

Substituted oxopyridine derivatives

The invention relates to substituted oxopyridine derivatives and to processes for their preparation, and also to their use for preparing medicaments for the treatment and/or prophylaxis of diseases, in particular vascular disorders, preferably thrombotic or thromboembolic disorders and/or thrombotic or thromboembolic complications.

Haemostasis is a protective mechanism of the organism, which helps to "seal" leaking damages in the blood vessel wall quickly and reliably. Thus, excessive loss of blood can often be avoided or kept to a minimum. After injury of a blood vessel, hemostasis is conducted mainly by activation and aggregation of platelets and activation the coagulation system, which consists of an enzymatic "waterfall" cascade leading one after another to the activation of the next coagulation factor until thrombin is formed, which leads to the generation of insoluble fibrin, which is an important part of the clot.

In the more recent past, the traditional theory of two separate starting points of the coagulation cascade (extrinsic and intrinsic path) has been modified owing to new findings: In these models, coagulation is initiated by binding of activated factor VIIa to tissue factor (TF). The resulting complex activates factor X, which in turn leads to generation of thrombin with subsequent production of fibrin and platelet activation (via PAR-1) as injury-sealing end products of haemostasis. Compared to the subsequent amplification/propagation phase, the thrombin production rate in this first phase is low and as a result of the occurrence of TFPI as inhibitor of the TF-FVIIa-FX complex is limited in time. A central component of the transition from initiation to amplification of coagulation and thereby thrombus propagation is factor XIa: in positive feedback loops, thrombin activates not only factor V and factor VIII, but also factor XI to factor XIa, which in turn converts factor IX into factor IXa, which in turn in a factor IXa/factor VIIIa complex generates factor Xa and finally to large amounts of thrombin, resulting in strong thrombus growth and stabilization of the thrombus. This is supported by TAFIa and FXIIIa, which are activated by thrombin as well and lead to inhibition of clot lysis and further clot stabilisation.

In addition to the stimulation via tissue factor, the coagulation system can be activated particularly on negatively charged surfaces, which include not only surface structures of foreign cells (e.g. bacteria) but also artificial surfaces such as vascular prostheses, stents and extracorporeal circulation. On these surfaces, factor XII (FXII) is activated to factor XIIa, which subsequently activates factor XI to factor XIa. This leads to further activation of the coagulation cascade as described above. In addition, factor XIIa also activates bound plasma prokallikrein to plasma kallikrein (PK) which, in a potentiation loop, firstly leads to further factor XII activation, overall resulting in amplification of the initiation of this intrinsic part of the coagulation cascade.

Uncontrolled activation of the coagulation system or defective inhibition of the activation processes may lead to the formation of local thrombi or emboli in vessels (e.g. arteries, veins, lymph vessels)

or in organ cavities (e.g. cardiac atrium). In addition, systemic hypercoagulability may lead to system-wide formation of microthrombi and finally to a consumption coagulopathy in the context of a disseminated intravascular coagulation. Thromboembolic complications may also occur in extracorporeal circulatory systems, such as haemodialysis, and also in vascular prostheses or
5 prosthetic heart valves and stents.

In the course of many cardiovascular and metabolic disorders, increased tendency for coagulation and platelet activation occur owing to either systemic factors such as hyperlipidaemia, diabetes, inflammation, infection or smoking, or to changes in blood flow with stasis, for example in diseased leg veins or in atrial fibrillation, or owing to pathological changes in vessel walls, for example endothelial
10 dysfunctions or atherosclerosis. This unwanted and excessive activation of coagulation may, by formation of fibrin- and platelet-rich thrombi, lead to thromboembolic disorders and thrombotic complications with often life-threatening events. Inflammation processes may also be involved by triggering the coagulation system. On the other hand, thrombin is known to activate inflammatory pathways, as well.

15 Accordingly, thromboembolic disorders are still the most frequent cause of morbidity and mortality in most industrialized countries.

The anticoagulants known from the prior art, that is to say substances for inhibiting or preventing blood coagulation, have various disadvantages. Accordingly, in practice, efficient treatment methods or the prophylaxis of thrombotic/thromboembolic disorders is found to be difficult and
20 unsatisfactory.

In the therapy and prophylaxis of thromboembolic disorders, use is made, firstly, of heparin which is administered parenterally or subcutaneously. Because of more favourable pharmacokinetic properties, preference is these days increasingly given to low-molecular-weight heparin; however, the known disadvantages described herein below encountered in heparin therapy cannot be avoided
25 either in this manner. Thus, heparin is orally ineffective and has only a comparatively short half-life. In addition, there is a high risk of bleeding, there may in particular be cerebral haemorrhages and bleeding in the gastrointestinal tract, and there may be thrombopaenia, alopecia medicamentosa or osteoporosis. Low-molecular-weight heparins do have a lower probability of leading to the development of heparin-induced thrombocytopenia; however, they can also only be administered
30 subcutaneously. This also applies to fondaparinux, a synthetically produced selective factor Xa inhibitor having a long half-life.

A second class of anticoagulants are the vitamin K antagonists. These include, for example, 1,3-indanediones and in particular compounds such as warfarin, phenprocoumon, dicumarol and other coumarin derivatives which non-selectively inhibit the synthesis of various products of vitamin K-
35 dependent coagulation factors in the liver. Owing to the mechanism of action, the onset of action is only very slow (latency to the onset of action 36 to 48 hours). The compounds can be administered

orally; however, owing to the high risk of bleeding and the narrow therapeutic index complicated individual adjustment and monitoring of the patient are required. In addition, other side-effects such as gastrointestinal problems, hair loss and skin necroses have been described.

Today, approaches for Non-vitamin K dependent oral anticoagulation (NOACs) are in clinical use, and have demonstrated their effectiveness in various studies. However, taking these medicaments can also lead to bleeding complications, particularly in predisposed patients.

Thus, for antithrombotic medicaments, the therapeutic window is of central importance: The interval between the therapeutically active dose for coagulation inhibition and the dose where bleeding may occur should be as large as possible so that maximum therapeutic activity is achieved at a minimum risk profile.

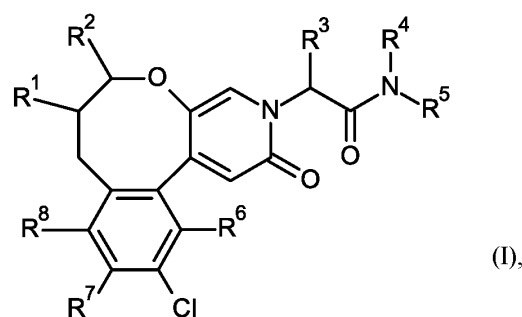
In various in vitro and in vivo models with, for example, antibodies as factor XIa inhibitors, but also in factor XIa knock-out animal models, the antithrombotic effect with small/no prolongation of bleeding time or extension of blood volume was confirmed. In clinical studies, elevated factor XIa concentrations were associated with an increased thrombotic event rate. In contrast, factor XI deficiency (haemophilia C) did not lead to spontaneous bleeding and was apparent only in the course of surgical operations and traumata, but did show protection with respect to certain thromboembolic events.

Furthermore, for many disorders the combination of antithrombotic and antiinflammatory principles may also be particularly attractive to prevent the mutual enhancement of coagulation and inflammation.

It is therefore an object of the present invention to provide novel compounds for the treatment of cardiovascular disorders, in particular of thrombotic or thromboembolic disorders and/or thrombotic or thromboembolic complications, in humans and animals, which compounds have a wide therapeutic window.

WO 2006/030032 describes inter alia substituted pyridinones as allosteric modulators of the mGluR2 receptor, and WO 2008/079787 describes substituted pyridin-2-ones and their use as glucokinase activators. WO 2014/154794, WO 2014/160592, WO 2015/011087, WO 2015/063093, WO 2016/046158, WO 2016/046157, WO 2016/046159, WO 2016/046164, WO 2016/046166, WO 2016/046156, WO 2017/005725 and WO 2017/037051 describe substituted pyridin-2-ones and their use as factor XIa inhibitors.

The invention provides compounds of the formula



in which

R¹ represents methyl, ethyl, difluoromethyl or trifluoromethyl,

R² represents hydrogen, methyl, difluoromethyl or trifluoromethyl,

5 or

R¹ and R² together with the carbon atoms to which they are attached form a cyclobutyl ring,

R³ represents methyl, ethyl or n-propyl,

where methyl may be substituted with one substituent selected from the group consisting of cyclopropyl, cyclobutyl, oxetan-2-yl, oxetan-3-yl, tetrahydrofuran-2-yl, tetrahydro-2H-pyran-2-yl, tetrahydro-2H-pyran-4-yl and 1,4-dioxan-2-yl,

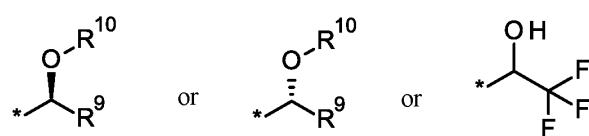
10

where oxetan-2-yl, tetrahydrofuran-2-yl, tetrahydro-2H-pyran-2-yl and 1,4-dioxan-2-yl may be substituted by 1 to 2 substituents independently of one another selected from the group consisting of fluorine and methyl,

or

15

where methyl may be substituted with one substituent of the group of the formula



where

* is the attachment site to the methyl group,

R⁹ represents methyl, ethyl, iso-propyl, cyclopropyl, difluoromethyl or trifluoromethyl,

20

R¹⁰ represents methyl or difluoromethyl,

and

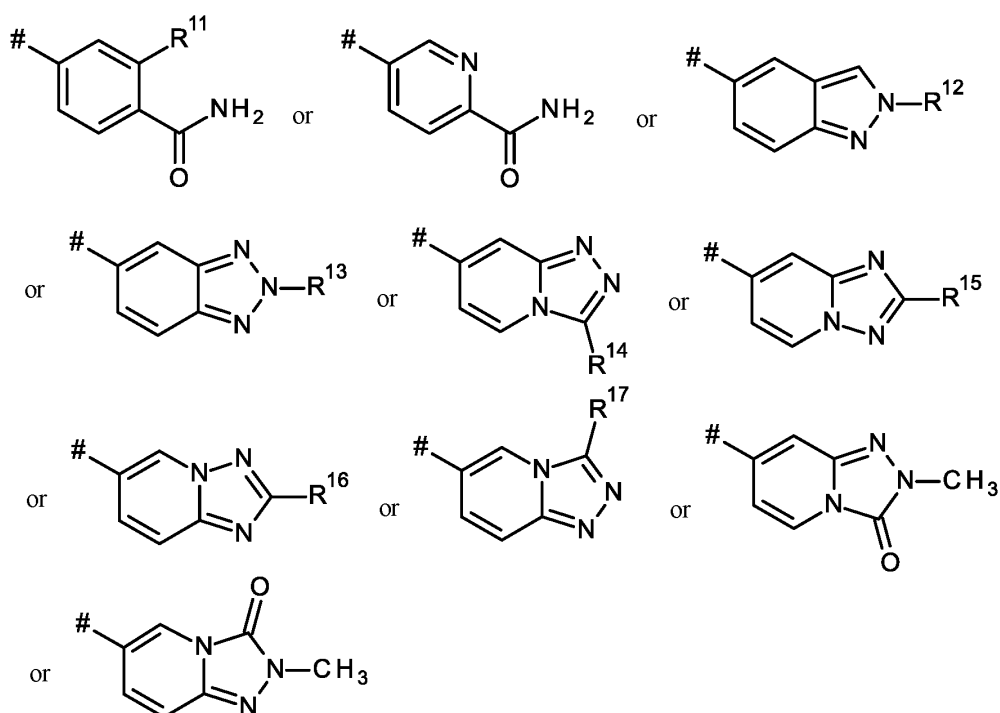
where ethyl may be substituted with one substituent selected from the group consisting of methoxy, ethoxy, iso-propoxy, tert-butoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, cyclopropyloxy and cyclobutyloxy,

where cyclopropyloxy and cyclobutyloxy may be substituted with one substituent selected from the group consisting of fluorine and methyl,

5

R⁴ represents hydrogen,

R⁵ represents a group of the formula



where

10

is the attachment site to the nitrogen atom,

R¹¹ represents hydrogen or fluorine,

R¹² represents methyl, difluoromethyl or trifluoromethyl,

R¹³ represents methyl, difluoromethyl or trifluoromethyl,

R¹⁴ represents hydrogen or methyl,

15

R¹⁵ represents hydrogen or methyl,

R¹⁶ represents hydrogen or methyl,

R¹⁷ represents hydrogen or methyl,

R⁶, R⁷ and R⁸ represent the following:

R⁶ represents hydrogen, fluorine or chlorine,

R⁷ represents hydrogen,

R⁸ represents hydrogen,

5 or

R⁶ represents hydrogen,

R⁷ represents fluorine or chlorine,

R⁸ represents hydrogen,

or

10 R⁶ represents hydrogen,

R⁷ represents hydrogen,

R⁸ represents fluorine,

and the salts thereof, the solvates thereof and the solvates of the salts thereof.

15 Compounds according to the invention are the compounds of the formula (I) and the salts, solvates and solvates of the salts thereof, and also the compounds encompassed by formula (I) and specified hereinafter as working example(s), and the salts, solvates and solvates of the salts thereof, to the extent that the compounds encompassed by formula (I) and specified hereinafter are not already salts, solvates and solvates of the salts.

20 The inventive compounds may, depending on their structure, exist in different stereoisomeric forms, i.e. in the form of configurational isomers or else, if appropriate, of conformational isomers (enantiomers and/or diastereomers, including those in the case of rotamers and atropisomers). The present invention therefore encompasses the enantiomers and diastereomers, and the respective mixtures thereof. The stereoisomerically uniform constituents can be isolated from such mixtures of enantiomers and/or diastereomers in a known manner; chromatography processes are preferably used
25 for this, especially HPLC chromatography on an achiral or chiral phase.

If the compounds according to the invention can occur in tautomeric forms, the present invention encompasses all the tautomeric forms.

30 In the context of the present invention, the term “enantiomerically pure” is understood to mean that the compound in question with respect to the absolute configuration of the chiral centre is present in an enantiomeric excess of more than 95%, preferably more than 97%. The enantiomeric excess (ee value) is calculated in this case by evaluation of the corresponding HPLC chromatogram on a chiral phase with the aid of the formula below:

$$ee = [E^A (\text{area}\%) - E^B (\text{area}\%)] \times 100\% / [E^A (\text{area}\%) + E^B (\text{area}\%)]$$

(E^A: enantiomer in excess, E^B: enantiomer in deficiency)

The present invention also encompasses all suitable isotopic variants of the compounds according to the invention. An isotopic variant of an inventive compound is understood here as meaning a
5 compound in which at least one atom within the inventive compound has been exchanged for another atom of the same atomic number, but with a different atomic mass than the atomic mass which usually or predominantly occurs in nature. Examples of isotopes which can be incorporated into a compound according to the invention are those of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine and iodine, such as ²H (deuterium), ³H (tritium), ¹³C, ¹⁴C, ¹⁵N, ¹⁷O,
10 ¹⁸O, ³²P, ³³P, ³³S, ³⁴S, ³⁵S, ³⁶S, ¹⁸F, ³⁶Cl, ⁸²Br, ¹²³I, ¹²⁴I, ¹²⁹I and ¹³¹I. Particular isotopic variants of a compound according to the invention, especially those in which one or more radioactive isotopes have been incorporated, may be beneficial, for example, for the examination of the mechanism of action or of the active ingredient distribution in the body; due to comparatively easy preparability and detectability, especially compounds labelled with ³H or ¹⁴C isotopes are suitable for this purpose.
15 In addition, the incorporation of isotopes, for example of deuterium, may lead to particular therapeutic benefits as a consequence of greater metabolic stability of the compound, for example an extension of the half-life in the body or a reduction in the active dose required; such modifications of the inventive compounds may therefore in some cases also constitute a preferred embodiment of the present invention. Isotopic variants of the compounds according to the invention can be prepared
20 by the processes known to those skilled in the art, for example by the methods described further below and the procedures described in the working examples, by using corresponding isotopic modifications of the respective reagents and/or starting compounds.

Preferred salts in the context of the present invention are physiologically acceptable salts of the compounds according to the invention. However, the invention also encompasses salts which themselves
25 are unsuitable for pharmaceutical applications but which can be used, for example, for the isolation or purification of the compounds according to the invention.

Physiologically acceptable salts of the compounds according to the invention include acid addition salts of mineral acids, carboxylic acids and sulfonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid,
30 toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of the compounds according to the invention also include salts of conventional bases, by way of example and with preference alkali metal salts (e.g. sodium and potassium
35 salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonium salts derived from ammonia or organic amines having 1 to 16 carbon atoms, by way of example and with preference

ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, *N*-methylmorpholine, arginine, lysine, ethylenediamine, *N*-methylpiperidine and choline.

- 5 Solvates in the context of the invention are described as those forms of the inventive compounds which form a complex in the solid or liquid state by coordination with solvent molecules. Hydrates are a specific form of the solvates in which the coordination is with water.

- The present invention additionally also encompasses prodrugs of the inventive compounds. The term "prodrugs" encompasses compounds which for their part may be biologically active or inactive but are converted during their residence time in the body into compounds according to the invention (for
10 example by metabolism or hydrolysis).

- In the context of the present invention, the term "treatment" or "treating" includes inhibition, retardation, checking, alleviating, attenuating, restricting, reducing, suppressing, repelling or healing of a disease, a condition, a disorder, an injury or a health problem, or the development, the course or the progression of such states and/or the symptoms of such states. The term "therapy" is understood
15 here to be synonymous with the term "treatment".

The terms "prevention", "prophylaxis" and "preclusion" are used synonymously in the context of the present invention and refer to the avoidance or reduction of the risk of contracting, experiencing, suffering from or having a disease, a condition, a disorder, an injury or a health problem, or a development or advancement of such states and/or the symptoms of such states.

- 20 The treatment or prevention of a disease, a condition, a disorder, an injury or a health problem may be partial or complete.

In the formulae of the group which may represent a substituent to the methyl group in R^3 , the end point of the line marked by * in each case does not represent a carbon atom or a CH_2 group, but is part of the bond to the atom to which the group is attached.

- 25 In the formulae of the group which may represent R^5 , the end point of the line marked by # in each case does not represent a carbon atom or a CH_2 group, but is part of the bond to the atom to which R^5 is attached.

Preference is given to compounds of the formula (I) in which

- R^1 represents methyl, ethyl or trifluoromethyl,
30 R^2 represents hydrogen or methyl,

or

R^1 and R^2 together with the carbon atoms to which they are attached form a cyclobutyl ring,

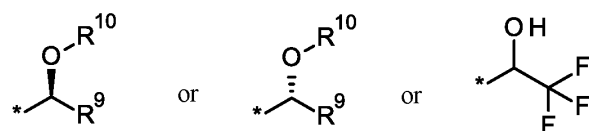
R^3 represents methyl, ethyl or n-propyl,

where methyl may be substituted with one substituent selected from the group consisting of cyclobutyl, tetrahydrofuran-2-yl, tetrahydro-2H-pyran-2-yl and 1,4-dioxan-2-yl,

where tetrahydrofuran-2-yl may be substituted by 1 to 2 substituents methyl,

or

5 where methyl may be substituted with one substituent of the group of the formula



where

* is the attachment site to the methyl group,

R⁹ represents methyl, cyclopropyl, difluoromethyl or trifluoromethyl,

10 R¹⁰ represents methyl or difluoromethyl,

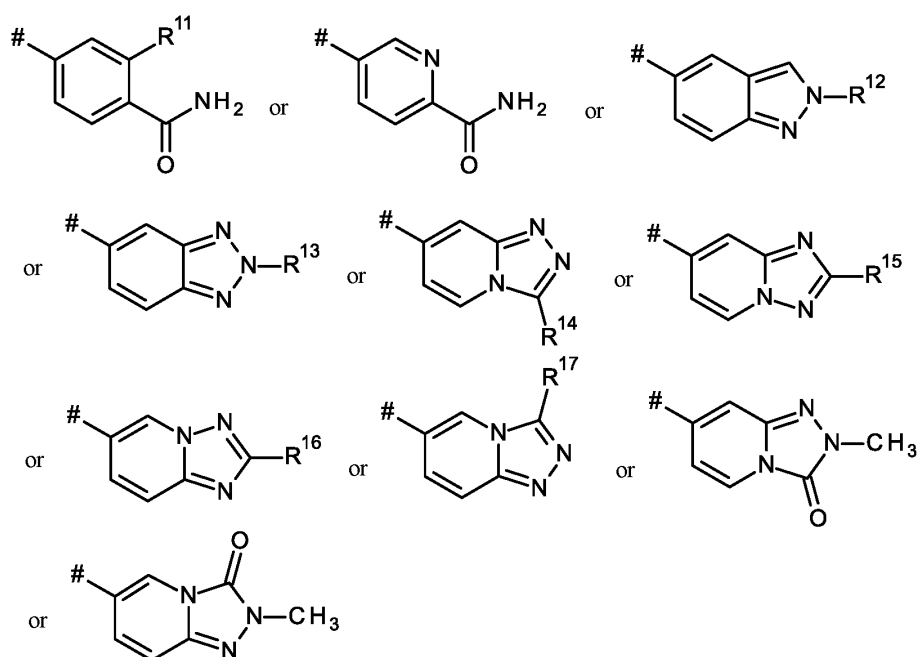
and

where ethyl may be substituted with one substituent selected from the group consisting of methoxy, iso-propoxy, tert-butoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, cyclopropyloxy and cyclobutyloxy,

15 where cyclopropyloxy and cyclobutyloxy may be substituted with one substituent selected from the group consisting of fluorine and methyl,

R⁴ represents hydrogen,

R⁵ represents a group of the formula



where

$\#$ is the attachment site to the nitrogen atom,

R^{11} represents hydrogen or fluorine,

5 R^{12} represents difluoromethyl or trifluoromethyl,

R^{13} represents methyl,

R^{14} represents hydrogen or methyl,

R^{15} represents hydrogen or methyl,

R^{16} represents hydrogen,

10 R^{17} represents hydrogen,

R^6 , R^7 and R^8 represent the following:

R^6 represents hydrogen, fluorine or chlorine,

R^7 represents hydrogen,

R^8 represents hydrogen,

15 and the salts thereof, the solvates thereof and the solvates of the salts thereof.

Preference is also given to compounds of the formula (I) in which

R^1 represents methyl, ethyl or trifluoromethyl,

R² represents hydrogen or methyl,

or

R¹ and R² together with the carbon atoms to which they are attached form a cyclobutyl ring,

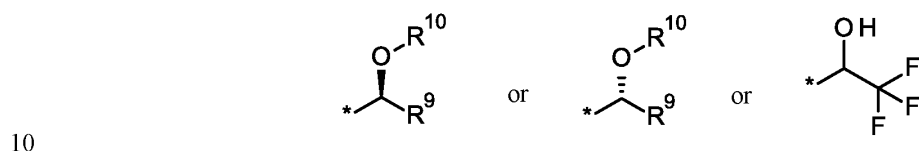
R³ represents methyl, ethyl or n-propyl,

5 where methyl may be substituted with one substituent selected from the group consisting of cyclobutyl, tetrahydrofuran-2-yl, tetrahydro-2H-pyran-2-yl and 1,4-dioxan-2-yl,

where tetrahydrofuran-2-yl may be substituted by 1 to 2 substituents methyl,

or

where methyl may be substituted with one substituent of the group of the formula



where

* is the attachment site to the methyl group,

R⁹ represents methyl, cyclopropyl, difluoromethyl or trifluoromethyl,

R¹⁰ represents methyl or difluoromethyl,

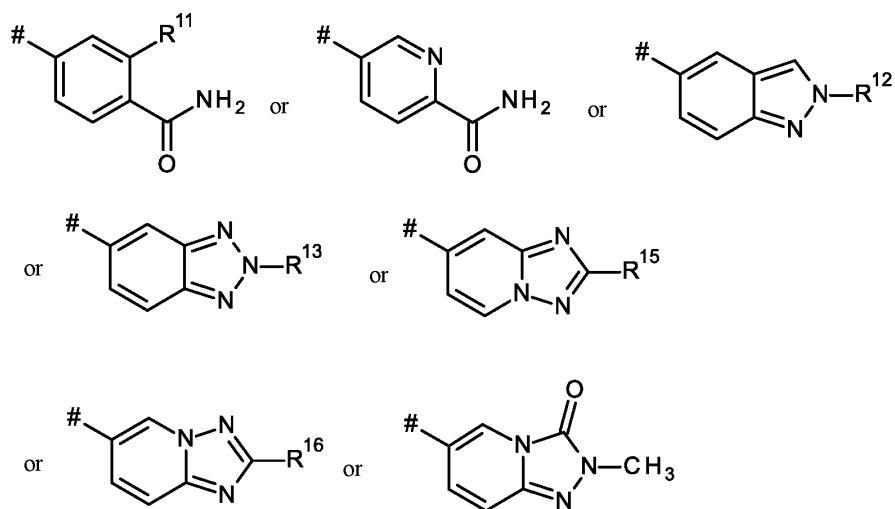
15 and

where ethyl may be substituted with one substituent selected from the group consisting of methoxy, iso-propoxy, tert-butoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, cyclopropyloxy and cyclobutyloxy,

20 where cyclopropyloxy and cyclobutyloxy may be substituted with one substituent selected from the group consisting of fluorine and methyl,

R⁴ represents hydrogen,

R⁵ represents a group of the formula



where

is the attachment site to the nitrogen atom,

R^{11} represents hydrogen or fluorine,

5 R^{12} represents difluoromethyl or trifluoromethyl,

R^{13} represents methyl,

R^{15} represents hydrogen or methyl,

R^{16} represents hydrogen,

R^6 , R^7 and R^8 represent the following:

10 R^6 represents hydrogen or fluorine,

R^7 represents hydrogen,

R^8 represents hydrogen,

and the salts thereof, the solvates thereof and the solvates of the salts thereof.

Preference is also given to compounds of the formula (I) in which

15 R^1 represents methyl or trifluoromethyl,

R^2 represents hydrogen,

or

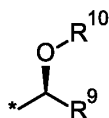
R^1 and R^2 together with the carbon atoms to which they are attached form a cyclobutyl ring,

R^3 represents methyl or ethyl,

where methyl is substituted with one substituent selected from the group consisting of tetrahydro-2H-pyran-2-yl and 1,4-dioxan-2-yl,

or

where methyl is substituted with one substituent of the group of the formula



5

where

* is the attachment site to the methyl group,

R⁹ represents methyl,

R¹⁰ represents methyl or difluoromethyl,

10

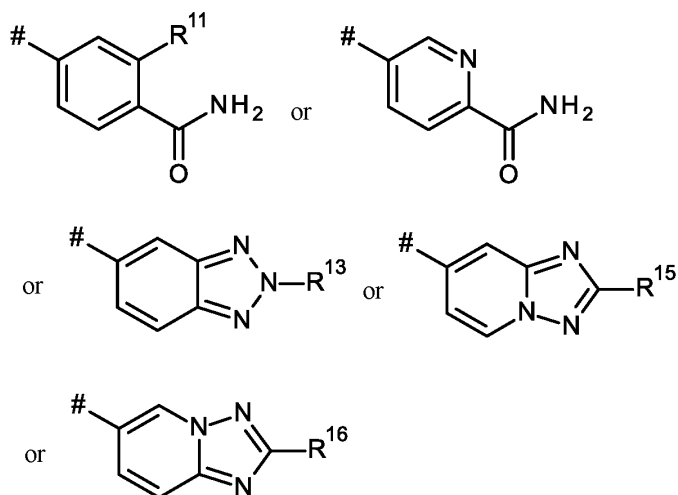
and

where ethyl is substituted with one substituent selected from the group consisting of methoxy, iso-propoxy, tert-butoxy, difluoromethoxy and cyclopropyloxy,

where cyclopropyloxy may be substituted with one substituent selected from the group consisting of fluorine and methyl,

15 R⁴ represents hydrogen,

R⁵ represents a group of the formula



where

is the attachment site to the nitrogen atom,

R^{11} represents hydrogen or fluorine,

R^{13} represents methyl,

R^{15} represents hydrogen or methyl,

R^{16} represents hydrogen,

5 R^6 , R^7 and R^8 represent the following:

R^6 represents hydrogen or fluorine,

R^7 represents hydrogen,

R^8 represents hydrogen,

and the salts thereof, the solvates thereof and the solvates of the salts thereof.

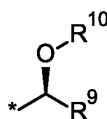
10 Preference is also given to compounds of the formula (I) in which

R^1 represents methyl or trifluoromethyl,

R^2 represents hydrogen,

R^3 represents methyl,

where methyl is substituted with one substituent of the group of the formula



15

where

* is the attachment site to the methyl group,

R^9 represents methyl,

R^{10} represents methyl or difluoromethyl,

20 R^4 represents hydrogen,

R^5 represents a group of the formula



where

is the attachment site to the nitrogen atom,

R¹¹ represents hydrogen,

R⁶, R⁷ and R⁸ represent the following:

R⁶ represents hydrogen or fluorine,

R⁷ represents hydrogen,

5 R⁸ represents hydrogen,

and the salts thereof, the solvates thereof and the solvates of the salts thereof.

Preference is also given to compounds of the formula (I) in which

R⁶, R⁷ and R⁸ represent the following:

R⁶ represents hydrogen or fluorine,

10 R⁷ represents hydrogen,

R⁸ represents hydrogen.

Preference is also given to compounds of the formula (I) in which

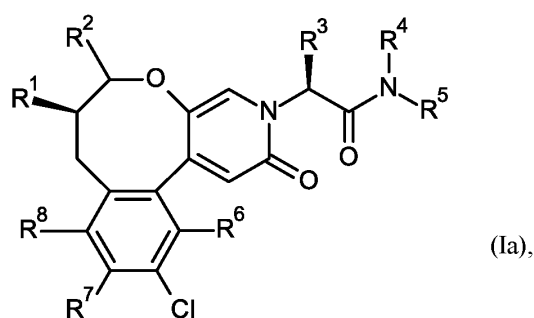
R⁶, R⁷ and R⁸ represent the following:

R⁶ represents hydrogen,

15 R⁷ represents hydrogen,

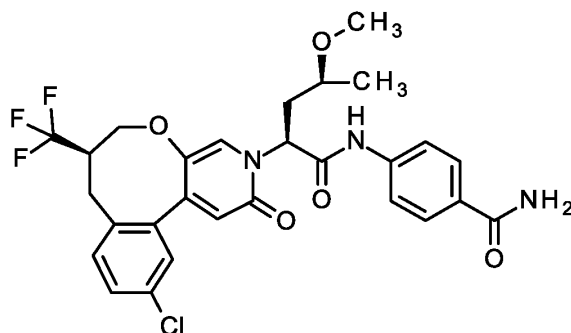
R⁸ represents hydrogen.

Also preferred are compounds having the formula (Ia)



in which R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are as defined above.

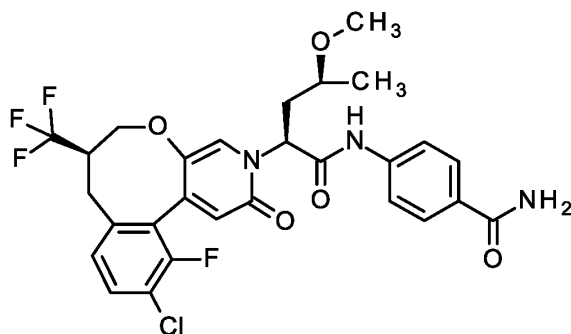
20 Preference is also given to the compound 4-((2*S*,4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-pentanoyl)amino)benzamide (single stereoisomer) of the formula below



or one of the salts thereof, solvates thereof or solvates of the salts thereof.

Preference is also given to the compound 4-({(2*S*,4*S*)-2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-

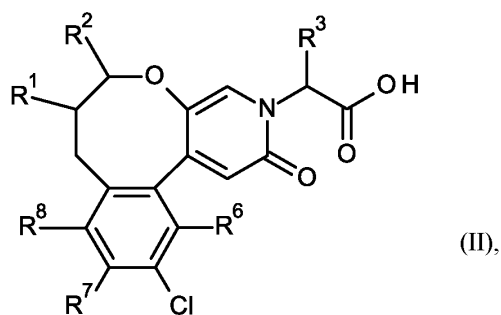
5 pentanoyl} amino)benzamide (single stereoisomer) of the formula below



or one of the salts thereof, solvates thereof or solvates of the salts thereof.

The invention further provides a method for preparing compounds of the formula (I), or salts thereof, solvates thereof or solvates of the salts thereof, wherein

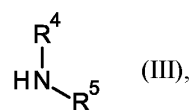
10 [A] the compounds of the formula



in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 are as defined above,

are reacted with compounds of the formula



in which

R^4 and R^5 are as defined above,

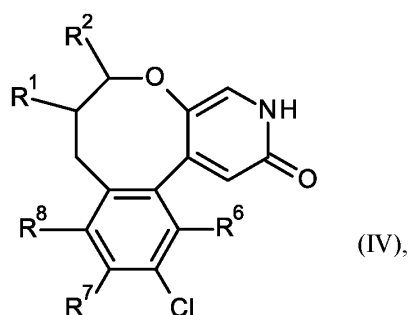
- 5 in the presence of a dehydrating agent to give compounds of the formula (I)

or

[B] the compounds of the formula (II) are converted in a one-pot reaction to the acid chloride of compounds of the formula (II) and then the acid chlorides are reacted with compounds of the formula (III) to give compounds of the formula (I)

- 10 or

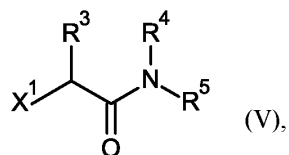
[C] the compounds of the formula



in which

R^1 , R^2 , R^6 , R^7 and R^8 are as defined above,

- 15 are reacted with compounds of the formula



in which

X^1 represents bromine, iodine or trifluoromethane-sulfonyloxy,

in the presence of a base to give compounds of the formula (I).

The reaction according to process [A] is generally carried out in inert solvents, if appropriate in the presence of a base, preferably in a temperature range from -20°C to 80°C at atmospheric pressure.

Alternatively, the reaction can also be carried out without a solvent only in one base if the base is a liquid at RT.

- 5 Suitable dehydrating agents here are, for example, carbodiimides such as *N,N'*-diethyl-, *N,N'*-dipropyl-, *N,N'*-diisopropyl-, *N,N'*-dicyclohexylcarbodiimide, *N*-(3-dimethylaminoisopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) (optionally in the presence of pentafluorophenol (PFP)), *N*-cyclohexylcarbodiimide-*N'*-propyloxymethyl-polystyrene (PS-carbodiimide) or carbonyl compounds such as carbonyldiimidazole, or 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-
10 1,2-oxazolium 3-sulfate or 2-tert-butyl-5-methyl-isoxazolium perchlorate, or acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or isobutyl chloroformate, or bis-(2-oxo-3-oxazolidinyl)phosphoryl chloride or benzotriazolyloxytri(dimethylamino)-phosphonium hexafluorophosphate, or *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), 2-(2-oxo-1-(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU),
15 (benzotriazol-1-yloxy)bisdimethylaminomethylum fluoroborate (TBTU) or *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluoro-phosphate (HATU), or 1-hydroxybenzotriazole (HOBt), or benzotriazol-1-yloxytris(dimethyl-amino)phosphonium hexafluorophosphate (BOP), or ethyl cyano(hydroxyimino)acetate (Oxyma), or (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU), or
20 *N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylidene]-*N*-methylmethanaminium hexafluorophosphate, or 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane-2,4,6-trioxide (T3P), or mixtures of these with bases, the condensation with HATU or with T3P being preferred.

