentrated under vacuum to give residue, which was purified by silica-gel chromatography (elute with EtOAc:PE = 50%) to afford compound **065a** (387 mg, 83.43% yield). MS obsd. (ESI⁺) [(M+H)⁺]: 585.1.

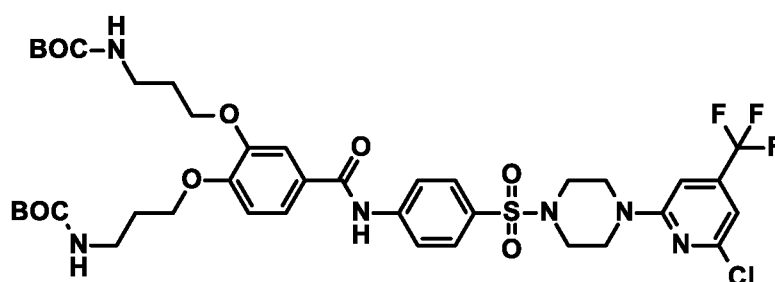
Step 2: N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3,4-dihydroxy-benzamide

**065b**

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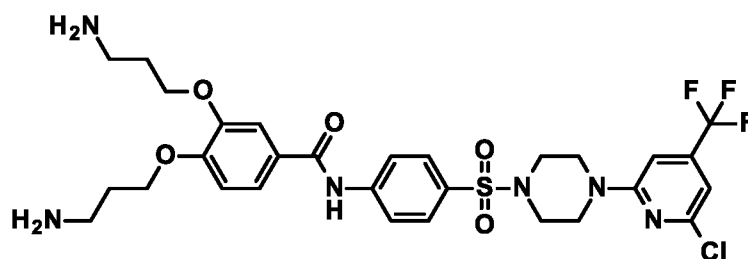
To a solution of compound (187.0 mg, 0.320 mmol) in DCM (4 mL) was added BBr₃ (240.24 mg, 0.960 mmol) dropwise at 25 °C. The resulted mixture was stirred for 2 hours at rt. After completion, MeOH (5mL) was added to quench the reaction. And then, the reaction mixture was concentrated and the residue was purified by prep-HPLC (TFA as additive) to afford compound **065b** (96 mg, 48.53% yield) as a light yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 557.1.

Step 3: *Tert*-butyl *N*-[3-[2-[3-(*tert*-butoxycarbonylamino)propoxy]-4-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenoxy]propyl]carbamate

**065c**

A mixture of compound **065b** (56.0 mg, 0.100 mmol), K₂CO₃ (20.0 mg) and *tert*-butyl *N*-(3-iodopropyl)carbamate (0.08 mL, 0.150 mmol) in DMF (1.4 mL) was stirred at 25 °C for 16 hours. And then, the mixture was poured into water (5 mL), extracted with EtOAc (8 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated under vacuum to give a residue, which was purified by prep-HPLC (TFA as additive) to afford the compound **065c** (45 mg, 46.23% yield) as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 871.3.

Step 4: 3,4-Bis(3-aminopropoxy)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

**065**

Compound **065c** (45.0 mg, 0.050 mmol) was dissolved in 4M TFA/dioxane (4 mL) and the mixture was stirred at rt for 4 hours. After completion, the reaction mixture was concentrated

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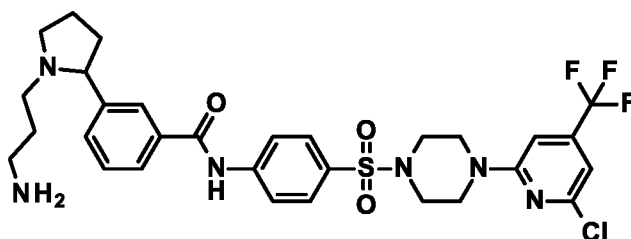
under vacuum to give residue, which was purified by prep-HPLC (TFA as additive) to afford

Example 065 (23 mg, 65.69% yield) as white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 671.3.

Example 065: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.67 (s, 1H), 8.08 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.70 – 7.59 (m, 2H), 7.16 – 7.05 (m, 2H), 6.97 (s, 1H), 4.16 (s, 4H),

5 3.72 (s, 4H), 2.99 (s, 8H), 2.04 (s, 4H). ¹⁹F NMR (376 MHz, DMSO) δ ppm -63.46 (s, 3F).

Example 066: 3-[1-(3-Aminopropyl)pyrrolidin-2-yl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



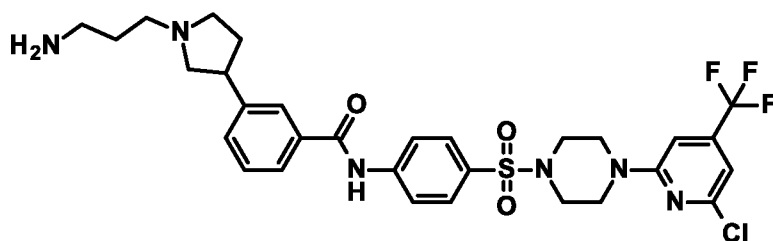
10

066

The title compound was prepared in analogy to the preparation of example **044** by replacing 6-*tert*-butoxycarbonyl-5,7-dihydropyrrolo[3,4-*b*]pyridine-3-carboxylic acid with compound **Int-19** and compound **Int-13** with compound **Int-1** in **step1**. **Example 066** (22.85 mg) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 651.2.

15 **Example 066:** ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.06 (d, *J* = 8.8 Hz, 2H), 7.88 (s, 1H), 7.84 (br d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.61 - 7.55 (m, 1H), 7.53 - 7.46 (m, 1H), 7.09 (s, 1H), 6.97 (s, 1H), 3.78 - 3.69 (m, 4H), 3.00 (br t, *J* = 4.5 Hz, 4H), 2.60 - 2.55 (m, 2H), 2.47 - 2.41 (m, 2H), 2.25 - 2.06 (m, 4H), 1.95 - 1.72 (m, 2H), 1.67 - 1.47 (m, 3H).

20 **Example 067: 3-[1-(3-Aminopropyl)pyrrolidin-3-yl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide**

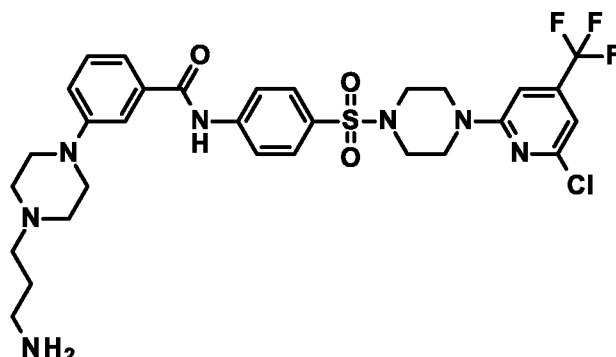


067

The title compound was prepared in analogy to the preparation of example **044** by replacing 6-*tert*-butoxycarbonyl-5,7-dihydropyrrolo[3,4-*b*]pyridine-3-carboxylic acid with compound **Int-20** and compound **Int-13** with compound **Int-1** in **step1**. **Example 067** (22.85 mg) was obtained. MS obsd. (ESI⁺) [(M+H)⁺]: 651.2.

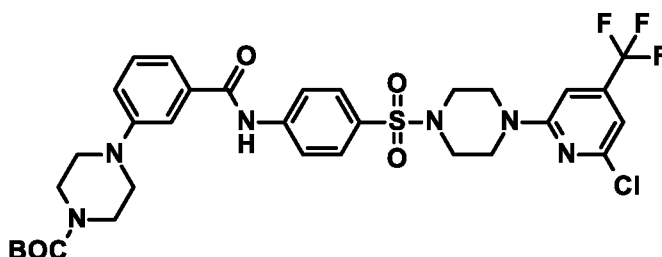
5 **Example 067:** ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.06 (d, *J* = 8.9 Hz, 2H), 7.86 - 7.79 (m, 1H), 7.77 (s, 3H), 7.59 - 7.52 (m, 1H), 7.49 - 7.42 (m, 1H), 7.13 - 7.05 (m, 1H), 6.99 - 6.93 (m, 1H), 3.72 (br s, 4H), 3.02 - 2.96 (m, 4H), 2.92 - 2.86 (m, 1H), 2.75 - 2.60 (m, 4H), 2.32 - 2.23 (m, 1H), 1.87 - 1.72 (m, 1H), 1.68 - 1.50 (m, 2H).

10 **Example 068:** 3-[4-(3-Aminopropyl)piperazin-1-yl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



068

Step 1: *Tert*-butyl 4-[3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]piperazine-1-carboxylate



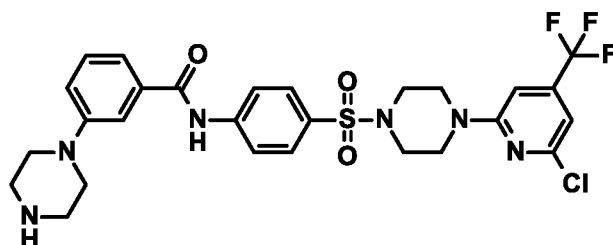
068a

A mixture of 3-(4-*tert*-butoxycarbonylpiperazin-1-yl)benzoic acid (300.0 mg, 0.980 mmol), 3-methylpyridine (182.39 mg, 1.96 mmol) and MsCl (0.11 mL, 1.47 mmol) in MeCN (5 mL) was stirred at 25 °C for 1 hour. And then, compound **Int-1** (412.1 mg, 0.980 mmol) was added to the mixture which was stirred at rt for another 2 hours. After completion, the mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic layer was

-123-

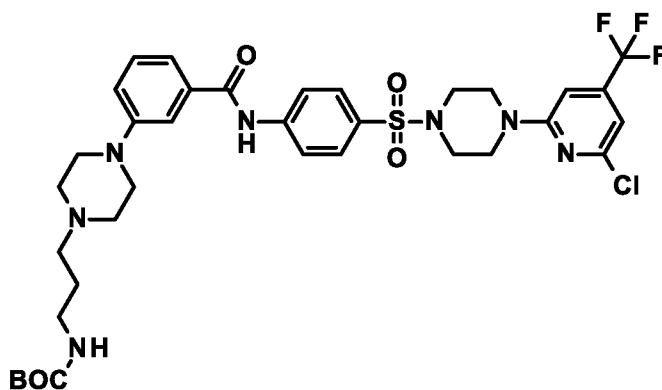
washed with brine (30 mL), dried with anhydrous Na₂SO₄ and concentrated under vacuum to give residue, which was purified by prep-HPLC(TFA as additive) to give compound **068a** (210 mg, 30.24% yield) as yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 709.2.

Step 2: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-piperazin-1-yl-benzamide

**068b**

The mixture of compound **068a** (210.0 mg, 0.300 mmol) in DCM (1 mL) and TFA (1.14 mL) was stirred at 25°C for 1 hour. After completion, the mixture was concentrated under vacuum to give compound **068b** (180 mg, 99.8% yield) as yellow oil, which was used directly in the next step. MS obsd. (ESI⁺) [(M+H)⁺]: 609.1.