- Bases are, for example, organic bases such as trialkylamines, for example triethylamine, *N*-
25 methylmorpholine, *N*-methylpiperidine, 4-dimethylaminopyridine or diisopropylethylamine, or pyridine, preference is given to condensation with diisopropylethylamine or pyridine.

- Inert solvents are, for example, halogenated hydrocarbons such as dichloromethane or trichloromethane, hydrocarbons such as benzene or toluene, or other solvents such as 1,4-dioxane,
diethyl ether, tetrahydrofuran, ethyl acetate, *N,N*-dimethylformamide, dimethyl sulfoxide or
30 acetonitrile, or mixtures of the solvents, preference being given to *N,N*-dimethylformamide or tetrahydrofuran.

The reaction according to process [B] is generally carried out in inert solvents, in the presence of a chlorination agent, preferably in a temperature range from -20°C to 80°C at atmospheric pressure.

- Inert solvents are, for example, halogenated hydrocarbons such as dichloromethane or
35 trichloromethane, hydrocarbons such as benzene or toluene, or other solvents such as 1,4-dioxane,

diethyl ether, tetrahydrofuran, ethyl acetate or N,N-dimethylformamide, or mixtures of the solvents, preference being given to dichloromethane.

Chlorination agents are, for example, 1-chloro-N,N,2-trimethylprop-1-en-1-amine, oxalyl chloride, sulfurous dichloride, preference being given to 1-chloro-N,N,2-trimethylprop-1-en-1-amine.

- 5 The reaction according to process [C] is generally carried out in inert solvents, preferably in a temperature range from room temperature to reflux of the solvents at atmospheric pressure.

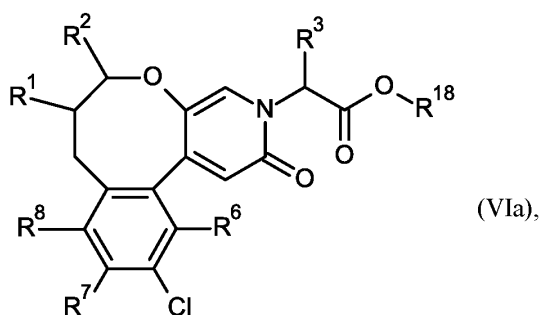
Bases are, for example, alkali metal hydroxides such as sodium hydroxide, lithium hydroxide or potassium hydroxide, or alkali metal carbonates such as caesium carbonate, sodium carbonate or potassium carbonate, or potassium tert-butoxide or sodium tert-butoxide, sodium hydride or a
10 mixture of these bases or a mixture of sodium hydride and lithium bromide, or organic bases such as 1,1,3,3-tetramethylguanidine or 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), preference is given to potassium carbonate or sodium hydride or 1,1,3,3-tetramethylguanidine.

Inert solvents are, for example, halogenated hydrocarbons such as dichloromethane,
15 trichloromethane, carbon tetrachloride or 1,2-dichloroethane, alcohols such as methanol, ethanol or 2-propanol, ethers such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, 1,4-dioxane or tetrahydrofuran, or other solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, pyridine or acetone, or mixtures of solvents, or mixtures of solvents with water, preference is given to N,N-dimethylformamide or to a mixture of acetone and 2-propanol.

- 20 The compounds of the formula (III) are known or can be synthesized from the corresponding starting compounds by known processes.

The compounds of the formula (V) are known, can be synthesized from the corresponding starting compounds by known processes or can be prepared analogously to the processes described in the Examples section.

- 25 The compounds of the formula (II) are known or can be prepared by reacting
[D] compounds of the formula



in which

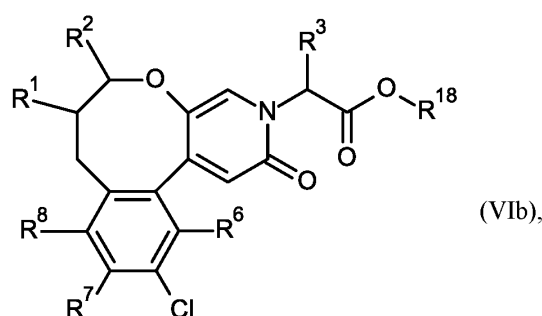
R^1 , R^2 , R^3 , R^6 , R^7 and R^8 are each as defined above and

R^{18} represents tert-butyl,

with an acid to give compounds of the formula (II)

5 or

[E] compounds of the formula



in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 are each as defined above and

10 R^{18} represents methyl, ethyl, tert-butyl or benzyl,

with a base to give compounds of the formula (II).

The reaction according to process [D] is generally carried out in inert solvents, preferably in a temperature range from 0°C to 60°C at atmospheric pressure.

Inert solvents are, for example, halogenated hydrocarbons such as dichloromethane, trichloromethane, carbon tetrachloride or 1,2-dichloroethane, or ethers such as tetrahydrofuran or 1,4-dioxane, preference being given to dichloromethane.

Acids are, for example, trifluoroacetic acid or hydrogen chloride in 1,4-dioxane, preference being given to trifluoroacetic acid.

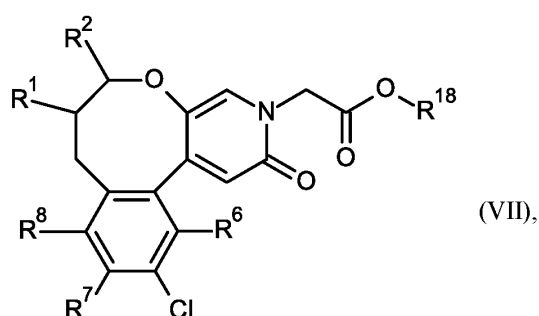
The reaction according to process [E] is generally carried out in solvents, preferably in a temperature range from room temperature up to reflux of the solvents at atmospheric pressure.

Inert solvents are, for example, alcohols such as methanol or ethanol, ethers such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, 1,4-dioxane or tetrahydrofuran, or mixtures of solvents, or mixtures of solvents with water, preference being given to a mixture of tetrahydrofuran and water.

Bases are, for example, alkali metal hydroxides such as sodium hydroxide, lithium hydroxide or potassium hydroxide, or alkali metal carbonates such as caesium carbonate, sodium carbonate or potassium carbonate, preference being given to lithium hydroxide.

The compounds of the formulae (VIa) and (VIb) together form the group of the compounds of the
5 formula (VI).

The compounds of the formula (VIa) are known or can be prepared by reacting compounds of the formula

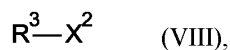


in which

10 R^1 , R^2 , R^6 , R^7 and R^8 are each as defined above and

R^{18} represents tert-butyl,

with compounds of the formula



in which

15 R^3 is as defined above and

X^2 represents chlorine, bromine, iodine or trifluoromethanesulfonyloxy.

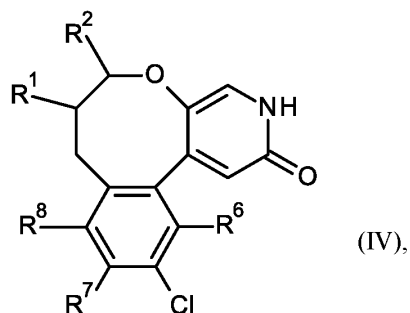
The reaction is generally carried out in inert solvents, in the presence of a base, preferably in a temperature range from -78°C to room temperature at atmospheric pressure.

Inert solvents are, for example, ethers such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, 1,4-dioxane or tetrahydrofuran, or mixtures of solvents, or mixtures of solvent
20 with water, preference is given to tetrahydrofuran.

Bases are, for example, potassium tert-butoxide or sodium tert-butoxide, sodium hydride, n-butyllithium, lithium bis(trimethylsilyl)amide or sodium bis(trimethylsilyl)amide, preference is given to lithium bis(trimethylsilyl)amide or sodium bis(trimethylsilyl)amide.

The compounds of the formula (VIII) are known or can be synthesized from the corresponding starting compounds by known processes.

The compounds of the formula (VII) are known or can be prepared by reacting compounds of the formula

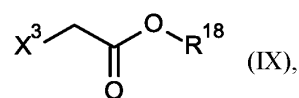


5

in which

R^1 , R^2 , R^6 , R^7 and R^8 are as defined above,

with compounds of the formula



10 in which

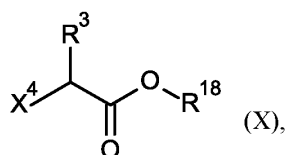
X^3 represents chlorine, bromine, iodine, methanesulfonyloxy or trifluoromethane-sulfonyloxy and

R^{18} represents tert-butyl.

The reaction is carried out as described for process [C].

15 The compounds of the formula (IX) are known or can be synthesized from the corresponding starting compounds by known processes.

In an alternative process, the compounds of the formula (VI) can be prepared by reacting compounds of the formula (IV) with compounds of the formula



20 in which

R³ is as defined above,

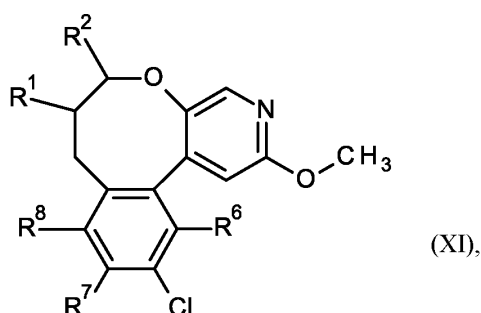
X⁴ represents chlorine, bromine, iodine, methanesulfonyloxy or trifluoromethane-sulfonyloxy and

R¹⁸ represents methyl, ethyl, tert-butyl or benzyl.

5 The reaction is carried out as described for process [C].

The compounds of the formula (X) are known, can be synthesized from the corresponding starting compounds by known processes or can be prepared analogously to the processes described in the Examples section.

10 The compounds of the formula (IV) are known or can be prepared by reacting compounds of the formula



in which

R¹, R², R⁶, R⁷ and R⁸ are as defined above,

15 with pyridinium hydrochloride or pyridinium hydrobromide or sodium iodide and an acid or lithium iodide and an acid or with a thiol, such as ethanethiol, and a base.

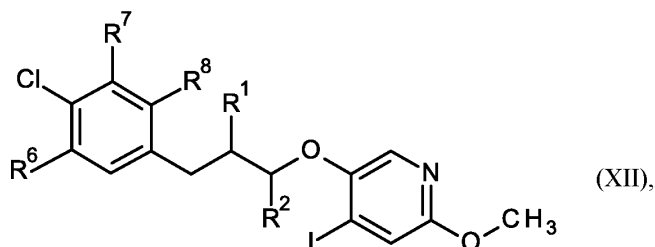
The reaction is generally carried out in inert solvents or without solvents, preferably in a temperature range of from 80°C to 120°C at atmospheric pressure.

20 Inert solvents are, for example, hydrocarbons such as benzene, or alcohols such as methanol, ethanol or 1-butanol, or other solvents such as nitromethane, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide or acetonitrile, or a mixture of the solvents, preference is given to N,N-dimethylformamide or 1-butanol.

Acids are, for example, 4-toluenesulfonic acid monohydrate, formic acid, acetic acid, trifluoroacetic acid, preference is given to acetic acid and 4-toluenesulfonic acid monohydrate.

25 Bases are, for example, potassium *tert*-butoxide or sodium *tert*-butoxide or sodium hydride, preference is given to sodium hydride.

The compounds of the formula (XI) are known or can be prepared by reacting compounds of the formula



in which

- 5 R^1 , R^2 , R^6 , R^7 and R^8 are as defined above,

with a base in the presence of a catalyst.

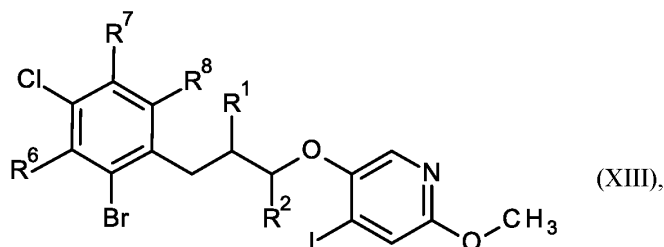
The reaction is generally carried out in inert and degassed solvents, preferably within a temperature range from 80°C to 150°C at atmospheric pressure.

- 10 Bases are, for example, alkali metal carbonates such as sodium carbonate or potassium carbonate, organic bases such as sodium pivalate, potassium pivalate, caesium pivalate, sodium acetate, potassium acetate, caesium acetate, preference is given to potassium pivalate or potassium acetate.

- Catalysts are, for example, palladium catalysts customary for CH-activation conditions, such as dichlorobis(triphenylphosphine)palladium, tetrakis(triphenylphosphine)palladium(0), palladium(II) acetate/triscyclohexylphosphine, bis(tri-*tert*-butylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium, bis(diphenylphosphaneferrocenyl)palladium(II) chloride, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene(1,4-naphthoquinone)palladium dimer, allyl(chloro)(1,3-dimesityl-1,3-dihydro-2H-imidazol-2-ylidene)palladium, palladium(II) acetate/
 15 dicyclohexyl(2',4',6'-triisopropyl-biphenyl-2-yl)phosphine, XPhos precatalyst [(2'-aminobiphenyl-2-yl)(chloro)palladium dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphane (1:1)], DavePhos precatalyst [Methanesulfonato 2-dicyclohexylphosphino-2-(*N,N*-dimethylamino)biphenyl(2'-amino-1,1'-biphenyl-2-yl) palladium(II)], PEPPSI®-catalysts such as [1,3-bis(2,6-di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride or [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride, preference being
 20 given to tetrakis(triphenylphosphine)palladium(0) or [1,3-bis(2,6-di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride.
 25

Inert solvents are, for example, ethers such as 1,4-dioxane, tetrahydrofuran or 1,2-dimethoxyethane, hydrocarbons such as benzene, xylene or toluene, or carboxamides such as *N,N*-dimethylformamide or *N,N*-dimethylacetamide, alkyl sulfoxides such as dimethyl sulfoxide, or mixtures of the solvents with water, preference is given to *N,N*-dimethylformamide or *N,N*-dimethylacetamide.

In an alternative process, the compounds of the formula (XI) can be prepared by reacting compounds of the formula



in which

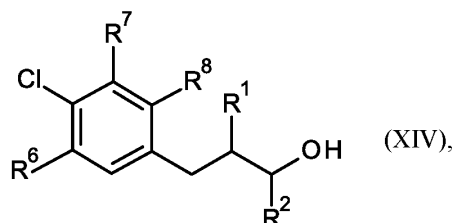
- 5 R^1 , R^2 , R^6 , R^7 and R^8 are as defined above,

with bis(pinacolato)diboran in the presence of a base and a catalyst.

The reaction is generally carried out in inert solvents, preferably within a temperature range from room temperature to 150°C at atmospheric pressure.

- Catalysts are, for example, palladium catalysts customary for Suzuki reaction conditions, preference
 10 being given to catalysts such as dichlorobis(triphenylphosphine)palladium, tetrakis(triphenylphosphine)palladium(0), bis(tri-*tert*-butylphosphine)palladium(0), palladium(II) acetate, palladium(II) acetate/triscyclohexylphosphine, tris(dibenzylideneacetone)dipalladium, bis(diphenylphosphaneferrocenyl)palladium(II) chloride, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene(1,4-naphthoquinone)palladium dimer, allyl(chloro)(1,3-dimesityl-1,3-dihydro-2H-
 15 imidazol-2-ylidene)palladium, palladium(II) acetate/ dicyclohexyl(2',4',6'-triisopropyl-biphenyl-2-yl)phosphine, [1,1-bis(diphenylphosphino)-ferrocene]palladium(II) chloride monodichloromethane adduct or XPhos precatalyst [(2'-aminobiphenyl-2-yl)(chloro)palladium dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphane (1:1)], preference being given to palladium(II) acetate or palladium(II) acetate/triscyclohexylphosphine or tetrakis(triphenylphosphine)palladium(0).
- 20 Bases are, for example, alkali metal carbonates such as caesium carbonate, potassium carbonate or sodium carbonate, alkali metal bicarbonates such as, sodium bicarbonate, alkali or alkaline earth metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide or potassium acetate, potassium *tert*-butoxide or potassium phosphate, where these may be present in aqueous solution, preference being given to an aqueous sodium bicarbonate solution or potassium acetate.
- 25 Inert solvents are, for example, ethers such as 1,4-dioxane, tetrahydrofuran or 1,2-dimethoxyethane, hydrocarbons such as benzene, xylene or toluene, or carboxamides such as N,N-dimethylformamide or N,N-dimethylacetamide, alkyl sulfoxides such as dimethyl sulfoxide, or N-methylpyrrolidone or acetonitrile, or mixtures of the solvents with alcohols such as methanol or ethanol and/or water, preference is given to N,N-dimethylformamide.

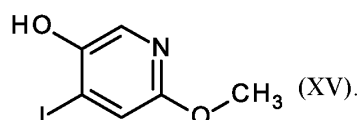
The compounds of the formula (XII) are known or can be prepared by reacting compounds of the formula



in which

- 5 R¹, R², R⁶, R⁷ and R⁸ are as defined above,

with a compound of the formula



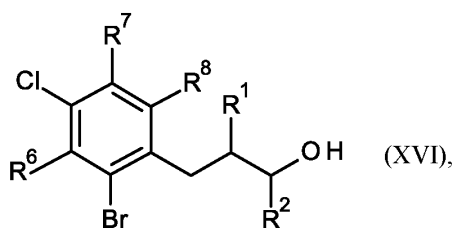
- The reaction is carried out in the presence of (tributylphosphoranylidene)-acetonitrile, in inert solvents such as benzene, xylene or toluene, preference is given to toluene, optionally in a microwave, preferably within a temperature range from 80°C to 160°C at atmospheric pressure to 3 bar or higher than 3 bar using a microwave,

or

- the reaction is carried out in the presence of an ester of the azodicarboxylic acid such as diisopropyl azodicarboxylate (DIAD) and organophosphorus compounds such as triphenylphosphine, in inert solvents such as tetrahydrofuran, 1,4-dioxane or dichloromethane, within a temperature range of 0°C to room temperature at atmospheric pressure.

The compounds of the formulae (XIV) and (XV) are known, can be synthesized from the corresponding starting compounds by known processes or can be prepared analogously to the processes described in the Examples section.

- 20 The compounds of the formula (XIII) are known or can be prepared by reacting compounds of the formula



in which

R^1 , R^2 , R^6 , R^7 and R^8 are as defined above,

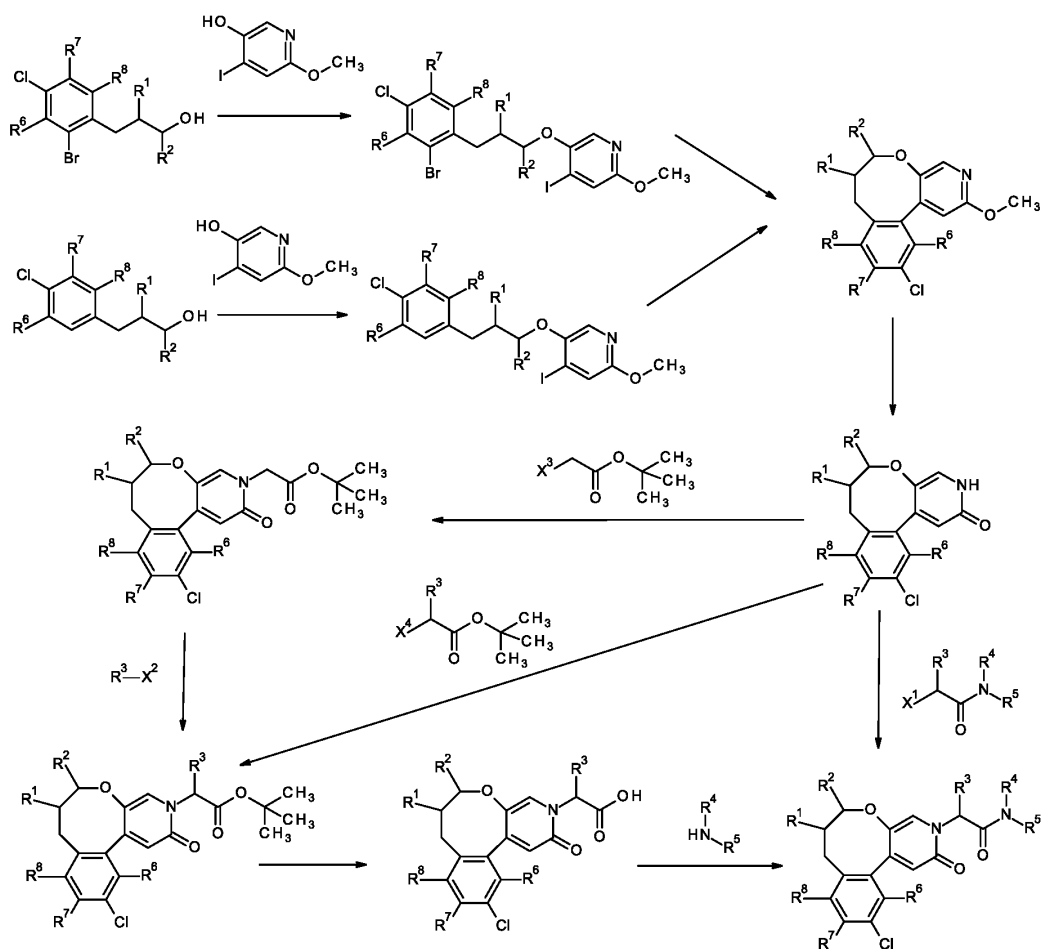
with a compound of the formula (XV).

The reaction is carried out as described for the reaction of compounds of the formula (XIV) with compounds of the formula (XV).

The compounds of the formula (XVI) are known, can be synthesized from the corresponding starting compounds by known processes or can be prepared analogously to the processes described in the Examples section.

The preparation of the starting compounds and of the compounds of the formula (I) can be illustrated by the synthesis scheme which follows.

Scheme:



The compounds according to the invention have an unforeseeable useful pharmacological activity spectrum and good pharmacokinetic properties. They are compounds that influence the proteolytic activity of the serine protease factor XIa (FXIa). The compounds according to the invention inhibit the enzymatic cleavage of FXIa-substrates, such as factor IX (FIX), which have essential roles in the activation of blood coagulation, in the aggregation of blood platelets via PAR-1 activation of the platelets, and in inflammatory processes, which particularly involve an increase in vascular permeability.

They are therefore suitable for use as medicaments for the treatment and/or prophylaxis of diseases in humans and animals.

The present invention further provides for the use of the compounds according to the invention for the treatment and/or prophylaxis of disorders, in particular vascular disorders, preferably thrombotic or thromboembolic disorders and/or thrombotic or thromboembolic complications.

Factor XIa (FXIa) is an important enzyme in the context of coagulation, which can be activated by both thrombin and factor XIIa (FXIIa), and is therefore involved in two essential processes of coagulation. It is a central component of the transition from initiation to amplification of the coagulation and propagation of the clot: in positive feedback loops, thrombin activates, in addition to factor V and factor VIII, also factor XI to factor XIa, whereby factor IX is converted into factor IXa, and, via the factor IXa/factor VIIIa complex generated in this manner, factor Xa and subsequently thrombin are formed, leading to strong thrombus growth and stabilization of the thrombus.

Moreover, factor XIa is an important component for the intrinsic initiation of coagulation: In addition to the stimulation via tissue factor (TF) in the extrinsic pathway, the coagulation system can be activated also particularly on negatively charged surfaces, which include not only surface structures of foreign cells (e.g. bacteria) but also artificial surfaces such as vascular prostheses, stents and parts of extracorporeal circulation systems. On these surfaces, factor XII (FXII) is activated to factor XIIa (FXIIa) which subsequently activates FXI to FXIa. This leads to further activation of the coagulation cascade as described above.

In contrast, thrombin generation triggered by TF/factor VIIa via factor X activation and finally thrombin formation, which represents the early physiological reaction to vascular wall injuries, remains uninfluenced. This could explain why no prolongations of bleeding times were found in FXIa knockout mice, as in rabbits and other species, with administration of FXIa inhibitor. This low bleeding tendency caused by the substance is of great advantage for use in humans, particularly in patients with increased risk of bleeding.

Accordingly, the compounds according to the invention are suitable for the treatment and/or prophylaxis of disorders or complications which may arise from the formation of clots.

For the purpose of the present invention, the "thrombotic or thromboembolic disorders and/or thrombotic or thromboembolic complications" include disorders and complications, which occur in the arterial, the venous vascular system and the lymphatic system, which can be treated with the compounds according to the invention. This includes in particular disorders in the coronary arteries
5 of the heart, such as acute coronary syndrome (ACS), myocardial infarction with ST segment elevation (STEMI) and without ST segment elevation (non-STEMI), stable angina pectoris, unstable angina pectoris, stent thrombosis, reocclusions and restenoses after coronary interventions such as angioplasty, stent implantation or aortocoronary bypass, disorders in the cerebrovascular arteries, such as transitory ischaemic attacks (TIA), ischemic strokes including cardioembolic strokes, such
10 as strokes due to atrial fibrillation, non-cardioembolic strokes, such as lacunar stroke, strokes due to large or small artery diseases, or strokes due to undetermined cause, cryptogenic strokes, embolic strokes, embolic strokes of undetermined source, or events of thrombotic and/or thromboembolic origin leading to stroke or TIA, and disorders of peripheral arteries, leading to peripheral artery disease, including peripheral artery occlusion, acute limb ischemia, amputation, reocclusions and
15 restenoses after interventions such as angioplasty, stent implantation or surgery and bypass.

In addition, this includes thrombotic or thromboembolic disorders in particular in veins of the extremities, kidneys, mesenterium, liver, brain and eye, leading to pulmonary embolisms, venous thromboembolisms and/or venous thrombosis.

Stimulation of the coagulation system may occur by various causes or associated disorders. In the
20 context of surgical interventions, immobility, confinement to bed, infections, inflammation or cancer or cancer therapy, inter alia, the coagulation system can be highly activated, and there may be thrombotic complications, in particular venous thromboses. The compounds according to the invention are therefore suitable for the prophylaxis of thrombosis in the context of surgical interventions in patients suffering from cancer. The compounds according to the invention are
25 therefore also suitable for the prophylaxis of thrombosis in patients having an activated coagulation system, for example in the situations described above.

The inventive compounds are therefore also suitable for the prevention and treatment of cardiogenic thromboembolisms, for example brain ischaemias, stroke and systemic thromboembolisms and ischaemias, in patients with acute, intermittent or persistent cardiac arrhythmias, for example atrial
30 fibrillation, and in patients undergoing cardioversion, and also in patients with heart valve disorders or with artificial heart valves.

In addition, the inventive compounds are suitable for the treatment and prevention of disseminated intravascular coagulation (DIC) which may occur in connection with sepsis inter alia, but also owing to surgical interventions, neoplastic disorders, burns or other injuries and may lead to severe organ
35 damage through microthrombosis.

Thromboembolic complications furthermore occur in microangiopathic haemolytical anaemias and by blood coming into contact with artificial surfaces in the context of extracorporeal circulation such as, for example, haemodialysis and ECMO ("extracorporeal membrane oxygenation"), LVAD ("left ventricular assist device") and similar devices, AV fistulas, vascular and heart valve prostheses.

- 5 Moreover, the compounds according to the invention are suitable for the treatment and/or prophylaxis of disorders involving microclot formation or fibrin deposits in cerebral blood vessels or asymptomatic, covert strokes, which may lead to dementia disorders such as vascular dementia or Alzheimer's disease. Here, the clot may contribute to the disorder both via occlusions and by binding disease-relevant factors.
- 10 Moreover, the compounds according to the invention are suitable for the treatment and/or prophylaxis of disorders where, in addition to the pro-coagulant component, the pro-inflammatory component also plays an essential role. Mutual enhancement of coagulation and inflammation in particular can be prevented by the compounds according to the invention, thus decisively lowering the probability of thrombotic complications. Therefore, the compounds according to the invention
- 15 are suitable for the treatment and/or prophylaxis in the context of atherosclerotic vascular disorders, inflammatory diseases, such as rheumatic disorders of the locomotor system, inflammatory disorders of the lung, such as pulmonary fibroses, inflammatory disorders of the kidney, such as glomerulonephritides, inflammatory disorders of the intestine, such as Crohn's disease or ulcerative colitis, or disorders, which may be present in the context of an underlying diabetic disease, such as
- 20 diabetic retinopathy or nephropathy.

Moreover, the compounds according to the invention can be used for inhibiting tumor growth and the formation of metastases, and also for the prophylaxis and/or treatment of thromboembolic complications, such as, for example, venous thromboembolisms, for cancer patients, in particular those undergoing major surgical interventions or chemo- or radiotherapy.

- 25 In addition, the inventive compounds are also suitable for the prophylaxis and/or treatment of pulmonary hypertension.

In the context of the present invention, the term "pulmonary hypertension" includes pulmonary arterial hypertension, pulmonary hypertension associated with disorders of the left heart, pulmonary hypertension associated with pulmonary disorders and/or hypoxia and pulmonary hypertension

30 owing to chronic thromboembolisms (CTEPH).

"Pulmonary arterial hypertension" includes idiopathic pulmonary arterial hypertension (IPAH, formerly also referred to as primary pulmonary hypertension), familial pulmonary arterial hypertension (FPAH) and associated pulmonary arterial hypertension (APAH), which is associated with collagenoses, congenital systemic-pulmonary shunt vitia, portal hypertension, HIV infections,

35 the ingestion of certain drugs and medicaments, with other disorders (thyroid disorders, glycogen

storage disorders, Morbus Gaucher, hereditary teleangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy), with disorders having a significant venous/capillary contribution, such as pulmonary-venooclusive disorder and pulmonary-capillary haemangiomatosis, and also persisting pulmonary hypertension of neonatants.

- 5 Pulmonary hypertension associated with disorders of the left heart includes a diseased left atrium or ventricle and mitral or aorta valve defects.

Pulmonary hypertension owing to chronic thromboembolisms (CTEPH) comprises the thromboembolic occlusion of proximal pulmonary arteries, the thromboembolic occlusion of distal pulmonary arteries and non-thrombotic pulmonary embolisms (tumour, parasites, foreign bodies).

- 10 The present invention further provides for the use of the inventive compounds for production of medicaments for the treatment and/or prophylaxis of pulmonary hypertension associated with sarcoidosis, histiocytosis X and lymphangiomatosis.

In addition, the compounds according to the invention may also be useful for the treatment of lung, liver and kidney fibrosis.

- 15 The compounds according to the invention are also suitable for the primary prophylaxis of thrombotic or thromboembolic disorders and/or thrombo-inflammatory disorders and/or disorders with increased vascular permeability in patients, in which gene mutations lead to enhanced activity of the enzymes or increased levels of the zymogens - and these are established by relevant tests/measurements of the enzyme activity or zymogen concentrations.

- 20 The present invention further provides for the use of the compounds according to the invention for the treatment and/or prophylaxis of disorders, especially the disorders mentioned above.

The present invention further provides for the use of the compounds according to the invention for production of a medicament for the treatment and/or prophylaxis of disorders, especially the disorders mentioned above.

- 25 The present invention further provides a method for the treatment and/or prophylaxis of disorders, especially the disorders mentioned above, using a therapeutically effective amount of a compound according to the invention.

The present invention further provides the compounds according to the invention for use in a method for the treatment and/or prophylaxis of disorders, especially the disorders mentioned above, using a

- 30 therapeutically effective amount of a compound according to the invention.

The present invention further provides medicaments comprising a compound according to the invention and one or more further active compounds.

In addition, the compounds according to the invention can also be used for preventing coagulation ex vivo, for example for the protection of organ transplants against damage caused by formation of

clots and for protecting the organ recipient against thromboemboli from the transplanted organ, for preserving blood and plasma products, for cleaning/pretreating catheters and other medical auxiliaries and instruments, for coating synthetic surfaces of medical auxiliaries and instruments used in vivo or ex vivo or for biological samples which may contain factor XIa.

- 5 The present invention furthermore provides a method for preventing the coagulation of blood in vitro, in particular in banked blood or biological samples which may comprise factor XIa, which method is characterized in that an anticoagulatory effective amount of the compound according to the invention is added.

10 The present invention further provides medicaments comprising a compound according to the invention and one or more further active compounds, in particular for the treatment and/or prophylaxis of the disorders mentioned above. Preferred examples of active compounds suitable for combinations include:

- 15 • lipid-lowering substances, especially HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors, for example lovastatin (Mevacor), simvastatin (Zocor), pravastatin (Pravachol), fluvastatin (Lescol) and atorvastatin (Lipitor);
- coronary therapeutics/vasodilators, especially ACE (angiotensin converting enzyme) inhibitors, for example captopril, lisinopril, enalapril, ramipril, cilazapril, benazepril, fosinopril, quinapril and perindopril, or AII (angiotensin II) receptor antagonists, for example embusartan, losartan, valsartan, irbesartan, candesartan, eprosartan and temisartan, or β -adrenoceptor antagonists, for
20 example carvedilol, alprenolol, bisoprolol, acebutolol, atenolol, betaxolol, carteolol, metoprolol, nadolol, penbutolol, pindolol, propanolol and timolol, or α -1-adrenoceptor antagonists, for example prazosine, bunazosine, doxazosine and terazosine, or diuretics, for example hydrochlorothiazide, furosemide, bumetanide, piretanide, torasemide, amiloride and dihydralazine, or calcium channel blockers, for example verapamil and diltiazem, or
25 dihydropyridine derivatives, for example nifedipin (Adalat) and nitrendipine (Bayotensin), or nitro preparations, for example isosorbide 5-mononitrate, isosorbide dinitrate and glycerol trinitrate, or substances causing an increase in cyclic guanosine monophosphate (cGMP), for example stimulators of soluble guanylate cyclase, for example riociguat;
- plasminogen activators (thrombolytics/fibrinolytics) and compounds which promote
30 thrombolysis/fibrinolysis such as inhibitors of the plasminogen activator inhibitor (PAI inhibitors) or inhibitors of the thrombin-activated fibrinolysis inhibitor (TAFI inhibitors) such as, for example, tissue plasminogen activator (t-PA, for example Actilyse®), streptokinase, reteplase and urokinase or plasminogen-modulating substances causing increased formation of plasmin;

- anticoagulatory substances (anticoagulants), for example heparin (UFH), low-molecular-weight heparins (LMW), for example tinzaparin, certoparin, parnaparin, nadroparin, ardeparin, enoxaparin, reviparin, dalteparin, danaparoid, semuloparin (AVE 5026), adomiparin (M118) and EP-42675/ORG42675;
- 5 • direct thrombin inhibitors (DTI) such as, for example, Pradaxa (dabigatran), atecegatran (AZD-0837), DP-4088, SSR-182289A, argatroban, bivalirudin and tanogitran (BIBT-986 and prodrug BIBT-1011), hirudin;
- direct factor Xa inhibitors, for example, rivaroxaban, apixaban, edoxaban (DU-176b), betrixaban (PRT-54021), R-1663, darexaban (YM-150), otamixaban (FXV-673/RPR-130673),
- 10 letaxaban (TAK-442), razaxaban (DPC-906), DX-9065a, LY-517717, tanogitran (BIBT-986, prodrug: BIBT-1011), idraparinix and fondaparinux,
- substances which inhibit the aggregation of platelets (platelet aggregation inhibitors, thrombocyte aggregation inhibitors), such as, for example, acetylsalicylic acid (such as, for example, aspirin), P2Y₁₂ antagonists such as, for example, ticlopidine (Ticlid), clopidogrel
- 15 (Plavix), prasugrel, ticagrelor, cangrelor, elinogrel, PAR-1 antagonists such as, for example, vorapaxar, PAR-4 antagonists, EP3 antagonists such as, for example, DG041;
- platelet adhesion inhibitors such as GPVI and/or GPIb antagonists such as, for example, Revacept or caplacizumab;
- fibrinogen receptor antagonists (glycoprotein-IIb/IIIa antagonists), for example abciximab,
- 20 eptifibatide, tirofiban, lamifiban, lefradafiban and fradafiban;
- recombinant human activated protein C such as, for example, Xigris or recombinant thrombomodulin;
- and also antiarrhythmics.