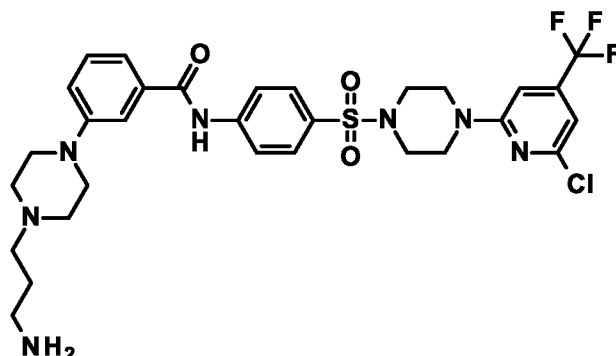
Step 3: *Tert*-butyl *N*-[3-[4-[3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]piperazin-1-yl]propyl]carbamate

**068c**

A mixture of compound **068b** (190.0 mg, 0.310 mmol), KI (0.0 mL, 0.030 mmol), DIPEA (0.11 mL, 0.620 mmol) and *tert*-butyl *N*-(3-chloropropyl)carbamate (90.62 mg, 0.470 mmol) in DMF (10 mL) was stirred at 80 °C for 16 hours. After completion, the mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine (50 mL), dried with anhydrous Na₂SO₄ and concentrated under vacuum to give crude, which was purified by prep-TLC(DCM/MeOH=10/1) to give compound **068c** (120 mg, 50.2% yield) as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 766.2.

-124-

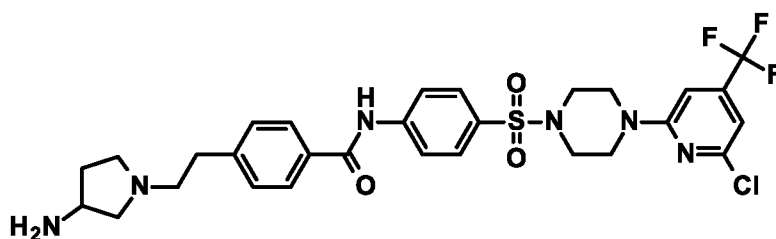
Step 4: 3-[4-(3-Aminopropyl)piperazin-1-yl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

**068**

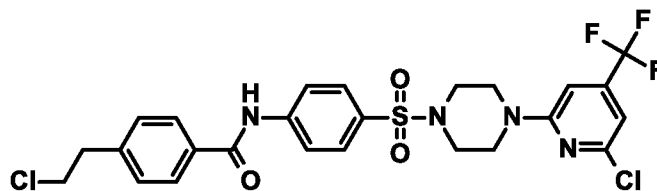
5 A mixture of compound **068c** (120.0 mg, 0.160 mmol) in DCM (1 mL) and TFA (0.6 mL) was stirred at rt for 1 hour. After completion, the mixture was concentrated under vacuum to give a residue, which was purified by prep-HPLC (NH_4HCO_3 as additive) to afford **Example 068** (65 mg, 62.01% yield) as a yellow solid. MS obsd. (ESI⁺) [(M+H)⁺]: 666.0.

Example 067: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 8.07 - 8.01 (m, 2H), 7.75 (s, 2H), 7.43 - 7.39 (m, 1H), 7.39 - 7.30 (m, 2H), 7.19 - 7.14 (m, 1H), 7.10 - 7.06 (m, 1H), 6.96 (s, 1H), 3.74 - 3.67 (m, 4H), 3.23 - 3.18 (m, 4H), 2.97 (s, 4H), 2.37 - 2.32 (m, 2H), 1.60 - 1.50 (m, 2H).

Example 069: 4-[2-(3-Aminopyrrolidin-1-yl)ethyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

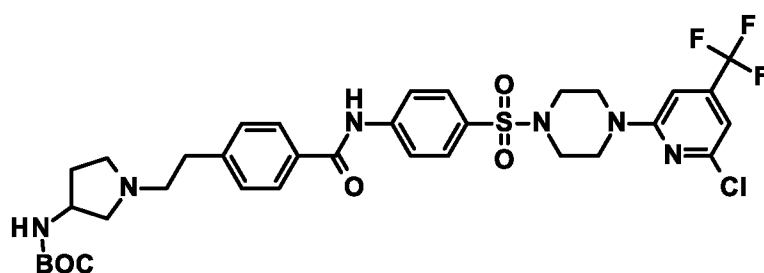
**069**

Step1: 4-(2-Chloroethyl)-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

**069a**

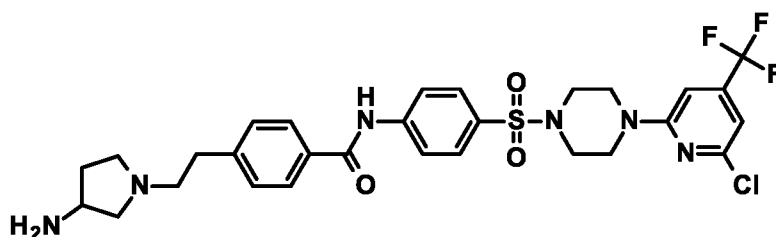
To a mixture of compound **Int-1** (1.26 g, 2.99 mmol) and TEA (1.51 g, 2.09 mL) in DCM (20 mL) was added a solution of 4-(2-chloroethyl)benzoyl chloride (1.03 g, 5.09 mmol) in DCM (3 mL) dropwise at 0 °C. The mixture was slowly warmed up to rt and stirred for 40 minutes. After completion, the mixture was quenched with water (30 mL) and extracted with DCM (30 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under vacuum to give crude product, which was purified by silica-gel chromatography (elute with EtOAc:PE = 10%) to afford compound **069a** (0.850 g, 48%). MS obsd. (ESI⁺) [(M+H)]⁺: 587.1

Step2: *Tert*-butyl *N*-[1-[2-[4-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]ethyl]pyrrolidin-3-yl]carbamate

**069b**

A mixture of *tert*-butyl pyrrolidin-3-ylcarbamate (66.6 mg, 357 μmol), compound **069a** (0.070 g, 119 μmol) and K₂CO₃ (49.4 mg, 357 μmol) in DMF (10 mL) was stirred at 80 °C for 2 hours. After completion, the mixture was diluted with EtOAc (10 mL), washed with water (10 mL). The organic was dried over anhydrous Na₂SO₄ and concentrated under vacuum to give crude compound **069b** (87.9 mg, 100%) which was used directly in the next step. MS obsd. (ESI⁺) [(M+H)]⁺: 736.9.

Step 3: 4-[2-(3-Aminopyrrolidin-1-yl)ethyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

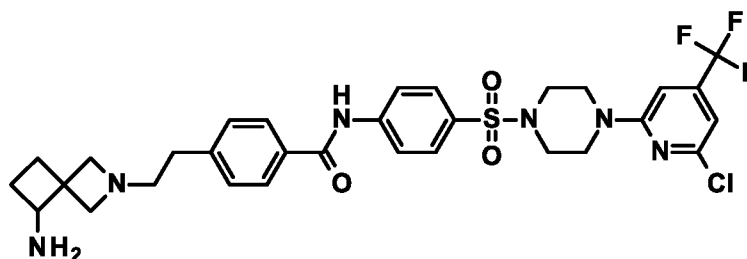
**069**

A mixture of compound **069b** (0.0879 g, 119 μmol) in TFA (1 mL) was stirred at rt for one hour. And then, the mixture was concentrated under vacuum to give a residue, which was purified by prep-HPLC (TFA as additive) to provide **Example 069** (8 mg, 10.5%) as a white solid. MS obsd. (ESI⁺) [(M+H)]⁺: 637.2

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Example 069: ^1H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.59 (s, 1H), 8.08 - 8.03 (m, 2H), 7.92 - 7.87 (m, 2H), 7.78 - 7.72 (m, 2H), 7.44 - 7.39 (m, 2H), 7.09 (s, 1H), 6.96 (s, 1H), 3.75 - 3.69 (m, 4H), 3.67 - 3.60 (m, 1H), 3.01 - 2.95 (m, 4H), 2.86 - 2.81 (m, 2H), 2.78 (br dd, J = 3.0, 8.6 Hz, 1H), 2.72 - 2.67 (m, 3H), 2.61 - 2.58 (m, 1H), 2.48 - 2.41 (m, 1H), 2.20 - 2.04 (m, 1H), 1.65 (br d, J = 4.2 Hz, 1H). ^{19}F NMR (376 MHz, DMSO-*d*₆) δ ppm -68.53 (s, 3F).

Example 070: 4-[2-(7-Amino-2-azaspiro[3.3]heptan-2-yl)ethyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

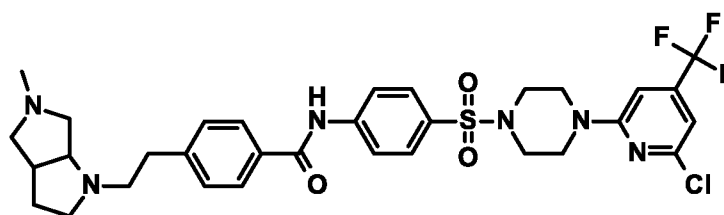


070

The title compound was prepared in analogy to the preparation of **Example 069** by replacing *tert*-butyl pyrrolidin-3-ylcarbamate with *tert*-butyl (2-azaspiro[3.3]heptan-5-yl)carbamate in **step2**. **Example 070** (3 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 663.1.

Example 070: ^1H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.62 (s, 1H), 8.07 (s, 1H), 8.05 (s, 1H), 8.00 - 7.95 (m, J = 8.1 Hz, 2H), 7.76 (d, J = 8.9 Hz, 2H), 7.48 - 7.40 (m, 2H), 7.09 (s, 1H), 6.97 (s, 1H), 4.14 - 3.92 (m, 4H), 3.75 - 3.70 (m, 4H), 3.45 (m, 3H), 3.01 - 2.96 (m, 4H), 2.94 - 2.86 (m, 2H), 2.22 (br d, J = 7.6 Hz, 1H), 2.16 - 2.01 (m, 2H), 1.90 (br d, J = 6.6 Hz, 1H). ^{19}F NMR (376 MHz, DMSO-*d*₆) δ ppm -68.44 (s, 3F).

Example 071: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-4-[2-(5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-*c*]pyrrol-1-yl)ethyl]benzamide



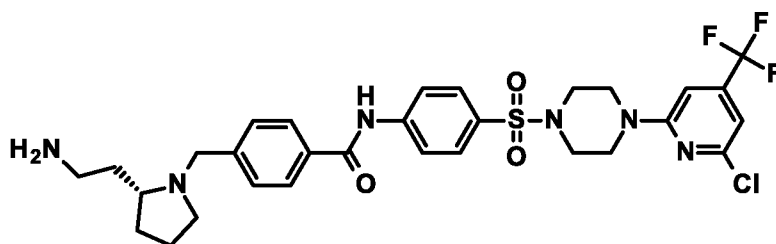
071

-127-

The title compound was prepared in analogy to the preparation of compound **069b** by replacing *tert*-butyl pyrrolidin-3-ylcarbamate with 5-methyloctahydropyrrolo[3,4-*b*]pyrrole in **step 2**. **Example 071** (4 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 676.8.

Example 071: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.59 (s, 1H), 8.09 - 8.04 (m, *J* = 8.9 Hz, 2H), 7.94 - 7.88 (m, *J* = 8.2 Hz, 2H), 7.77 - 7.73 (m, *J* = 8.9 Hz, 2H), 7.46 - 7.39 (m, *J* = 8.3 Hz, 2H), 7.09 (s, 1H), 6.96 (s, 1H), 3.75 - 3.69 (m, 4H), 3.24 - 3.17 (m, 2H), 3.14 - 3.04 (m, 2H), 3.01 - 2.97 (m, 4H), 2.93 - 2.80 (m, 5H), 2.70 - 2.63 (m, 2H), 2.52 (br s, 3H), 2.44 - 2.33 (m, 1H), 2.02 (br s, 1H), 1.56 (br t, *J* = 11.3 Hz, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -68.55 (s, 2F)

Example 072: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-4-[(2*S*)-2-(2-aminoethyl)pyrrolidin-1-yl]methyl]benzamide



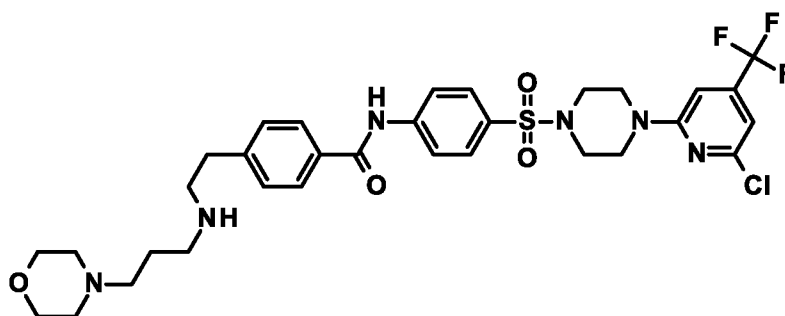
072

The title compound was prepared in analogy to the preparation of **Example 001** by replacing compound *tert*-butyl *N*-(3-aminopropyl)carbamate with *tert*-butyl *N*-[2-[(2*R*)-pyrrolidin-2-yl]ethyl]carbamate in **step 1**. **Example 072** (31 mg) was obtained as a pink solid. MS obsd. (ESI⁺) [(M+H)⁺]: 651.1.

Example 072: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.09 - 8.01 (m, 2H), 7.95 - 7.88 (m, 2H), 7.77 - 7.70 (m, 2H), 7.50 - 7.42 (m, 2H), 7.11 - 7.05 (m, 1H), 6.95 (s, 1H), 4.08 - 4.02 (m, 1H), 3.75 - 3.70 (m, 4H), 3.26 - 3.21 (m, 1H), 3.03 - 2.95 (m, 4H), 2.82 - 2.68 (m, 4H), 2.11 - 2.00 (m, 1H), 1.95 - 1.75 (m, 2H), 1.61 (br s, 2H), 1.52 - 1.39 (m, 2H).

Example 073: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-4-[2-(3-morpholinopropylamino)ethyl]benzamide

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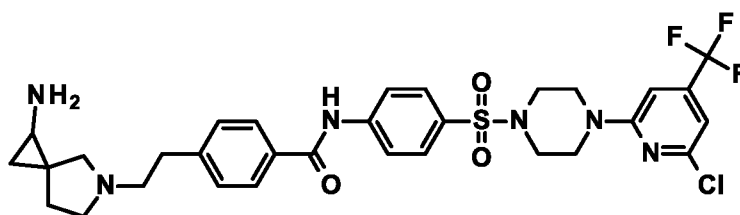
**073**

The title compound was prepared in analogy to the preparation of compound **069b** by replacing *tert*-butyl pyrrolidin-3-ylcarbamate with 3-morpholinopropan-1-amine in **step2**.

Example 073 (10 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 695.2.

Example 073: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.62 (s, 1H), 8.10 - 8.03 (m, *J* = 8.9 Hz, 2H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.79 - 7.73 (m, *J* = 8.9 Hz, 2H), 7.48 - 7.40 (m, 2H), 7.11 - 7.07 (m, 1H), 6.97 (s, 1H), 4.00 (br s, 2H), 3.82 - 3.61 (m, 8H), 3.24 (br s, 4H), 3.07 - 2.95 (m, 10H), 2.00 (br s, 2H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -68.35 (s, 3F).

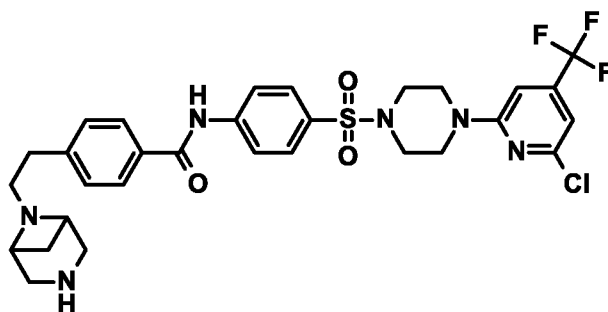
Example 074: 4-[2-(2-Amino-5-azaspiro[2.4]heptan-5-yl)ethyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

**074**

The title compound was prepared in analogy to the preparation of **Example 069** by replacing *tert*-butyl pyrrolidin-3-ylcarbamate with *tert*-butyl (5-azaspiro[2.4]heptan-1-yl)carbamate hydrochloride in **step 2**. **Example 074** (5.5 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 663.1.

Example 074: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.62 (s, 1H), 8.09 - 8.04 (m, *J* = 8.8 Hz, 2H), 8.00 - 7.95 (m, 2H), 7.78 - 7.74 (m, *J* = 8.8 Hz, 2H), 7.49 - 7.43 (m, 2H), 7.09 (s, 1H), 6.97 (s, 1H), 3.74 - 3.69 (m, 4H), 3.47 - 3.43 (m, 2H), 3.25 - 3.15 (m, 2H), 3.13 - 3.03 (m, 2H), 2.99 (br t, *J* = 4.6 Hz, 4H), 2.88 - 2.68 (m, 2H), 2.59 - 2.52 (m, 1H), 2.03 (br s, 2H), 1.26 - 1.13 (m, 1H), 1.11 - 0.97 (m, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -68.42 (s, 3F).

Example 075: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-4-[2-(3,6-diazabicyclo[3.1.1]heptan-6-yl)ethyl]benzamide

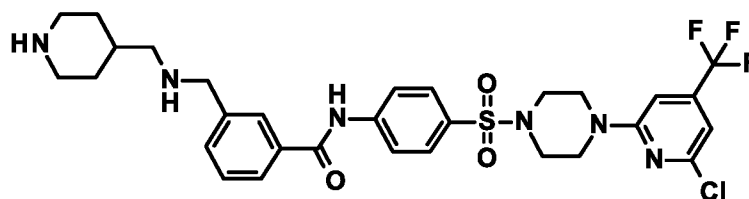


075

5 The title compound was prepared in analogy to the preparation of **Example 069** by replacing *tert*-butyl pyrrolidin-3-ylcarbamate with *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane-3-carboxylate in **step2**. **Example 075** (3 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 649.1.

Example 075: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.62 (s, 1H), 8.09 - 8.04 (m, *J* = 8.8 Hz, 2H), 7.99 - 7.94 (m, *J* = 8.2 Hz, 2H), 7.78 - 7.74 (m, *J* = 8.8 Hz, 2H), 7.50 - 7.44 (m, *J* = 8.3 Hz, 2H), 7.11 - 7.08 (m, 1H), 6.98 - 6.96 (m, 1H), 3.74 - 3.70 (m, 4H), 3.50 - 3.38 (m, 8H), 3.01 - 2.97 (m, 4H), 2.60 - 2.52 (m, 4H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -68.31 (s, 3F).

Example 076: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[(4-piperidylmethylamino)methyl]benzamide

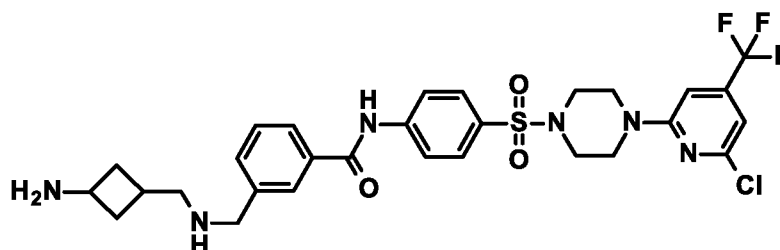


076

15 The title compound was prepared in analogy to the preparation of **Example 001** by replacing compound *tert*-butyl *N*-(3-aminopropyl)carbamate with *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate and **Int-2** with **Int-3** in **step 1**. **Example 076** (10 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 651.1.

20 **Example 076:** ¹H NMR (CD₃OD, 400 MHz) δ ppm 8.01 (s, 1H), 7.9-8.0 (m, 3H), 7.7-7.7 (m, 2H), 7.65 (d, 1H, *J* = 7.8 Hz), 7.5-7.6 (m, 1H), 6.82 (s, 1H), 6.73 (s, 1H), 4.24 (s, 2H), 3.6-3.7 (m, 4H), 3.34 (br d, 2H, *J* = 13.0 Hz), 2.9-3.0 (m, 8H), 1.9-2.1 (m, 3H), 1.3-1.5 (m, 2H). ¹⁹F NMR (376 MHz, CD₃OD) δ ppm -66.48 (s, 3F).

Example 077: 3-[[3-(Aminocyclobutyl)methylamino]methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide



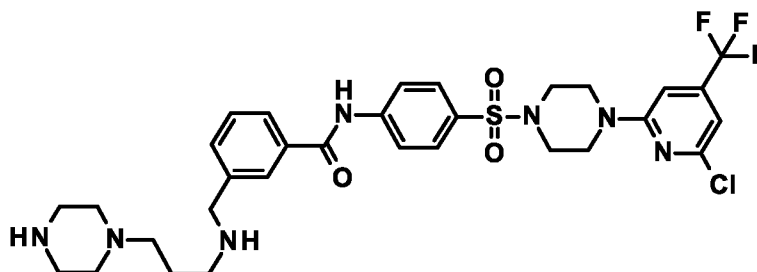
5

077

The title compound was prepared in analogy to the preparation of **Example 001** by replacing compound *tert*-butyl *N*-(3-aminopropyl)carbamate with *tert*-butyl *N*-[(3-aminocyclobutyl)methyl]carbamate and **Int-2** with **Int-3** in **step 1**. Example **077** (10 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 637.1.

Example 077: ¹H NMR (CD₃OD, 400 MHz) δ ppm 8.0-8.0 (m, 1H), 7.8-8.0 (m, 3H), 7.7-7.8 (m, 2H), 7.6-7.7 (m, 1H), 7.5-7.6 (m, 1H), 6.82 (s, 1H), 6.73 (s, 1H), 4.1-4.3 (m, 2H), 3.6-3.8 (m, 5H), 3.1-3.2 (m, 1H), 3.09 (d, 1H, *J* = 6.8 Hz), 3.0-3.0 (m, 4H), 2.4-2.6 (m, 2H), 2.2-2.4 (m, 2H), 1.8-2.0 (m, 1H). ¹⁹F NMR (376 MHz, CD₃OD) δ ppm -66.48 (s, 3F).

Example 078: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[(3-piperazin-1-ylpropylamino)methyl]benzamide

**078**

The title compound was prepared in analogy to the preparation of **Example 001** by replacing compound *tert*-butyl *N*-(3-aminopropyl)carbamate with *tert*-butyl 4-(3-aminopropyl)piperazine-1-carboxylate and **Int-2** with **Int-3** in **step 1**. Example **078** (12 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 680.2.