25 “Combinations” for the purpose of the invention mean not only dosage forms which contain all the components (so-called fixed combinations) and combination packs which contain the components separate from one another, but also components which are administered simultaneously or sequentially, provided that they are used for prophylaxis and/or treatment of the same disease. It is likewise possible to combine two or more active ingredients with one another, meaning that they are thus each in two-component or multicomponent combinations.

30 The inventive compounds can act systemically and/or locally. For this purpose, they can be administered in a suitable manner, for example by the oral, parenteral, pulmonal, nasal, sublingual, lingual, buccal, rectal, dermal, transdermal, conjunctival or otic route, or as an implant or stent.

The inventive compounds can be administered in administration forms suitable for these administration routes.

Suitable administration forms for oral administration are those which function according to the prior art and deliver the inventive compounds rapidly and/or in modified fashion, and which contain the inventive compounds in crystalline and/or amorphized and/or dissolved form, for example tablets (uncoated or coated tablets, for example having enteric coatings or coatings which are insoluble or dissolve with a delay, which control the release of the compound according to the invention), tablets which disintegrate rapidly in the mouth, or films/wafers, films/lyophilisates, capsules (for example hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can be accomplished with avoidance of a resorption step (for example by an intravenous, intraarterial, intracardiac, intraspinal or intralumbar route) or with inclusion of a resorption (for example by an intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal route). Administration forms suitable for parenteral administration include preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilizates or sterile powders.

Preference is given to oral administration.

Suitable administration forms for the other administration routes are, for example, pharmaceutical forms for inhalation (including powder inhalers, nebulizers), nasal drops, solutions or sprays; tablets for lingual, sublingual or buccal administration, films/wafers or capsules, suppositories, preparations for the ears or eyes, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (for example patches), milk, pastes, foams, dusting powders, implants or stents.

The inventive compounds can be converted to the administration forms mentioned. This can be accomplished in a manner known per se by mixing with inert, nontoxic, pharmaceutically suitable excipients. These excipients include carriers (for example microcrystalline cellulose, lactose, mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersing or wetting agents (for example sodium dodecylsulfate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (e.g. antioxidants, for example ascorbic acid), colourants (e.g. inorganic pigments, for example iron oxides) and flavour and/or odour correctants.

The present invention further provides medicaments comprising at least one inventive compound, preferably together with one or more inert nontoxic pharmaceutically suitable excipients, and the use thereof for the purposes mentioned above.

In the case of parenteral administration, it has generally been found to be advantageous to administer amounts of about 5 to 250 mg every 24 hours to achieve effective results. In the case of oral administration, the amount is about 5 to 500 mg every 24 hours.

In spite of this, it may be necessary, if appropriate, to deviate from the amounts specified, specifically depending on body weight, administration route, individual behaviour towards the active ingredient, type of formulation, and time or interval of administration.

- 5 Unless stated otherwise, the percentages in the tests and examples which follow are percentages by weight; parts are parts by weight. Solvent ratios, dilution ratios and concentration data for the liquid/liquid solutions are based in each case on volume. "w/v" means "weight/volume". For example, "10% w/v" means: 100 ml of solution or suspension comprise 10 g of substance.

A) Examples**Abbreviations:**

Boc	<i>tert</i> -Butyloxycarbonyl
br s	broad singlet (in NMR)
br d	broad doublet (in NMR)
br t	broad triplet (in NMR)
cv	column volume
d	day(s), doublet (in NMR)
TLC	thin-layer chromatography
DCI	direct chemical ionization (in MS)
dd	doublet of doublets (in NMR)
ddd	doublet of doublets of doublets (in NMR)
DMSO	dimethyl sulfoxide
eq.	equivalent(s)
ESI	electrospray ionization (in MS)
h	hour(s)
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HPLC	high-pressure, high-performance liquid chromatography
LC/MS	liquid chromatography-coupled mass spectroscopy
m	multiplet (in NMR)
min	minute(s)
MS	mass spectroscopy
NMR	nuclear magnetic resonance spectroscopy
q	quartet or quadruplet (in NMR)
quin	quintet (in NMR)
RP	reverse phase (in HPLC)
RT	room temperature
R _t	retention time (in HPLC)
s	singlet (in NMR)
sxt	sextet (in NMR)
SFC	supercritical fluid chromatography (with supercritical carbon dioxide as a eluent)
t	triplet (in NMR)
TFA	trifluoroacetic acid
T3P	2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide

HPLC, LC-MS and GC methods:

Method 1: Instrument: Waters ACQUITY SQD UPLC system; column: Waters Acquity UPLC HSS T3 C18 1.8 μm , 50 mm $\times$ 1.0 mm; eluent A: water + 0.025% formic acid, eluent B: acetonitrile + 0.025% formic acid; gradient: 0.0 min 10% B $\rightarrow$ 1.2 min 95% B $\rightarrow$ 2.0 min 95% B; oven: 50°C; flow rate: 0.40 ml/min; UV detection: 210-400 nm.

Method 2: Instrument: Thermo Scientific DSQII; GC: Thermo Scientific Trace GC Ultra; column: Restek RTX-35MS, 15 m $\times$ 200 μm $\times$ 0.33 μm ; constant helium flow rate: 1.20 ml/min; oven: 60°C; inlet: 220°C; gradient: 60°C, 30°C/min $\rightarrow$ 300°C (maintained for 3.33 min).

Method 3: Instrument: Waters ACQUITY SQD UPLC system; column: Waters Acquity UPLC HSS T3 C18 1.8 μm , 50 mm $\times$ 1.0 mm; eluent A: water + 0.025% formic acid, eluent B: acetonitrile + 0.025% formic acid; gradient: 0.0 min 5% B $\rightarrow$ 6.0 min 95% B $\rightarrow$ 7.5 min 95% B; oven: 50°C; flow rate: 0.35 ml/min; UV detection: 210-400 nm.

Method 4: Instrument: Thermo Scientific FT-MS; UHPLC: Thermo Scientific UltiMate 3000; column: Waters HSS T3 C18 1.8 μm , 75 mm $\times$ 2.1 mm; eluent A: water + 0.01% formic acid; eluent B: acetonitrile + 0.01% formic acid; gradient: 0.0 min 10% B $\rightarrow$ 2.5 min 95% B $\rightarrow$ 3.5 min 95% B; oven: 50°C; flow rate: 0.90 ml/min; UV detection: 210-400 nm.

Method 5: Instrument: Agilent MS Quad 6150; HPLC: Agilent 1290; column: Waters Acquity UPLC HSS T3 1.8 μm , 50 mm $\times$ 2.1 mm; eluent A: water + 0.025% formic acid, eluent B: acetonitrile + 0.025% formic acid; gradient: 0.0 min 10% B $\rightarrow$ 0.3 min 10% B $\rightarrow$ 1.7 min 95% B $\rightarrow$ 3.0 min 95% B; oven: 50°C; flow rate: 1.20 ml/min; UV detection: 205-305 nm.

Method 6: Instrument: Waters MS SQ detector 2; GC: Agilent A7890; column: Restek RTX-35 MS, 15 m $\times$ 200 μm $\times$ 0.33 μm , gas: helium; oven: 60°C; flow rate: 1.20 ml/min; inlet: 240°C; gradient: 30°C/min $\rightarrow$ 300°C.

Method 7: Instrument: Shimadzu LCMS-2020; column: CORTECS C18 2.7 μm , 50 mm $\times$ 2.1 mm; eluent A: water + 0.1% formic acid, eluent B: acetonitrile + 0.1% formic acid; gradient: 0.0 min 5% B $\rightarrow$ 2.0 min 95% B $\rightarrow$ 3.0 min 95% B; oven: 40°C; flow rate: 1.0 ml/min; UV detection: 210-400 nm.

Method 8: Instrument: Shimadzu LCMS-2020; column: CORTECS C18 2.7 μm , 2.1 mm $\times$ 50 mm; eluent A: water + 0.1% formic acid, eluent B: acetonitrile + 0.1% formic acid; gradient: 0.0 min 5% B $\rightarrow$ 1.2 min 100% B $\rightarrow$ 2.0 min 100% B; oven: 40°C; flow rate: 1.0 ml/min; UV detection: 210-400 nm.

Method 9: Instrument: Shimadzu LCMS-2020; column: Kinetex EVO-C18 2.6 μm , 3.0 mm $\times$ 50 mm; eluent A: water + 0.2% ammonium hydroxide, eluent B: acetonitrile; gradient: 0.0 min 10%

B → 2.0 min 95% B → 3.0 min 95% B; oven: 45°C; flow rate: 1.2 ml/min; UV detection: 210-400 nm.

Method 10: Instrument: Shimadzu LCMS-2020; column: CORTECS C18 2.7 µm, 50 mm × 2.1 mm; eluent A: water + 0.09% formic acid, eluent B: acetonitrile + 0.1% formic acid, gradient: 0.0 min 5% B → 1.2 min 100% B → 2.0 min 100% B; oven: 40°C; flow rate: 1.0 ml/min; UV detection: 210-400 nm.

Method 11: Instrument: Shimadzu LC-MS-2020; column: Ascentis Express C18 2.7 µm, 50 mm × 2.1 mm; eluent A: water with 0.05% trifluoroacetic acid, eluent B: acetonitrile with 0.05% trifluoroacetic acid; gradient: 0.0 min 5% B → 1.2 min 100% B → 1.7 min 100% B → 1.75 min 5% B → 2.0 min 5% B; oven: 40°C; flow rate: 1.5 ml/min; UV detection: 210-400 nm.

Method 12: Instrument: Shimadzu LC-MS-2020; column: Ascentis Express C18 2.7 µm, 50 mm × 3.0 mm; eluent A: water with 0.05% trifluoroacetic acid, eluent B: acetonitrile with 0.05% trifluoroacetic acid; gradient: 0.0 min 5% B → 1.2 min 95% B → 1.7 min 95% B → 1.8 min 5% B → 2.0 min 5% B; oven: 40°C; flow rate: 1.5 ml/min; UV detection: 210-400 nm.

Method 13: Instrument: Shimadzu LCMS-2020; column: Kinetex EVO C18 2.6 µm, 50 mm × 3.0 mm; eluent A: water + 0.03% ammonium hydroxide, eluent B: acetonitrile, gradient: 0.0 min 10% B → 1.1 min 95% B → 2.0 min 95% B; oven: 40°C; flow rate: 1.2 ml/min; UV detection: 210-400 nm.

Method 14: Instrument: Shimadzu LCMS-2020; column: Kinetex EVO C18 2.6 µm, 50 mm × 3.0 mm; eluent A: water + 0.03% ammonium hydroxide, eluent B: acetonitrile, gradient: 0.0 min 10% B → 2.0 min 95% B → 3.0 min 95% B; oven: 40°C; flow rate: 1.2 ml/min; UV detection: 210-400 nm.

Method 15: Instrument: Waters Single Quad MS; HPLC: Waters UPLC Acquity; column: Waters BEH C18 1.7 µm, 50 mm × 2.1 mm; eluent A: water + 0.025% ammonia, eluent B: acetonitrile; gradient: 0.0 min 8% B → 0.1 min 8% B → 1.8 min 95% B → 3.5 min 95% B; oven: 50°C; flow rate: 0.45 ml/min; UV detection: 210-400 nm.

Method 16: Instrument: Waters TOF instrument; UPLC: Waters Acquity I-CLASS; column: Waters HSST3 C18 1.8 µm, 50 mm × 2.1 mm; eluent A: water + 0.01% formic acid; eluent B: acetonitrile + 0.01% formic acid; gradient: 0.0 min 2% B → 0.5 min 2% B → 7.5 min 95% B → 10.0 min 95% B; oven: 50°C; flow rate: 1.00 ml/min; UV detection: 210-400 nm.

Method 17: Instrument: Waters TOF instrument; UPLC: Waters Acquity I-CLASS; column: Waters Acquity UPLC Peptide BEH C18, 300 Å, 1.7 µm, 150 mm × 2.1 mm; eluent A: water + 0.01% formic acid, eluent B: acetonitrile + 0.01% formic acid; gradient: 0.0 min 90% A → 0.25 min 90% A → 8.0 min 45% A → 10.0 min 2% A → 12.0 min 2% A; oven: 50°C; flow rate: 0.475 ml/min; UV detection: 210 nm.

Method 18: Instrument: Waters TOF instrument; UPLC: Waters Acquity I-CLASS; column: Waters Acquity UPLC HSS T3, 1.8 μm , 50 mm x 1 mm; eluent A: water + 0.01% formic acid, eluent B: acetonitrile + 0.01% formic acid; gradient: 0.0 min 95% A $\rightarrow$ 6.0 min 5% A $\rightarrow$ 7.5 min 5% A; oven: 50°C; flow rate: 0.35 ml/min; UV detection: 210 nm.

- 5 Method 19: Instrument: Shimadzu LCMS-2020; column: Poroshell HPH C18 2.7 μm , 50 mm x 3.0 mm; eluent A: water 6.5 mM ammonium carbonate, eluent B: acetonitrile, gradient: 0.0 min 10% B $\rightarrow$ 2.1 min 95% B $\rightarrow$ 2.7 min 95% B $\rightarrow$ 2.75 min 10% B; oven: 40°C; flow rate: 1.2 ml/min; UV detection: 190-400 nm.

- 10 Microwave: The microwave reactor used was a "single-mode" instrument of the Emrys™ Optimizer type.

- When compounds according to the invention are purified by preparative HPLC by the above-described methods in which the eluents contain additives, for example trifluoroacetic acid, formic acid or ammonia, the compounds according to the invention may be obtained in salt form, for example as trifluoroacetate, formate or ammonium salt, if the compounds according to the invention contain a sufficiently basic or acidic functionality. Such a salt can be converted to the corresponding free base or acid by various methods known to the person skilled in the art.

- 20 In the case of the synthesis intermediates and working examples of the invention described hereinafter, any compound specified in the form of a salt of the corresponding base or acid is generally a salt of unknown exact stoichiometric composition, as obtained by the respective preparation and/or purification process. Unless specified in more detail, additions to names and structural formulae, such as "hydrochloride", "trifluoroacetate", "sodium salt" or " $x \text{ HCl}$ ", " $x \text{ CF}_3\text{COOH}$ ", " $x \text{ Na}^+$ " should not therefore be understood in a stoichiometric sense in the case of such salts, but have merely descriptive character with regard to the salt-forming components present therein.

This applies correspondingly if synthesis intermediates or working examples or salts thereof were obtained in the form of solvates, for example hydrates, of unknown stoichiometric composition (if they are of a defined type) by the preparation and/or purification processes described.

- 30 In NMR spectra of mixtures of stereoisomers, numbers mentioned with "/" indicate that the stereoisomers show separate signals for the respective hydrogen atom, i.e. "... / ... (2s, 1H)" means that one hydrogen atom is represented by 2 singlets, each singlet from one or more different stereoisomer(s).

General Synthesis Methods

General Method 1: Etherification using sodium hydride

The respective alcohol (1.0 eq.) and the respective bromide (1.0-1.25 eq.) were dissolved in tetrahydrofuran (0.2-0.4 M) and cooled to 0°C. Then sodium hydride (60% dispersion in mineral oil, 1.5-3.0 eq.) was added and stirring was continued for 1-3 h at 0°C and overnight at RT. The reaction mixture was diluted with ethyl acetate and saturated aqueous ammonium chloride solution, subsequently washed with water and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was either purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate mixtures or dichloromethane / methanol mixtures) or preparative HPLC (reversed phase, eluent: water / acetonitrile gradients or water / methanol gradients).

General Method 2: Mitsunobu reaction using (tributylphosphoranylidene)acetonitrile

(Tributylphosphoranylidene)acetonitrile (1.5-3.0 eq.) was added to a solution of the respective primary or secondary alcohol (1.0 eq.) and the respective phenol (1.0-1.5 eq.) in toluene (0.1-0.5 M) in a microwave vessel. The reaction vessel was then sealed, placed into a microwave reactor, irradiated at 100 to 160°C and stirred at this temperature for 1-8 h. The reaction mixture was then cooled to RT and concentrated under reduced pressure. The crude product was either purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate mixtures or dichloromethane / methanol mixtures) or preparative HPLC (reversed phase, eluent: water / acetonitrile gradients or water / methanol gradients).

General Method 3a: Ring closure using Miyaura borylation reaction and Suzuki reaction

The respective ether (1.0 eq.), bis(pinacolato)diboron (1.25-2.0 eq.), palladium(II) acetate (0.03-0.1 eq.), tricyclohexylphosphine (0.1-0.15 eq.) and potassium acetate (3.0-4.5 eq.) were dissolved in *N,N*-dimethylformamide (0.25-0.4 M) and argon was passed through the resulting suspension for 10 min. The reaction mixture was heated to 80-100°C and stirred at this temperature overnight, followed by the addition of saturated aqueous sodium bicarbonate solution (5-7 ml/mmol of the respective ether) and tetrakis(triphenylphosphine)palladium(0) (0.03-0.05 eq.). Stirring was then continued at 80-100°C for additional 2-72 h and the reaction mixture was either filtered over silica gel and eluted with dichloromethane or extracted with ethyl acetate, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was either purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate mixtures or dichloromethane / methanol mixtures) or preparative HPLC (reversed phase, eluent: water / acetonitrile gradients or water / methanol gradients).

General Method 3b: Ring closure using CH-activation

The respective ether (1.0 eq.) and potassium pivalate or potassium acetate (2.0-6.0 eq.) were

dissolved in *N,N*-dimethylacetamide (0.01-0.1 M) and argon was passed through the mixture for 10 min. Subsequently, tetrakis(triphenylphosphine)palladium(0) (0.05-0.2 eq.) was added and the mixture was stirred for 2-48 h at 100-150°C. The residue was diluted with water and extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous
5 magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was either purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate mixtures or dichloromethane / methanol mixtures) or preparative HPLC (reversed phase, eluent: water / acetonitrile gradients or water / methanol gradients).

General Method 4: Pyridinone formation using acetic acid and sodium iodine

10 The respective 2-methoxypyridine derivative (1.0 eq.) was dissolved in acetic acid (0.05-0.2 M), sodium iodide (2.0-4.0 eq.) was added and the resulting mixture was stirred at 80-100°C for 2-24 h. Then dichloromethane and saturated aqueous sodium bicarbonate solution were added and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered and
15 concentrated under reduced pressure. The crude product was then purified either by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate mixtures or dichloromethane / methanol mixtures) or preparative HPLC (reversed phase, eluent: water / acetonitrile gradients or water / methanol gradients) or used in the subsequent reaction without further purification.

General Method 5: Pyridinone formation using 4-toluenesulfonic acid monohydrate and lithium iodine

The respective 2-methoxypyridine derivative (1.0 eq.) was dissolved in 1-butanol (0.1-0.25 M), 4-toluenesulfonic acid monohydrate (1.5-2.5 eq.) and lithium iodide (5.0-10.0 eq.) were added and the resulting mixture was stirred at 80-100°C for 2-6 h. The reaction mixture was then concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic
25 layer was separated, washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified either by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate mixtures or dichloromethane / methanol mixtures) or preparative HPLC (reversed phase, eluent: water / acetonitrile gradients or water / methanol gradients) or used in the subsequent reaction without
30 further purification.

General Method 6: Pyridinone formation using ethanethiol and sodium hydride

The respective 2-methoxypyridine derivative (1.0 eq.) was dissolved in *N,N*-dimethylformamide (0.1-0.25 M) followed by the addition of ethanethiol (6.0-10.0 eq.). The mixture was cooled to 0°C, sodium hydride (60% dispersion in mineral oil, 3.0-5.0 eq.) was added, stirring was continued at 0°C
35 for 10-20 min and then heated to 80-100°C overnight. Subsequently, water was added, the mixture

was neutralized to pH 7 by slow addition of aqueous hydrochloric acid (1 N) and extracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC (reversed phase, eluent: water / acetonitrile gradients or water / methanol gradients).

5 General Method 7: Alkylation of pyridinone derivatives with α -bromo-ester and α -bromo-amide derivatives

The respective pyridinone derivative (1.0 eq.) was dissolved in a 4:1 mixture of 2-propanol and acetone (0.05-0.15 M) and 1,1,3,3-tetramethylguanidine (3.0-5.0 eq.) was added at RT. After stirring or shaking for 15 min, the respective α -bromo-ester or α -bromo-amide derivative (1.0-2.5 eq.) was added and stirring or shaking was continued overnight at RT. The crude mixture was then directly purified by preparative HPLC or concentrated under reduced pressure and the crude mixture was purified by preparative HPLC (reversed phase, eluent: water / acetonitrile gradients or water / methanol gradients).

General Method 8: Synthesis of triflate derivatives

15 A solution of trifluoromethanesulfonic anhydride (1.1-1.3 eq.) in dichloromethane (0.1-0.25 M) under argon atmosphere was cooled to -78°C and a solution of the corresponding alcohol (1.0 eq.) and trimethylamine or pyridine (1.1-1.5 eq.) in dichloromethane (0.75-1.0 M) was added slowly. Stirring was continued at -78°C for 0.5-2 h before the mixture was warmed to RT, diluted with methyl *tert*-butyl ether and washed with a 3:1 mixture of a saturated aqueous sodium chloride solution and
20 aqueous hydrochloric acid (1 N). The organic phase was then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain the crude product, which was used in the subsequent reaction without further purification.

General Method 9: α -Alkylation of *N*-substituted pyridinone derivatives with triflate or bromide derivatives

25 Under argon atmosphere, the respective *N*-substituted pyridinone derivative (1.0 eq.) was dissolved in tetrahydrofuran (0.1-0.2 M). At -78°C , a solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (1 M, 1.15-1.5 eq.) was added dropwise. After 20-30 min, the respective triflate or bromide derivative (1.15-1.5 eq.) dissolved in tetrahydrofuran (0.2-0.4 M) was added slowly. The mixture was stirred at -78°C for 15-30 min and for 0.5-1.0 h at RT. Then the mixture was cooled to
30 -78°C before glacial acetic acid (1.5-3.0 eq.) was added. The reaction mixture was concentrated under reduced pressure and the crude product was either purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate mixtures or dichloromethane / methanol mixtures) or preparative HPLC (reversed phase, eluent: water / acetonitrile gradients or water / methanol gradients) or used in the subsequent reaction without further purification.

General Method 10: Ester cleavage using lithium hydroxide

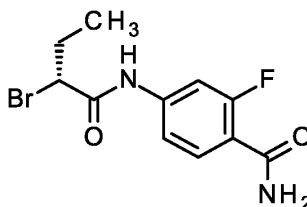
The respective ester (1.0 eq.) was dissolved in tetrahydrofuran (0.05-0.15 M) and an aqueous solution of lithium hydroxide or sodium hydroxide (0.3-1.0 M, 5.0-10.0 eq.) was added. The reaction mixture was stirred at RT for 2 h up to overnight and acidified by addition of aqueous solution of hydrochloric acid (1 N). The resulting crude product was filtered and subsequently washed with water and cyclohexane or directly concentrated under reduced pressure. The residue was then purified by preparative HPLC (reversed phase, eluent: water / acetonitrile gradients or water / methanol gradients) or used in the subsequent reaction without further purification.

General Method 11: Amide coupling using T3P/pyridine

To a solution of the respective carboxylic acid (1 eq.) and the respective amine (1.1-1.5 eq.) in pyridine (about 0.1 M) was added T3P (50% solution in *N,N*-dimethylformamide or in ethyl acetate, 1.5-4.0 eq.) at RT and the mixture was then stirred at RT or heated to 50-80°C. Alternatively, to a solution of the respective carboxylic acid (1.0 eq.) in pyridine (about 0.1 M) was added T3P (50% solution in *N,N*-dimethylformamide or in ethyl acetate, 1.5-4 eq.) and the solution was stirred for 1 to 10 min at RT. The respective amine (1.1-1.5 eq.) was then added and the reaction mixture was stirred at RT or heated to 50-80°C. After stirring at the respective temperature for 1-48 h, the reaction mixture was cooled to RT and either directly concentrated under reduced pressure or diluted with water, extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified either by column chromatography (cyclohexane / ethyl acetate mixtures or dichloromethane / methanol mixtures) or preparative HPLC (reversed phase, eluent: water / acetonitrile gradients or water / methanol gradients).

Starting compounds**Example 1.1A**

4-{[(2*R*)-2-Bromobutanoyl]amino}-2-fluorobenzamide (single stereoisomer)



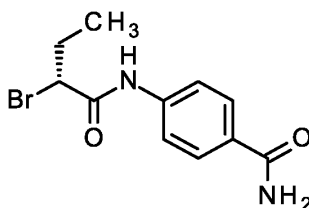
(2*R*)-2-Bromobutanoic acid (single stereoisomer) (3.5 g, 21.2 mmol, 1.1 eq.), pyridine (1.7 ml, 21.2 mmol, 1.1 eq.) and T3P (17.2 ml, 50% solution in ethyl acetate, 28.9 mmol, 1.5 eq.) were added under argon atmosphere at 0-5°C to a suspension of 4-amino-2-fluorobenzamide (3.0 g, 19.3 mmol) in tetrahydrofuran (30 ml). The reaction mixture was allowed to warm to RT and stirred for 30 min.

The reaction mixture was then cooled to 10°C, mixed dropwise with water (35 ml), stirred for 15 min, followed by the addition of further water (25 ml), and stirred for 30 min. The forming precipitate was filtered, washed with water and dried *in vacuo*. Yield: 5.23 g (90% of theory). From the combined filtrates, further precipitate formed which was filtered, washed with water and dried *in vacuo*. Yield: 0.5 g (9% of theory).

both batches: LC-MS (method 4): $R_t = 1.25$ min; MS (ESIpos): $m/z = 303$ $[M+H]^+$

Example 1.2A

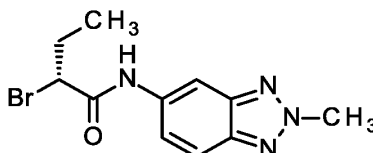
4-[(2*R*)-2-Bromobutanoyl]amino}benzamide (single stereoisomer)



- 10 (2*R*)-2-Bromobutanoic acid (single stereoisomer) (3.97 g, 23.8 mmol, 1.1 eq.) was added slowly under argon atmosphere to an ice-cooled suspension of 4-aminobenzamide (3.00 g, 21.6 mmol) in tetrahydrofuran (22 ml), followed by the addition of pyridine (1.9 ml, 23.8 mmol, 1.1 eq.) and T3P (19 ml, 50% solution in ethyl acetate, 32.4 mmol, 1.5 eq.) at a temperature of 0-5°C. The reaction mixture was allowed to warm to RT and stirred at RT for 30 min. Water (35 ml) was added dropwise
- 15 at 10°C. The reaction mixture was stirred for 15 min, followed by addition of further water (25 ml), and stirred for another 30 min. The forming precipitate was filtered, washed with water and dried *in vacuo*. The precipitate was suspended in a mixture of dichloromethane / ethyl acetate, filtered (the filtrate was discarded), suspended in tetrahydrofuran, filtered and dried *in vacuo*. Yield: 5.72 g (93% of theory). Further crystallization from the second filtrate yielded another 210 mg (3% of theory).
- 20 main batch: LC-MS (method 4): $R_t = 1.12$ min; MS (ESIpos): $m/z = 285$ $[M+H]^+$
- main batch: $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.52 (s, 1H), 7.94-7.81 (m, 3H), 7.66 (d, 2H), 7.26 (br s, 1H), 4.48 (t, 1H), 2.17-1.88 (m, 2H), 0.96 (t, 3H).

Example 1.3A

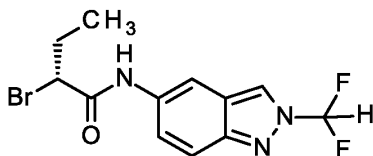
(2*R*)-2-Bromo-*N*-(2-methyl-2*H*-benzotriazol-5-yl)butanamide (single stereoisomer)



- (2*R*)-2-Bromobutanoic acid (single stereoisomer) (695 mg, 4.16 mmol, 1.1 eq.) was added slowly under argon atmosphere to an ice-cooled suspension of 2-methyl-2*H*-benzotriazol-5-amine (590 mg, 3.78 mmol) in tetrahydrofuran (3.8 ml), followed by the addition of pyridine (337 μ l, 4.16 mmol, 1.1 eq.) and T3P (3.38 ml, 50% solution in ethyl acetate, 5.67 mmol, 1.5 eq.) at a temperature of 0-5°C. The reaction mixture was allowed to warm to RT and stirred at RT for 30 min. Water (25 ml) was added dropwise at 10°C. The reaction mixture was stirred for 15 min, followed by addition of ethyl acetate (15 ml). After phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine (15 ml), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Yield: 980 mg (85% of theory).
- LC-MS (method 1): R_t = 0.82 min; MS (ESIpos): m/z = 297 $[M+H]^+$
- 1H -NMR (400 MHz, DMSO- d_6): δ [ppm] = 10.55 (s, 1H), 8.36 (d, 1H), 7.89 (d, 1H), 7.43 (dd, 1H), 4.51 (t, 1H), 4.46 (s, 3H), 2.19-1.91 (m, 2H), 0.98 (t, 3H).

Example 1.4A

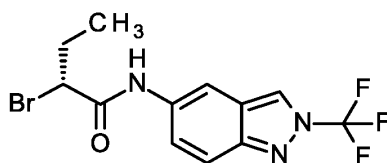
(2*R*)-2-Bromo-*N*-[2-(difluoromethyl)-2*H*-indazol-5-yl]butanamide (single stereoisomer)



- General Method 11 was carried out with 2-(difluoromethyl)-2*H*-indazol-5-amine hydrochloride (24.0 mg, 109 μ mol, 1.0 eq.), (2*R*)-2-bromobutanoic acid (single stereoisomer) (20.1 mg, 120 μ mol, 1.1 eq.), pyridine (9.7 μ l, 120 μ mol, 1.1 eq.) and T3P (98 μ l, 50% solution in ethyl acetate, 160 μ mol, 1.5 eq.) in tetrahydrofuran (300 μ l) including the following variations of the procedure: The mixture was stirred at 0°C for the addition of the reagents and at RT for 30 min. Water was added at 10°C to the reaction mixture and stirring was continued for 15 min. The crude mixture was extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and used in the subsequent reaction without further purification. Yield: 59.0 mg (quantitative of theory).
- LC-MS (method 5): R_t = 1.12 min; MS (ESIpos): m/z = 332 $[M+H]^+$

Example 1.5A

(2*R*)-2-Bromo-*N*-[2-(trifluoromethyl)-2*H*-indazol-5-yl]butanamide (single stereoisomer)

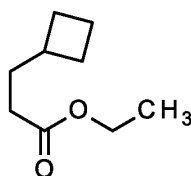


General Method 11 was carried out with 2-(trifluoromethyl)-2*H*-indazol-5-amine hydrochloride (65.3 mg, 272 μ mol, 1.0 eq.), (2*R*)-2-bromobutanoic acid (single stereoisomer) (50.0 mg, 299 μ mol, 1.1 eq.), pyridine (24 μ l, 300 μ mol, 1.1 eq.) and T3P (240 μ l, 50% solution in ethyl acetate, 410 μ mol, 1.5 eq.) in tetrahydrofuran (500 μ l) including the following variations of the procedure: The mixture was stirred at 0°C for the addition of the reagents and at RT for 30 min. Subsequently, additional amounts of (2*R*)-2-bromobutanoic acid (22.7 mg, 136 μ mol, 0.5 eq.) and T3P (81 μ l, 50% solution in ethyl acetate, 136 μ mol, 0.5 eq.) were added and stirring was continued for 30 min. Water was added at 10°C to the reaction mixture and stirring was continued for 15 min. The crude mixture was extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and used in the subsequent reaction without further purification. Yield: 181 mg (quantitative of theory).

LC-MS (method 5): R_t = 1.25 min; MS (ESIpos): m/z = 350 $[M+H]^+$

Example 1.6A

Ethyl 3-cyclobutylpropanoate

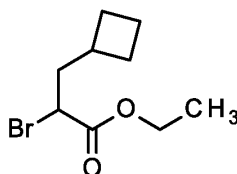


To a solution of 3-cyclobutylpropanoic acid (1.00 g, 7.80 mmol, 1.0 eq.) in ethanol (15 ml) was added thionyl chloride (850 μ l, 12 mmol, 1.5 eq.) at 0°C. The resulting mixture was then warmed to RT and stirred overnight. The crude mixture was diluted with ethyl acetate, washed with saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used in the subsequent reaction without further purification. Yield: 1.02 g (84% of theory).

GC-MS (method 6): R_t = 3.15 min; MS (APCIpos): m/z = 157 $[M+H]^+$

Example 1.6B

Ethyl 2-bromo-3-cyclobutylpropanoate (racemate)

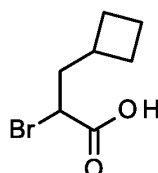


To a solution of diisopropylamine (1.3 ml, 9.0 mmol, 1.4 eq.) in tetrahydrofuran (20 ml) was added a solution of *n*-butyllithium (3.1 ml, 2.5 M in hexane, 7.7 mmol, 1.2 eq.) at 0°C. After stirring at this temperature for 30 min, the mixture was cooled to -78°C and a solution of ethyl 3-cyclobutylpropanoate (1.00 g, 6.40 mmol, 1.0 eq.) in tetrahydrofuran (20 ml) was added dropwise. The mixture was stirred at -78°C for 45 min, followed by the addition of 1,2-dibromo-1,1,2,2-tetrachloroethane (2.50 g, 7.68 mmol, 1.2 eq.) in tetrahydrofuran (10 ml). The resulting mixture was allowed to warm to RT over a period of 1 h, quenched by the addition of saturated aqueous solution of ammonium chloride and extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 98:2 to 9:1). Yield: 540 mg (41% purity, 15% of theory).