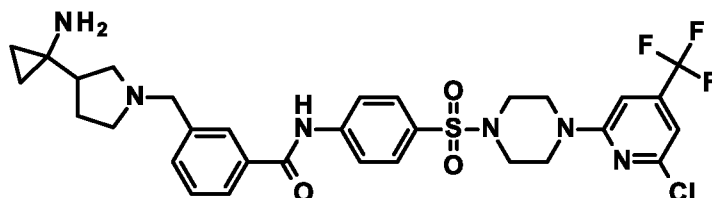
Example 078: ¹H NMR (CD₃OD, 400 MHz) δ 8.0-8.0 (m, 1H), 7.9-8.0 (m, 3H), 7.7-7.7 (m, 2H), 7.6-7.7 (m, 1H), 7.5-7.6 (m, 1H), 6.83 (s, 1H), 6.73 (s, 1H), 4.23 (s, 2H), 3.6-3.7 (m, 4H), 3.1-3.2

25

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(m, 4H), 3.1-3.1 (m, 2H), 3.0-3.0 (m, 4H), 2.62 (br s, 4H), 2.49 (t, 2H, $J = 6.6$ Hz), 1.8-1.9 (m, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ ppm -66.49 (s, 3F).

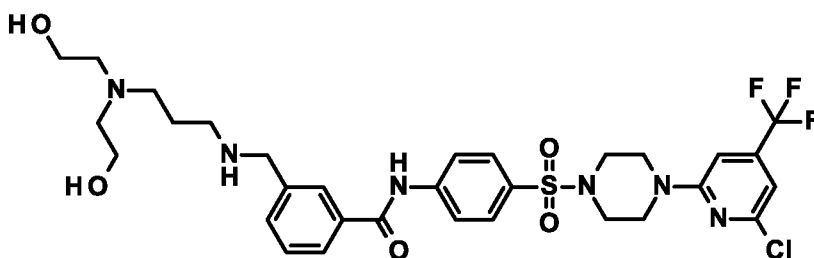
Example 079: 3-[[3-(1-Aminocyclopropyl)pyrrolidin-1-yl]methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

**079**

The title compound was prepared in analogy to the preparation of **Example 001** by replacing *tert*-butyl *N*-(3-aminopropyl)carbamate with *tert*-butyl *N*-(1-pyrrolidin-3-ylcyclopropyl)carbamate and compound **Int-2** with compound **Int-3** in step 1. **Example 079** (46 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 663.1.

Example 079: ^1H NMR (CD_3OD , 400 MHz) δ ppm 8.02 (s, 1H), 7.9-8.0 (m, 3H), 7.6-7.8 (m, 3H), 7.5-7.6 (m, 1H), 6.82 (s, 1H), 6.73 (s, 1H), 4.4-4.5 (m, 2H), 3.6-3.7 (m, 4H), 3.5-3.6 (m, 1H), 3.3-3.5 (m, 2H), 3.0-3.0 (m, 4H), 2.9-3.1 (m, 1H), 2.7-2.9 (m, 1H), 2.17 (br dd, 1H, $J = 5.1$, 11.7 Hz), 1.6-1.8 (m, 1H), 0.89 (s, 4H). ^{19}F NMR (376 MHz, CD_3OD) δ ppm -66.47 (s, 3F).

Example 080: 3-[[3-[Bis(2-hydroxyethyl)amino]propylamino]methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

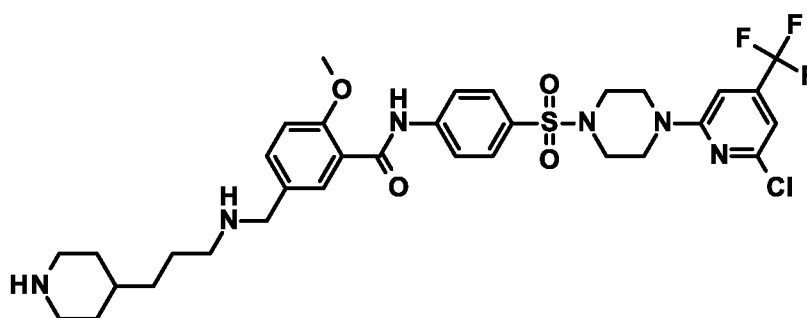
**080**

The title compound was prepared in analogy to the step of preparation compound **001a** by replacing compound *tert*-butyl *N*-(3-aminopropyl)carbamate with 2-[3-aminopropyl(2-hydroxyethyl)amino]ethanol and **Int-2** with **Int-3**. **Example 080** (18 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 699.1.

Example 080: ^1H NMR (CD_3OD , 400 MHz) δ ppm 8.0-8.0 (m, 1H), 7.9-8.0 (m, 3H), 7.7-7.7 (m, 2H), 7.6-7.7 (m, 1H), 7.5-7.6 (m, 1H), 6.83 (s, 1H), 6.73 (s, 1H), 4.23 (s, 2H), 3.6-3.7 (m, 4H), 3.1-3.2 (m, 4H), 3.1-3.1 (m, 2H), 3.0-3.0 (m, 4H), 2.64-2.60 (m, 4H), 2.49 (t, 2H, $J = 6.6$ Hz), 1.8-1.9 (m, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ ppm -66.49 (s, 3F).

5

Example 081: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methoxy-5-[[3-(4-piperidyl)propylamino]methyl]benzamide

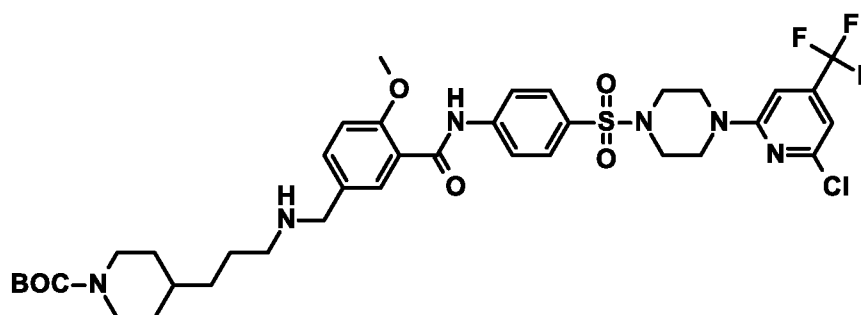


10

081

Step 1: *Tert*-butyl 4-[3-[[3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbonyl]-4-methoxy-phenyl]methylamino]propyl]piperidine-1-carboxylate

15

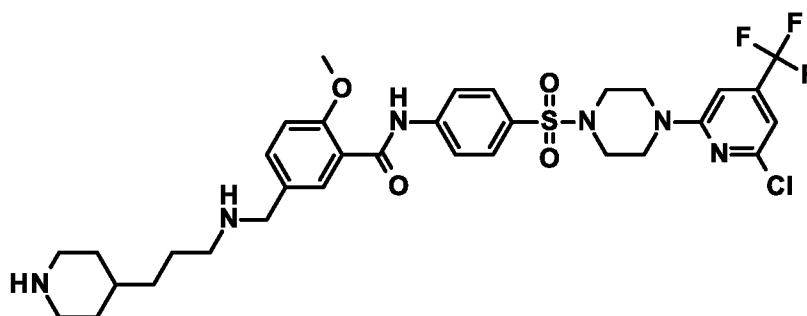


081a

A mixture of compound **056a** (60 mg, 99.4 μmol), DIPEA (38.6 mg, 298 μmol) and *tert*-butyl 4-(3-aminopropyl)piperidine-1-carboxylate (48.2 mg, 199 μmol) in THF (5 mL) was stirred at 80 $^{\circ}\text{C}$ overnight. The mixture was diluted with EtOAc (20), washed with water (10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give crude compound **081a** (80 mg, 100%) which was used directly in next step. MS obsd. (ESI^+) $[(\text{M}+\text{H})]^+$: 809.0

20

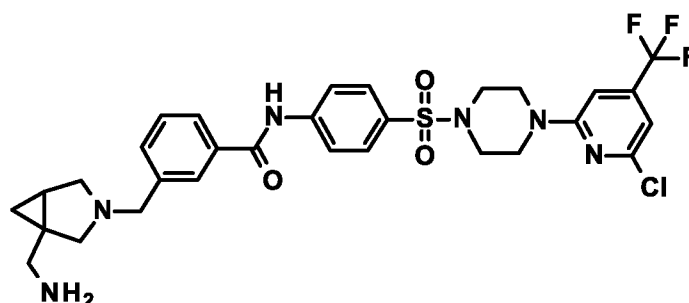
Step 2: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methoxy-5-[[3-(4-piperidyl)propylamino]methyl]benzamide

**081**

5 A mixture of compound **081a** (80 mg, 98.8 μmol) in TFA (1 mL) was stirred at rt for 2 hours. The mixture was concentrated under vacuum to give residue which was purified by HPLC (TFA as additive) to give **Example 081** (3 mg, 4%) as white solid. MS obsd. (ESI⁺) [(M+H)]⁺: 709.1.

Example 081: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.57 - 10.53 (m, 1H), 8.73 - 8.69 (m, 1H), 8.01 - 7.95 (m, 2H), 7.78 - 7.74 (m, 4H), 7.11 - 7.07 (m, 1H), 6.99 - 6.96 (m, 1H), 4.17 - 4.14 (m, 1H), 3.92 - 3.91 (m, 3H), 3.73 - 3.71 (m, 4H), 3.00 - 2.99 (m, 4H), 2.89 - 2.86 (m, 4H), 1.79 - 1.76 (m, 2H), 1.62 - 1.56 (m, 5H), 1.27 - 1.23 (m, 5H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -68.46 (s, 3F).

15 **Example 082:** 3-[[1-(Aminomethyl)-3-azabicyclo[3.1.0]hexan-3-yl]methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

**082**

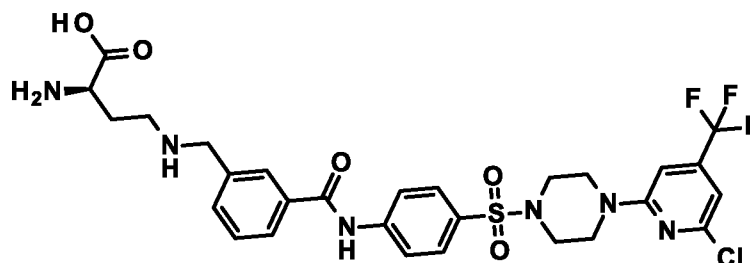
20 The title compound was prepared in analogy to the preparation of **Example 001** by replacing compound *tert*-butyl *N*-(3-aminopropyl)carbamate with *tert*-butyl *N*-(3-azabicyclo[3.1.0]hexan-1-ylmethyl)carbamate and compound **Int-2** with compound **Int-3** in **step 1**. **Example 082** (26.1 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)]⁺: 649.2.