GC-MS (method 6): $R_t = 4.33$ min; MS (APCIpos): $m/z = 235$ $[M+H]^+$

Example 1.6C

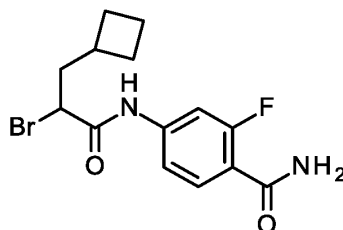
2-Bromo-3-cyclobutylpropanoic acid (racemate)



General Method 10 was carried out with ethyl 2-bromo-3-cyclobutylpropanoate (racemate) (530 mg, 41% purity, 924 μ mol, 1.0 eq.) and lithium hydroxide (111 mg, 4.62 mmol, 5.0 eq.) in a mixture of tetrahydrofuran / water (2:1, 9 ml) including the following variations of the procedure: The reaction mixture was stirred at RT for 2 h, then acidified by the addition of aqueous hydrochloric acid (1 N) and extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used in the subsequent reaction without further purification.

Example 1.6D

4-(2-Bromo-3-cyclobutylpropanamido)-2-fluorobenzamide (racemate)



General Method 11 was carried out two times with crude product of 2-bromo-3-cyclobutylpropanoic acid (racemate) (50.0 mg, 0.24 mmol, 1.0 eq.), 4-amino-2-fluorobenzamide (55.8 mg, 0.36 mmol, 1.5 eq.) and T3P (0.56 ml, 50% solution in ethyl acetate, 0.97 mmol, 4.0 eq.) in pyridine (3 ml) and

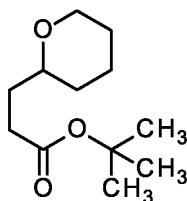
5 crude product of 2-bromo-3-cyclobutylpropanoic acid (racemate) (410 mg, 1.98 mmol, 1.0 eq.), 4-amino-2-fluorobenzamide (458 mg, 2.97 mmol, 1.5 eq.) and T3P (4.6 ml, 50% solution in ethyl acetate, 7.9 mmol, 4.0 eq.) in pyridine (20 ml) including the following variations of the procedure: The two reaction mixtures were combined, washed with saturated aqueous solution of ammonium chloride and water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced

10 pressure. The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 33.0 mg (91% purity, 4% of theory).

LC-MS (method 5): $R_t = 1.16$ min; MS (ESIpos): $m/z = 343$ $[M+H]^+$

Example 1.7A

tert-Butyl 3-(tetrahydro-2*H*-pyran-2-yl)propanoate (racemate)



15

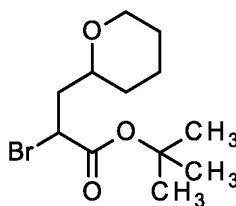
Tetrahydro-2*H*-pyran-2-ylmethanol (racemate) (20.0 g, 172 mmol, 1.0 eq.), *tert*-butyl acetate (230 ml, 1.7 mol, 10.0 eq.), bis(1,5-cyclooctadiene)diiridium(I) dichloride (5.78 g, 8.61 mmol, 0.1 eq.), triphenylphosphine (6.77 g, 25.8 mmol, 0.2 eq.) and potassium *tert*-butanolate (38.6 g, 344 mmol, 2.0 eq.) were dissolved in degassed *tert*-butanol (200 ml) and stirred at 100°C for 6 days.

20 The reaction mixture was filtered and washed repeatedly with ethyl acetate. After removal of the volatiles under reduced pressure, the crude mixture was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate with 0.1% *N,N*-diisopropylethylamine: 100:0 to 98:2 to 96:4). Yield: 8.40 g (23% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 3.88-3.80 (m, 1H), 3.32-3.24 (m, 1H), 3.20-3.13 (m, 1H), 2.29-2.13 (m, 2H), 1.78-1.67 (m, 1H), 1.63-1.49 (m, 3H), 1.47-1.35 (m, 3H), 1.39 (s, 9H), 1.18-1.06 (m, 1H).

Example 1.7B

- 5 *tert*-Butyl 2-bromo-3-(tetrahydro-2*H*-pyran-2-yl)propanoate (mixture of stereoisomers)

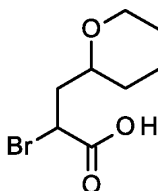


- N,N*-Diisopropylamine (7.7 ml, 55 mmol, 1.4 eq.) was dissolved in tetrahydrofuran (120 ml) and cooled to 0°C before a solution of *n*-butyllithium (19 ml, 2.5 M in hexane, 47 mmol, 1.2 eq.) was added. The mixture was stirred at 0°C for 30 min, then cooled to -78°C, followed by the dropwise addition of *tert*-butyl 3-(tetrahydro-2*H*-pyran-2-yl)propanoate (racemate) (8.40 g, 39.2 mmol, 1.0 eq.) in tetrahydrofuran (62 ml). Stirring was continued at -78°C for 45 min, 1,2-dibromo-1,1,2,2-tetrafluoroethane (12.2 g, 47.0 mmol, 1.2 eq.) in tetrahydrofuran (62 ml) was added dropwise and the mixture was warmed to RT over 1 h. After addition of saturated aqueous solution of ammonium chloride, the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate with 0.1% *N,N*-diisopropylethylamine: 100:0 to 96:4 to 70:30). Yield: 7.00 g (61% of theory).
- 10
- 15

GC-MS (method 6): *R*_t = 5.38 / 5.50 min; MS (APCIpos): *m/z* = 239 [M-*t*Bu+H]⁺

Example 1.7C

- 20 2-Bromo-3-(tetrahydro-2*H*-pyran-2-yl)propanoic acid (mixture of stereoisomers)

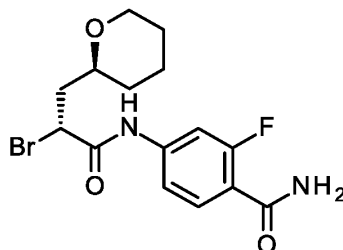


- tert*-Butyl 2-bromo-3-(tetrahydro-2*H*-pyran-2-yl)propanoate (mixture of stereoisomers) (7.00 g, 23.9 mmol, 1.0 eq.) was dissolved in trifluoroacetic acid (140 ml) and stirred at RT for 2 h. The reaction mixture was concentrated under reduced pressure and coevaporated three times with toluene.
- 25 The crude product was used in the subsequent reaction without further purification. Yield: 5.65 g (quantitative of theory).

GC-MS (method 6): $R_t = 5.53$ min; MS (APCIpos): $m/z = 239$ $[M+H]^+$

Example 1.7D

4-({(2*R*)-2-Bromo-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)-2-fluorobenzamide (single stereoisomer)



5

General Method 11 was carried out with 4-amino-2-fluorobenzamide (3.68 g, 23.9 mmol, 1.0 eq.), 2-bromo-3-(tetrahydro-2*H*-pyran-2-yl)propanoic acid (mixture of stereoisomers) (5.66 g, 23.9 mmol, 1.0 eq.), pyridine (2.1 ml, 26 mmol, 1.1 eq.) and T3P (21 ml, 50% solution in ethyl acetate, 36 mmol, 1.5 eq.) in tetrahydrofuran (43 ml) including the following variations of the procedure: After stirring
10 at RT overnight, the reaction mixture was worked up by addition of water, extracted with ethyl acetate, washed with brine, dried and concentrated under reduced pressure. Stereoisomer separation of the crude mixture gave:

single stereoisomer 1 (chiral SFC: $R_t = 1.52$ min): 1.87 g,

single stereoisomer 2 (the title compound 1.7D) (chiral SFC: $R_t = 1.66$ min, 99% de): 1.90 g (21%
15 of theory),

single stereoisomer 3 (chiral SFC: $R_t = 1.30$ min): 1.18 g,

single stereoisomer 4 (chiral SFC: $R_t = 1.34$ min): 1.15 g.

Separation method 1: SFC: column: Daicel Chiralpak AD 20 μ m, 450 mm x 50 mm; eluent: 75% carbon dioxide / 25% 2-propanol; temperature: 40°C; flow rate: 400 ml/min; UV detection: 210 nm.

20 Separation method 2: Single stereoisomer 3 and single stereoisomer 4 eluted as a mixture in the first separation. This mixture was then separated according to the following conditions: SFC: column: Daicel Chiralpak AD 20 μ m, 450 mm x 50 mm; eluent: 20% carbon dioxide / 80% 2-propanol; temperature: 40°C; flow rate: 400 ml/min; UV detection: 210 nm.

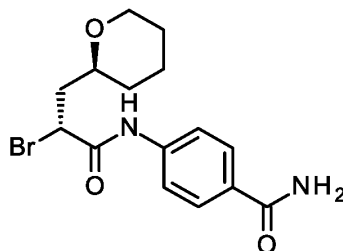
Analysis method: SFC: column: Daicel Chiralpak AD-H 5 μ m, 250 mm x 4.6 mm; eluent: 80%
25 carbon dioxide / 20% methanol; flow rate: 3.0 ml/min; UV detection: 210 nm.

LC-MS (method 1): $R_t = 0.82$ min; MS (ESIpos): $m/z = 373$ $[M+H]^+$

¹H-NMR (500 MHz, DMSO-*d*₆): δ [ppm] = 10.71 (s, 1H), 7.72-7.66 (m, 1H), 7.65-7.59 (m, 1H), 7.57-7.46 (m, 2H), 7.43-7.26 (m, 1H), 4.80-4.66 (m, 1H), 3.88 (d, 1H), 3.54-3.41 (m, 1H), 3.40-3.33 (m, 1H), 2.11-1.95 (m, 2H), 1.88-1.69 (m, 1H), 1.61 (d, 1H), 1.53-1.38 (m, 3H), 1.31-1.21 (m, 1H).

Example 1.8A

- 5 4-({(2*R*)-2-Bromo-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)benzamide (single stereoisomer)



General Method 11 was carried out with 4-aminobenzamide (5.95 g, 43.7 mmol, 1.0 eq.), 2-bromo-3-(tetrahydro-2*H*-pyran-2-yl)propanoic acid (mixture of stereoisomers) (11.4 g, 48.1 mmol, 1.1 eq.),
10 pyridine (3.9 ml, 48.1 mmol, 1.1 eq.) and T3P (39 ml, 50% solution in ethyl acetate, 66 mmol, 1.5 eq.) in tetrahydrofuran (79 ml) including the following variations of the procedure: After stirring at RT overnight, the reaction mixture was worked up by addition of water, extracted with ethyl acetate, washed with brine, dried and concentrated under reduced pressure. Stereoisomer separation of the crude mixture gave:

- 15 single stereoisomer 1 (the title compound 1.8A) (chiral SFC: R_t = 1.52 min, 99% de): 2.71 g (17% of theory),

single stereoisomer 2 (chiral SFC: R_t = 1.66 min): 3.29 g,

single stereoisomer 3 (chiral SFC: R_t = 1.30 min): 1.43 g,

single stereoisomer 4 (chiral SFC: R_t = 1.34 min): 1.45 g.

- 20 Separation method 1: SFC: column: Daicel Chiralpak AD 20 μ m, 450 mm x 50 mm; eluent: 75% carbon dioxide / 25% 2-propanol; temperature: 40°C; flow rate: 400 ml/min; UV detection: 210 nm.

Separation method 2: Single stereoisomer 3 and single stereoisomer 4 eluted as a mixture in the first separation. This mixture was then separated according to the following conditions: SFC: column: Daicel Chiralpak AD 20 μ m, 450 mm x 50 mm; eluent: 20% carbon dioxide / 80% 2-propanol;

- 25 temperature: 40°C; flow rate: 400 ml/min; UV detection: 210 nm.

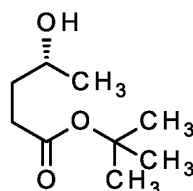
Analysis method: SFC: column: Daicel Chiralpak AD-H 5 μ m, 250 mm x 4.6 mm; eluent: 80% carbon dioxide / 20% methanol; flow rate: 3.0 ml/min; UV detection: 210 nm.

LC-MS (method 1): R_t = 0.75 min; MS (ESIpos): m/z = 355 [M+H]⁺

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 10.58 (s, 1H), 7.95-7.82 (m, 3H), 7.71-7.63 (m, 2H), 7.29 (br s, 1H), 4.81 (dd, 1H), 3.92 (d, 1H), 3.58-3.43 (m, 1H), 3.42-3.37 (m, 1H), 2.12-1.99 (m, 2H), 1.80 (d, 1H), 1.64 (d, 1H), 1.57-1.41 (m, 4H), 1.37-1.22 (m, 1H).

Example 1.9A

- 5 *tert*-Butyl (4*R*)-4-hydroxypentanoate (single stereoisomer)

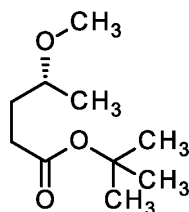


- To a stirred solution of lithium diisopropylamide (86 ml, 2.0 M in tetrahydrofuran / *n*-hexane, 170 mmol, 2.0 eq.) in tetrahydrofuran (250 ml) was added *tert*-butyl acetate (20.0 g, 172 mmol, 2.0 eq.) dropwise at -78°C. After stirring for 0.5 h, the mixture was warmed to -40°C, diethylaluminum chloride (170 ml, 1.0 M in hexane, 170 mmol, 2.0 eq.) was added over a period of 20 min and stirring was continued for further 15 min. Subsequently, (2*R*)-2-methyloxirane (single stereoisomer) (5.00 g, 86.1 mmol, 1.0 eq.) was added and the mixture was stirred at -40°C for 5 h, followed by the addition of saturated aqueous solution of ammonium chloride and ice in aqueous hydrochloric acid (6 N) at -20°C. The mixture was extracted with diethyl ether and the combined organic layers were washed with saturated aqueous solution of sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: *n*-hexane / ethyl acetate 4:1). Yield: 8.0 g (90% purity, 48% of theory).

- ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 4.43 (d, 1H), 3.62-3.49 (m, 1H), 2.33-2.14 (m, 2H), 1.61-1.46 (m, 2H), 1.39 (s, 9H), 1.03 (d, 3H).

Example 1.9B

- tert*-Butyl (4*R*)-4-methoxypentanoate (single stereoisomer)



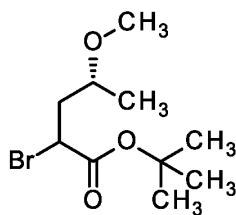
- To a suspension of *tert*-butyl (4*R*)-4-hydroxypentanoate (single stereoisomer) (9.00 g, 95% purity, 49.1 mmol, 1.0 eq.) and freshly prepared silver(I) oxide (34.1 g, 147 mmol, 3.0 eq.) in 1,2-dichloroethane (150 ml) was added iodomethane (31 ml, 490 mmol, 10.0 eq.) at 0°C. After

stirring at 40°C for 72 h, the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: *n*-hexane / ethyl acetate 8:1 to 1:1). Yield: 1.90 g (20% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 3.28-3.21 (m, 1H), 3.18 (s, 3H), 2.20 (t, 2H), 1.71-1.50 (m, 2H), 1.39 (s, 9H), 1.04 (d, 3H).

Example 1.9C

tert-Butyl (4*R*)-2-bromo-4-methoxypentanoate (mixture of two diastereomers)

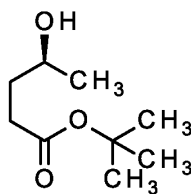


To a solution of *tert*-butyl (4*R*)-4-methoxypentanoate (single stereoisomer) (1.70 g, 8.58 mmol, 1.0 eq.) in tetrahydrofuran (70 ml) was added lithium diisopropylamide (6.4 ml, 2.0 M in tetrahydrofuran, 13 mmol, 1.5 eq.) at -78°C. After stirring at -78°C for 15 min, a solution of 1,2-dibromo-1,1,2,2-tetrachloroethane (6.98 g, 21.4 mmol, 2.5 eq.) in tetrahydrofuran (10 ml) was added dropwise. The resulting mixture was slowly allowed to warm to RT over a period of 1 h and stirred for further 2 h before water was added. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (silica gel, eluent: petroleum ether / ethyl acetate 8:1). Yield: 0.95 g (90% purity, 37% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 4.40-4.28 (m, 1H), 3.47-3.36 / 3.34-3.26 (2m, 1H), 3.21 / 3.18 (2s, 3H), 2.21-1.86 (m, 2H), 1.43 / 1.42 (2s, 9H), 1.15-1.05 (m, 3H).

Example 1.10A

tert-Butyl (4*S*)-4-hydroxypentanoate (single stereoisomer)



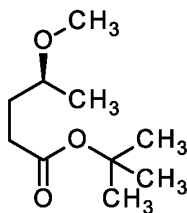
tert-Butyl acetate (4.00 g, 34.4 mmol, 2.0 eq.) was added dropwise at -78°C to a stirred solution of lithium diisopropylamide (17.2 ml, 34.4 mmol, 2 M in tetrahydrofuran / *n*-hexane, 2.0 eq.) in

tetrahydrofuran (50 ml). After stirring for 0.5 h, the mixture was warmed to -40°C. Diethylaluminum chloride (34.4 ml, 34.4 mmol, 1 M in *n*-hexane, 2.0 eq.) was added over a period of 5 min and stirring was continued for further 15 min. Subsequently, (2*S*)-2-methyloxirane (single stereoisomer) (1.00 g, 17.2 mmol, 1.0 eq.) was added and the mixture was stirred at -40°C for 5 h, followed by the addition of saturated aqueous solution of ammonium chloride and ice in aqueous hydrochloric acid (6 N) at -20°C. The mixture was extracted with diethyl ether. The combined organic layers were washed with saturated aqueous solution of sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: *n*-hexane / ethyl acetate 4:1). Yield: 1.50 g (90% purity, 45% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 4.45 (d, 1H), 3.64-3.46 (m, 1H), 2.34-2.12 (m, 2H), 1.61-1.45 (m, 2H), 1.40 (s, 9H), 1.04 (d, 3H).

Example 1.10B

tert-Butyl (4*S*)-4-methoxypentanoate (single stereoisomer)



15

Iodomethane (61.3 g, 432 mmol, 10.0 eq.) was added at 0°C to a suspension of *tert*-butyl (4*S*)-4-hydroxypentanoate (single stereoisomer) (8.00 g, 43.2 mmol, 1.0 eq.) and freshly prepared silver(I) oxide (30.0 g, 130 mmol, 3.0 eq.) in 1,2-dichloroethane (150 ml). After stirring at 40°C for 72 h, the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: *n*-hexane / ethyl acetate 8:1 to 1:1). Yield: 2.20 g (26% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 3.28-3.21 (m, 1H), 3.18 (s, 3H), 2.20 (t, 2H), 1.68-1.54 (m, 2H), 1.39 (s, 9H), 1.04 (d, 3H).

Alternative synthetic route:

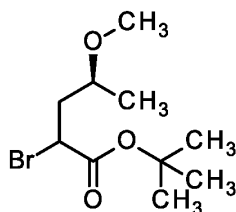
N,N,N',N'-Tetramethylnaphthalene-1,8-diamine (14.36 g, 66.99 mmol, 1.1 eq., weighed out in glove box!) was added under argon atmosphere at 0-4°C to a solution of *tert*-butyl (4*S*)-4-hydroxypentanoate (single stereoisomer) (13.10 g, 60.90 mmol) in dichloromethane (260 ml). The reaction mixture was stirred at RT for 30 min, cooled again to 0-4°C, mixed with trimethyloxonium tetrafluoroborate (19.91 g, 127.89 mmol, 2.1 eq., weighed out in glove box!), stirred for 30 min at 0-4°C and then for 60 min while allowing to warm to RT. The reaction mixture was quenched with

- water (250 ml) and diluted with dichloromethane (150 ml). The precipitate was filtered off and discarded. After phase separation, the aqueous phase was extracted two times with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure (at >100 mbar and <25°C). The residue was purified by
- 5 column chromatography (silica gel, eluent: cyclohexane / ethyl acetate gradient, eluent evaporation at >80 mbar and <30°C). Yield: 10.13 g (88% of theory).

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 3.28-3.22 (m, 1H), 3.19 (s, 3H), 2.20 (t, 2H), 1.64-1.57 (m, 2H), 1.39 (s, 9H), 1.05 (d, 3H).

Example 1.10C

- 10 *tert*-Butyl (4*S*)-2-bromo-4-methoxypentanoate (mixture of two diastereomers)

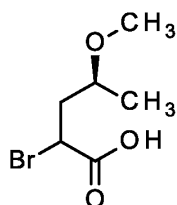


- Lithium diisopropylamide (5.7 ml, 11.4 mmol, 2.0 M in tetrahydrofuran, 1.5 eq.) was added at -78°C to a solution of *tert*-butyl (4*S*)-4-methoxypentanoate (single stereoisomer) (1.50 g, 7.6 mmol, 1.0 eq.) in tetrahydrofuran (60 ml). After stirring at -78°C for 15 min, a solution of 1,2-dibromo-1,1,2,2-tetrachloroethane (6.16 g, 18.9 mmol, 2.5 eq.) in tetrahydrofuran (8 ml) was added dropwise. The resulting mixture was slowly allowed to warm to RT over a period of 1 h and stirred for further 2 h before water was added. The aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative thin-layer
- 15 chromatography (silica gel, eluent: petroleum ether / ethyl acetate 8:1). Yield: 0.94 g (85% purity, 40% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 4.41-4.28 (m, 1H), 3.47-3.36 / 3.35-3.25 (2m, 1H), 3.21 / 3.18 (2s, 3H), 2.21-1.85 (m, 2H), 1.43 / 1.42 (2s, 9H), 1.15-1.05 (m, 3H).

Example 1.10D

- 25 (4*S*)-2-Bromo-4-methoxypentanoic acid (mixture of two diastereomers)



Trifluoroacetic acid (13.3 ml, 172.6 mmol, 20 eq.) was added dropwise under argon atmosphere to an ice-cooled solution of *tert*-butyl (4*S*)-2-bromo-4-methoxypentanoate (mixture of two diastereomers) (2.7 g, 85% purity, 8.6 mmol) in dichloromethane (50 ml). The reaction mixture was stirred at RT for 2 h, followed by the addition of further trifluoroacetic acid (3.3 ml, 43.2 mmol, 5.0 eq.). After stirring for another 1 h, the reaction mixture was concentrated *in vacuo* and coevaporated with dichloromethane. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate gradient). Yield: 1.37 g (75% of theory).

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 4.41-4.36 (m, 1H), 3.48-3.40 / 3.35-3.28 (2m, 1H), 3.23 / 3.19 (2s, 3H), 2.17-2.02 / 1.96-1.89 (2m, 2H), 1.12 / 1.10 (2d, 3H).

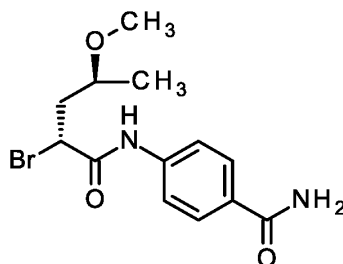
Alternative synthetic route:

Lithium hydroxide monohydrate (233 g, 5.55 mol, 2.1 eq.) was added at RT to a solution of methyl (4*S*)-2-bromo-4-methoxypentanoate (mixture of two diastereomers) (625 g, 94% purity, 2.61 mol) in a mixture of tetrahydrofuran / water (3:1, 6.1 l). The reaction mixture was stirred at RT overnight and mixed with 1 N aqueous hydrochloric acid (5 l). The aqueous phase was extracted with 2-methyltetrahydrofuran. The organic phase was dried and evaporated under reduced pressure. The crude material was used without further purification. Yield: 595 g (94% purity, quantitative of theory).

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 12.9 (br s, 1H, two diastereomers), 4.44-4.30 (m, 1H, two diastereomers), 3.47-3.40 (m, 1H, major diastereomer), 3.37-3.27 (m, 1H, minor diastereomer), 3.22 (s, 3H, major diastereomer), 3.18 (s, 3H, minor diastereomer), 2.17-2.00 (m, 2H, two diastereomers), 1.11 (d, 3H, major diastereomer), 1.09 (d, 3H, minor diastereomer).

Example 1.10E

4-[(2*R*,4*S*)-2-Bromo-4-methoxypentanoyl]amino}benzamide (single stereoisomer)



(4*S*)-2-Bromo-4-methoxypentanoic acid (mixture of two diastereomers) (1.37 g, 6.5 mmol), pyridine (579 μ l, 7.2 mmol, 1.1 eq.) and T3P (5.7 ml, 50% solution in ethyl acetate, 9.8 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of 4-aminobenzamide (975 mg, 7.2 mmol, 1.1 eq.) in tetrahydrofuran (25 ml). The reaction mixture was stirred at RT for 2 h, quenched with water and diluted with ethyl acetate. After phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: dichloromethane / methanol gradient). Yield: 1.91 g (86% of theory).

10 LC-MS (method 4): R_t = 1.18 min; MS (ESIpos): m/z = 329 $[M+H]^+$

Diastereomer separation of 1910 mg of 4-{[(4*S*)-2-bromo-4-methoxypentanoyl]amino}benzamide (mixture of two diastereomers) gave

single stereoisomer 1 (the title compound Example 1.10E) (chiral HPLC: R_t = 11.7 min, >99% de): 901 mg,

15 single stereoisomer 2 (chiral HPLC: R_t = 14.0 min, 89% de): 576 mg.

Separation method: HPLC: column: Daicel Chiralpak IE 5 μ m, 250 mm x 20 mm; eluent: 80% *n*-heptane / 20% ethanol; temperature: 40°C; flow rate: 15 ml/min; UV detection: 220 nm.

Analysis method: HPLC: column: Daicel Chiralpak IE 5 μ m, 250 mm x 4.6 mm; eluent: 80% *iso*-hexane / 20% ethanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.

20 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.56 (s, 1H), 7.92-7.81 (m, 3H), 7.65 (d, 2H), 7.25 (br s, 1H), 4.75 (t, 1H), 3.54-3.44 (m, 1H), 3.26 (s, 3H), 2.10-2.02 (m, 2H), 1.15 (d, 3H).

Alternative synthetic route:

Under nitrogen atmosphere, 4-aminobenzamide (419 g, 3.08 mol, 1.17 eq.) in tetrahydrofuran (6.1 l) was treated at RT with (4*S*)-2-bromo-4-methoxypentanoic acid (mixture of two diastereomers) (591 g, 94% purity, 2.63 mol), pyridine (249 ml, 3.08 mol, 1.17 eq.) and T3P (50% in ethyl acetate, 2.51 l, 4.21 mol). After 4 h stirring at RT, the reaction mixture was diluted with ethyl acetate (7.0 l) and afterwards with water (8.0 l). After extraction and phase separation, the aqueous phase was reextracted with ethyl acetate (7.0 l). The combined organic phases were washed with saturated

aqueous sodium chloride solution (6.0 l). The residue was suspended in diisopropyl ether (7.5 l) and ethyl acetate (550 ml) and stirred for 2.5 h at RT. The mixture was filtered under reduced pressure. Methanol was added under stirring to allow for a good filtration. The obtained solid was washed with diisopropyl ether and dried under air atmosphere. This material was triturated with acetonitrile at 5 80°C for 20 min. The suspension was slowly allowed to reach RT and then cooled down to 0°C. After stirring for 1 h, the suspension was filtered under reduced pressure, the residue was washed with cold acetonitrile and then dried under air atmosphere (yield: 81 g). The filtrate from the first filtration was concentrated under reduced pressure and the obtained residue was triturated with acetonitrile (5.0 l) at 80°C for 20 min. The suspension was slowly allowed to reach RT and then 10 cooled down to 0°C. After stirring for 1 h, the suspension was filtered under reduced pressure, the residue was washed with cold acetonitrile and then dried under air atmosphere (yield: 451 g). The combined filtrates were concentrated under reduced pressure and the obtained residue was dissolved with acetonitrile (1.0 l) at 60°C. The suspension was slowly allowed to reach RT and then cooled 15 down to 0°C. After stirring for 1 h, the suspension was filtered under reduced pressure, the residue was washed with cold acetonitrile and then dried under air atmosphere. This material was dissolved in dichloromethane and methanol and loaded onto Isolute®. This material was purified *via* column chromatography (Biotage Isolera LS, 1.5 kg SNAP-Ultra cartridge, eluent: dichloromethane / 20% acetone (1 cv), 20% - 60% acetone gradient (10 cv), 60% acetone (2 cv) to yield 63 g. Diastereomer separation of all crude products (81 g, 451 g and 63 g) *via* SFC gave the product as single 20 stereoisomer. Combined yield: 266 g (31% of theory, >99% de).

Separation method: SFC: column: Chiralpak AY, 20 µm, 250 mm x 50 mm, eluent: isocratic 82% carbon dioxide / 18% methanol, 5 min, temperature: 30°C; flow rate: 350 ml/min; UV detection: 210 nm; backpressure 100 bar and SFC: column: Chiralpak AZ 20 µm, 350 mm x 50 mm, eluent: isocratic 65% carbon dioxide / 35% methanol; 5 min, temperature: 30°C; flow rate: 350 ml/min; UV 25 detection: 210 nm; backpressure: 100 bar.

Chiral SFC: $R_t = 1.56$ min, >99% de

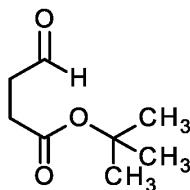
Analysis method: SFC: column: Chiralcel AY-3, 3 µm, 100 mm x 4.6 mm, eluent: isocratic 80% carbon dioxide / 20% methanol; 10 min, temperature: 40°C; flow rate: 3.0 ml/min; UV detection: 210 nm; backpressure: 130 bar.

30 LC-MS (method 4): $R_t = 1.16$ min; MS (ESIpos): $m/z = 329, 331$ $[M+H]^+$

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.5 (br s, 1H), 7.85 (br d, 3H), 7.65 (br d, 2H), 7.23 (br s, 1H), 4.75 (br t, 1H), 3.57-3.43 (m, 1H), 3.26 (s, 3H), 2.07 (br t, 2H), 1.15 (br d, 3H).

Example 1.11A

tert-Butyl 4-oxobutanoate

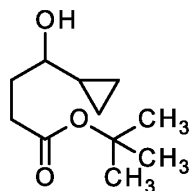


3,3,3-Triacetoxy-3-iodophthalide (123.7 g, 291.6 mmol, 2.0 eq.) was added in portions at 0°C to a mixture of *tert*-butyl 4-hydroxybutanoate (23.4 g, 145.8 mmol, 1.0 eq.) and sodium bicarbonate (24.5 g, 291.6 mmol, 2.0 eq.) in dichloromethane (500 ml). After stirring at RT for 2 h, the reaction mixture was quenched by the addition of a mixture of saturated aqueous solution of sodium carbonate and sodium thiosulfate (1:1), stirred for further 30 min and extracted with dichloromethane. The combined organic phases were washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 95:5). Yield: 15.4 g (63% of theory).

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 9.79 (s, 1H), 2.76-2.68 (m, 2H), 2.59-2.50 (m, 2H), 1.43 (s, 9H).

Example 1.11B

tert-Butyl 4-cyclopropyl-4-hydroxybutanoate (racemate)



15

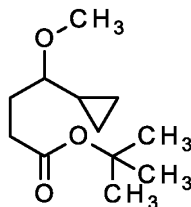
Cyclopropylmagnesium bromide (185.0 ml, 1.0 M in tetrahydrofuran, 185.0 mmol, 2.0 eq.) was added under argon atmosphere at -10°C to a stirred solution of *tert*-butyl 4-oxobutanoate (15.4 g, 92.5 mmol) in tetrahydrofuran (300 ml). The reaction mixture was allowed to warm to RT within a period of 1 h, stirred for another 1 h, quenched with aqueous solution of aqueous hydrochloric acid (2 N), diluted with ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 90:10). Yield: 5.88 g (85% purity, 27% of theory).

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 4.55-4.30 (m, 1H), 2.89-2.72 (m, 1H), 2.39-2.13 (m, 2H), 1.82-1.52 (m, 2H), 1.39 (s, 9H), 0.88-0.67 (m, 1H), 0.45-0.05 (m, 4H).

25

Example 1.11C

tert-Butyl 4-cyclopropyl-4-methoxybutanoate (racemate)

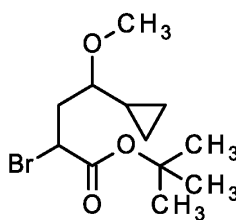


Iodomethane (34.82 g, 245.3 mmol, 10.0 eq.) was added under argon atmosphere at RT to a mixture of *tert*-butyl 4-cyclopropyl-4-hydroxybutanoate (racemate) (5.78 g, 85% purity, 24.5 mmol) and freshly prepared silver(I) oxide (17.05 g, 73.6 mmol, 3.0 eq.) in 1,2-dichloroethane (100 ml). After stirring at 45°C for 24 h, the resulting mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was re-dissolved in 1,2-dichloroethane (100 ml), followed by the addition of silver(I) oxide (8.53 g, 36.8 mmol, 1.5 eq.) and iodomethane (17.41 g, 122.7 mmol, 5.0 eq.) under argon atmosphere at RT. The resulting mixture was stirred at 45°C for 48 h and filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 99:1 to 80:20). Yield: 1.44 g (27% of theory).

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 3.38 (s, 3H), 2.53-2.42 (m, 1H), 2.42-2.28 (m, 2H), 1.97-1.77 (m, 2H), 1.44 (s, 9H), 0.84-0.69 (m, 1H), 0.68-0.54 (m, 1H), 0.53-0.31 (m, 2H), 0.14-0.02 (m, 1H).

Example 1.11D

tert-Butyl 2-bromo-4-cyclopropyl-4-methoxybutanoate (mixture of stereoisomers)



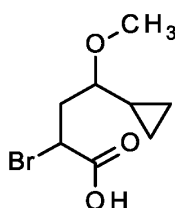
Lithium diisopropylamide (4.9 ml, 2.0 M in tetrahydrofuran, 9.9 mmol, 1.5 eq.) was added under argon atmosphere at -78°C to a solution of *tert*-butyl 4-cyclopropyl-4-methoxybutanoate (racemate) (1.44 g, 6.6 mmol) in tetrahydrofuran (20 ml). The resulting mixture was stirred at -78°C for 1 h, followed by the dropwise addition of a solution of 1,2-dibromo-1,1,2,2-tetrachloroethane (2.57 g, 7.9 mmol, 1.2 eq.) in tetrahydrofuran (10 ml) at -78°C. The resulting mixture was allowed to warm to RT, stirred further for 2 h, quenched with saturated aqueous solution of ammonium chloride and

extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography (silica gel, eluent: petroleum ether / ethyl acetate 80:20). Yield: 1.52 g (80% purity, 63% of theory).

- 5 ¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 4.42-4.33 (m, 1H), 3.43 / 3.36 (2s, 3H), 2.74-2.61 (m, 1H), 2.57-2.49 / 2.44-2.34 (2m, 1H), 2.29-2.19 (m, 1H), 1.47 (s, 9H), 0.87-0.72 (m, 1H), 0.71-0.60 (m, 1H), 0.53-0.36 (m, 2H), 0.19-0.03 (m, 1H).

Example 1.11E

2-Bromo-4-cyclopropyl-4-methoxybutanoic acid (mixture of stereoisomers)



10

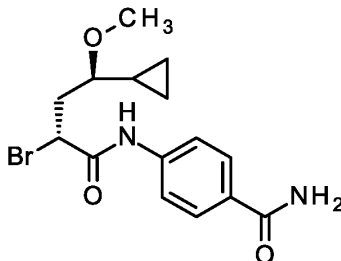
Trifluoroacetic acid (6.2 ml, 80.2 mmol, 20 eq.) was added dropwise under argon atmosphere to an ice-cooled solution of *tert*-butyl 2-bromo-4-cyclopropyl-4-methoxybutanoate (mixture of stereoisomers) (1.47 g, 80% purity, 4.01 mmol) in dichloromethane (40 ml). The reaction mixture was stirred at RT for 1.5 h, concentrated *in vacuo* and coevaporated two times with dichloromethane.

- 15 The residue was purified by column chromatography (silica gel, eluent: dichloromethane / methanol gradient). Yield: 641 mg (67% of theory).

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 13.15 (br s, 1H), 4.44-4.34 (m, 1H), 3.32 / 3.27 (2s, 3H), 3.04-2.97 / 2.85-2.79 / 2.72-2.62 (3m, 1H), 2.35-2.28 / 2.28-2.21 (2m, 1H), 2.19-2.11 / 2.07-2.00 (2m, 1H), 0.88-0.73 (m, 1H), 0.64-0.53 (m, 1H), 0.50-0.36 (m, 2H), 0.12-0.0 (m, 1H).

Example 1.11F

4-{[(2*R*,4*R*)-2-Bromo-4-cyclopropyl-4-methoxybutanoyl]amino}benzamide (single stereoisomer)



2-Bromo-4-cyclopropyl-4-methoxybutanoic acid (mixture of stereoisomers) (641 mg, 2.70 mmol), pyridine (241 µl, 2.97 mmol, 1.1 eq.) and T3P (2.37 ml, 50% solution in ethyl acetate, 4.06 mmol,

1.5 eq.) were added under argon atmosphere at RT to a solution of 4-aminobenzamide (368 mg, 2.70 mmol, 1.0 eq.) in tetrahydrofuran (15 ml). The reaction mixture was stirred at RT for 1.5 h before additional 4-aminobenzamide (110 mg, 0.81 mmol, 0.3 eq.) and T3P (316 μ l, 50% solution in ethyl acetate, 0.54 mmol, 0.2 eq.) were added and stirred for another 1 h. The reaction mixture
5 was quenched with water and diluted with ethyl acetate. After phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Yield: 941 mg.

Stereoisomer separation of 941 mg of 4-(2-bromo-4-cyclopropyl-4-methoxybutan-amido)benzamide (mixture of stereoisomers) gave

10 mixture of two stereoisomers 1+2 (chiral SFC: R_t = 2.81 min): 197 mg,

single stereoisomer 3 (chiral SFC: R_t = 3.25 min, 98% ee): 134 mg,

single stereoisomer 4 (the title compound Example 1.11F) (chiral SFC: R_t = 3.58 min, 98% ee): 123 mg.

Separation method: SFC: column: Daicel OJ-H, 250 mm x 20 mm; eluent: 89% carbon dioxide /
15 11% ethanol; temperature: 40°C; flow rate: 80 ml/min; UV detection: 210 nm.

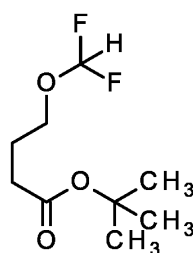
Analysis method: SFC: column: Daicel OJ-3, 50 mm x 4.6 mm; eluent: 90% carbon dioxide / 10% methanol; temperature: 40°C; flow rate: 3 ml/min; UV detection: 210 nm.

LC-MS (method 4): R_t = 1.38 min; MS (ESI^{neg}): m/z = 353 [M-H]⁻

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 10.55 (s, 1H), 7.89-7.81 (m, 3H), 7.65 (d, 2H), 7.23 (br
20 s, 1H), 4.74 (dd, 1H), 3.36 (s, 3H), 2.70 (dt, 1H), 2.26-2.13 (m, 2H), 0.84-0.76 (m, 1H), 0.65-0.57 (m, 1H), 0.49-0.41 (m, 2H), 0.06-0.0 (m, 1H).

Example 1.12A

tert-Butyl 4-(difluoromethoxy)butanoate



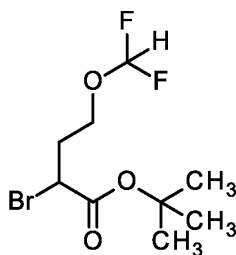
25 [Bromo(difluoro)methyl](trimethyl)silane (5.28 ml, 29.6 mmol, 2.0 eq.) was added dropwise under argon atmosphere at RT to a solution of *tert*-butyl 4-hydroxybutanoate (2.50 g, 14.8 mmol) and potassium acetate (5.82 g, 59.3 mmol, 4.0 eq.) in a mixture of dichloromethane (8.7 ml) and water (8.7 ml). The reaction mixture was stirred overnight and diluted with dichloromethane and water.

After phase separation, the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used without further purification. Yield: 3.82 g.

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 6.63 (t, 1H), 3.82 (t, 2H), 2.27 (t, 2H), 1.83-1.75 (m, 2H),
5 1.40 (s, 9H).

Example 1.12B

tert-Butyl 2-bromo-4-(difluoromethoxy)butanoate (racemate)

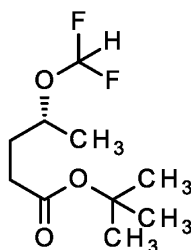


A solution of *n*-butyllithium (12.2 ml, 1.6 M in hexane, 19.5 mmol, 1.2 eq.) was added dropwise
10 under argon atmosphere at 0°C to a solution of diisopropylamine (3.2 ml, 22.8 mmol, 1.4 eq.) in
tetrahydrofuran (25 ml). The reaction mixture was stirred at 0°C for 30 min and cooled to -78°C. A
solution of *tert*-butyl 4-(difluoromethoxy)butanoate (3.8 g, 90% purity, 16.3 mmol) in
tetrahydrofuran (12.5 ml) was added dropwise and stirred at -78°C for 30 min. A solution of 1,2-
15 dibromo-1,1,2,2-tetrafluoroethane (5.1 g, 19.5 mmol, 1.2 eq.) was added dropwise and stirred at -
78°C for 10 min. The reaction mixture was allowed to warm to RT, stirred for another 1 h and
quenched with saturated aqueous solution of ammonium chloride. After phase separation, the
aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with
brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The
residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate
20 gradient). Yield: 1.7 g (36% of theory).

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 6.59 (t, 1H), 4.35-4.30 (m, 1H), 3.90-3.80 (m, 2H), 2.30-
2.22 (m, 1H), 2.10-2.02 (m, 1H).

Example 1.13A

tert-Butyl (4*R*)-4-(difluoromethoxy)pentanoate (single stereoisomer)



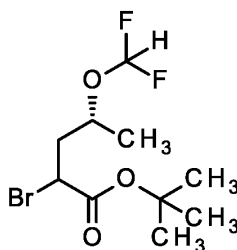
[Bromo(difluoro)methyl](trimethyl)silane (6.64 g, 32.7 mmol, 3.0 eq.) and potassium hydrogen difluoride (5.11 g, 65.4 mmol, 6.0 eq.) were added at RT to a mixture of *tert*-butyl (4*R*)-4-hydroxypentanoate (single stereoisomer) (2.00 g, 10.9 mmol) in dichloromethane (7 ml) and water
 5 (7 ml) in a plastic bottle. After stirring at RT for 10 h, the reaction mixture was diluted with dichloromethane and washed with water and brine. The organic phase was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. Yield: 2.17 g (85% of theory).

¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 6.22 (t, 1H), 4.37-4.26 (m, 1H), 2.41-2.31 (m, 2H), 1.89-
 10 1.77 (m, 2H), 1.46 (s, 9H), 1.31 (d, 3H).

¹⁹F-NMR (376 MHz, CDCl₃): δ [ppm] = -80.81 (q, 2F).

Example 1.13B

tert-Butyl (4*R*)-2-bromo-4-(difluoromethoxy)pentanoate (mixture of two diastereomers)



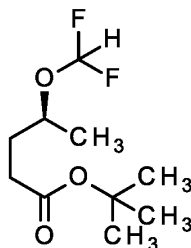
Lithium diisopropylamide (3.9 ml, 2.0 M in tetrahydrofuran, 7.7 mmol, 1.2 eq.) was added at -78°C under argon atmosphere to a solution of *tert*-butyl (4*R*)-4-(difluoromethoxy) pentanoate (single stereoisomer) (1.50 g, 6.4 mmol) in tetrahydrofuran (20 ml). The resulting mixture was stirred at -78°C for 1 h, followed by the dropwise addition of a solution of 1,2-dibromo-1,1,2,2-tetrachloroethane (2.30 g, 7.1 mmol, 1.1 eq.) in tetrahydrofuran (8 ml) at -78°C. The resulting
 20 mixture was allowed to warm to RT, stirred further for 4 h, quenched with saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness *in vacuo*. The crude product was purified by preparative thin layer chromatography (silica gel, eluent: petroleum ether / ethyl acetate 83:17). Yield: 0.85 g (85% purity, 37% of theory).

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ [ppm] = 6.44-5.96 (m, 1H), 4.59-4.40 (m, 1H), 4.38-4.21 (m, 1H), 2.39-2.01 (m, 2H), 1.51 / 1.44 (2s, 9H), 1.36 / 1.32 (2d, 3H).

$^{19}\text{F-NMR}$ (376 MHz, CDCl_3): δ [ppm] = -84.64 - -79.29 (m, 2F).

Example 1.14A

- 5 *tert*-Butyl (4*S*)-4-(difluoromethoxy)pentanoate (single stereoisomer)

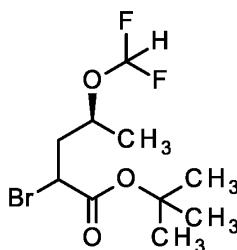


- A mixture of *tert*-butyl (4*S*)-4-hydroxypentanoate (single stereoisomer) (3.00 g, 16.2 mmol, 1.0 eq.) in dichloromethane (10 ml) and water (10 ml) was added into a plastic bottle, followed by the addition of [bromo(difluoro)methyl](trimethyl)silane (9.86 g, 48.6 mmol, 3.0 eq.) and potassium hydrogen difluoride (7.58 g, 97.1 mmol, 6.0 eq.) at RT. After stirring at RT for 10 h, the reaction mixture was diluted with dichloromethane, washed with water, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and used in the subsequent reaction without further purification. Yield: 3.50 g (92% of theory).

- $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ [ppm] = 6.47-5.97 (m, 1H), 4.39-4.18 (m, 1H), 2.39-2.25 (m, 2H), 1.90-1.72 (m, 2H), 1.45 (s, 9H), 1.30 (d, 3H).

Example 1.14B

tert-Butyl (4*S*)-2-bromo-4-(difluoromethoxy)pentanoate (mixture of two diastereomers)



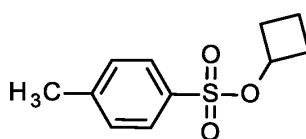
- Lithium diisopropylamide (8.9 ml, 2.0 M in tetrahydrofuran, 17.8 mmol, 1.2 eq.) was added at -78°C to a solution of *tert*-butyl (4*S*)-4-(difluoromethoxy)pentanoate (single stereoisomer) (3.50 g, 14.8 mmol, 1.0 eq.) in tetrahydrofuran (40 ml). After stirring at -78°C for 1 h, 1,2-dibromo-1,1,2,2-tetrachloroethane (5.79 g, 17.8 mmol, 1.2 eq.) in tetrahydrofuran (15 ml) was added. The resulting mixture was allowed to warm to RT and stirred for further 4 h. The reaction mixture was quenched

with saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified preparative thin-layer chromatography (silica gel, eluent: petroleum ether / ethyl acetate 91:9). Yield: 2.09 g (45% of theory).

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ [ppm] = 6.48-5.92 (m, 1H), 4.52-4.44 (m, 1H), 4.36-4.22 (m, 1H), 2.44-1.98 (m, 2H), 1.49 / 1.49 (2s, 9H), 1.36 / 1.32 (2d, 3H).

Example 1.15A

Cyclobutyl 4-methylbenzene-1-sulfonate



10

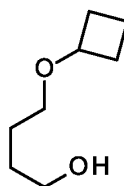
A solution of cyclobutanol (13 ml, 170 mmol, 1.0 eq.) in pyridine (86 ml) was cooled to 0°C, then 4-methylbenzene-1-sulfonyl chloride (34.9 g, 183 mmol, 1.1. eq.) was added in portions and stirring was continued for 80 min. Subsequently, the reaction mixture was poured to a mixture of ice and water, extracted with dichloromethane, washed with saturated aqueous solution of sodium bicarbonate and water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was then taken up in *n*-heptane and concentrated again for three times. The crude product was used in the subsequent step without further purification. Yield: 33.9 g (90% of theory).

15

GC-MS (method 6): R_t = 6.65 min; MS (APCIpos): m/z = 227 $[\text{M}+\text{H}]^+$

20 Example 1.15B

4-(Cyclobutyloxy)butan-1-ol



A solution of butane-1,4-diol (39.8 g, 442 mmol, 10.0 eq.) and potassium hydroxide (4.96 g, 88.4 mmol, 2.0 eq.) in 1,4-dioxane (220 ml) was heated to 105°C before a solution of cyclobutyl 4-methylbenzene-1-sulfonate (10.0 g, 44.2 mmol, 1.0 eq.) in 1,4-dioxane (46 ml) was added. The mixture was stirred at 105°C for 4 h, then diatomaceous earth was added and the suspension was

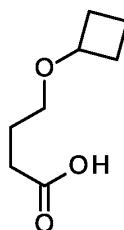
25

concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 1:1 to 3:7 to 1:9). Yield: 7.1 g (71% purity, 79% of theory).

GC-MS (method 6): $R_t = 3.61$ min; MS (APCIpos): $m/z = 145$ $[M+H]^+$

Example 1.15C

5 4-(Cyclobutyloxy)butanoic acid

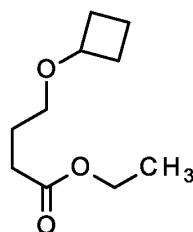


To a solution of chromium trioxide (11.1 g, 111 mmol, 8.0 eq.) in water (30 ml) at 0°C was added sulfuric acid (9.7 ml) and water (60 ml). The resulting mixture was stirred at 0°C for 15 min and then transferred to a solution of 4-(cyclobutyloxy)butan-1-ol (2.00 g, 13.9 mmol, 1.0 eq.) in acetone (40 ml) at RT. Stirring was continued at RT for 16 h, followed by the addition of water and extraction with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used in the subsequent step without further purification. Yield: 1.30 g of crude product.

GC-MS (method 6): $R_t = 4.05$ min; MS (APCIpos): $m/z = 159$ $[M+H]^+$

15 Example 1.15D

Ethyl 4-(cyclobutyloxy)butanoate

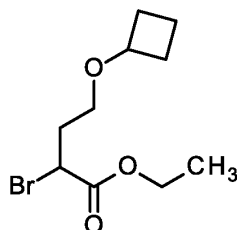


To a crude mixture of 4-(cyclobutyloxy)butanoic acid (1.30 g, 8.22 mmol, 1.0 eq.) in ethanol (29 ml) at 0°C was added dropwise thionyl chloride (1.2 ml, 16 mmol, 2.0 eq.). The resulting mixture was allowed to warm to RT and stirring was continued for 4 h before the mixture was concentrated under reduced pressure and coevaporated with toluene. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 9:1 to 4:1 to 7:3 to 3:1 to 1:1). Yield: 100 mg (76% purity, 5% of theory) and 270 mg (86% purity, 15% of theory).

GC-MS (method 6): $R_t = 4.15$ min; MS (APCIpos): $m/z = 187$ $[M+H]^+$

Example 1.15E

Ethyl 2-bromo-4-(cyclobutyloxy)butanoate (racemate)

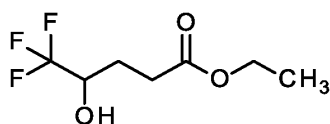


To a solution of diisopropylamine (280 μ l, 2.0 mmol, 1.4 eq.) in tetrahydrofuran (4.6 ml) was added
5 a solution of *n*-butyllithium (700 μ l, 2.5 M in hexane, 1.7 mmol, 1.2 eq.) at 0°C. After stirring at this
temperature for 30 min, the mixture was cooled to -78°C and a solution of 1,2-dibromo-1,1,2,2-
tetrachloroethane (566 mg, 1.74 mmol, 1.2 eq.) in tetrahydrofuran (4.6 ml) was added dropwise. The
mixture was stirred at -78°C for 45 min, followed by the addition of further 1,2-dibromo-1,1,2,2-
tetrachloroethane (566 mg, 1.74 mmol, 1.2 eq.) in portions. The resulting mixture was allowed to
10 warm to RT over a period of 1 h, quenched by the addition of saturated aqueous solution of
ammonium chloride and extracted with dichloromethane. The combined organic layers were dried
over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was
purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 98:2 to 96:4 to
94:6 to 92:8 to 9:1). Yield: 120 mg (75% purity, 23% of theory).

15 GC-MS (method 6): R_t = 5.13 min; MS (APCIpos): m/z = 266 $[M+H]^+$

Example 1.16A

Ethyl 5,5,5-trifluoro-4-hydroxypentanoate (racemate)

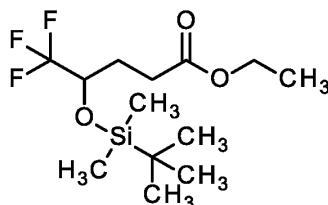


To a solution of ethyl 5,5,5-trifluoro-4-oxopentanoate (4.00 g, 20.2 mmol, 1.0 eq.) in ethanol (40 ml)
20 was added sodium borohydride (3.82 g, 100.9 mmol, 5.0 eq.) in portions at 0°C. After stirring at RT
for 5 h, the reaction mixture was poured into a mixture of aqueous hydrochloric acid (0.5 N) and
ethyl acetate and stirred for 10 min. The aqueous solution was extracted with ethyl acetate, the
combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate,
filtered and concentrated under reduced pressure. The residue was purified by column
25 chromatography (silica gel, eluent: petroleum ether / ethyl acetate 92:8). Yield: 1.65 g (39% of
theory).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 6.22 (d, 1H), 4.06 (q, 2H), 4.01-3.89 (m, 1H), 2.48-2.41 (m, 2H), 1.90-1.79 (m, 1H), 1.73-1.60 (m, 1H), 1.18 (t, 3H).

Example 1.16B

Ethyl 4-[[*tert*-butyl(dimethyl)silyl]oxy]-5,5,5-trifluoropentanoate (racemate)



5

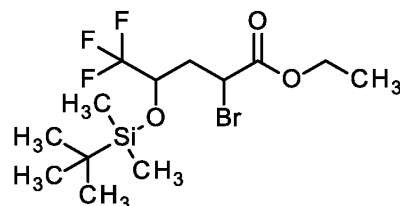
To a solution of ethyl 5,5,5-trifluoro-4-hydroxypentanoate (racemate) (1.10 g, 5.3 mmol, 1.0 eq.) in acetonitrile (15 ml) were added imidazole (1.40 g, 21.1 mmol, 4.0 eq.) and *tert*-butyldimethylsilyl chloride (2.40 g, 15.8 mmol, 3.0 eq.) at RT. The mixture was then heated to reflux and stirred at this temperature for 7 h. After concentrating under reduced pressure, the residue was dissolved in ethyl acetate and washed with water and brine. The organic phase was then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether). Yield: 1.30 g (75% of theory).

10

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ [ppm] = 4.16 (q, 2H), 4.11-4.01 (m, 1H), 2.55-2.37 (m, 2H), 2.09-1.84 (m, 2H), 1.27 (t, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H).

Example 1.16C

Ethyl 2-bromo-4-[[*tert*-butyl(dimethyl)silyl]oxy]-5,5,5-trifluoropentanoate (mixture of stereoisomers)



To a solution of ethyl 4-[[*tert*-butyl(dimethyl)silyl]oxy]-5,5,5-trifluoropentanoate (racemate) (1.30 g, 4.0 mmol, 1.0 eq.) in tetrahydrofuran (20 ml) was added a solution of lithium diisopropylamide (2.0 ml, 2.0 M in tetrahydrofuran, 4.0 mmol, 1.0 eq.) at -78°C . After stirring at -78°C for 1 h, a solution of 1,2-dibromo-1,1,2,2-tetrachloroethane (1.42 g, 4.4 mmol, 1.1 eq.) in tetrahydrofuran (6 ml) was added. The resulting mixture was allowed to warm to RT and stirred further for 4 h. Water was then added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and

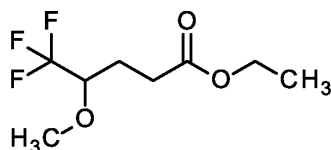
25

concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 98:2). Yield: 1.10 g (69% purity, 49% of theory).

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 4.39-4.04 (m, 3H), 2.72-2.41 (m, 1H), 2.37-2.21 (m, 1H), 2.13-1.79 (m, 1H), 1.45-1.17 (m, 3H), 0.94-0.88 (m, 9H), 0.23-0.00 (m, 6H).

5 Example 1.17A

Ethyl 5,5,5-trifluoro-4-methoxypentanoate (racemate)

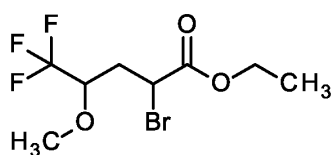


To a solution of ethyl 5,5,5-trifluoro-4-hydroxypentanoate (racemate) (3.0 g, 14.4 mmol, 1.0 eq.) in 1,2-dichloroethane (40 ml) were added freshly prepared silver(I) oxide (10.0 g, 43.2 mmol, 3.0 eq.) and iodomethane (9.0 ml, 140 mmol, 10.0 eq.) at RT and the mixture was heated to 35°C. After stirring for 54 h at this temperature, the reaction mixture was cooled to RT, filtered through Celite® and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 96:4). Yield: 600 mg (20% of theory).

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 4.07 (q, 2H), 3.97-3.80 (m, 1H), 3.45 (s, 3H), 2.48-2.40 (m, 2H), 1.96-1.82 (m, 1H), 1.81-1.62 (m, 1H), 1.19 (t, 3H).

Example 1.17B

Ethyl 2-bromo-5,5,5-trifluoro-4-methoxypentanoate (mixture of stereoisomers)



20

To a solution of ethyl 5,5,5-trifluoro-4-methoxypentanoate (racemate) (2.20 g, 10.1 mmol, 1.0 eq.) in tetrahydrofuran (40 ml) was added a solution of lithium diisopropylamide (6.0 ml, 2.0 M in tetrahydrofuran, 12.1 mmol, 1.0 eq.) at -78°C. After stirring at -78°C for 1 h, 1,2-dibromo-1,1,2,2-tetrachloroethane (3.93 g, 12.1 mmol, 1.2 eq.) in tetrahydrofuran (15 ml) was added, the resulting mixture was allowed to warm to RT and stirring was continued for 2 h. The reaction mixture was treated with saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by preparative thin-

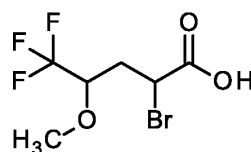
25

layer chromatography (silica gel, eluent: petroleum ether / ethyl acetate 91:9). Yield: 1.46 g (84% purity, 42% of theory).

¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 4.55-4.42 (m, 1H), 4.34-4.21 (m, 2H), 4.00-3.74 (m, 1H), 3.63 (d, 2H), 3.51 (s, 1H), 2.38 (s, 1H), 2.34-2.22 (m, 1H), 1.41-1.24 (m, 3H). Additional signals of
5 minor diastereomer visible.

Example 1.17C

2-Bromo-5,5,5-trifluoro-4-methoxypentanoic acid (mixture of stereoisomers)

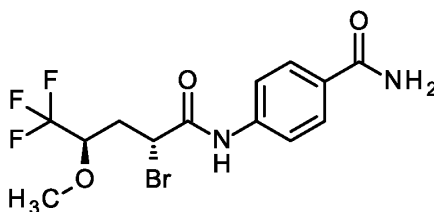


General Method 10 was carried out with ethyl 2-bromo-5,5,5-trifluoro-4-methoxypentanoate
10 (mixture of stereoisomers) (1.26 g, 84% purity, 3.61 mmol, 1.0 eq.) and lithium hydroxide (432 mg, 18.1 mmol, 5.0 eq.) in a mixture of tetrahydrofuran / water (3.6:1, 115 ml). The crude mixture was used in the subsequent reaction without further purification. Yield: 1.10 g (85% purity, 99% of theory).

GC-MS (method 6): R_t = 3.51 / 3.56 min; MS (APCIpos): m/z = 265 [M+H]⁺

Example 1.17D

4-[(2*R*,4*R*)-2-Bromo-5,5,5-trifluoro-4-methoxypentanoyl]amino}benzamide (single stereoisomer)



General Method 11 was carried out with 4-aminobenzamide (518 mg, 3.81 mmol, 1.0 eq.), 2-bromo-5,5,5-trifluoro-4-methoxypentanoic acid (mixture of stereoisomers) (1.13 g, 85% purity, 4.19 mmol,
20 0.95 eq.), T3P (3.4 ml, 50% solution in ethyl acetate, 5.71 mmol, 1.5 eq.) and pyridine (339 µl, 4.19 mmol, 1.1 eq.) in tetrahydrofuran (15 ml) for 1 h including the following variations of the procedure: Iced water was added to the reaction mixture which was then extracted with dichloromethane and concentrated under reduced pressure. The crude mixture was purified by column chromatography (silica gel, eluent: dichloromethane / methanol 98:2 to 80:20). Yield: 910
25 mg (91% purity, 57% of theory).

Stereoisomer separation of 910 mg of 4-[(2-bromo-5,5,5-trifluoro-4-methoxypentanoyl)amino]-benzamide (mixture of stereoisomers) gave:

single stereoisomer 1 (the title compound 1.17D) (chiral SFC: $R_t = 2.44$ min, 99% de): 53.1 mg (4% of theory),

5 single stereoisomer 2 (chiral SFC: $R_t = 2.72$ min): 46.6 mg,

single stereoisomer 3 (chiral SFC: $R_t = 3.46$ min): 215 mg,

single stereoisomer 4 (chiral SFC: $R_t = 7.83$ min): 259 mg.

Separation method 1: SFC: column: Daicel Chiralpak IE 5 μm , 250 mm x 20 mm; eluent: 80% carbon dioxide / 20% methanol; temperature: 35°C; flow rate: 80 ml/min; UV detection: 210 nm.

10 Separation method 2: Single stereoisomer 1 and single stereoisomer 2 eluted as a mixture in the first separation, this mixture was then separated according to the following conditions: SFC: column: Daicel Chiralpak IF 5 μm , 250 mm x 20 mm; eluent: 88% carbon dioxide / 12% methanol; temperature: 35°C; flow rate: 80 ml/min; UV detection: 210 nm.

Analysis method: SFC: column: Daicel Chiralpak IE-3 3 μm , 250 mm x 4.6 mm; eluent: 90% carbon

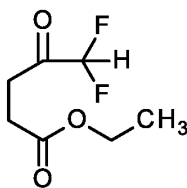
15 dioxide / 10% methanol; flow rate: 3.0 ml/min; UV detection: 210 nm.

LC-MS (method 5): $R_t = 1.04$ min; MS (ESIpos): $m/z = 383$ $[\text{M}+\text{H}]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.73 (s, 1H), 7.92-7.83 (m, 3H), 7.67 (d, 2H), 7.27 (br s, 1H), 4.72 (dd, 1H), 3.90-3.82 (m, 1H), 3.44 (s, 3H), 2.64-2.56 (m, 1H), 2.22-2.14 (m, 1H).

Example 1.18A

20 Ethyl 5,5-difluoro-4-oxopentanoate



[Bromo(difluoro)methyl](trimethyl)silane (74.04 g, 364.5 mmol, 1.5 eq.), triphenylphosphine (70.12 g, 267.3 mmol, 1.1 eq.) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (62.30 g, 486.1 mmol, 2.0 eq.) were added under argon atmosphere at RT to a solution of ethyl 4-chloro-4-oxobutanoate (40.0 g, 243.0 mmol, 1.0 eq.) in acetonitrile (240 ml). After stirring for 5 h at RT, the resulting mixture was quenched with water (200 ml) and pyridine (76.90 g, 972.1 mmol, 4.0 eq.). After stirring for further 1.5 h at 80°C, the reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was diluted with water and extracted with methyl *tert*-butyl ether. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate,

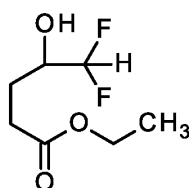
filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica, gel, eluent: petroleum ether / ethyl acetate 95:5). Yield: 15.20 g (70% purity, 22% of theory).

¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 5.94-5.60 (m, 1H), 4.23-4.07 (m, 2H), 2.98-2.94 (m, 1H),
5 2.71-2.64 (m, 2H), 2.14-2.06 (m, 1H), 1.30-1.22 (m, 3H).

¹⁹F-NMR (376 MHz, CDCl₃): δ [ppm] = -127.60 (s, 2F).

Example 1.18B

Ethyl 5,5-difluoro-4-hydroxypentanoate (racemate)



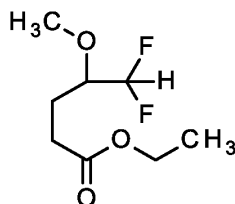
10 Sodium borohydride (2.23 g, 59.1 mmol, 1.0 eq.) was added at 0°C to a solution of ethyl 5,5-difluoro-4-oxopentanoate (15.20 g, 70% purity, 59.1 mmol) in tetrahydrofuran (140 ml) and ethanol (20 ml). After stirring at 0°C for 2 h, the reaction mixture was quenched with aqueous hydrochloric acid (3 N) at 0°C and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered
15 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 90:10). Yield: 5.40 g (48% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 5.96-5.67 (m, 1H), 5.53 (d, 1H), 4.08-4.00 (m, 2H), 3.69-3.53 (m, 1H), 2.48-2.32 (m, 2H), 1.82-1.69 (m, 1H), 1.64-1.51 (m, 1H), 1.18 (t, 3H).

¹⁹F-NMR (376 MHz, DMSO-*d*₆): δ [ppm] = -128.80 (q, 2F).

Example 1.18C

Ethyl 5,5-difluoro-4-methoxypentanoate (racemate)



Iodomethane (40.39 g, 284.6 mmol, 10.0 eq.) was added under argon atmosphere at RT to a mixture of ethyl 5,5-difluoro-4-hydroxypentanoate (racemate) (5.40 g, 28.5 mmol, 1.0 eq.) and freshly
25 prepared silver(I) oxide (19.78 g, 85.4 mmol, 3.0 eq.) in dichloroethane (80 ml). After stirring at

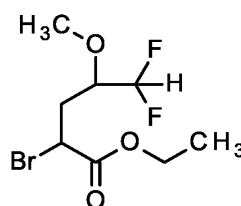
45°C for 72 h, the resulting mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 95:5). Yield: 2.40 g (90% purity, 39% of theory).

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 5.84-5.45 (m, 1H), 4.17-4.09 (m, 2H), 3.47 (s, 3H), 3.42-3.36 (m, 1H), 2.54-2.40 (m, 2H), 2.03-1.89 (m, 1H), 1.88-1.74 (m, 1H), 1.28 (t, 3H).

¹⁹F-NMR (282 MHz, CDCl₃): δ [ppm] = -126.70 (d, 2F).

Example 1.18D

Ethyl 2-bromo-5,5-difluoro-4-methoxypentanoate (mixture of stereoisomers)

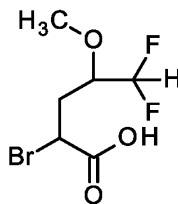


- 10 Lithium diisopropylamide solution (8.0 ml, 2.0 M in tetrahydrofuran, 16.0 mmol, 1.2 eq.) was added under argon atmosphere at -78°C to a solution of ethyl 5, 5-difluoro-4-methoxypentanoate (racemate) (2.90 g, 90% purity, 13.3 mmol, 1.0 eq.) in tetrahydrofuran (70 ml). The resulting mixture was stirred at -78°C for 1 h, followed by the addition of a solution of 1,2-dibromo-1,1,2,2-tetrachloroethane (5.20 g, 16.0 mmol, 1.2 eq.) in tetrahydrofuran (20 ml) dropwise at the same temperature.
- 15 warming to RT and stirring for further 2 h, the reaction mixture was quenched with saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (silica gel, eluent: petroleum ether / ethyl acetate 80:20). Yield: 1.85 g (85% purity, 43% of theory).
- 20 ¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 5.87-5.70 (m, 1H), 4.50-4.22 (m, 3H), 3.66-3.42 (m, 4H), 2.23-2.16 (m, 2H), 1.35-1.26 (m, 3H).

¹⁹F-NMR (376 MHz, CDCl₃): δ [ppm] = -126.60 (s, 2F).

Example 1.18E

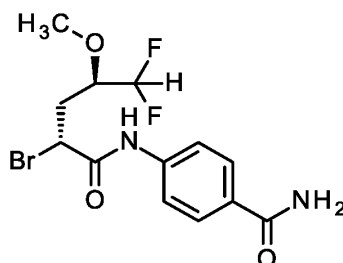
2-Bromo-5,5-difluoro-4-methoxypentanoic acid (mixture of stereoisomers)



Lithium hydroxide (255 mg, 10.6 mmol, 2.0 eq.) was added at RT to a solution of ethyl 2-bromo-5,5-difluoro-4-methoxypentanoate (mixture of stereoisomers) (1.72 g, 85% purity, 5.3 mmol) in a mixture of tetrahydrofuran and water (3:1, 20 ml). The reaction mixture was stirred at RT for 100 min and then acidified with aqueous hydrochloric acid (1 N). After removing all volatiles under reduced pressure, the resulting mixture was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure (at <30°C and >100 mbar). The crude product was used without further purification. Yield: 1.65 g.

Example 1.18F

4-{[(2*R*,4*R*)-2-Bromo-5,5-difluoro-4-methoxypentanoyl]amino}benzamide (single stereoisomer)



2-Bromo-5,5-difluoro-4-methoxypentanoic acid (mixture of stereoisomers) (1.65 g, 90% assumed purity of crude material, 6.0 mmol), pyridine (0.53 ml, 6.6 mmol, 1.1 eq.) and T3P (5.3 ml, 50% solution in ethyl acetate, 9.0 mmol, 1.5 eq.) were added under argon atmosphere at RT to a mixture of 4-aminobenzamide (817 mg, 6.0 mmol, 1.0 eq.) in tetrahydrofuran (20 ml). The reaction mixture was stirred at RT for 1 h, mixed with water, stirred for additional 15 min and mixed with additional water. After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was crystallized with dichloromethane, filtered and dried *in vacuo*. Yield: 993 mg (94% purity, 43% of theory). The combined mother liquids were concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: dichloromethane / methanol gradient). Yield: 297 mg (13% of theory).

LC-MS (method 4): $R_t = 1.26$ min; MS (ESIpos): $m/z = 365$ $[M+H]^+$

Stereoisomer separation of 1410 mg of 4-[(2-bromo-5,5-difluoro-4-methoxypentanoyl)amino]-benzamide (mixture of stereoisomers) gave

mixture of two stereoisomers 1+2 (chiral SFC 1: $R_t = 1.34 / 1.45$ min): 290 mg,

single stereoisomer 3 (the title compound Example 1.18F) (chiral SFC 1: $R_t = 1.18$ min, >98% ee): 330 mg,

single stereoisomer: (chiral SFC 2: R_t = 1.40 min): 410 mg.