Example 082: ¹H NMR (CD₃OD, 400 MHz) δ 8.0-8.0 (m, 1H), 7.96 (d, 1H, *J* = 7.8 Hz), 7.9-7.9 (m, 2H), 7.7-7.7 (m, 2H), 7.64 (d, 1H, *J* = 7.9 Hz), 7.5-7.6 (m, 1H), 6.82 (s, 1H), 6.73 (s, 1H),

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4.3-4.5 (m, 2H), 3.6-3.7 (m, 4H), 3.4-3.6 (m, 4H), 3.32 (d, 1H, $J = 13.8$ Hz), 2.9-3.1 (m, 5H), 1.89 (br s, 1H), 0.9-1.3 (m, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ ppm -66.48 (s, 3F).

Example 083: (2*R*)-2-Amino-4-[[3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]methylamino]butanoic acid

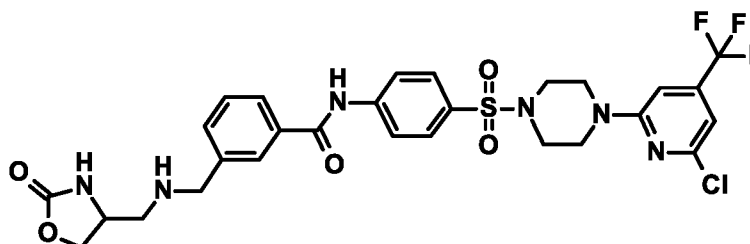


083

The title compound was prepared in analogy to the preparation of **Example 001** by replacing compound *tert*-butyl *N*-(3-aminopropyl)carbamate with (2*R*)-4-amino-2-(*tert*-butoxycarbonylamino)butanoic acid and compound **Int-2** with compound **Int-3** in **step 1**. Example **084** (2 mg) was obtained as a white solid. MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 655.1.

Example 083: ^1H NMR (CD_3OD , 400 MHz) δ ppm 8.11 (t, 1H, $J = 1.5$ Hz), 8.0-8.1 (m, 3H), 7.8-7.9 (m, 2H), 7.7-7.8 (m, 1H), 7.6-7.7 (m, 1H), 6.94 (s, 1H), 6.85 (s, 1H), 4.36 (s, 2H), 4.09 (dd, 1H, $J = 5.2, 8.4$ Hz), 3.7-3.8 (m, 4H), 3.3-3.5 (m, 2H), 3.1-3.2 (m, 4H), 2.2-2.5 (m, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ ppm -66.49 (s, 3F).

Example 084: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[[2-oxooxazolidin-4-yl]methylamino]methyl]benzamide



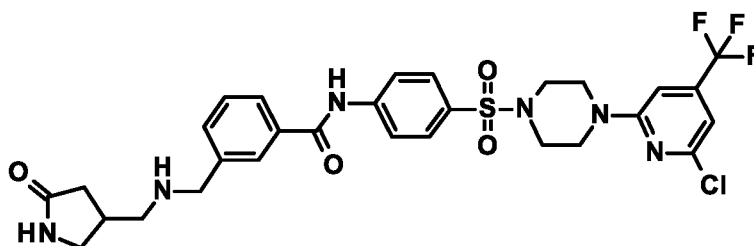
084

The title compound was prepared in analogy to the step of preparation compound **001a** by replacing *tert*-butyl *N*-(3-aminopropyl)carbamate with 4-(aminomethyl)oxazolidin-2-one and

compound **Int-2** with compound **Int-3** in **step 1**. **Example 084** (20 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 653.1.

Example 084: ¹H NMR (CD₃OD, 400 MHz) δ ppm 7.8-8.0 (m, 2H), 7.7-7.8 (m, 2H), 7.7-7.7 (m, 2H), 7.3-7.5 (m, 2H), 6.83 (s, 1H), 6.73 (s, 1H), 4.3-4.4 (m, 2H), 3.6-3.7 (m, 5H), 3.3-3.4 (m, 3H), 3.10 (dd, 1H, *J* = 5.7, 9.1 Hz), 3.0-3.0 (m, 4H). ¹⁹F NMR (376 MHz, CD₃OD) δ ppm -66.49 (s, 3F).

Example 085: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[[5-oxopyrrolidin-3-yl)methylamino]methyl]benzamide



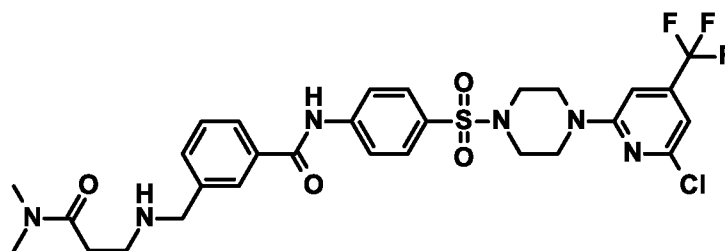
085

The title compound was prepared in analogy to the preparation of compound **001a** in **step 1** by replacing compound *tert*-butyl *N*-(3-aminopropyl)carbamate with 4-(aminomethyl)pyrrolidin-2-one and compound **Int-2** with compound **Int-3**. **Example 085** (32 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 651.2.

Example 085: ¹H NMR (CD₃OD, 400 MHz) δ ppm 8.01 (s, 1H), 7.9-8.0 (m, 1H), 7.9-7.9 (m, 2H), 7.7-7.8 (m, 2H), 7.65 (d, 1H, *J* = 7.8 Hz), 7.5-7.6 (m, 1H), 6.83 (s, 1H), 6.73 (s, 1H), 4.24 (s, 2H), 3.6-3.7 (m, 4H), 3.50 (dd, 1H, *J* = 7.9, 10.1 Hz), 3.15 (dd, 2H, *J* = 3.6, 7.3 Hz), 3.08 (dd, 1H, *J* = 6.6, 10.1 Hz), 3.0-3.0 (m, 4H), 2.79 (quind, 1H, *J* = 7.7, 15.3 Hz), 2.44 (dd, 1H, *J* = 8.8, 16.9 Hz), 2.12 (dd, 1H, *J* = 7.7, 16.9 Hz). ¹⁹F NMR (376 MHz, CD₃OD) δ ppm -66.49 (s, 3F).

Example 086: *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[[[3-(dimethylamino)-3-oxo-propyl]amino]methyl]benzamide

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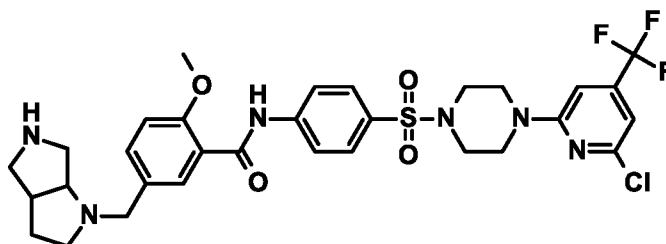
**086**

The title compound was prepared in analogy to the preparation compound **001a** by replacing compound *tert*-butyl *N*-(3-aminopropyl)carbamate with 3-amino-*N,N*-dimethylpropanamide and compound **Int-2** with compound **Int-3**. **Example 086** (32 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 653.1.

Example 086: ¹H NMR (CD₃OD, 400 MHz) δ ppm 8.00 (s, 1H), 7.9-8.0 (m, 3H), 7.71 (d, 2H, *J* = 8.8 Hz), 7.65 (d, 1H, *J* = 7.8 Hz), 7.5-7.6 (m, 1H), 6.82 (s, 1H), 6.73 (s, 1H), 4.26 (s, 2H), 3.6-3.7 (m, 4H), 3.0-3.0 (m, 4H), 2.94 (s, 3H), 2.86 (s, 3H), 2.8-2.8 (m, 2H), 2.73 (t, 2H, *J* = 6.2 Hz).

¹⁹F NMR (376 MHz, CD₃OD) δ ppm -66.48 (s, 3F).

Example 087: 5-(3,3a,4,5,6,6a-Hexahydro-2*H*-pyrrolo[3,4-*b*]pyrrol-1-ylmethyl)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methoxy-benzamide

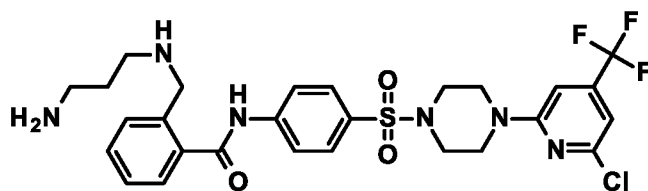
**087**

The title compound was prepared in analogy to the preparation of **Example 081** by replacing *tert*-butyl 4-(3-aminopropyl)piperidine-1-carboxylate with *tert*-butyl 2,3,3a,4,6,6a-hexahydro-1*H*-pyrrolo[2,3-*c*]pyrrole-5-carboxylate in **step 1**. **Example 087** (20 mg) was obtained as a white solid. MS obsd. (ESI⁺) [(M+H)⁺]: 679.0.

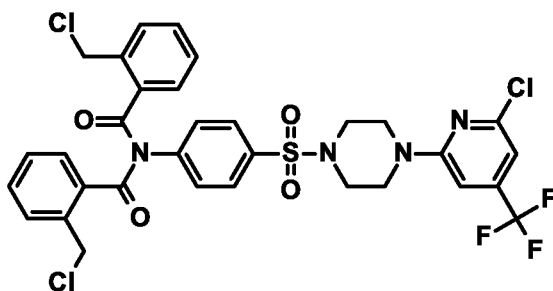
Example 087: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.46 (s, 1H), 7.91 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.9 Hz, 2H), 7.49 (d, *J* = 2.1 Hz, 1H), 7.38 (dd, *J* = 2.2, 8.4 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 7.02 (s, 1H), 6.90 (s, 1H), 3.83 - 3.76 (m, 4H), 3.68 - 3.61 (m, 4H), 3.38 - 3.36 (m, 2H), 3.13 - 3.02 (m, 3H), 2.93 - 2.89 (m, 4H), 2.79 - 2.63 (m, 3H), 2.12 - 1.99 (m, 1H), 1.96 - 1.85 (m, 1H), 1.43 - 1.32 (m, 1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -68.53 (s, 3F).

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Example 088: 2-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

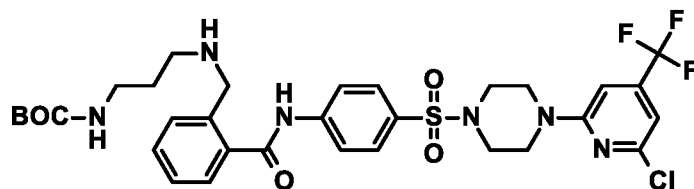
**088**

Step 1: 2-(Chloromethyl)-N-[2-(chloromethyl)benzoyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

**088a**

To a mixture of compound **Int-1** (400mg, 950 μ mol) and TEA (288 mg, 2.85 mmol) in DCM (5 mL) was added 2-(chloromethyl)benzoyl chloride (216 mg, 1.14 mmol) dropwise at rt and the mixture was stirred at rt for 2 hours. After completion, the mixture was quenched with saturated NaHCO_3 aq. (40 mL), extracted with DCM (30 mL $\times$ 3). The combined organic layer was concentrated under vacuum to give crude, which was purified by silica-gel chromatography (elute with EtOAc:PE = 10%) to afford compound **088a** (200mg, 29 % yield) as white solid. MS obsd. (ESI^+) $[(\text{M}+\text{H})^+]$: 725.2.