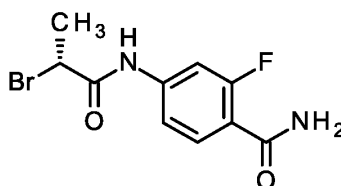
Separation method: SFC: column: Chiralpak AD-H 5 μ m, 250 mm x 20 mm; eluent: carbon dioxide / ethanol, gradient: 0 min 80% carbon dioxide, 5.00-8.43 min 70% carbon dioxide, 8.53-11.31 min 80% carbon dioxide; temperature: 40°C; flow rate: 100 ml/min; UV detection: 210 nm.

- 5 Analysis method: SFC 1: column: Chiralpak AD-H, 50 mm x 4.6 mm; eluent: 80% carbon dioxide / 20% ethanol; temperature: 40°C; flow rate: 3 ml/min; UV detection: 210 nm. SFC 2: column: Chiralpak AD-H, 50 mm x 4.6 mm; eluent: 60% carbon dioxide / 40% ethanol; temperature: 40°C; flow rate: 3 ml/min; UV detection: 210 nm.

- $^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.61 (s, 1H), 7.90-7.81 (m, 3H), 7.65 (d, 2H), 7.24 (br s, 1H), 6.17 (dt, 1H), 4.76 (dd, 1H), 3.71-3.62 (m, 1H), 3.49 (s, 3H), 2.21-2.11 (m, 2H).
- 10

Example 1.19A

4-{[(2*R*)-2-Bromopropanoyl]amino}-2-fluorobenzamide (single stereoisomer)



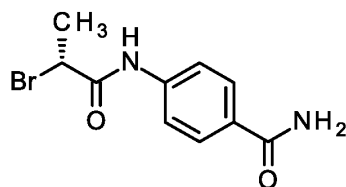
- (2*R*)-2-Bromopropanoic acid (single stereoisomer) (4.0 g, 26.1 mmol), pyridine (2.3 ml, 28.8 mmol, 1.1 eq.) and T3P (22.9 ml, 50% solution in ethyl acetate, 39.2 mmol, 1.5 eq.) were added under argon atmosphere at RT to a mixture of 4-amino-2-fluorobenzamide (4.0 g, 26.1 mmol, 1.0 eq.) in tetrahydrofuran (60 ml). The reaction mixture was stirred at RT for 1 h, mixed with water and stirred for additional 1 h. The forming precipitate was filtered, washed with water and dried *in vacuo*. Yield: 5.7 g (75% of theory). The combined filtrates were extracted with ethyl acetate. The combined
- 20 organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was crystallized from water and the precipitate dried *in vacuo*. Yield: 1.5 g (20% of theory).

main batch: LC-MS (method 1): R_t = 0.61 min; MS (ESIpos): m/z = 289 $[\text{M}+\text{H}]^+$

- main batch: $^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.68 (s, 1H), 7.70 (t, 1H), 7.64 (dd, 1H), 7.57-7.46 (m, 2H), 7.36 (dd, 1H), 4.69 (q, 1H), 1.76 (d, 3H).
- 25

Example 1.20A

4-{[(2*R*)-2-Bromopropanoyl]amino}benzamide (single stereoisomer)



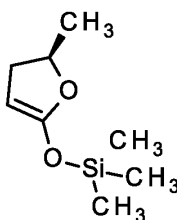
(2*R*)-2-Bromopropanoic acid (single stereoisomer) (1.00 g, 6.54 mmol), pyridine (0.58 ml, 7.19 mmol, 1.1 eq.) and T3P (5.73 ml, 50% solution in ethyl acetate, 9.81 mmol, 1.5 eq.) were added under argon atmosphere at RT to a mixture of 4-aminobenzamide (890 mg, 6.54 mmol, 1.0 eq.) in tetrahydrofuran (15 ml). The reaction mixture was stirred at RT for 30 min. After removing all volatiles under reduced pressure, the residue was mixed with additional water. The forming precipitate was filtered, washed with water and dried *in vacuo*. Yield: 1.77 g (quantitative of theory).

LC-MS (method 15): $R_t = 0.97$ min; MS (ESIpos): $m/z = 271$ $[M+H]^+$

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.52 (s, 1H), 7.87 (br s, 1H), 7.86 (d, 2H), 7.66 (d, 2H), 7.26 (br s, 1H), 4.71 (q, 1H), 1.76 (d, 3H).

Example 1.21A

Trimethyl{[(5*R*)-5-methyl-4,5-dihydrofuran-2-yl]oxy}silane (single stereoisomer)

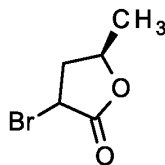


Under argon atmosphere, *n*-butyllithium solution (3.34 l, 1.6 M in hexanes, 5.35 mol, 1.1 eq.) was added at 0°C within 1.5 h to a solution of diisopropylethylamine (818 ml, 5.84 mol, 1.2 eq.) in tetrahydrofuran (5.0 l) and stirred for 30 min at 0°C before cooled to -78°C. A solution of (5*R*)-5-methyldihydrofuran-2(3*H*)-one (single stereoisomer) (487 g, 4.86 mol) in tetrahydrofuran (500 ml) was added at -78°C within 1 h and the reaction mixture stirred at -78°C for 90 min, followed by the dropwise addition of chloro(trimethyl)silane (803 ml, 6.32 mol, 1.3 eq.). The reaction mixture was stirred at -78°C for 1 h and allowed to warm to RT overnight while stirring was continued. The suspension was decanted and the filtrate evaporated under reduced pressure and again suspended in *n*-pentane. The mixture was stirred for 30 min at -10°C and filtered. The filtrate was evaporated under reduced pressure. The crude material was used without further purification. Yield: 759 g (85% purity, 79% of theory).

$^1\text{H-NMR}$ (600 MHz, CDCl_3): δ [ppm] = 4.53-4.46 (m, 1H), 3.45 (t, 1H), 2.63 (ddd, 1H), 2.10 (ddd, 1H), 1.20 (d, 3H), 0.12 (s, 9H).

Example 1.21B

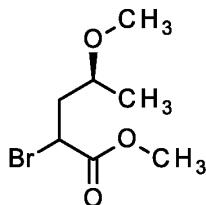
(5*R*)-3-Bromo-5-methyldihydrofuran-2(3*H*)-one (mixture of two diastereomers)



- Bromine (197 ml, 3.83 mol, 1.0 eq.) was added slowly at -78°C to a solution of trimethyl{[(5*R*)-5-methyl-4,5-dihydrofuran-2-yl]oxy}silane (single stereoisomer) (759 g, 87% purity, 3.83 mol) in dichloromethane (7.6 l). The reaction mixture was allowed to warm to RT overnight while stirring was continued and then concentrated under reduced pressure. The residue was purified with a thin-film vacuum evaporator (dosing of crude material: 50 ml/min, 107°C, 0.5 mbar). Yield: 563 g (*trans/cis*: about 2:1, about 80% purity, about 66% of theory).
- 10 ¹H-NMR (600 MHz, CDCl₃): δ [ppm] = 4.80-4.67 (m, 1H, *trans*-diastereomer), 4.59-4.47 (m, 2H, *cis*-diastereomer), 4.35 (dd, 1H, *trans*-diastereomer), 2.93 (ddd, 1H, *cis*-diastereomer), 2.46 (ddd, 1H, *trans*-diastereomer), 2.42-2.35 (m, 1H, *cis*-diastereomer), 2.30-2.20 (m, 1H, *trans*-diastereomer), 2.15-2.04 (m, 1H, *cis*-diastereomer), 1.38 (d, 3H, *cis*-diastereomer), 1.34 (d, 3H, *trans*-diastereomer).

15 **Example 1.21C**

Methyl (4*S*)-2-bromo-4-methoxypentanoate (mixture of two diastereomers)



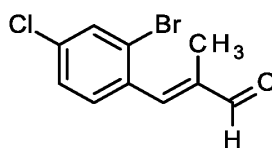
- Trimethoxymethane (688 ml, 6.28 mol, 2.5 eq.) followed by sulfuric acid (16.7 ml, 314 mmol, 0.125 eq.) were added at RT to a solution of (5*R*)-3-bromo-5-methyldihydrofuran-2(3*H*)-one (mixture of two diastereomers) (563 g, about 80% purity, 2.51 mol) in methanol (5.1 l). The reaction mixture was stirred at 50°C for 24 h and concentrated under reduced pressure. Afterwards, trimethoxymethane (688 ml, 6.28 mol, 2.5 eq.) followed by sulfuric acid (16.7 ml, 314 mmol, 0.125 eq.) were again added at RT to a solution of the crude material in methanol (5.1 l). The reaction mixture was stirred at 50°C for 24 h and concentrated under reduced pressure. This procedure was repeated one more time to allow for complete conversion of the reaction. The resulting residue was mixed with ethyl acetate and the mixture washed with 0.5 N aqueous sodium hydroxide solution. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure.
- 20
- 25

The crude material was used without further purification. Yield: 625 g (94% purity, quantitative of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 4.55-4.43 (m, 1H, two diastereomers), 3.68 (s, 3H, minor diastereomer), 3.67 (s, 3H, major diastereomer), 3.46-3.37 (m, 1H, major diastereomer), 3.34-3.25 (m, 1H, minor diastereomer), 3.19 (s, 3H, major diastereomer), 3.15 (s, 3H, minor diastereomer), 2.22-2.05 (m, 1H, major diastereomer), 1.99-1.90 (m, 1H, minor diastereomer), 1.11-1.05 (m, 3H, two diastereomers).

Example 2.1A

3-(2-Bromo-4-chlorophenyl)-2-methylprop-2-enal (*E/Z* mixture)



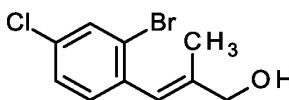
10

Propionaldehyde (3.6 ml, 50.1 mmol, 1.1 eq.) was added dropwise at RT to a mixture of 2-bromo-4-chlorobenzaldehyde (10.0 g, 45.6 mmol) and sodium hydroxide (0.18 g, 4.6 mmol, 0.1 eq.) in methanol (100 ml). The mixture was stirred at RT for 1 h, followed by the addition of acetic acid to adjust the pH value to 6. The resulting mixture was stirred further 16 h and then concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 10:1). Yield: 6.0 g (50% of theory).

LC-MS (method 10): *R*_t = 1.28 min; MS (ESIpos): *m/z* = 259 [M+H]⁺
¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 9.70 (s, 1H), 7.93-7.91 (m, 1H), 7.59-7.56 (m, 2H), 7.52-7.50 (m, 1H), 1.81 / 1.81 (2s, 3H).

Example 2.1B

3-(2-Bromo-4-chlorophenyl)-2-methylprop-2-en-1-ol (*E/Z* mixture)



A mixture of 3-(2-bromo-4-chlorophenyl)-2-methylprop-2-enal (*E/Z* mixture) (10.0 g, 38.5 mmol, 1.0 eq.) in tetrahydrofuran (90 ml) was added at 0°C to a suspension of sodium borohydride (7.29 g, 192.7 mmol, 5.0 eq.) in tetrahydrofuran (10 ml) and methanol (10 ml). The reaction mixture was stirred at RT for 3 h, followed by addition of aqueous hydrochloric acid to adjust the pH value to 6. The volatiles were removed under reduced pressure and the aqueous phase was extracted with ethyl

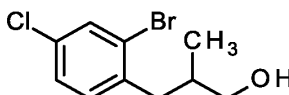
25

acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 10:1). Yield: 5.7 g (55% of theory).

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 7.78 (d, 1H), 7.47 (dd, 1H), 7.37 (d, 1H), 6.44 (br s, 1H),
5 5.12 (t, 1H), 4.05-3.98 (m, 2H), 1.67 (s, 3H).

Example 2.1C

3-(2-Bromo-4-chlorophenyl)-2-methylpropan-1-ol (racemate)

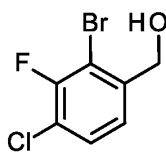


Tris(triphenylphosphine)rhodium(I) chloride (3.2 g, 3.4 mmol, 0.3 eq.) was added at RT under
10 nitrogen atmosphere to a mixture of 3-(2-bromo-4-chlorophenyl)-2-methylprop-2-en-1-ol (*E/Z*
mixture) (3.0 g, 11.5 mmol, 1.0 eq.) in ethanol (30 ml). The resulting mixture was purged with
hydrogen gas and stirred at RT for 48 h under hydrogen gas atmosphere (2 bar). The reaction mixture
was filtered through Celite® and the filtrate concentrated under reduced pressure. The residue was
purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 20:1). Yield:
15 1.90 g (59% of theory).

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 7.71 (d, 1H), 7.41 (dd, 1H), 7.33 (d, 1H), 4.57 (t, 1H),
3.32-3.26 (m, 2H, partially concealed), 2.85-2.76 (m, 1H), 2.49-2.39 (m, 1H), 1.93-1.79 (m, 1H),
0.82 (d, 3H).

Example 2.2A

20 (2-Bromo-4-chloro-3-fluorophenyl)methanol



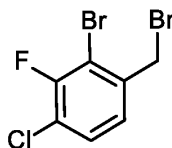
2-Bromo-4-chloro-3-fluorobenzoic acid (5.00 g, 19.7 mmol, 1.0 eq.) was dissolved in
tetrahydrofuran (150 ml), cooled to 0°C and a solution of borane tetrahydrofuran complex (59 ml,
1.0 M in tetrahydrofuran, 59 mmol, 3.0 eq.) was added dropwise. The mixture was stirred at 0°C for
25 1 h and at RT for 2 days. Further amounts of borane tetrahydrofuran complex solution (30 ml, 1.0 M
in tetrahydrofuran, 30 mmol, 1.5 eq.) were added at 0°C and stirring was continued at RT overnight.
The reaction mixture was diluted with ethyl acetate and saturated aqueous sodium bicarbonate
solution, extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and

filtered. The filtrate was concentrated under reduced pressure and the crude product was used in the subsequent step without further purification. Yield: 4.49 g (95% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.71-7.58 (m, 1H), 7.44-7.32 (m, 1H), 5.67-5.56 (t, 1H), 4.58-4.44 (d, 2H).

5 Example 2.2B

2-Bromo-1-(bromomethyl)-4-chloro-3-fluorobenzene

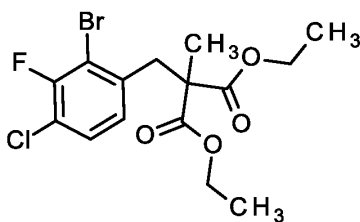


To a solution of (2-bromo-4-chloro-3-fluorophenyl)methanol (9.16 g, 66% purity, 25.2 mmol, 1.0 eq.) in diethyl ether (120 ml) at 0-5°C was added a solution of phosphorous tribromide (3.6 ml, 38 mmol, 1.5 eq.) in diethyl ether (40 ml). The mixture was stirred at RT for 4 days, followed by the addition of further amounts of phosphorous tribromide (12 ml, 130 mmol, 5.0 eq.) at 0°C. Stirring was continued at RT for 0.5 h, followed by the addition of saturated aqueous sodium bicarbonate solution at 0°C. The mixture was extracted with dichloromethane and ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was used in the subsequent step without further purification. Yield: 10.26 g (quantitative of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.74-7.59 (m, 1H), 7.57-7.47 (m, 1H), 4.81-4.73 (s, 2H).

Example 2.2C

Diethyl [(2-bromo-4-chloro-3-fluorophenyl)methyl](methyl)propanedioate



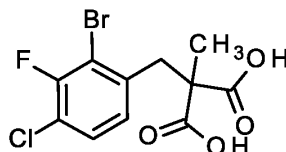
20

2-Bromo-1-(bromomethyl)-4-chloro-3-fluorobenzene (10.3 g, 33.9 mmol, 1.0 eq.), diethyl methylmalonate (6.21 g, 35.6 mmol, 1.1 eq.) and caesium carbonate (13.3 g, 40.7 mmol, 1.2 eq.) were dissolved in *N,N*-dimethylformamide (30 ml) and stirred at 70°C overnight. The mixture was diluted with water, extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was used in the subsequent step without further purification. Yield: 11.81 g (54% purity, 48% of theory).

GC-MS (method 6): $R_t = 7.41$ min; MS (APCIpos): $m/z = 397$ $[M+H]^+$

Example 2.2D

[(2-Bromo-4-chloro-3-fluorophenyl)methyl](methyl)propanedioic acid

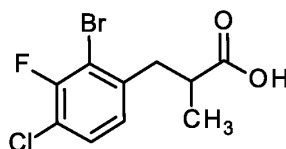


- 5 Diethyl [(2-bromo-4-chloro-3-fluorophenyl)methyl](methyl)propanedioate (11.8 g, 54% purity, 16.1 mmol, 1.0 eq.) was dissolved in ethanol (100 ml), an aqueous solution of sodium hydroxide (97 ml, 1.0 M, 97 mmol, 6.0 eq.) was added and the mixture was stirred at RT overnight and at 80°C for 3 days. The mixture was concentrated under reduced pressure, the residue was treated with aqueous hydrogen chloride (1 N) and extracted with dichloromethane and ethyl acetate. The
- 10 combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used in the subsequent step without further purification. Yield: 7.01 g (50% purity, 64% of theory).

LC-MS (method 1): $R_t = 0.85$ min; MS (ESI_{neg}): $m/z = 339$ $[M-H]^-$

Example 2.2E

- 15 3-(2-Bromo-4-chloro-3-fluorophenyl)-2-methylpropanoic acid (racemate)

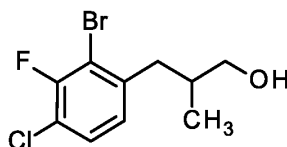


- [(2-Bromo-4-chloro-3-fluorophenyl)methyl](methyl)propanedioic acid (7.00 g, 50% purity, 10.3 mmol, 1.0 eq.) was dissolved in acetic acid (100 ml) and stirred at 120°C overnight. The mixture was then concentrated under reduced pressure, dissolved in acetonitrile and water, filtered and the
- 20 filtrate was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 2.52 g (77% purity, 64% of theory).

LC-MS (method 1): $R_t = 1.03$ min; MS (ESI_{neg}): $m/z = 293$ $[M-H]^-$

Example 2.2F

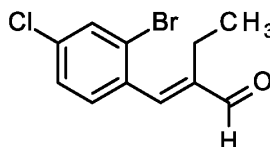
3-(2-Bromo-4-chloro-3-fluorophenyl)-2-methylpropan-1-ol (racemate)



- 3-(2-Bromo-4-chloro-3-fluorophenyl)-2-methylpropanoic acid (racemate) (2.40 g, 77% purity, 6.25 mmol, 1.0 eq.) was dissolved in tetrahydrofuran (60 ml), cooled to 0°C and a solution of borane tetrahydrofuran complex (19 ml, 1.0 M in tetrahydrofuran, 19 mmol, 3.0 eq.) was added dropwise.
- 5 The mixture was stirred at 0°C for 1 h and at RT overnight. The reaction mixture was diluted with ethyl acetate and saturated aqueous sodium bicarbonate solution, extracted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 99:1 to 40:60). Yield: 1.65 g (87% purity, 82% of theory).
- 10 ¹H-NMR (500 MHz, DMSO-*d*₆): δ [ppm] = 7.59-7.47 (m, 1H), 7.24-7.11 (m, 1H), 4.58 (t, 1H), 3.31-3.21 (m, 2H), 2.90-2.82 (m, 1H), 2.49-2.46 (m, 1H), 1.96-1.79 (m, 1H), 0.82 (d, 3H).

Example 2.3A

2-[(2-Bromo-4-chlorophenyl)methylidene]butanal (*E/Z* mixture)

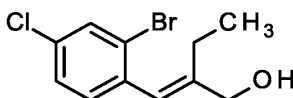


- 15 To a solution of 2-bromo-4-chlorobenzaldehyde (10.0 g, 45.6 mmol, 1.0 eq.) and sodium hydroxide (182 mg, 4.56 mmol, 0.1 eq.) in methanol (40 ml) was added butanal (4.5 ml, 50 mmol, 1.1 eq.) dropwise at RT. The mixture was stirred at RT overnight, followed by addition of water. The mixture was partially concentrated under reduced pressure, dried over anhydrous sodium sulfate, filtered and washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude mixture
- 20 was used in the subsequent step without further purification. Yield: 12.8 g (86% purity, 78% of theory).

¹H-NMR (500 MHz, DMSO-*d*₆): δ [ppm] = 9.67 (s, 1H), 7.93 (d, 1H), 7.59 (dd, 1H), 7.54-7.42 (m, 2H), 2.26 (q, 2H), 0.96 (t, 3H).

Example 2.3B

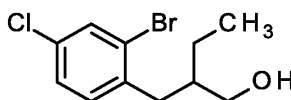
- 25 2-[(2-Bromo-4-chlorophenyl)methylidene]butan-1-ol (*E/Z* mixture)



- To a suspension of sodium borohydride (2.68 g, 70.9 mmol, 2.0 eq.) in tetrahydrofuran (10 ml) and methanol (10 ml) was added a solution of 2-[(2-bromo-4-chlorophenyl)methylidene]butanal (*E/Z* mixture) (11.3 g, 86% purity, 35.5 mmol, 1.0 eq.) in tetrahydrofuran (90 ml) dropwise at 0°C. The resulting mixture was stirred at RT for 3 h and cooled to 0°C, followed by the addition of aqueous hydrogen chloride (1 N) to adjust the pH value to 6. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was used in the subsequent step without further purification. Yield: 10.58 g (86% purity, 93% of theory).
- ¹H-NMR (500 MHz, DMSO-*d*₆): δ [ppm] = 7.73 (d, 1H), 7.43 (dd, 1H), 7.28 (d, 1H), 6.38 (s, 1H), 4.09-3.94 (m, 2H), 2.06 (q, 2H), 1.98 (s, 1H), 0.96 (t, 3H).

Example 2.3C

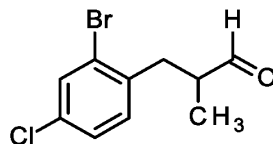
2-(2-Bromo-4-chlorobenzyl)butan-1-ol (racemate)



- To a solution of 2-[(2-bromo-4-chlorophenyl)methylidene]butan-1-ol (*E/Z* mixture) (10.6 g, 86% purity, 33.0 mmol, 1.0 eq.) in dichloromethane (200 ml) was added tris(triphenylphosphine)rhodium(I) chloride (1.53 g, 1.65 mmol, 0.1 eq.) under argon atmosphere. The resulting mixture was purged with hydrogen gas and stirred at 22°C for 48 h under a hydrogen atmosphere at 50 bar. The reaction mixture was filtered through Celite® and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 100:0 to 65:35). Yield: 8.84 g (77% purity, 74% of theory).
- ¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 7.68 (d, 1H), 7.39 (dd, 1H), 7.35-7.28 (m, 1H), 4.46 (t, 1H), 3.32-3.24 (m, 2H), 2.70-2.65 (m, 1H), 2.63-2.57 (m, 1H), 1.69-1.56 (m, 1H), 1.44-1.35 (m, 1H), 1.24 (s, 1H), 0.86 (t, 3H).

Example 2.4A

- 3-(2-Bromo-4-chlorophenyl)-2-methylpropanal (racemate)



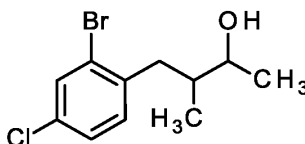
To a solution of 3-(2-bromo-4-chlorophenyl)-2-methylpropan-1-ol (racemate) (5.0 g, 18.4 mmol, 1.0 eq.) in dichloromethane (100 ml) were added 3,3,3-triacetoxy-3-iodophthalide (19.5 g, 46.0 mmol, 2.5 eq.) and sodium hydrogen carbonate (11.6 g, 138.0 mmol, 7.5 eq.) at 0°C. After stirring

- at RT for 3 h, the reaction mixture was quenched with a mixture (1:1) of a saturated aqueous solution of sodium thiosulfate and a saturated aqueous solution of sodium carbonate and extracted with dichloromethane. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was
- 5 purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 97:3). Yield: 3.90 g (85% purity, 68% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 9.66 (s, 1H), 7.74 (d, 1H), 7.44-7.37 (m, 2H), 3.16-3.11 (m, 1H), 2.78-2.64 (m, 2H), 1.01 (d, 3H).

Example 2.4B

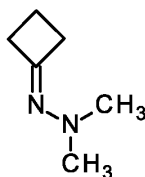
- 10 4-(2-Bromo-4-chlorophenyl)-3-methylbutan-2-ol (mixture of stereoisomers)



- To a solution of 3-(2-bromo-4-chlorophenyl)-2-methylpropanal (racemate) (4.2 g, 90% purity, 14.4 mmol, 1.0 eq.) in tetrahydrofuran (80 ml) was added methylmagnesium bromide (14.5 ml, 3.0 M in 2-methyl tetrahydrofuran, 43.3 mmol, 3.0 eq.) at 0°C under nitrogen atmosphere. After stirring
- 15 at 0°C for 2 h, the reaction mixture was quenched with water and stirred for 10 min. The mixture was then extracted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 87:13) to give 2.8 g of 4-(2-bromo-4-chlorophenyl)-3-methylbutan-2-ol (mixture of stereoisomers) in 63% purity. In order to remove
- 20 side products, the crude product was dissolved in dichloromethane (15 ml), treated with imidazole (0.66 g, 9.7 mmol, 0.7 eq.) and *tert*-butyldimethylsilyl chloride (0.73 g, 4.8 mmol, 0.35 eq.), stirred at RT for 2 h and filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: *n*-hexane / ethyl acetate 94:6). Yield: 1.47 g (83% purity, 30% of theory).
- 25 ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.71-7.68 (m, 1H), 7.41-7.37 (m, 1H), 7.35-7.28 (m, 1H), 4.51-4.45 (m, 1H), 3.57-3.50 (m, 1H), 2.93-2.79 (m, 1H), 2.49-2.34 (m, 1H), 1.77-1.68 (m, 1H), 1.16-1.05 (m, 3H), 0.75-0.67 (m, 3H).

Example 2.5A

2-Cyclobutylidene-1,1-dimethylhydrazine



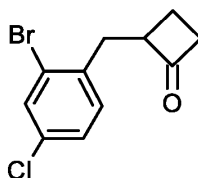
A solution of cyclobutanone (1.00 g, 14.3 mmol) and 1,1-dimethylhydrazine (1.1 ml, 14 mmol, 1.0 eq.) in tetrahydrofuran (6.0 ml) was stirred at 60°C for 2.5 h under microwave irradiation. All volatiles were removed at 30°C *in vacuo* (>50 mbar). The residue was purified by Kugelrohr distillation (75°C, 20 mbar). Yield: 1.08 g (67% of theory).

GC-MS (method 2): $R_t = 1.79$ min; $m/z = 112$ $[M]^+$

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ [ppm] = 3.02-2.87 (m, 4H), 2.58 (s, 6H), 1.98 (quin, 2H).

Example 2.5B

2-[(2-Bromo-4-chlorophenyl)methyl]cyclobutan-1-one (racemate)



10

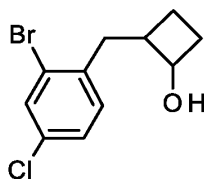
A solution of *n*-butyllithium (6.1 ml, 1.6 M in hexane, 9.8 mmol, 1.1 eq.) was added under argon atmosphere at -10°C to a solution of 2-cyclobutylidene-1,1-dimethylhydrazine (1.00 g, 8.92 mmol) in tetrahydrofuran (40 ml). The reaction mixture was stirred at -10°C for 1 h, followed by the addition of a solution of 2-bromo-1-(bromomethyl)-4-chlorobenzene (3.13 g, 81% purity, 8.92 mmol, 1.0 eq.) in tetrahydrofuran (10 ml). The reaction mixture was stirred at RT for 20 h, diluted with aqueous hydrochloric acid (2 N) and stirred at RT for 1 h. After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate mixtures). Yield: 1.89 g (77% of theory).

20

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 7.72 (d, 1H), 7.43 (dd, 1H), 7.38 (d, 1H), 3.73-3.61 (m, 1H), 3.15-2.97 (m, 2H), 2.95-2.81 (m, 2H), 2.06 (qd, 1H), 1.77-1.64 (m, 1H).

Example 2.5C

trans-2-[(2-Bromo-4-chlorophenyl)methyl]cyclobutan-1-ol (racemate)



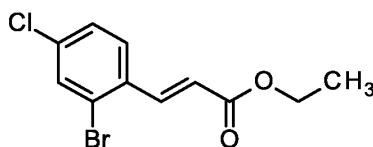
Sodium borohydride (505 mg, 13.3 mmol, 1.0 eq.) was added at 0°C to a solution of 2-[(2-bromo-4-chlorophenyl)methyl]cyclobutan-1-one (racemate) (3.65 g, 13.3 mmol) in a mixture of dichloromethane / methanol (2:1, 67 ml). The reaction mixture was stirred at 5°C for 1 h and diluted with water. After phase separation, the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate mixtures). Yield: 1.03 g (27% of theory) of the *cis*-product and 2.67 g (72% of theory) of the desired *trans*-product (the title compound Example 2.5C).

10 LC-MS (method 4): $R_t = 2.00$ min; MS (ESIpos): $m/z = 299$ $[M+Na]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 7.68 (d, 1H), 7.39 (dd, 1H), 7.36 (d, 1H), 5.03 (d, 1H), 3.71 (quin, 1H), 2.91 (dd, 1H), 2.69 (dd, 1H), 2.35-2.20 (m, 1H), 2.08-1.99 (m, 1H), 1.65-1.51 (m, 2H), 1.15-1.01 (m, 1H).

Example 2.6A

15 Ethyl 3-(2-bromo-4-chlorophenyl)prop-2-enoate (*E/Z* mixture)

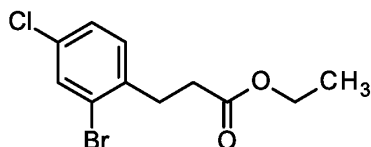


While cooling in an iced water bath, ethoxycarbonylmethylenetriphenylphosphorane (47.6 g, 136.7 mmol, 1.5 eq.) was added dropwise to a solution of 2-bromo-4-chlorobenzaldehyde (20.0 g, 91.1 mmol) in dichloromethane (200 ml). After stirring at RT for 2 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 6:1). Yield: 26.0 g (98% of theory).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 7.94 (d, 0.8H), 7.84 (d, 0.8H), 7.80 (d, 1H), 7.50 (dd, 0.8H), 7.45 (dd, 0.2H), 7.42 (d, 0.2H), 7.06 (d, 0.2H), 6.68 (d, 0.8H), 6.18 (d, 0.2H), 4.21 (q, 1.6H), 4.04 (q, 0.4H), 1.26 (t, 2.4H), 1.10 (t, 0.6H).

Example 2.6B

Ethyl 3-(2-bromo-4-chlorophenyl)propanoate

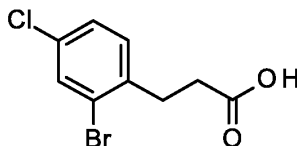


- Chlorotris(triphenylphosphine)rhodium(I) (12.3 g, 13.3 mmol, 0.15 eq.) was added under nitrogen atmosphere to a solution of ethyl 3-(2-bromo-4-chlorophenyl)prop-2-enoate (*E/Z* mixture) (26.0 g, 88.9 mmol) in ethanol (250 ml). The resulting mixture was purged with hydrogen for 5 min and stirred at RT for 12 h under hydrogen atmosphere (2 bar). The mixture was filtered through Celite® and the filtrate concentrated under reduced pressure. The residue was re-dissolved in ethanol (100 ml), followed by the addition of chlorotris(triphenylphosphine)rhodium(I) (6.2 g, 6.7 mmol, 0.075 eq.) under nitrogen atmosphere. The resulting mixture was purged with hydrogen for 5 min and stirred at RT for 15 h under hydrogen atmosphere (2 bar). The reaction mixture was filtered through Celite® and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 100% petroleum ether). Yield: 25.6 g (97% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.73 (d, 1H), 7.43 (dd, 1H), 7.38 (d, 1H), 4.06 (m, 2H), 2.95 (t, 2H), 2.62 (t, 2H), 1.17 (t, 3H).

Example 2.6C

- 3-(2-Bromo-4-chlorophenyl)propanoic acid

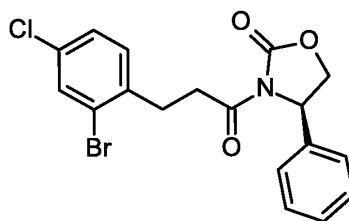


- A solution of sodium hydroxide (31.9 g, 798.4 mmol, 4.0 eq.) in water (250 ml) was added to a stirred solution of ethyl 3-(2-bromo-4-chlorophenyl) propanoate (60.0 g, 199.6 mmol) in ethanol (400 ml). After stirring at RT for 15 h, the reaction mixture was concentrated under reduced pressure. The mixture was adjusted to pH 3 with aqueous hydrochloric acid (4 N) and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. Yield: 54.0 g (98% of theory).

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 12.25 (s, 1H), 7.71 (s, 1H), 7.45-7.34 (m, 2H), 2.91 (t, 2H), 2.53 (t, 2H).

- Example 2.6D**

(4*R*)-3-[3-(2-Bromo-4-chlorophenyl)propanoyl]-4-phenyl-1,3-oxazolidin-2-one (single stereoisomer)



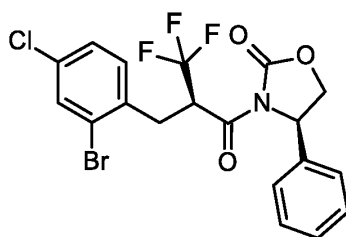
N,N-Dimethylformamide (0.62 g, 8.5 mmol, 0.1 eq.) was added to a suspension of 3-(2-bromo-4-chlorophenyl)propanoic acid (22.5 g, 85.4 mmol) in thionyl chloride (60 ml). After stirring at 80°C for 4 h, the reaction mixture was evaporated to dryness to give 24.0 g of 3-(2-bromo-4-chlorophenyl)propanoyl chloride.

A solution of *n*-butyllithium (35.7 ml, 2.5 M in hexane, 89.4 mmol, 1.05 eq.) was added at -78°C under nitrogen atmosphere to a stirred solution of (4*R*)-4-phenyl-1,3-oxazolidin-2-one (single stereoisomer) (13.9 g, 85.1 mmol, 1.0 eq.) in tetrahydrofuran (300 ml). The resulting mixture was stirred at -78°C for 30 min, followed by the addition of a solution of 3-(2-bromo-4-chlorophenyl)propanoyl chloride (24.0 g, 85.1 mmol) in tetrahydrofuran (200 ml) at -78°C. After stirring at RT for 5 h, the reaction mixture was quenched with saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 10:1). Yield: 29.5 g (85% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.71 (d, 1H), 7.44-7.25 (m, 7H), 5.46 (dd, 1H), 4.74 (t, 1H), 4.17 (dd, 1H), 3.28-3.11 (m, 2H), 2.99-2.85 (m, 2H).