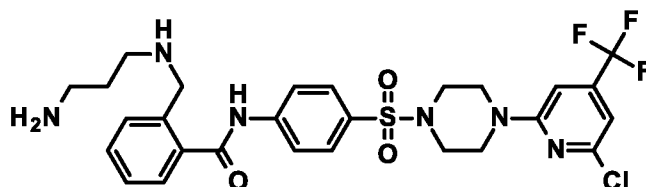
Step 2: *Tert*-butyl N-[3-[[2-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbonyl]phenyl]methylamino]propyl]carbamate

**088b**

A mixture of compound **089a** (120mg, 165 μ mol), *tert*-butyl (3-aminopropyl)carbamate (43.2 mg, 248 μ mol) and DIEA (64 mg, 496 μ mol) in THF (5 mL) was heated at 70 $^{\circ}\text{C}$ for 10 hours. After completion, the mixture was diluted with DCM (20 mL), washed with NaHCO_3 aq. (20 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum to give crude

compound **088b** (118mg, 100 % yield), which was used in the next step directly. MS obsd. (ESI⁺) [(M+H)⁺]: 711.2.

Step 3: 2-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide

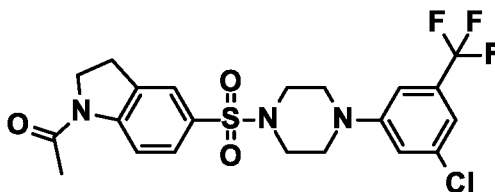


088

A crude solution of compound **088** (70mg, 98.4 μ mol) in TFA (10 mL) was stirred at rt for 2 hour. And then, the reaction mixture was concentrated and the residue was purified by prep-HPLC (TFA as additive) to afford **Example 088** (10mg, 15.8 % yield). MS obsd. (ESI⁺) [(M+H)⁺]: 611.1.

Example 088: ¹H NMR (CD₃OD, 400 MHz) δ ppm 7.9-7.9 (m, 2H), 7.8-7.9 (m, 1H), 7.7-7.7 (m, 2H), 7.5-7.6 (m, 3H), 6.83 (s, 1H), 6.74 (s, 1H), 4.20 (s, 2H), 3.6-3.7 (m, 4H), 3.1-3.2 (m, 2H), 2.9-3.0 (m, 6H), 2.05 (quin, 2H, *J*=7.7 Hz). ¹⁹F NMR (376 MHz, CD₃OD) δ ppm -66.48 (s, 3F).

Compound **F-1**, disclosed in the literature (Bioorganic Chemistry 102 (2020) 104055) and reported having LPS synthesis pathway inhibition activity and displaying antibiotic activity against efflux-deficient *E. coli* strains, was chosen as reference compound in present invention.



Compound **F-1**

BIOLOGICAL EXAMPLES

Example 089: Minimal Inhibitory Concentration Protocol (MIC) Assay:

The antibacterial activity of the compounds of the present invention was evaluated against the commonly used quality control strain *Escherichia coli* ATCC 25922 and the rifampin-resistant mutant strain *Klebsiella pneumonia* ATCC 43816. Both were originally derived from human clinical samples and are available from ATCC (American Type Culture Collection). The *in vitro* potency of compounds to inhibit *Escherichia coli* (ATCC 25922) and *Klebsiella*

pneumonia (ATCC 43816) growth was assessed by the MIC (Minimal Inhibitory Concentration) broth dilution method. Specifically compound dilutions were prepared from 10 mM DMSO stock solutions as follows: i) serial 2-fold dilution in 20 μ L DMSO were prepared in a master plate (Greiner, Cat No: 651201), ii) 180 μ L sterile distilled water was added to each aliquot and
 5 iii) 10 μ L diluted compounds were transferred into a new assay plate (Costar, 3599).

Vials of each test microorganisms were maintained frozen in the vapor phase of a liquid nitrogen freezer. Single-use frozen vials of the two strains *Escherichia coli* ATCC 25922 (KWIKSTIK, 0335K) and *Klebsiella pneumonia* ATCC 43816, with predetermined CFU/mL, were taken out from the freezer, thawed at room temperature, and diluted in Cation-Adjusted
 10 Mueller Hinton Broth (CAMHB) to achieve a final inoculum of 5×10^5 CFU/ mL. 90 μ L bacteria containing broth was dispensed to the assay plate containing the pre-dispensed compound dilutions and mixed by pipetting 5 times.

Then the assay plates were incubated for 20 hours at 35 °C in ambient air. Following incubation, the MIC (μ g/mL), the lowest concentration of drug that inhibits visible growth of the
 15 microorganism was read with the help of a magnification mirror and recorded.

Table 1: MIC values of the compounds of this invention against *E. coli* and *K. pneumonia*

Example No.	MIC (μ g/mL)		Example No.	MIC (μ g/mL)	
	<i>Escherichia coli</i> ATCC 25922	<i>Klebsiella pneumoniae</i> ATCC43816		<i>Escherichia coli</i> ATCC 25922	<i>Klebsiella pneumoniae</i> ATCC43816
F-1	>24	>24	044	0.91	1.8
001	0.51	1.5	045	0.91	3.6
002	1.8	5.4	046	0.47	0.47
003	1.4	3.8	047	1.1	2.3
004	1.9	3.8	048	0.48	0.97
005	1.9	7.7	050	1	1
006	3.7	15	051	0.56	1.1
007	0.97	0.97	052	1.1	2.3
008	N.A.	7.7	053	0.44	0.89
009	5.4	11	054	0.48	0.95
010	5.3	11	055	0.45	0.91
011	3.8	7.6	056	3.8	3.8
012	1.8	3.6	057	1	2
013	0.94	N.A.	058	3.8	3.8
014	15	30	059	1.9	3.8
015	1.9	3.8	060	0.48	1.9
016	1.9	3.8	061	0.53	1.1
017	0.97	0.97	062	2.1	4.2
018	0.64	2.6	063	4.3	4.3
019	2.6	5.2	064	2.1	4.2
020	1.2	2.5	065	0.26	0.52

021	3.9	7.8	066	0.51	1
022	3.9	3.9	067	0.51	1
023	4.2	4.2	068	1	2.1
024	0.48	0.96	069	1.2	2.3
025	1.3	5.1	070	1.2	2.4
026	3.9	7.8	071	4.2	4.2
027	4	4	072	1	2
028	4.6	9.3	073	1.4	2.9
029	1.9	3.8	074	2.8	2.8
030	4	8	075	2.7	5.5
031	3.9	3.9	076	0.69	2.7
032	7.1	7.1	077	0.68	2.7
033	3.6	3.6	078	1.4	5.7
034	0.92	0.92	079	1.1	2.2
035	3.7	7.5	080	1.4	2.9
036	3.7	7.4	081	1.5	2.9
037	3.7	7.5	082	0.69	1.4
038	3.7	7.4	084	4.8	4.8
040	2.1	8.3	085	1.2	N.A.
041	1	8.3	086	2.4	N.A.
042	0.99	2	087	1.2	2.5
043	4.2	2.1	088	1.3	2.6

Example 090: Human microsome stability assay

The human microsomal stability assay is used for early assessment of metabolic stability of a test compound in human liver microsomes.

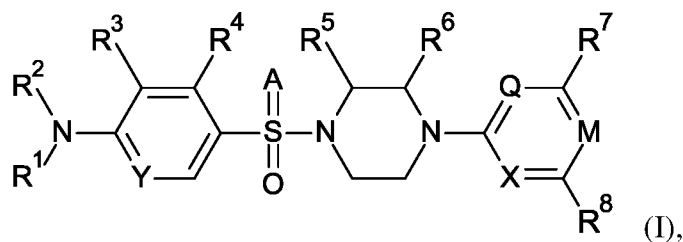
- 5 Human liver microsomes (Cat.NO.: 452117, Corning, USA) were pre-incubated with test compound for 10 minutes at 37°C in 100 mM potassium phosphate buffer, pH 7.4. The reactions were initiated by adding NADPH regenerating system. The final incubation mixtures contained 1 µM test compound, 0.5 mg/mL liver microsomal protein, 1 mM MgCl₂, 1 mM NADP, 1 unit/mL isocitric dehydrogenase and 6 mM isocitric acid in 100 mM potassium phosphate buffer, pH 7.4.
- 10 After incubation times of 0, 3, 6, 9, 15 and 30 minutes at 37°C, 300 µL of cold acetonitrile (including internal standard) was added to 100 µL incubation mixture to terminate the reaction. Following precipitation and centrifugation, the amount of compound remaining in the samples were determined by LC-MS/MS. Controls of no NADPH regenerating system at zero and 30 minutes were also prepared and analyzed. The compounds of present invention showed good
- 15 human liver microsome stability determined in the above assay, results are shown in Table 2 below. (Human microsome clearance: <7 mL/min/kg (low); 7-16.2 mL/min/kg (medium); >16.2 mL/min/kg (high))

Table 2: Human microsome clearance values of the compounds of this invention

Example No.	Clearance of Human microsome (mL/min/kg)	Example No.	Clearance of Human microsome (mL/min/kg)
F-1	14	039	9.4
001	6.2	041	6.2
012	6.2	043	6.2
020	8.8	068	6.2
034	6.2	078	6.2

CLAIMS

1. A compound of formula (I),



wherein

5 R^1 is COR^9 ; wherein

R^9 is ((hydroxy C_{1-6} alkyl)amino) C_{1-6} alkyl,

1-oxa-2,9-diazaspiro[4.5]dec-2-enyl,

4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazinyl,

4,6-dihydropyrrolo[3,4-c]pyrazolyl substituted by C_{1-6} alkyl,

10 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl,

indanyl substituted by amino or amino C_{1-6} alkylamino,

isoindolinyl,

piperazinyl C_{1-6} alkyl,

pyrazolo[1,5-a]pyrimidinyl,

15 pyrazolyl substituted once or twice by the substituents independently selected from

amino C_{1-6} alkyl, azetidiny, C_{1-6} alkyl and carboxy,

pyridinyl substituted by (amino C_{1-6} alkylamino) C_{1-6} alkyl, or

phenyl substituted once or twice by the substituents independently selected from

((amino(carboxy) C_{1-6} alkyl)amino) C_{1-6} alkyl, ((amino C_{1-6} alkyl)-3-

20 azabicyclo[3.1.0]hexanyl) C_{1-6} alkyl, ((amino C_{1-6} alkyl)pyrrolidinyl) C_{1-6} alkyl,

((amino C_{3-7} cycloalkyl) C_{1-6} alkylamino) C_{1-6} alkyl, ((amino C_{3-7}

7cycloalkyl)pyrrolidinyl) C_{1-6} alkyl, ((oxooxazolidinyl) C_{1-6} alkylamino) C_{1-6} alkyl,

((oxopyrrolidinyl) C_{1-6} alkylamino) C_{1-6} alkyl, ((piperidinyl) C_{1-6} alkylamino) C_{1-6}

6alkyl, (3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[3,4-b]pyrrolyl) C_{1-6} alkyl, (3,6-

25 diazabicyclo[3.1.1]heptanyl) C_{1-6} alkyl, (amino-2-azaspiro[3.3]heptanyl) C_{1-6}

6alkyl, (amino-5-azaspiro[2.4]heptanyl) C_{1-6} alkyl, (amino C_{1-6} alkyl)piperazinyl,