Example 2.6E

(4*R*)-3-[(2*R*)-2-[(2-Bromo-4-chlorophenyl)methyl]-3,3,3-trifluoropropanoyl]-4-phenyl-1,3-oxazolidin-2-one (single stereoisomer)



A solution of lithium bis(trimethylsilyl)amide (75.8 ml, 1.0 M in tetrahydrofuran, 75.8 mmol, 1.05 eq.) was added at -78°C under nitrogen atmosphere to a stirred solution of (4*R*)-3-[3-(2-bromo-4-chlorophenyl)propanoyl]-4-phenyl-1,3-oxazolidin-2-one (single stereoisomer) (29.5 g, 72.2 mmol) in tetrahydrofuran (300 ml). After stirring at -78°C for 30 min, 1-trifluoromethyl-1,2-

benziodoxol-3(1*H*)-one (24.0 g, 75.8 mmol, 1.05 eq.) was added to the mixture at -78°C. The resulting mixture was allowed to warm to RT during 1 h and stirred further 4 h. The reaction mixture was quenched with saturated aqueous solution of sodium carbonate and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 22.5 g of crude product, which was triturated with methanol and stirred for 30 min. The solid was collected by filtration, washed with methanol and dried under air atmosphere. Yield: 16.0 g (46% of theory).

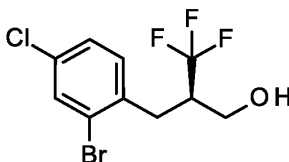
LC-MS (method 10): $R_t = 1.26$ min; MS (ESIpos): $m/z = 478$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 7.80 (d, 1H), 7.48 (dd, 1H), 7.44-7.37 (m, 2H), 7.37-7.31 (m, 2H), 7.30-7.24 (m, 2H), 5.50-5.37 (m, 2H), 4.66 (t, 1H), 4.20 (dd, 1H), 3.34-3.16 (m, 2H).

$^{19}\text{F-NMR}$ (376 MHz, $\text{DMSO-}d_6$): δ [ppm] = -65.71 (s, 3F).

Example 2.6F

(2*R*)-2-[(2-Bromo-4-chlorophenyl)methyl]-3,3,3-trifluoropropan-1-ol (single stereoisomer)



Sodium borohydride (3.4 g, 90.4 mmol, 5.0 eq.) was added at 0°C to a stirred solution of (4*R*)-3-[(2*R*)-2-(2-bromo-4-chlorobenzyl)-3,3,3-trifluoropropanoyl]-4-phenyl-1,3-oxazolidin-2-one (single stereoisomer) (8.9 g, 18.1 mmol) in tetrahydrofuran (60 ml) and water (20 ml). After stirring at RT for 5 h, the reaction mixture was quenched with saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 5:1). Yield: 4.5 g (75% of theory).

Chiral SFC: $R_t = 1.11$ min, >99% ee

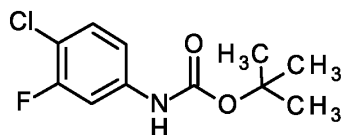
Analysis method: SFC: column: Chiralpak AD-3 3 μm , 100 mm x 3 mm, eluent: carbon dioxide (A), methanol with 0.1% DEA (B), gradient: 5% to 20% B in 2 min, hold 1 min at 20% B; temperature: 35°C; flow rate: 2.0 ml/min; UV detection: 254 nm.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 7.75 (d, 1H), 7.50-7.40 (m, 2H), 5.02 (t, 1H), 3.64-3.44 (m, 2H), 3.03-2.93 (m, 2H), 2.75-2.59 (m, 1H).

$^{19}\text{F-NMR}$ (376 MHz, $\text{DMSO-}d_6$): δ [ppm] = -67.19 (s, 3F).

Example 2.7A

tert-Butyl (4-chloro-3-fluorophenyl)carbamate

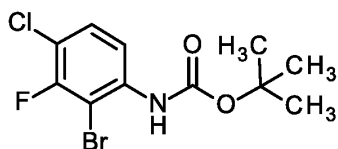


To a mixture of 4-chloro-3-fluoroaniline (15.0 g, 103 mmol, 1.0 eq.) in water (150 ml) was added
5 di-*tert*-butyl dicarbonate (26 ml, 110 mmol, 1.1 eq.). The resulting mixture was stirred at RT for
24 h, extracted with diethyl ether, dried over anhydrous sodium sulfate, filtered and concentrated
under reduced pressure. The crude product was used in the subsequent reaction without further
purification. Yield: 21.6 g (85% of theory).

LC-MS (method 1): $R_t = 1.12$ min; MS (ESI^{neg}): $m/z = 244$ [M-H]⁻

10 **Example 2.7B**

tert-Butyl (2-bromo-4-chloro-3-fluorophenyl)carbamate

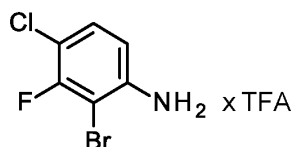


A solution of *tert*-butyllithium (88 ml, 1.7 M in pentane, 150 mmol, 1.5 eq.) in tetrahydrofuran (350
ml) was cooled to -78°C, a solution of *tert*-butyl (4-chloro-3-fluorophenyl)carbamate (24.4 g, 99.4
15 mmol, 1.0 eq.) in tetrahydrofuran (150 ml) was added dropwise over a period of 90 min. Stirring was
continued at this temperature for 60 min, before 1,2-dibromoethane (10 ml, 120 mmol, 1.2 eq.) was
added dropwise. The resulting mixture was stirred at -78°C for 1.5 h, at RT overnight and then treated
with a saturated aqueous solution of ammonium chloride, extracted with ethyl acetate, dried over
anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was
20 purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 20:1 to 10:1).
Yield: 15.9 g (49% of theory).

LC-MS (method 3): $R_t = 4.20$ min; MS (ESI^{neg}): $m/z = 323$ [M-H]⁻

Example 2.7C

2-Bromo-4-chloro-3-fluoroaniline trifluoroacetate

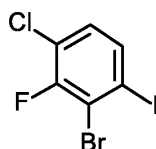


To a solution of *tert*-butyl (2-bromo-4-chloro-3-fluorophenyl)carbamate (15.9 g, 49.0 mmol, 1.0 eq.) in dichloromethane (200 ml) was added trifluoroacetic acid (19 ml, 240 mmol, 5.0 eq.) and the resulting mixture was stirred at RT overnight. The mixture was then concentrated under reduced pressure and the remaining residual was dissolved for two times in dichloromethane followed by evaporation. The crude product was used in the subsequent reaction without further purification. Yield: 15.1 g (87% of theory).

LC-MS (method 15): $R_t = 1.62$ min; MS (ESI^{neg}): $m/z = 222$ [M-H-TFA]⁻

Example 2.7D

10 2-Bromo-4-chloro-3-fluoro-1-iodobenzene

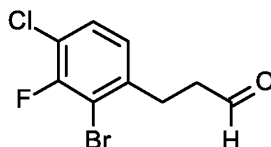


A solution of 2-bromo-4-chloro-3-fluoroaniline trifluoroacetate in water (320 ml) was cooled to 0°C, followed by the dropwise addition of sulfuric acid (60 ml). A solution of sodium nitrite (3.27 g, 47.4 mmol, 1.1 eq.) in water (30 ml) was added to the mixture and the resulting suspension was stirred for 1 h while the temperature was kept at 5-10°C. Subsequently, a solution of potassium iodide (9.38 g, 56.5 mmol, 1.3 eq.) in water (50 ml) was added under vigorous stirring. The reaction mixture was allowed to warm to RT and extracted with ethyl acetate. The combined organic phases were washed with aqueous solutions of sodium hydroxide (1 N), sodium thiosulfate (1 N), hydrogen chloride (1 N) and a saturated aqueous sodium bicarbonate solution. The washed organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 50:1). Yield: 12.1 g (82% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.81 (dd, 1H), 7.43 (dd, 1H).

Example 2.7E

25 3-(2-Bromo-4-chloro-3-fluorophenyl)propanal

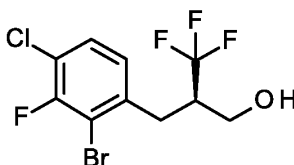


2-Bromo-4-chloro-3-fluoro-1-iodobenzene (9.00 g, 26.3 mmol, 1.0 eq.), palladium(II) acetate (118 mg, 526 μ mol, 0.02 eq.), tetra-*N*-butylammonium chloride (7.31 g, 26.3 mmol, 1.0 eq.) and sodium bicarbonate (5.52 g, 65.8 mmol, 2.5 eq.) were dissolved in *N,N*-dimethylformamide (60 ml) and argon was passed through the resulting suspension for 10 min. After addition of prop-2-en-1-ol (2.7 ml, 39 mmol, 1.5 eq.), the mixture was heated to 40°C and stirred at this temperature overnight, subsequently followed by the addition diethyl ether and water. The aqueous phase was extracted with diethyl ether and the combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was used in the subsequent step without further purification. Yield: 6.29 g (82% purity, 74% of theory).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 9.72 (s, 1H), 7.56 (dd, 1H), 7.25 (dd, 1H), 2.98 (t, 2H), 2.81 (t, 2H).

Example 2.7F

(2*R*)-2-(2-Bromo-4-chloro-3-fluorobenzyl)-3,3,3-trifluoropropan-1-ol (single stereoisomer)



15

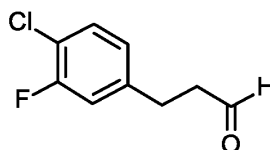
Argon was passed through a mixture of 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (3.53 g, 10.7 mmol, 1.0 eq.), (5*R*)-5-benzyl-2,2,3-trimethyl-4-oxoimidazolidin-1-ium trifluoroacetate (single stereoisomer) (711 mg, 2.14 mmol, 0.2 eq.) and copper(I) chloride (52.9 mg, 535 μ mol, 0.05 eq.) for 10 min. The mixture was cooled to -20°C before a solution of 3-(2-bromo-4-chloro-3-fluorophenyl)propanal (4.50 g, 82% purity, 13.9 mmol, 1.3 eq.) in chloroform (30 ml) was added. The resulting mixture was stirred at -20°C for 5 h and kept in the freezer at -18°C overnight. Additional amounts of 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (2.12 g, 6.41 mmol, 0.6 eq.), (5*R*)-5-benzyl-2,2,3-trimethyl-4-oxoimidazolidin-1-ium trifluoroacetate (single stereoisomer) (355 mg, 1.07 mmol, 0.1 eq.) and copper(I) chloride (265 mg, 2.67 mmol, 0.25 eq.) were added and the mixture was stirred at -20°C for additional 5.5 h. After cooling to -78°C, precooled dichloromethane (45 ml, -78°C) was added and the mixture was treated with sodium borohydride (4.04 g, 107 mmol, 10.0 eq.) and precooled methanol (21 ml, -78°C). Stirring was continued at -78°C for 1 h, followed by the addition of a saturated aqueous solution of ammonium chloride and warming of the reaction mixture to RT. The aqueous phase was then extracted with dichloromethane and the

combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 3.68 g (76% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.61 (dd, 1H), 7.33 (dd, 1H), 5.03 (t, 1H), 3.62-3.46 (m, 2H), 3.10-2.99 (m, 2H), 2.76-2.64 (m, 1H).

Example 2.8A

3-(4-Chloro-3-fluorophenyl)propanal

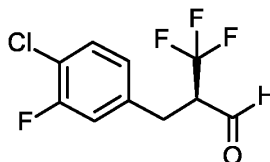


1-Chloro-2-fluoro-4-iodobenzene (10.0 g, 39.0 mmol, 1.0 eq.), tetra-*N*-butylammonium chloride (10.8 g, 39.0 mmol, 1.0 eq.) and sodium bicarbonate (8.19 g, 97.5 mmol, 2.5 eq.) were dissolved in *N,N*-dimethylformamide (80 ml) and argon was passed through the resulting suspension for 10 min. After addition of palladium(II) acetate (175 mg, 780 μmol, 0.02 eq.) and prop-2-en-1-ol (4.0 ml, 58 mmol, 1.5 eq.), the mixture was heated to 50°C and stirred at this temperature for 4 h, followed by the addition of methyl *tert*-butyl ether and water. After phase separation, the aqueous phase was extracted with methyl *tert*-butyl ether. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was used in the subsequent step without further purification. Yield: 6.55 g (90% of theory).

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 9.70 (t, 1H), 7.51-7.40 (m, 1H), 7.31-7.27 (m, 1H), 7.10 (dd, 1H), 2.89-2.84 (m, 2H), 2.83-2.77 (m, 2H).

Example 2.8B

(2*R*)-2-(4-Chloro-3-fluorobenzyl)-3,3,3-trifluoropropanal (single stereoisomer)



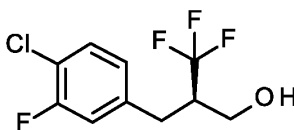
Argon was passed through a mixture of 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (10.6 g, 32.2 mmol, 1.0 eq.), (5*R*)-5-benzyl-2,2,3-trimethyl-4-oxoimidazolidin-1-ium trifluoroacetate (single stereoisomer) (2.14 g, 6.43 mmol, 0.2 eq.) and copper(I) chloride (239 mg, 2.41 mmol, 0.075 eq.) for 10 min. The mixture was cooled to -20°C before a solution of 3-(4-chloro-3-

fluorophenyl)propanal (6.00 g, 32.2 mmol, 1.0 eq.) in chloroform (70 ml) was added. The resulting mixture was kept in the freezer at -18°C for 72 h and stirred at -20°C for additional 4 h. The mixture was then immediately purified by column chromatography (silica gel, eluent: dichloromethane / methanol 98:2 to 80:20). Yield: 5.94 g (73% of theory).

- 5 ¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 9.69 (t, 1H), 7.52 (dd, 1H), 7.42 (dd, 1H), 7.19 (dd, 1H), 4.21-4.12 (m, 1H), 3.26 (dd, 1H), 3.04 (dd, 1H).

Example 2.8C

(2*R*)-2-(4-Chloro-3-fluorobenzyl)-3,3,3-trifluoropropan-1-ol (single stereoisomer)

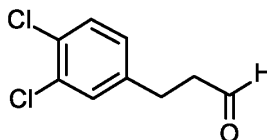


- 10 (2*R*)-2-(4-Chloro-3-fluorobenzyl)-3,3,3-trifluoropropanal (single stereoisomer) (3.00 g, 11.8 mmol, 1.0 eq.) was dissolved in dichloromethane (21 ml) and cooled to -78°C. Subsequently, the mixture was treated with sodium borohydride (5.83 g, 58.9 mmol, 5.0 eq.) and precooled methanol (10 ml, -78°C). Stirring was continued at -78°C for 1 h, followed by the addition of a saturated aqueous ammonium chloride solution and warming to RT. The aqueous phase was then extracted with
15 dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 1.86 g (60% of theory).

- ¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 7.51 (dd, 1H), 7.37 (dd, 1H), 7.17 (dd, 1H), 4.96 (t, 1H),
20 3.57-3.52 (m, 1H), 3.50-3.40 (m, 1H), 2.92-2.84 (m, 2H), 2.77-2.64 (m, 1H).

Example 2.9A

3-(3,4-Dichlorophenyl)propanal



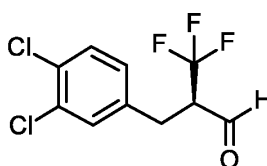
- 1,2-Dichloro-4-iodobenzene (5.00 g, 18.0 mmol, 1.0 eq.), tetra-*N*-butylammonium chloride (4.99 g,
25 18.0 mmol, 1.0 eq.) and sodium bicarbonate (3.77 g, 44.9 mmol, 2.5 eq.) were dissolved in *N,N*-dimethylformamide (30 ml) and argon was passed through the resulting suspension for 10 min. After addition of palladium(II) acetate (80.6 mg, 359 μmol, 0.02 eq.) and prop-2-en-1-ol (1.8 ml, 27 mmol, 1.5 eq.), the mixture was heated to 50°C and stirred at this temperature for 5 h, followed by the

addition of methyl *tert*-butyl ether and water. After phase separation, the aqueous phase was extracted with methyl *tert*-butyl ether. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 80:20). Yield: 2.56 g (69% of theory).

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 9.69 (t, 1H), 7.53-7.50 (m, 2H), 7.23 (dd, 1H), 2.86-2.79 (m, 4H).

Example 2.9B

(2*R*)-2-(3,4-Dichlorobenzyl)-3,3,3-trifluoropropanal (single stereoisomer)



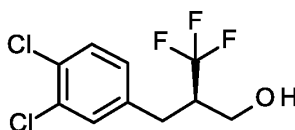
10

Argon was passed through a mixture of 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (4.06 g, 12.3 mmol, 1.0 eq.), (5*R*)-5-benzyl-2,2,3-trimethyl-4-oxoimidazolidin-1-ium trifluoroacetate (single stereoisomer) (818 mg, 2.46 mmol, 0.2 eq.) and copper(I) chloride (239 mg, 2.41 mmol, 0.075 eq.) for 10 min. The mixture was cooled to -20°C before a solution of 3-(3,4-dichlorophenyl)propanal (2.55 g, 12.3 mmol, 1.0 eq.) in chloroform (35 ml) was added. The resulting mixture was stirred at -20°C for 5 h, kept in the freezer at -18°C overnight and stirred at -20°C for additional 3 h. The mixture was then immediately purified by column chromatography (silica gel, eluent: dichloromethane / methanol 98:2 to 80:20). Yield: 2.20 g (68% of theory).

15

Example 2.9C

(2*R*)-2-(3,4-Dichlorobenzyl)-3,3,3-trifluoropropan-1-ol (single stereoisomer)



(2*R*)-2-(3,4-Dichlorobenzyl)-3,3,3-trifluoropropanal (single stereoisomer) (2.20 g, 8.12 mmol, 1.0 eq.) was dissolved in dichloromethane (20 ml) and cooled to -78°C. Subsequently, the mixture was treated with sodium borohydride (4.02 g, 40.6 mmol, 5.0 eq.) and precooled methanol (5.0 ml, -78°C). Stirring was continued at -78°C for 1.5 h, followed by the addition of saturated aqueous ammonium chloride solution and warming to RT. The aqueous phase was then extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered

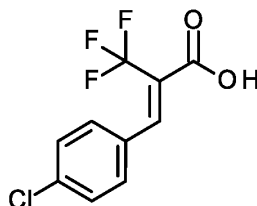
25

and concentrated under reduced pressure. The crude mixture was used in the subsequent step without further purification. Yield: 1.82 g (62% purity, 51% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.62-7.55 (m, 2H), 7.33-7.26 (m, 1H), 4.98 (t, 1H), 3.58-3.43 (m, 2H), 2.91-2.84 (m, 2H), 2.78-2.66 (m, 1H).

5 **Example 2.10A**

(2*Z*)-3-(4-Chlorophenyl)-2-(trifluoromethyl)prop-2-enoic acid



Under nitrogen atmosphere, titanium tetrachloride (470 g, 2.48 mol) in dichloromethane (200 ml) was added dropwise at 0°C to a stirred mixture of 3,3,3-trifluoropropanoic acid (210 g, 1.64 mol) and 4-chlorobenzaldehyde (251 g, 1.79 mol) in tetrahydrofuran (1 l). The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere, followed by the dropwise addition of triethylamine (684 ml, 4.92 mol) over 1 h. The resulting mixture was stirred for additional 12 h at RT. The reaction was repeated in parallel for another 4 batches. The reaction mixtures were separately quenched with ice/water (5 l) and the resulting mixtures were combined and extracted three times with dichloromethane (5 l). The combined organic layers were washed two times with saturated aqueous ammonium chloride solution (5 l), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was slurried with petroleum ether (500 ml). The precipitated solids were collected by filtration, washed with petroleum ether (500 ml) and dried *in vacuo*. Yield: 1070 g (52% of theory).

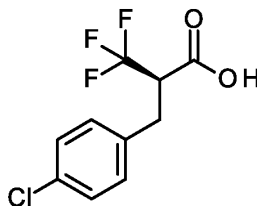
LC-MS (method 19): *R*_t = 1.01 min; MS (ES): *m/z* = 249 [M-H]⁺

¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 11.92 (br s, 1H), 8.22 (s, 1H), 7.47-7.39 (m, 4H).

¹⁹F-NMR (376 MHz, CDCl₃): δ [ppm] = -58.2 (s, 3F).

Example 2.10B

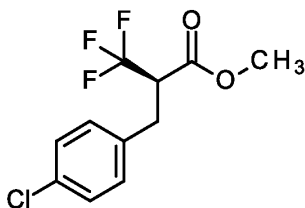
(2*R*)-2-(4-Chlorobenzyl)-3,3,3-trifluoropropanoic acid (single stereoisomer)



- (S)-2,6-Diethyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (20.9 g, 53.9 mmol, 0.010 eq.) [Y. Li *et al.*, *Angew. Chem. Int. Ed.* **2013**, *101*, 6748-6752] in 2-propanol / water (4:1, 4.5 l) was treated at RT with bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (10.9 g, 26.9 mmol, 0.015 eq.) and stirred for 2 min. Afterwards, triphenyl phosphine (4.71 g, 18.0 mmol, 0.010 eq.) was added and stirring was continued for another 10 min. (2Z)-3-(4-chlorophenyl)-2-(trifluoromethyl)prop-2-enoic acid (450 g, 1.80 mol) and morpholine (15.7 ml, 180 mmol, 0.10 eq.) were added and the reaction mixture was transferred to a 7 l autoclave. Stirring was continued at a hydrogen pressure of 20 bar for 24 h at RT. The reaction mixture was filtered over diatomaceous earth and the 2-propanol was mostly removed under reduced pressure. The residue was treated with 1 N aqueous hydrogen chloride solution (1.0 l) and water (1.0 l). The mixture was extracted with ethyl acetate (4.5 l) and after phase separation the aqueous phase was extracted with ethyl acetate (3 x 2.5 l). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was used in the subsequent reaction without further purification. Yield: 482 g (94% purity, quantitative of theory, >97% ee).
- LC-MS (method 17): $R_t = 6.82$ min; MS (ESIpos): $m/z = 253$ $[M+H]^+$
- Chiral SFC: $R_t = 0.87$ min, >97% ee
- Analysis method: SFC: column: Chiralpak AD-3, 3 μ m, 100 mm x 4.6 mm, eluent: isocratic 95% carbon dioxide / 5% methanol, 10 min, temperature: 40°C; flow rate: 3.0 ml/min; UV detection: 210 nm, backpressure: 130 bar.
- ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 13.34 (br s, 1H), 7.46-7.19 (m, 4H), 3.79 (td, 1H), 3.14-2.97 (m, 2H).

Example 2.10C

Methyl (2*R*)-2-(4-chlorobenzyl)-3,3,3-trifluoropropanoate (single stereoisomer)



- Methanol (3.6 l) was treated dropwise with thionyl chloride (346 ml, 4.75 mol, 2.0 eq.) at -10°C. After stirring for another 10 min at 0°C, (2*R*)-2-(4-chlorobenzyl)-3,3,3-trifluoropropanoic acid (single stereoisomer) (600 g, 2.38 mol) was added and the reaction mixture was stirred for 3 h under reflux. The reaction mixture was concentrated under reduced pressure and the residue was redissolved in ethyl acetate (4.0 l). The organic phase was washed with saturated aqueous sodium bicarbonate (3.0 l) and 10% aqueous sodium chloride solution (2.5 l), dried over anhydrous sodium

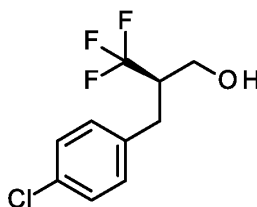
sulfate, filtered and concentrated under reduced pressure. The residue was redissolved in dichloromethane, treated with silica gel (3.0 kg) and the mixture was concentrated under reduced pressure. This material was purified by flash column chromatography (9.0 kg silica gel, eluent: petroleum ether / dichloromethane 8:2). Yield: 493 g (78% of theory).

- 5 GC-MS (method 2): $R_t = 3.91$ min; MS (EIpos): $m/z = 266$ $[M]^+$

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 7.40-7.34 (m, 2H), 7.33-7.28 (m, 2H), 4.07-3.96 (m, 1H), 3.61 (s, 3H), 3.18-3.05 (m, 2H).

Example 2.10D

(2*R*)-2-(4-Chlorobenzyl)-3,3,3-trifluoropropan-1-ol (single stereoisomer)



10

Two experiments of the same scale were run in parallel; the purification was carried out with the combined reaction mixtures.

- Methyl (2*R*)-2-(4-chlorobenzyl)-3,3,3-trifluoropropanoate (single stereoisomer) (171 g, 641 mmol) in tetrahydrofuran (3.2 l) was treated under argon with lithium aluminium hydride (673 ml, 2.4 M solution in tetrahydrofuran, 673 ml, 1.62 mol, 2.52 eq.) at -10°C within 10 min. Afterwards, the reaction mixture was stirred while allowing to warm up to RT. The reaction mixture was diluted with *tert*-butylmethyl ether (700 ml), cooled to 0°C and carefully treated dropwise with water (61.4 ml) under stirring. Afterwards, the reaction mixture was carefully treated dropwise with 15% aqueous sodium hydroxide solution (61.4 ml) and finally again with water (184 ml). The reaction mixture was warmed to RT, stirred for 15 min and then treated with anhydrous magnesium sulfate (1.4 kg). After stirring for another 15 min, the reaction mixture was filtered under reduced pressure and the filter cake was washed with *tert*-butylmethyl ether (1.7 l). The organic phase was concentrated under reduced pressure to yield the crude material. The combined crude material from two batches was subjected to column chromatography (8.0 kg silica gel, eluent: dichloromethane). Yield for the combined two batches: 271.4 g (89% of theory, >95% ee).

- 25 GC-MS (method 2): $R_t = 4.23$ min; MS (EIpos): $m/z = 238$ $[M]^+$

Chiral SFC: $R_t = 0.85$ min, >95% ee

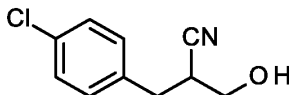
Analysis method: SFC: column: Chiralcel OD-3, 3 μm , 100 mm x 4.6 mm, eluent: isocratic 90% carbon dioxide / 10% isopropanol, 10 min, temperature: 40°C ; flow rate: 3.0 ml/min; UV detection:

210 nm, backpressure: 130 bar.

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 7.39-7.34 (m, 2H), 7.33-7.29 (m, 2H), 5.00 (t, 1H), 3.61-3.45 (m, 2H), 2.93-2.81 (m, 2H), 2.63 (ddt, 1H).

Example 2.11A

5 2-(4-Chlorobenzyl)-3-hydroxypropanenitrile (racemate)

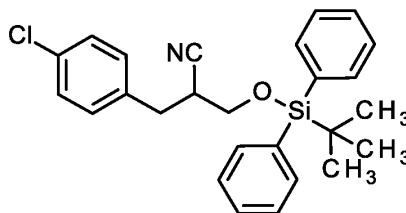


Lithium bis(trimethylsilyl)amide (1.41 l, 1.0 M in tetrahydrofuran, 1.41 mol, 2.0 eq.) was added at -78°C to solution of 3-hydroxypropanenitrile (50.0 g, 704 mmol) in tetrahydrofuran (500 ml) and the reaction mixture was stirred at -78°C for 1 h, followed by addition of 1-(bromomethyl)-4-chlorobenzene (145 g, 704 mmol, 1.0 eq.) in tetrahydrofuran (200 ml) at -78°C. The reaction mixture was stirred at -78°C for 1 h and then at 0°C for 1 h. The mixture was diluted with saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 20:1 to 10:1). Yield: 55.0 g (90% purity, 36% of theory).

¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 7.16 (d, 2H), 7.07-7.02 (m, 2H), 3.61 (q, 2H), 2.79 (s, 3H), 2.49-2.42 (m, 1H).

Example 2.11B

3-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-(4-chlorobenzyl)propanenitrile (racemate)



20

tert-Butyl(chloro)diphenylsilane (72.2 ml, 77.3 g, 281 mmol, 1.0 eq.) was added at RT to a solution of 2-(4-chlorobenzyl)-3-hydroxypropanenitrile (racemate) (55.0 g, 90% purity, 252 mmol), 4-dimethylaminopyridine (1.72 g, 14.1 mmol, 0.055 eq.) and imidazole (57.4 g, 843.4 mmol, 3.3 eq.) in dichloromethane (750 ml). The reaction mixture was stirred at RT for 12 h. Subsequently, the mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under

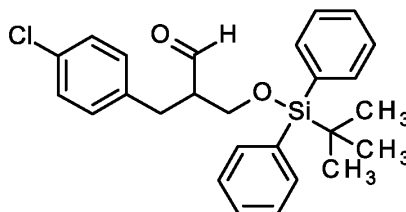
25

reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 20:1 to 10:1). Yield: 75.0 g (87% purity, 59% of theory).

¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 7.60-7.53 (m, 4H), 7.37-7.27 (m, 6H), 7.18 (d, 2H), 7.04 (d, 2H), 3.66 (d, 2H), 2.92-2.83 (m, 2H), 2.83-2.73 (m, 1H), 1.02 (s, 9H).

5 Example 2.11C

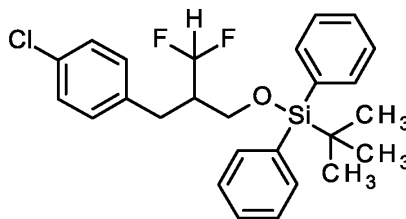
3-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-(4-chlorobenzyl)propanal (racemate)



A solution of diisobutylaluminium hydride (618 ml, 1.0 M in toluene, 4.6 eq.) was added at -70°C to a solution of 3-{[*tert*-butyl(diphenyl)silyl]oxy}-2-(4-chlorobenzyl)propanenitrile (racemate) (67.0 g, 87% purity, 133 mmol) in toluene (1.0 l) and the reaction mixture was stirred at 0°C for 2 h. The mixture was diluted with saturated potassium sodium tartrate solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used in the subsequent reaction without further purification. Yield: 80.0 g.

15 Example 2.11D

tert-Butyl[2-(4-chlorobenzyl)-3,3-difluoropropoxy]diphenylsilane (racemate)

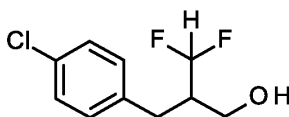


(Diethylamino)sulfur trifluoride (72.6 ml, 88.5 g, 549 mmol, 3.0 eq.) was added at -70°C to a solution of crude 3-{[*tert*-butyl(diphenyl)silyl]oxy}-2-(4-chlorobenzyl)propanal (racemate) (80.0 g, 183 mmol) in dichloromethane (1.0 l) and the reaction mixture was stirred at RT for 2 h. The mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 100:0 to 20:1). Yield: 17.0 g (65% purity, 18% of theory over two steps).

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ [ppm] = 7.63-7.55 (m, 4H), 7.48-7.37 (m, 6H), 7.22-7.17 (m, 2H), 7.02 (d, 2H), 6.05 (d, 1H), 3.74-3.67 (m, 1H), 3.64-3.58 (m, 1H), 2.98-2.84 (m, 1H), 2.78-2.69 (m, 1H), 2.32-2.11 (m, 1H), 1.11-1.08 (m, 9H).

Example 2.11E

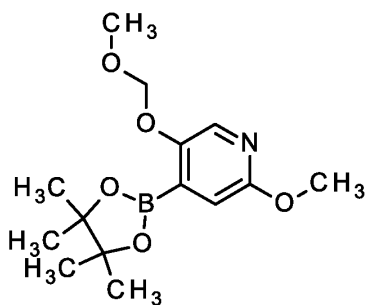
- 5 2-(4-Chlorobenzyl)-3,3-difluoropropan-1-ol (racemate)



- A solution of *tetra-N*-butylammonium fluoride (74.1 ml, 1.0 M in tetrahydrofuran, 74.1 mmol, 3.1 eq.) was added at -30°C to solution of *tert*-butyl[2-(4-chlorobenzyl)-3,3-difluoropropoxy]diphenylsilane (racemate) (17.0 g, 65% purity, 24.1 mmol) in tetrahydrofuran (180 ml) and the reaction mixture was stirred at RT for 2 h. The mixture was filtered and concentrated under reduced pressure to give a residue which was dissolved in ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative HPLC. Yield: 5.50 g (99% of theory).
- 15 $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ [ppm] = 7.34-7.28 (m, 2H), 7.17 (d, 2H), 6.35-5.56 (m, 1H), 3.89-3.59 (m, 2H), 3.13-2.56 (m, 2H), 2.45-2.13 (m, 1H), 1.55 (br s, 1H).

Example 3.1A

2-Methoxy-5-(methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

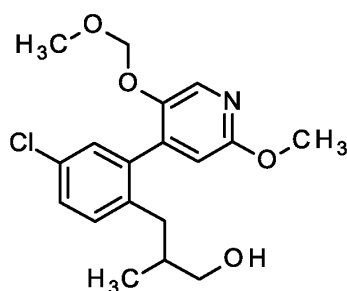


- 20 A solution of *tert*-butyllithium (22.2 ml, 1.6 M in pentane, 35.4 mmol, 2.0 eq.) was added at -78°C under nitrogen atmosphere to a solution of 2-methoxy-5-(methoxymethoxy)pyridine (3.0 g, 17.7 mmol, 1.0 eq.) in tetrahydrofuran (60 ml). After stirring at -78°C for 0.5 h, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.96 g, 21.3 mmol, 1.2 eq.) was added dropwise. The reaction mixture was stirred at -78°C for 2 h, quenched with methanol at -78°C and then concentrated under

reduced pressure. The crude product was used in the subsequent step without further purification.
Yield: 5.25 g.

Example 3.1B

3-{4-Chloro-2-[2-methoxy-5-(methoxymethoxy)pyridin-4-yl]phenyl}-2-methylpropan-1-ol
(racemate)

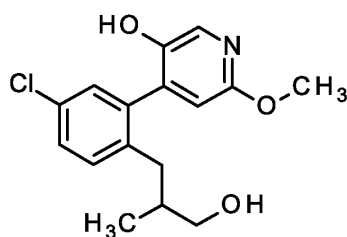


2-Methoxy-5-(methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (crude product from previous step, 7.39 g, 25.0 mmol, 2.0 eq.), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (0.92 g, 1.3 mmol, 0.1 eq.) and sodium carbonate (3.98 g, 37.6 mmol, 3.0 eq.) were added under nitrogen atmosphere to a solution of 3-(2-bromo-4-chlorophenyl)-2-methylpropan-1-ol (racemate) (3.3 g, 12.5 mmol, 1.0 eq.) in 1,4-dioxane (100 ml) and water (15 ml). The resulting mixture was stirred at 90°C for 2 h, cooled to RT and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 1:1). Yield: 3.6 g (87% purity, 72% of theory).

LC-MS (method 11): $R_t = 1.14$ min; MS (ESIpos): $m/z = 352$ $[M+H]^+$

Example 3.1C

4-[5-Chloro-2-(3-hydroxy-2-methylpropyl)phenyl]-6-methoxypyridin-3-ol (racemate)



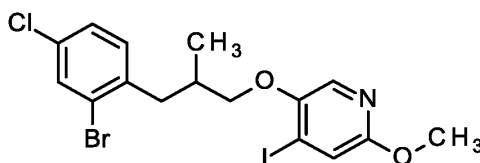
Aqueous hydrochloric acid (6.0 ml, 3 N) was added to a solution of 3-{4-chloro-2-[2-methoxy-5-(methoxymethoxy)pyridin-4-yl]phenyl}-2-methylpropan-1-ol (racemate) (2.2 g, 87% purity, 5.4 mmol, 1.0 eq.) in tetrahydrofuran (30 ml). The reaction mixture was stirred at 60°C for 3 h and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 1:1). Yield: 1.60 g (83% purity, 80% of theory).