(amino C_{1-6} alkyl)pyrrolidinyl, (amino C_{1-6} alkylamino) C_{1-6} alkyl,

(aminopyrrolidinyl) C_{1-6} alkyl, (C_{1-6} alkyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-

30 c]pyrrolyl) C_{1-6} alkyl, (diamino C_{1-6} alkylcarbonyl)amino, (morpholinyl C_{1-6}

6alkylamino) C_{1-6} alkyl, (piperazinyl C_{1-6} alkylamino) C_{1-6} alkyl, (piperidinyl C_{1-6}

- alkylamino)C₁₋₆alkyl, [((C₁₋₆alkyl)₂aminocarbonylC₁₋₆alkyl)amino]C₁₋₆alkyl, [(hydroxyC₁₋₆alkyl)₂amino]C₁₋₆alkylamino]C₁₋₆alkyl, 2,5-diazabicyclo[2.2.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, aminoC₁₋₆alkoxy, aminoC₁₋₆alkyl, aminopyrrolidinyl, azetidinyC₁₋₆alkoxy, azetidinyC₁₋₆alkylamino, C₁₋₆alkylcarbonyloxy, C₁₋₆alkoxy, carboxy, hydroxy and piperazinyl;
- R² is H;
- R³ is H, hydroxy or C₁₋₆alkoxy; or
- R² and R³ together with the atoms they are attached to form a pyrrolidinyl;
- 10 R⁴ is H, hydroxy or C₁₋₆alkoxy;
- R⁵ is H or C₁₋₆alkyl;
- R⁶ is H or C₁₋₆alkyl; or
- R⁵ and R⁶ together with the atoms they are attached to form a C₃₋₇cycloalkyl;
- R⁷ is halogen, cyano, haloC₁₋₆alkyl or C₁₋₆alkoxycarbonyl;
- 15 R⁸ is H, halogen, cyano, amino, C₃₋₇cycloalkoxy, C₁₋₆alkyl, C₁₋₆alkoxy or haloC₁₋₆alkyl;
- Y is CH or N;
- A is O, N(CN), or N(C₁₋₆alkyl);
- Q is CH or N;
- X is CH or N;
- 20 M is N or CR¹⁰; wherein R¹⁰ is H, halogen, C₁₋₆alkyl or C₃₋₇cycloalkyl; with the proviso that Q, X and M are not N simultaneously; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

- 25 R¹ is COR⁹; wherein
- R⁹ is 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl, indanyl substituted by amino or aminoC₁₋₆alkylamino, isoindolinyl, pyrazolo[1,5-a]pyrimidinyl,
- 30 pyridinyl substituted by (aminoC₁₋₆alkylamino)C₁₋₆alkyl, or phenyl substituted once or twice by the substituents independently selected from ((aminoC₁₋₆alkyl)-3-azabicyclo[3.1.0]hexanyl)C₁₋₆alkyl, (aminoC₁₋₆alkyl)pyrrolidinyl, (aminoC₁₋₆alkylamino)C₁₋₆alkyl, aminoC₁₋₆alkoxy,

aminoC₁₋₆alkyl, aminopyrrolidinyl, azetidinyC₁₋₆alkoxy, carboxy and piperazinyl.

3. A compound according to claim 1 or 2, wherein R¹ is COR⁹; wherein R⁹ is 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl, aminoindanyl, (3-aminopropylamino)indanyl, isoindolinyl, pyrazolo[1,5-a]pyrimidinyl, ((3-aminopropylamino)methyl)pyridinyl, ((3-aminopropylamino)methyl)phenyl, ((3-aminopropylamino)ethyl)phenyl, carboxyphenyl, (aminoethoxy)phenyl, (azetidin-3-ylmethoxy)phenyl, (aminopyrrolidin-1-yl)phenyl, (aminoethyl)phenyl, (piperazin-1-yl)phenyl, (3-aminopropoxy)₂phenyl, (1-(3-aminopropyl)pyrrolidin-2-yl)phenyl, (1-(3-aminopropyl)pyrrolidin-3-yl)phenyl or [[1-(aminomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)methyl]phenyl.
4. A compound according to any one of claims 1-3, wherein R² is H; R³ is H; or R² and R³ together with the atoms they are attached to form a pyrrolidinyl.
5. A compound according to any one of claims 1-4, wherein R⁴ is H; R⁵ is H; and R⁶ is H.
6. A compound according to any one of claims 1-5, wherein R⁷ is halogen or haloC₁₋₆alkyl.
7. A compound according to any one of claims 1-6, wherein R⁷ is bromo, trifluoromethyl or difluoroethyl.
8. A compound according to any one of claims 1-7, wherein R⁸ is halogen or C₁₋₆alkyl.
9. A compound according to any one of claims 1-8, wherein R⁸ is chloro or methyl.
10. A compound according to any one of claims 1-9, wherein Y is CH.
11. A compound according to any one of claims 1-10, wherein A is O.
12. A compound according to any one of claims 1-11, wherein X is N.
13. A compound according to any one of claims 1-12, wherein M is CH.

14. A compound according to claim 1 or 2, wherein

R¹ is COR⁹; wherein

R⁹ is 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl,

5 indanyl substituted by amino or aminoC₁₋₆alkylamino,
isoindolinyl,
pyrazolo[1,5-a]pyrimidinyl,
pyridinyl substituted by (aminoC₁₋₆alkylamino)C₁₋₆alkyl, or
phenyl substituted once or twice by the substituents independently selected from
10 ((aminoC₁₋₆alkyl)-3-azabicyclo[3.1.0]hexanyl)C₁₋₆alkyl, (aminoC₁₋₆alkyl)pyrrolidinyl, (aminoC₁₋₆alkylamino)C₁₋₆alkyl, aminoC₁₋₆alkoxy,
aminoC₁₋₆alkyl, aminopyrrolidinyl, azetidinyC₁₋₆alkoxy, carboxy and
piperazinyl;

R² is H;

15 R³ is H; or

R² and R³ together with the atoms they are attached to form a pyrrolidinyl;

R⁴ is H;

R⁵ is H;

R⁶ is H;

20 R⁷ is halogen or haloC₁₋₆alkyl;

R⁸ is halogen or C₁₋₆alkyl;

Y is CH;

A is O;

Q is CH or N;

25 X is N;

M is CH;

or a pharmaceutically acceptable salt thereof.

15. A compound according to claim 14, wherein

30 R¹ is COR⁹; wherein R⁹ is 6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl, aminoindanyl, (3-aminopropylamino)indanyl, isoindolinyl, pyrazolo[1,5-a]pyrimidinyl, ((3-aminopropylamino)methyl)pyridinyl, ((3-aminopropylamino)methyl)phenyl, ((3-aminopropylamino)ethyl)phenyl, carboxyphenyl, (aminoethoxy)phenyl, (azetidin-3-

ylmethoxy)phenyl, (aminopyrrolidin-1-yl)phenyl, (aminoethyl)phenyl, (piperazin-1-yl)phenyl, (3-aminopropoxy)₂phenyl, (1-(3-aminopropyl)pyrrolidin-2-yl)phenyl, (1-(3-aminopropyl)pyrrolidin-3-yl)phenyl or [[1-(aminomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)methyl]phenyl;

- 5 R² is H;
R³ is H; or
R² and R³ together with the atoms they are attached to form a pyrrolidinyl;
R⁴ is H;
R⁵ is H;
- 10 R⁶ is H;
R⁷ is bromo, trifluoromethyl or difluoroethyl;
R⁸ is chloro or methyl;
Y is CH;
A is O;
- 15 Q is CH or N;
X is N;
M is CH;
or a pharmaceutically acceptable salt thereof.
- 20 16. A compound selected from:
4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;
4-[(3-Aminopropylamino)methyl]-N-[4-[4-[4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;
- 25 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[5-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;
4-[(3-Aminopropylamino)methyl]-N-[4-[4-[3-chloro-5-(trifluoromethyl) phenyl]piperazin-1-yl]sulfonylphenyl]benzamide;
- 30 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[2-chloro-6-(trifluoromethyl)pyrimidin-4-yl]piperazin-1-yl]sulfonylphenyl]benzamide;
4-[(3-Aminopropylamino)methyl]-N-[4-[4-[2-amino-6-(trifluoromethyl)pyrimidin-4-yl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[(3-Aminopropylamino)methyl]-N-[4-[4-(4-bromo-6-chloro-2-pyridyl)piperazin-1-yl]sulfonylphenyl]benzamide;

4-[(3-Aminopropylamino)methyl]-N-[4-[4-[5-cyclopropyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

5 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-(cyclopropoxy)-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-ethoxy-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

10 4-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-ethyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[(3-Aminopropylamino)methyl]-N-[4-[4-[4-(trifluoromethyl)pyrimidin-2-yl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-[5-methyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

15 4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-(4,5-dichloro-2-pyridyl)piperazin-1-yl]sulfonylphenyl]benzamide;

4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-[4-cyano-6-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

20 4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-[6-cyano-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[2-(3-Aminopropylamino)ethyl]-N-[4-[4-[6-chloro-4-(1,1-difluoroethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-methyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

25 Methyl 2-[4-[4-[[3-[(3-aminopropylamino)methyl]benzoyl]amino]phenyl]sulfonylpiperazin-1-yl]-6-chloro-pyridine-4-carboxylate;

3-[(3-Aminopropylamino)methyl]-N-[4-[4-(6-chloro-4-cyano-2-pyridyl)piperazin-1-yl]sulfonylphenyl]benzamide;

30 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-2-methyl-piperazin-1-yl]sulfonylphenyl]benzamide;

3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-3-methyl-piperazin-1-yl]sulfonylphenyl]benzamide;

3-[(3-Aminopropylamino)methyl]-N-[4-[[5-[6-chloro-4-(trifluoromethyl)-2-pyridyl]-2,5-diazabicyclo[4.2.0]octan-2-yl]sulfonyl]phenyl]benzamide;

3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

5 3-[2-(3-Aminopropylamino)ethyl]-N-[4-[S-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-N-cyano-sulfonimidoyl]phenyl]benzamide;

3-[(3-aminopropylamino)methyl]-N-[4-[S-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]-N-methyl-sulfonimidoyl]phenyl]benzamide;

10 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-3-methoxy-phenyl]benzamide;

3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-3-hydroxy-phenyl]benzamide;

4-[(3-Aminopropylamino)methyl]-N-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-2-pyridyl]benzamide;

15 3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-2-methoxy-phenyl]benzamide;

3-[(3-Aminopropylamino)methyl]-N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonyl-2-hydroxy-phenyl]benzamide;

20 N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methyl-4,6-dihydropyrrolo[3,4-c]pyrazole-5-carboxamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-1-methyl-4,6-dihydropyrrolo[3,4-c]pyrazole-5-carboxamide;

[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-pyrazolo[1,5-a]pyrimidin-3-yl-methanone;

25 4-[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]-2-methyl-pyrazole-3-carboxylic acid;

[1-(Azetidin-3-yl)pyrazol-4-yl]-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]methanone;

30 [1-(3-Aminopropyl)pyrazol-4-yl]-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]methanone;

[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)methanone;

[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-(1-oxa-2,9-diazaspiro[4.5]dec-2-en-3-yl)methanone;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-piperazin-1-yl-acetamide;

5 1-[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindolin-1-yl]-2-(2-hydroxyethylamino)ethanone;

2-[5-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]benzoic acid;

10 [2-Acetoxy-4-[5-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylindoline-1-carbonyl]phenyl] acetate;

N-[4-[4-[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]piperazin-1-yl]sulfonylphenyl]-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxamide;

N-[4-[4-[6-methyl-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxamide;

15 *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]isoindoline-5-carboxamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-(2,5-diazabicyclo[2.2.1]heptan-2-yl)benzamide;

20 3-(2-Aminoethoxy)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

3-(Azetidin-3-ylmethylamino)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

3-(Azetidin-3-ylmethoxy)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

25 *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[(3*R*)-3-aminopyrrolidin-1-yl]benzamide;

N-[4-[4-[6-Chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[3,6-diazabicyclo[3.2.0]heptan-3-yl]benzamide;

30 3-(2-Aminoethyl)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-piperazin-1-yl-benzamide;

2-Amino-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]indane-5-carboxamide;

5-(Aminomethyl)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-hydroxy-benzamide;

5 *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-(2,4-diaminobutanoylamino)benzamide;

4-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]pyridine-2-carboxamide;

10 6-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]pyridine-2-carboxamide;

5-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]pyridine-3-carboxamide;

2-(3-Aminopropylamino)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]indane-5-carboxamide;

15 3-(3-Aminopropylamino)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]indane-5-carboxamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methoxy-5-[(5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-1-yl)methyl]benzamide;

20 1-(3-Aminopropylamino)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]indane-5-carboxamide;

3,4-bis(3-Aminopropoxy)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

3-[1-(3-Aminopropyl)pyrrolidin-2-yl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

25 3-[1-(3-Aminopropyl)pyrrolidin-3-yl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

3-[4-(3-Aminopropyl)piperazin-1-yl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

30 4-[2-(3-Aminopyrrolidin-1-yl)ethyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

4-[2-(7-Amino-2-azaspiro[3.3]heptan-2-yl)ethyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-4-[2-(5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-1-yl)ethyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-4-[[2*S*)-(2-aminoethyl)pyrrolidin-1-yl]methyl]benzamide;

5 *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-4-[2-(3-morpholinopropylamino)ethyl]benzamide;

4-[2-(2-Amino-5-azaspiro[2.4]heptan-5-yl)ethyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

10 *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-4-[2-(3,6-diazabicyclo[3.1.1]heptan-6-yl)ethyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[(4-piperidylmethylamino)methyl]benzamide;

3-[(3-Aminocyclobutyl)methylamino]methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

15 *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[(3-piperazin-1-ylpropylamino)methyl]benzamide;

3-[[3-(1-Aminocyclopropyl)pyrrolidin-1-yl]methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

20 3-[[3-[Bis(2-hydroxyethyl)amino]propylamino]methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methoxy-5-[[3-(4-piperidyl)propylamino]methyl]benzamide;

3-[[1-(Aminomethyl)-3-azabicyclo[3.1.0]hexan-3-yl]methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

25 (2*R*)-2-Amino-4-[[3-[[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]carbamoyl]phenyl]methylamino]butanoic acid;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[[2-oxooxazolidin-4-yl)methylamino]methyl]benzamide;

30 *N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[[5-oxopyrrolidin-3-yl)methylamino]methyl]benzamide;

N-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-3-[[[3-(dimethylamino)-3-oxo-propyl]amino]methyl]benzamide;

-152-

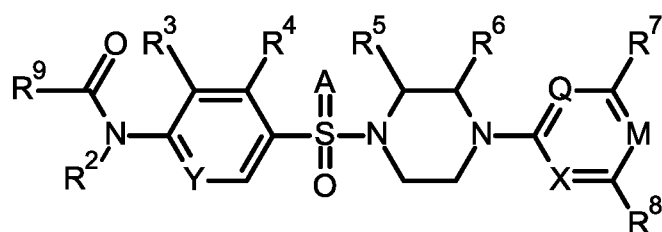
5-(3,3a,4,5,6,6a-Hexahydro-2*H*-pyrrolo[3,4-*b*]pyrrol-1-ylmethyl)-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]-2-methoxy-benzamide; and

2-[(3-Aminopropylamino)methyl]-*N*-[4-[4-[6-chloro-4-(trifluoromethyl)-2-pyridyl]piperazin-1-yl]sulfonylphenyl]benzamide;

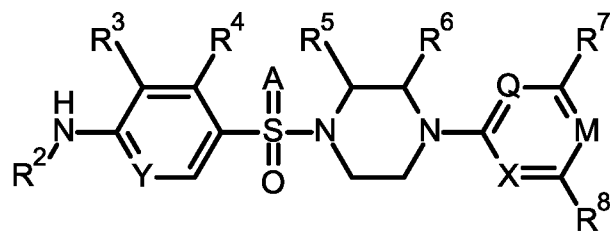
5 or a pharmaceutically acceptable salt thereof.

17. A process for the preparation of a compound according to any one of claims 1 to 16 comprising any of the following steps:

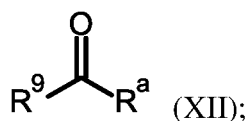
a) formation of compound of formula (Ia),



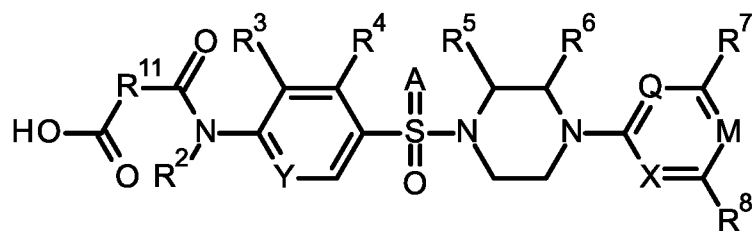
10 (Ia), via coupling reaction or acylation reaction between compound of formula (IX),



(IX), and compound of formula (XII),



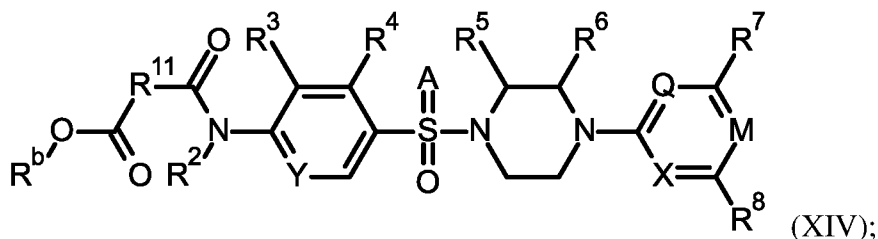
b) formation of compound of formula (Ib),



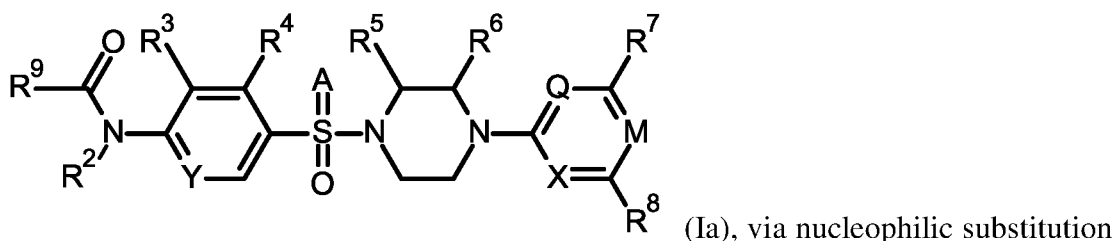
15 (Ib), via hydrolysis of

-153-

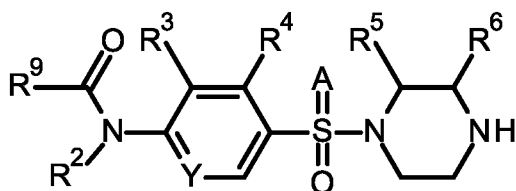
compound of formula (XIV),



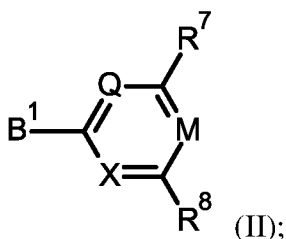
c) formation of compound of formula (Ia),



5 between compound of formula (XVIII),



(XVIII), and compound of formula (II),



wherein

10 in step a), coupling reaction was conducted in the presence of a condensation reagent, wherein the condensation reagent is TCFH; the acylation reaction was conducted in the presence of a base, wherein the base is TEA;

in step b), the hydrolysis reaction was conducted in the presence of a base, wherein the base is LiOH;

15 in step c), the nucleophilic substitution reaction was conducted in the presence of a base, wherein the base is Cs₂CO₃;

wherein B¹ is halogen; PG¹ is a protecting group, such as *tert*-butoxycarbonyl or benzyloxycarbonyl group; PG² is a protecting group, such as acetyl group; R^a is halogen or OH;

R^b is C₁₋₆alkyl, such as methyl or ethyl, R¹¹ is pyrazolylene, phenylene or aminoC₁₋₆alkylaminoC₁₋₆alkylene; R² to R⁹, Y, A, Q, X and M are defined as in any one of claims 1 to 15.

18. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 16 for
5 use as therapeutically active substance.

19. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 16 and a therapeutically inert carrier.

10 20. The use of a compound according to any one of claims 1 to 16 for the inhibition of LpxH.

21. The use of a compound according to any one of claims 1 to 16 for the treatment or prophylaxis of bacterial infection, particularly the bacteria is gram-negative bacteria.

15 22. The use of a compound according to any one of claims 1 to 16 for the preparation of a medicament for the treatment or prophylaxis of bacterial infection, particularly the bacteria is gram-negative bacteria.

20 23. The use of a compound according to claim 21 or 22, wherein the gram-negative bacteria is selected from *Enterobacteriaceae*, *Neisseria gonorrhoeae*, *Haemophilus influenzae*, *Helicobacter pylorus*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

24. The use of a compound according to claim 23, wherein the gram-negative bacteria is *Enterobacteriaceae*, wherein *Enterobacteriaceae* is *Klebsiella pneumoniae* or *Escherichia coli*.

25

25. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 16 for use in the treatment or prophylaxis of bacterial infection, particularly the bacteria is gram-negative bacteria.

30 26. A compound according to claim 25, wherein the gram-negative bacteria is selected from *Enterobacteriaceae*, *Neisseria gonorrhoeae*, *Haemophilus influenzae*, *Helicobacter pylorus*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

27. A compound according to claim 26, wherein the gram-negative bacteria is *Enterobacteriaceae*, wherein *Enterobacteriaceae* is *Klebsiella pneumoniae* or *Escherichia coli*.

28. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 16,
5 when manufactured according to a process of claim 17.

29. A method for the treatment or prophylaxis of bacterial infection, particularly the bacteria is gram-negative bacteria, which method comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 16, to a patient in need thereof.

International application No
PCT/EP2023/055251

1

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2023/055251

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/072369 A1 (UNIV DUKE [US]) 15 April 2021 (2021-04-15) page 1, paragraph 3 page 22 - page 25; compounds 16, 25, 27-30, 33-39 page 140; claim 1 -----	1-29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2023/055251

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010121212 A2	21-10-2010	US 2012034186 A1 WO 2010121212 A2	09-02-2012 21-10-2010
WO 2021072369 A1	15-04-2021	NONE	