LC-MS (method 12): $R_t = 0.79$ min; MS (ESIpos): $m/z = 308$ $[M+H]^+$

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): δ [ppm] = 9.33 (s, 1H), 7.78 (s, 1H), 7.39-7.35 (m, 1H), 7.30-7.27 (m, 1H), 7.13 (d, 1H), 6.54 (s, 1H), 4.48-4.31 (br s, 1H), 3.77 (s, 3H), 3.15-2.98 (m, 2H), 2.63-2.56 (m, 1H), 2.19-2.11 (m, 1H), 1.61-1.52 (m, 1H), 0.60 (d, 3H).

5 Example 3.1D

5-[3-(2-Bromo-4-chlorophenyl)-2-methylpropoxy]-4-iodo-2-methoxypyridine (racemate)



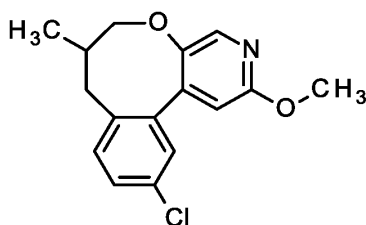
3-(2-Bromo-4-chlorophenyl)-2-methylpropan-1-ol (racemate) (2.0 g, 7.2 mmol, 1.0 eq.) and (tributylphosphoranylidene)acetonitrile (2.62 g, 10.8 mmol, 1.5 eq.) were added at RT to a suspension of 4-iodo-6-methoxypyridin-3-ol (1.82 g, 7.2 mmol, 1.0 eq.) in toluene (10 ml). The reaction mixture was irradiated at 160°C for 2 h in a microwave reactor and then cooled to RT. The above reaction procedure was repeated for three more batches (altogether 8.02 g (28.9 mmol) 3-(2-Bromo-4-chlorophenyl)-2-methylpropan-1-ol (racemate)). The four batches were combined and concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 19:1). Yield: 11.87 g (81% of theory).

LC-MS (method 13): $R_t = 1.63$ min; MS (ESIpos): $m/z = 496$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 7.77-7.70 (m, 2H), 7.42 (dd, 1H), 7.38-7.30 (m, 2H), 3.98-3.86 (m, 2H), 3.78 (s, 3H), 3.08-2.99 (m, 1H), 2.73-2.63 (m, 1H), 2.35-2.20 (m, 1H), 1.02 (d, 3H).

Example 3.1E

11-Chloro-2-methoxy-7-methyl-7,8-dihydro-6H-[3]benzoxocino[2,1-c]pyridine (racemate)



Diisopropyl diazene-1,2-dicarboxylate (2.1 g, 10.4 mmol, 2.4 eq.) was added dropwise at 0°C to a suspension of 4-[5-chloro-2-(3-hydroxy-2-methylpropyl)phenyl]-6-methoxypyridin-3-ol (racemate) (1.6 g, 83% purity, 4.4 mmol) and triphenylphosphine (2.7 g, 10.4 mmol, 2.4 eq.) in tetrahydrofuran (80 ml). The resulting mixture was stirred under nitrogen atmosphere at RT for 3 h and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 10:1). Yield: 0.6 g (91% purity, 43% of theory).

LC-MS (method 12): $R_t = 1.27$ min; MS (ESIpos): $m/z = 290$ $[M+H]^+$

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): δ [ppm] = 8.05 / 8.03 (2s, 1H), 7.47-7.31 (m, 3H), 6.78 / 6.73 (2s, 1H), 4.49-4.43 (m, 1H), 3.86 (s, 3H), 3.45-3.38 (m, 1H), 2.70-2.57 (m, 1H), 2.21-2.13 (m, 1H), 2.03-1.96 (m, 1H), 0.90-0.83 (d, 3H). Additional signals of minor rotamers were also detected.

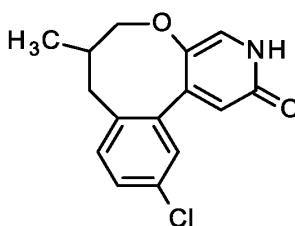
Alternative synthetic route:

Bis(pinacolato)diboron (6.14 g, 24.2 mmol, 2.0 eq.), palladium(II) acetate (0.27 g, 1.2 mmol, 0.1 eq.), tricyclohexylphosphine (0.51 g, 1.8 mmol, 0.15 eq.) and potassium acetate (3.56 g, 36.2 mmol, 3.0 eq.) were added to a solution of 4-[3-(2-bromo-4-chlorophenyl)-2-methylpropoxy]-5-iodo-2-methoxypyridine (racemate) (6.00 g, 12.1 mmol, 1.0 eq.) in *N,N*-dimethylformamide (60 ml). The resulting mixture was purged with nitrogen for 5 min, stirred at 80°C for 15 h under nitrogen atmosphere, treated with 5 ml of saturated aqueous solution of sodium bicarbonate and stirred at 80°C for further 2 h. After cooling to RT, the reaction mixture was diluted with ethyl acetate and filtered through Celite®. The filtrate was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 19:1). Yield: 1.2 g (34% of theory).

LC-MS (method 13): $R_t = 1.38$ min; MS (ESIpos): $m/z = 290$ $[M+H]^+$

Example 3.1F

11-Chloro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (racemate)



4-Toluenesulfonic acid monohydrate (2.72 g, 14.3 mmol, 1.8 eq.) and lithium iodide (5.32 g, 39.7 mmol, 5.0 eq.) were added at RT to a solution of 11-chloro-2-methoxy-7-methyl-7,8-dihydro-6*H*-[3]benzoxocino[2,1-*c*]pyridine (racemate) (2.30 g, 7.9 mmol) in 1-butanol (20 ml). After stirring at 85°C for 12 h, the mixture was concentrated under reduced pressure. The residue was dissolved in

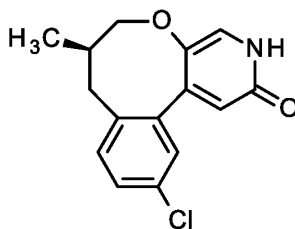
dichloromethane, washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: dichloromethane / methane 19:1). Yield: 1.78 g (79% of theory).

LC-MS (method 14): $R_t = 1.21$ min; MS (ESIpos): $m/z = 276$ $[M+H]^+$

- 5 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 11.56-11.25 (br s, 1H), 7.50-7.36 (m, 3H), 7.34-7.27 (m, 1H), 6.33-6.25 (m, 1H), 4.45-4.35 / 4.23-4.16 (2m, 1H), 3.86-3.78 / 3.3-3.25 (2m, 1H, partially concealed), 2.86-2.78 / 2.72-2.59 (2m, 1H), 2.29 (dd, 1H), 2.07-1.90 (m, 1H), 0.94-0.80 (m, 3H). Additional signals of minor rotamers were also detected.

Example 3.1G

- 10 (7*R*)-11-Chloro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer)



Enantiomer separation of 1.74 g of 11-chloro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (racemate), Example 3.1F gave

- 15 single stereoisomer 1 (the title compound Example 3.1G) (chiral HPLC: $R_t = 3.00$ min, >99% ee): 603 mg (86% purity),

single stereoisomer 2 (chiral HPLC: $R_t = 5.79$ min): 552 mg.

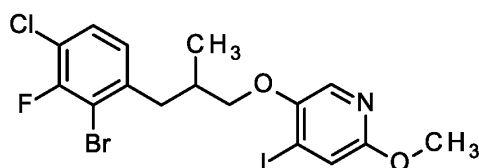
Separation method: HPLC: column: Daicel Chiralpak AS-H 5 μm , 250 mm x 20 mm; eluent: 15% *n*-heptane / 85% ethanol; temperature: 40°C; flow rate: 20 ml/min; UV detection: 220 nm.

- 20 Analysis method: HPLC: column: Daicel Chiralpak AS-3 3 μm , 50 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% ethanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.

LC-MS (method 4): $R_t = 1.52$ min; MS (ESIpos): $m/z = 276$ $[M+H]^+$

Example 3.2A

5-[3-(2-Bromo-4-chloro-3-fluorophenyl)-2-methylpropoxy]-4-iodo-2-methoxypyridine (racemate)

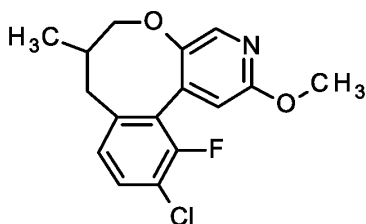


General Method 2 was carried out three times with 3-(2-bromo-4-chloro-3-fluorophenyl)-2-methylpropan-1-ol (racemate) (500 mg, 1.78 mmol, 1.0 eq.), 4-iodo-6-methoxypyridin-3-ol (446 mg, 1.78 mmol, 1.0 eq.) and (tributylphosphoranylidene)acetonitrile (643 mg, 2.66 mmol, 1.5 eq.) in toluene (14 ml) at 120°C including the following variations of the procedure: The three reaction mixtures were combined, concentrated under reduced pressure and the crude mixture was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 96:4 to 70:30). Yield: 2.01 g (92% purity, 68% of theory).

LC-MS (method 3): $R_t = 5.21$ min; MS (ESIpos): $m/z = 516$ $[M+H]^+$

10 **Example 3.2B**

11-Chloro-12-fluoro-2-methoxy-7-methyl-7,8-dihydro-6H-[3]benzoxocino[2,1-c]pyridine (racemate)

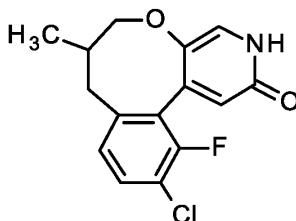


General Method 3a was carried out two times with 5-[3-(2-bromo-4-chloro-3-fluorophenyl)-2-methylpropoxy]-4-iodo-2-methoxypyridine (racemate) (1.00 g, 92% purity, 1.79 mmol, 1.0 eq.), bis(pinacolato)diboron (636 mg, 2.50 mmol, 1.4 eq.), potassium acetate (526 mg, 5.36 mmol, 3.0 eq.), palladium(II) acetate (20.0 mg, 89.0 μ mol, 0.05 eq.) and tricyclohexylphosphine (50.1 mg, 179 μ mol, 0.1 eq.) in *N,N*-dimethylformamide (26 ml) including the following variations of the procedure: After stirring at 80°C overnight, tetrakis(triphenylphosphine)palladium(0) (103.7 mg, 89.0 μ mol, 0.05 eq.) and saturated aqueous sodium bicarbonate solution (12.5 ml) were added to each of the two reaction mixtures. Stirring was then continued at 85°C for 1 h, the two reaction mixtures were combined, water was added and the combined mixtures were extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 485 mg (84% purity, 37% of theory).

LC-MS (method 3): $R_t = 3.89$ min; MS (ESIpos): $m/z = 308$ $[M+H]^+$

Example 3.2C

11-Chloro-12-fluoro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (racemate)



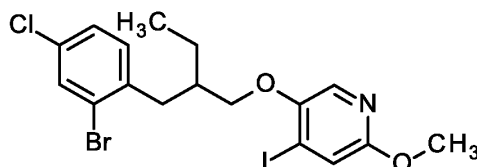
- General Method 4 was carried with 11-chloro-12-fluoro-2-methoxy-7-methyl-7,8-dihydro-6*H*-[3]benzoxocino[2,1-*c*]pyridine (racemate) (480 mg, 84% purity, 1.31 mmol, 1.0 eq.) and sodium iodine (393 mg, 2.62 mmol, 2.0 eq.) in acetic acid (15 ml) at 100°C for 4 h including the following variations of the procedure: The crude mixture was purified by preparative column chromatography (silica gel, eluent: dichloromethane / methanol 100:0 to 90:10), followed by purification by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95).
- Yield: 200 mg (92% purity, 48% of theory).

LC-MS (method 3): $R_t = 2.37$ min; MS (ESIpos): $m/z = 294$ $[M+H]^+$

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 11.49 (br s, 1H), 7.70-7.47 (m, 2H), 7.30-7.17 (m, 1H), 6.40 / 6.37 (2d, 1H), 4.44-4.36 / 3.84-3.79 (2m, 1H), 4.24-4.19 / 3.33-3.28 (2m, 1H), 2.74-2.66 / 2.72-2.67 (2m, 1H), 2.31-2.18 (m, 1H), 2.05-1.88 (m, 1H), 0.88 / 0.81 (2d, 3H).

15 **Example 3.3A**

5-[2-(2-Bromo-4-chlorobenzyl)butoxy]-4-iodo-2-methoxypyridine (racemate)

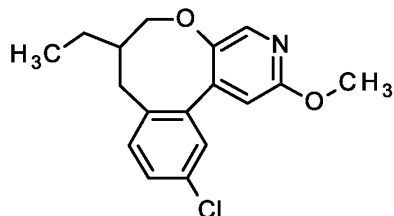


- General Method 2 was carried out two times with 2-(2-bromo-4-chlorobenzyl)butan-1-ol (racemate) (500 mg, 77% purity, 1.39 mmol, 1.0 eq.), 4-iodo-6-methoxypyridin-3-ol (453 mg, 1.80 mmol, 1.3 eq.) and (tributylphosphoranylidene)acetonitrile (502 mg, 2.08 mmol, 1.5 eq.) in toluene (15 ml) at 120°C including the following variations of the procedure: The two reaction mixtures were combined and purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 100:0 to 65:35). Yield: 750 mg (63% purity, 33% of theory).

LC-MS (method 1): $R_t = 1.62$ min; MS (ESIpos): $m/z = 510$ $[M+H]^+$

Example 3.3B

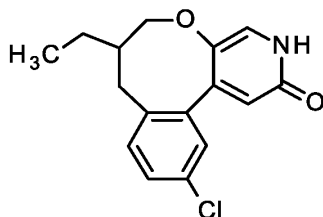
11-Chloro-7-ethyl-2-methoxy-7,8-dihydro-6H-[3]benzoxocino[2,1-c]pyridine (racemate)



- General Method 3a was carried out with 5-[2-(2-bromo-4-chlorobenzyl)butoxy]-4-iodo-2-methoxypyridine (racemate) (750 mg, 63% purity, 925 μmol , 1.0 eq.), bis(pinacolato)diboron (352 mg, 1.39 mmol, 1.5 eq.), palladium(II) acetate (10.4 mg, 46.3 μmol , 0.1 eq.), tricyclohexylphosphine (26.0 mg, 92.5 μmol , 0.1 eq.) and potassium acetate (272 mg, 2.78 mmol, 3.0 eq.) in *N,N*-dimethylformamide (14 ml) including the following variations of the procedure: After stirring at 80°C overnight, tetrakis(triphenylphosphine)palladium(0) (53.7 mg, 46.3 μmol , 0.1 eq.) and saturated aqueous sodium bicarbonate solution (6.5 ml) were added to the reaction mixture. Stirring was then continued at 85°C for 3 days. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate, filtered over silica gel (eluent: ethyl acetate) and used in the subsequent step without further purification. Yield: 600 mg (52% purity).
- LC-MS (method 1): $R_t = 1.31$ min; MS (ESIpos): $m/z = 304$ $[\text{M}+\text{H}]^+$

Example 3.3C

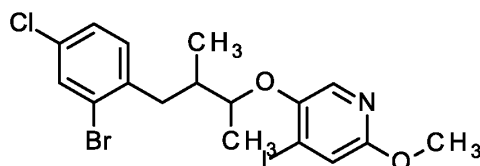
11-Chloro-7-ethyl-7,8-dihydro-3H-[3]benzoxocino[2,1-c]pyridin-2(6H)-one (racemate)



- General Method 4 was carried out with 11-chloro-7-ethyl-2-methoxy-7,8-dihydro-6H-[3]benzoxocino[2,1-c]pyridine (racemate) (600 mg, 52% purity, 1.03 mmol, 1.0 eq.) and sodium iodide (462 mg, 3.08 mmol, 3.0 eq.) in acetic acid (15 ml) at 100°C for 2 h including the following variations of the procedure: The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 57 mg (66% purity, 13% of theory) and 15 mg (86% purity, 4% of theory).
- LC-MS (method 1): $R_t = 0.89$ min; MS (ESIpos): $m/z = 290$ $[\text{M}+\text{H}]^+$

Example 3.4A

5-{{[4-(2-Bromo-4-chlorophenyl)-3-methylbutan-2-yl]oxy}-4-iodo-2-methoxypyridine (mixture of stereoisomers)

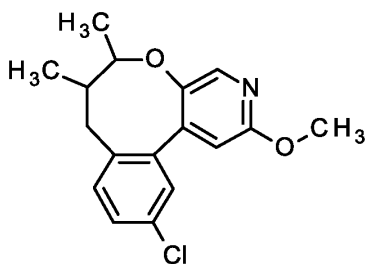


- 5 General Method 2 was carried out with 4-(2-bromo-4-chlorophenyl)-3-methylbutan-2-ol (mixture of stereoisomers) (500 mg, 91% purity, 1.64 mmol, 1.0 eq.), 4-iodo-6-methoxypyridin-3-ol (416 mg, 1.64 mmol, 1.0 eq.) and (tributylphosphoranylidene)acetonitrile (475 mg, 1.97 mmol, 1.2 eq.) in toluene (15 ml) at 120°C including the following variations of the procedure: After stirring for 1 h, additional amounts of (tributylphosphoranylidene)acetonitrile (198 mg, 820 µmol, 0.5 eq.) were
- 10 added and stirring was continued at 120°C for 1 h. The crude mixture was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 98:2 to 80:20). Yield: 670 mg (78% of theory).

LC-MS (method 1): $R_t = 1.61$ min; MS (ESIpos): $m/z = 510$ $[M+H]^+$

Example 3.4B

- 15 11-Chloro-2-methoxy-6,7-dimethyl-7,8-dihydro-6H-[3]benzoxocino[2,1-c]pyridine (mixture of stereoisomers)



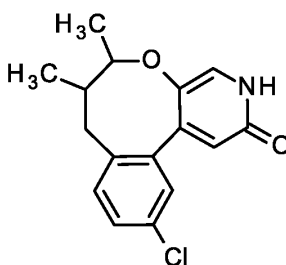
- General Method 3a was carried out with 5-{{[4-(2-bromo-4-chlorophenyl)-3-methylbutan-2-yl]oxy}-4-iodo-2-methoxypyridine (mixture of stereoisomers) (670 mg, 1.29 mmol, 1.0 eq.),
- 20 bis(pinacolato)diboron (457 mg, 1.80 mmol, 1.4 eq.), palladium(II) acetate (14.4 mg, 64.3 µmol, 0.05 eq.) and potassium acetate (379 mg, 3.86 mmol, 3.0 eq.) in *N,N*-dimethylformamide (16 ml) including the following variations of the procedure: After stirring at 80°C overnight, tetrakis(triphenylphosphine)palladium(0) (74.6 mg, 64.3 µmol, 0.05 eq.) and a saturated aqueous sodium bicarbonate solution (7.7 ml) were added to the reaction mixture. Stirring was then continued
- 25 at 85°C overnight. The reaction mixture was filtered over a mixture of silica gel and anhydrous

sodium sulfate and eluted with a mixture (1:1) of dichloromethane and ethyl acetate. The filtrate was concentrated under reduced pressure, water was added and the combined mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and used in the next step without further purification. Yield: 552 mg (63% purity, 89% of theory).

- 5 LC-MS (method 1): $R_t = 1.34$ min; MS (ESIpos): $m/z = 304$ $[M+H]^+$

Example 3.4C

11-Chloro-6,7-dimethyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (mixture of stereoisomers)

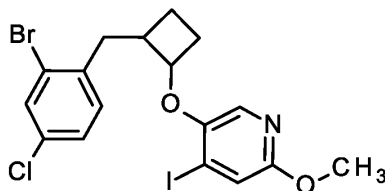


- 10 General Method 4 was carried out with 11-chloro-2-methoxy-6,7-dimethyl-7,8-dihydro-6*H*-[3]benzoxocino[2,1-*c*]pyridine (mixture of stereoisomers) (550 mg, 63% purity, 1.14 mmol, 1.0 eq.) and sodium iodide (513 mg, 3.42 mmol, 3.0 eq.) in acetic acid (20 ml) at 100°C for 2 h including the following variations of the procedure: The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 157 mg
- 15 (75% purity, 36% of theory).

LC-MS (method 3): $R_t = 2.52$ min; MS (ESIpos): $m/z = 290$ $[M+H]^+$

Example 3.5A

5-({*cis*-2-[(2-Bromo-4-chlorophenyl)methyl]cyclobutyl}oxy)-4-iodo-2-methoxypyridine (racemate)



20

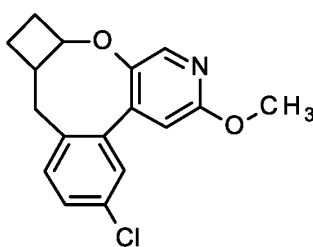
4-Iodo-6-methoxypyridin-3-ol (2.41 g, 9.62 mmol, 1.0 eq.), *trans*-2-[(2-bromo-4-chlorophenyl)methyl]-cyclobutan-1-ol (racemate) (2.65 g, 9.62 mmol) and (tributylphosphoranylidene)-acetonitrile (2.52 ml, 9.62 mmol, 1.0 eq.) were dissolved in toluene (53 ml) and equally distributed into three microwave vials which were sealed afterwards. The reaction

mixtures were heated at 120°C for 45 min under microwave irradiation. The three mixtures were combined and all volatiles removed *in vacuo*. The residue was dissolved in ethyl acetate and washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate mixtures). Yield: 2.69 g (54% of theory).

LC-MS (method 4): $R_t = 2.90 / 2.98$ min; MS (ESIpos): $m/z = 508$ $[M+H]^+$

Example 3.5B

cis-6-Chloro-3-methoxy-9a,10,11,11a-tetrahydro-9*H*-cyclobuta[4,5][3]benzoxocino[2,1-*c*]pyridine (racemate)



10

Bis(pinacolato)diboron (5.17 g, 20.35 mmol, 1.5 eq.), potassium acetate (3.99 g, 40.70 mmol, 3.0 eq.), palladium(II) acetate (305 mg, 1.36 mmol, 0.1 eq.) and tricyclohexylphosphine (380 mg, 1.36 mmol, 0.1 eq.) were added to a solution of 5-({*cis*-2-[(2-bromo-4-chlorophenyl)methyl]cyclobutyl}oxy)-4-iodo-2-methoxypyridine (racemate) (6.90 g, 13.57 mmol) in *N,N*-dimethylformamide (136 ml, degassed before in a flame-dried flask). The reaction mixture was stirred at 100°C overnight. Tetrakis(triphenylphosphine)palladium(0) (784 mg, 0.68 mmol, 0.05 eq.), solid sodium bicarbonate (5.70 g, 67.84 mmol, 5.0 eq.) and water (0.93 ml) were added. The reaction mixture was stirred at 100°C overnight, allowed to come to RT, diluted with ethyl acetate and filtered through Celite®. The filter cake was washed with ethyl acetate. The combined filtrates were concentrated under reduced pressure. The residue was dissolved ethyl acetate, washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was used without further purification in the next step. Yield: 8.50 g.

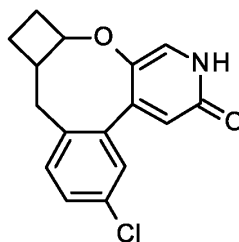
20

LC-MS (method 4): $R_t = 2.42$ min; MS (ESIpos): $m/z = 302$ $[M+H]^+$

Example 3.5C

cis-6-Chloro-9a,10,11,11a-tetrahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-*c*]pyridin-3(9*H*)-one (racemate)

25

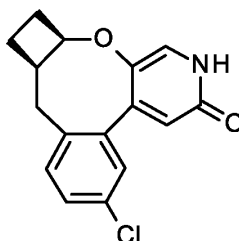


Sodium iodide (10.3 g, 68.8 mmol) was added to a solution of *cis*-6-chloro-3-methoxy-9a,10,11,11a-tetrahydro-9*H*-cyclobuta[4,5][3]benzoxocino[2,1-*c*]pyridine (racemate) (crude product from previous step, calculated with 50% purity: 8.3 g, 13.8 mmol) in acetic acid (208 ml). The resulting mixture was stirred at 80°C overnight. All volatiles were removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with phosphate buffer (pH 7) and filtered. After phase separation, the organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate mixtures). The residue was suspended in acetonitrile, filtered and dried *in vacuo*. Yield: 1.14 g (91% purity, 26% of theory).

LC-MS (method 4): $R_t = 1.58$ min; MS (ESIpos): $m/z = 288$ $[M+H]^+$

Example 3.5D

(9a*R*,11a*R*)-6-Chloro-9a,10,11,11a-tetrahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-*c*]pyridin-3(9*H*)-one (single stereoisomer)



Enantiomer separation of 1.13 g of *cis*-6-chloro-9a,10,11,11a-tetrahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-*c*]pyridin-3(9*H*)-one (racemate), Example 3.5C gave single stereoisomer 1 (chiral SFC: $R_t = 2.08$ min, 85% ee): 404 mg, single stereoisomer 2 (the title compound Example 3.5D) (chiral SFC: $R_t = 2.23$ min, 93% ee): 406 mg.

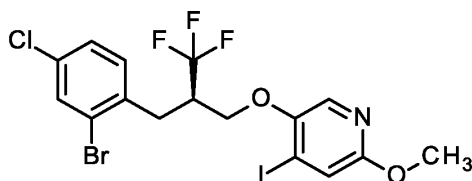
Separation method: SFC: column: Daicel Chiralpak OZ-H 5 μ m, 250 mm x 30 mm; eluent: 60% carbon dioxide / 40% methanol; temperature: 40°C; flow rate: 100 ml/min; UV detection: 210 nm.

Analysis method: SFC: column: Daicel Chiralpak OZ-H 3 μm , 100 mm x 4.6 mm; eluent: 70% carbon dioxide / 30% methanol; temperature: 40°C; flow rate: 3 ml/min; UV detection: 210 nm.

LC-MS (method 4): $R_t = 1.59$ min; MS (ESIpos): $m/z = 288$ $[\text{M}+\text{H}]^+$

Example 3.6A1

- 5 5-[(2*R*)-2-[(2-Bromo-4-chlorophenyl)methyl]-3,3,3-trifluoropropoxy]-4-iodo-2-methoxypyridine (single stereoisomer)



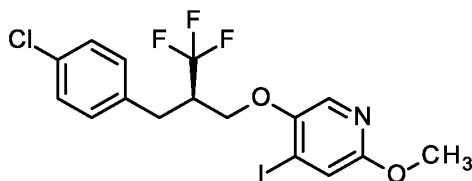
- (Tributylphosphoranylidene)acetonitrile (3.2 g, 13.3 mmol, 1.5 eq.) and (2*R*)-2-(2-bromo-4-chlorobenzyl)-3,3,3-trifluoropropan-1-ol (single stereoisomer) (3.0 g, 8.8 mmol) were added at RT to a solution of 4-iodo-6-methoxypyridin-3-ol (2.2 g, 8.8 mmol, 1.0 eq.) in toluene (15 ml). The resulting mixture was irradiated at 160°C for 2 h in a microwave reactor and then cooled to RT. The above reaction operation was repeated analogously for ten further batches. The eleven batches, altogether 33.0 g (97.3 mmol) of (2*R*)-2-(2-bromo-4-chlorobenzyl)-3,3,3-trifluoropropan-1-ol (single stereoisomer), were combined, diluted with ethyl acetate and washed with water and brine.
- 15 The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 9:1). Yield: 23.4 g (43% of theory).

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ [ppm] = 7.60 (d, 1H), 7.50 (s, 1H), 7.30-7.17 (m, 3H), 4.18 (dd, 1H), 3.94-3.86 (m, 1H), 3.84 (s, 3H), 3.37-3.23 (m, 2H), 3.07-2.93 (m, 1H).

- 20 $^{19}\text{F-NMR}$ (282 MHz, CDCl_3): δ [ppm] = -68.71 (s, 3F).

Example 3.6A2

- 5-[(2*R*)-2-(4-Chlorobenzyl)-3,3,3-trifluoropropoxy]-4-iodo-2-methoxypyridine (single stereoisomer)

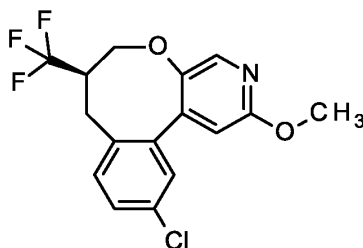


- 25 Under argon atmosphere, a mixture of (2*R*)-2-(4-chlorobenzyl)-3,3,3-trifluoropropan-1-ol (single stereoisomer) (558 g, 2.34 mol) and 4-iodo-6-methoxypyridin-3-ol (1.76 kg, 7.01 mol, 3.0 eq.) in

- toluene (5.6 l) was treated dropwise (addition time: 1 h) under reflux with (tributylphosphoranylidene)acetonitrile (847 g, 3.51 mol, 1.5 eq.). The reaction mixture was stirred for 2 h under reflux, cooled to 0°C and then methanol (366 ml) was added. The reaction mixture was diluted with toluene to a volume of 14.2 l and then washed with 2 N aqueous sodium hydroxide solution (3 x 5.3 l). The organic phase was washed with 10% aqueous sodium chloride solution (7.1 l) and then concentrated under reduced pressure. The crude material was divided into two equal portions which were purified by column chromatography (12.0 kg silica gel, eluent: dichloromethane / petroleum ether 3:2, then dichloromethane). Yield: 811 g (74% of theory). Recovery of excess 4-iodo-6-methoxypyridin-3-ol: The combined basic water phases were washed with toluene (7.0 l). The water phase was neutralized by addition of concentrated aqueous hydrogen chloride solution and the precipitate was then collected by filtration under reduced pressure. The filter cake was washed with water and then dried over phosphorus pentoxide under reduced pressure. The crude material was further purified by column chromatography (silica gel, eluent: dichloromethane / acetone 4:1) to yield pure 4-iodo-6-methoxypyridin-3-ol.
- LC-MS (method 4): $R_t = 2.64$ min; MS (ESIpos): $m/z = 471$ $[M+H]^+$
- $^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 7.70 (s, 1H), 7.39-7.31 (m, 5H), 4.22 (dd, 1H), 3.89 (dd, 1H), 3.77 (s, 3H), 3.19 (dt, 1H), 3.14-3.04 (m, 2H).

Example 3.6B

- (7*R*)-11-Chloro-2-methoxy-7-(trifluoromethyl)-7,8-dihydro-6*H*-[3]benzoxocino[2,1-*c*]pyridine (single stereoisomer)



- Bis(pinacolato)diboron (4.6 g, 18.2 mmol, 2.0 eq.), palladium(II) acetate (0.20 g, 0.9 mmol, 0.1 eq.), tricyclohexylphosphine (0.38 g, 1.4 mmol, 0.15 eq.) and potassium acetate (2.67 g, 27.2 mmol, 3.0 eq.) were added to a solution of 5-{[(2*R*)-2-(2-bromo-4-chlorobenzyl)-3,3,3-trifluoropropyl]oxy}-4-iodo-2-methoxypyridine (single stereoisomer) (5.0 g, 9.1 mmol) in *N,N*-dimethylformamide (100 ml). The resulting mixture was purged with nitrogen for 5 min and stirred at 80°C for 15 h under nitrogen atmosphere. After cooling to RT, the reaction mixture was diluted with ethyl acetate and filtered through Celite®. The filtrate was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column

chromatography (silica gel, eluent: petroleum ether / ethyl acetate 19:1). Yield: 0.86 g (28% of theory).

LC-MS (method 7): $R_t = 1.79$ min; MS (ESIpos): $m/z = 346$ $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ [ppm] = 8.08 (s, 1H), 7.42-7.39 (m, 1H), 7.33-7.24 (m, 2H), 6.69 (s, 1H), 4.90-4.75 (m, 1H), 3.98 (s, 3H), 3.96-3.89 (m, 1H), 3.06 (d, 1H), 2.88-2.63 (m, 1H), 2.60-2.51 (m, 1H).

$^{19}\text{F-NMR}$ (376 MHz, CDCl_3): δ [ppm] = -70.92 (s, 3F).

Alternative synthetic route:

Two experiments of the same scale were run in parallel; the purification was carried out with the combined reaction mixtures.

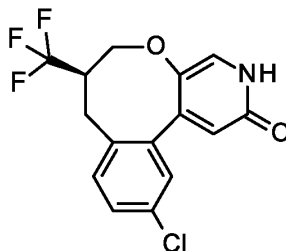
Under argon atmosphere, a 10 l round bottom flask was charged with potassium pivalate (44.6 g, 318 mmol, 1.5 eq.) in *N,N*-dimethylacetamide (600 ml) and then the flask was evacuated and back-filled with argon three times. The mixture was heated to 150°C (oil bath temperature: 180°C). A second 5 l round bottom flask was charged with 5-[(2*R*)-2-(4-chlorobenzyl)-3,3,3-trifluoropropoxy]-4-iodo-2-methoxypyridine (single stereoisomer) (100 g, 212 mmol) in *N,N*-dimethylacetamide (3.2 l) and the flask was evacuated and back-filled with argon three times. Tetrakis(triphenylphosphine)palladium(0) (24.5 g, 21.2 mmol, 0.10 eq.) was added and then the mixture was added *via* pump addition (flow rate: 60 ml/min) to the preheated potassium pivalate in *N,N*-dimethylacetamide (throughout the addition the temperature was always kept above 140°C). After the addition, the reaction mixture was stirred for another 3.5 h at 150°C. The reaction mixture was diluted with *tert*-butylmethyl ether (20 l) and 10% aqueous sodium chloride solution (20 l) was added. After stirring, the two phases were filtered over diatomaceous earth. After phase separation, the organic phase was washed with 10% aqueous sodium chloride solution (12 l), dried over sodium sulfate, filtered and concentrated under reduced pressure. The combined crude material from two batches was dissolved in dichloromethane and purified by column chromatography (8.0 kg silica gel, eluent: petroleum ether / ethyl acetate 19:1). The obtained material (65.5 g) was triturated with methanol (350 ml), the solid was filtered und reduced pressure and washed with cold methanol (2 x 50 ml). The combined mother liquors were concentrated under reduced pressure and the residue was triturated with cold methanol (100 ml). The solid was washed with cold methanol (2 x 20 ml) and dried. Yield for the combined two batches: 41.6 g (29% of theory). The combined mother liquors were concentrated under reduced pressure and the residue was triturated with cold methanol (100 ml). The solid was washed with cold methanol (2 x 20 ml) and dried under air atmosphere. Yield for the combined two batches: 2.5 g (94% purity, 2% of theory). Combined overall yield for the two batches: 44.1 g (31% of theory).

LC-MS (method 18): $R_t = 3.96$ min; MS (ESIpos): $m/z = 344$ $[M+H]^+$

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 8.15 (s, 1H), 7.58-7.30 (m, 3H), 6.81 (s, 1H), 4.68 (br s, 1H), 4.22-4.03 / 4.02-3.91 (2m, 1H), 3.88 (s, 3H), 3.25-3.15 / 3.11-2.82 (2m, 2H), 2.74-2.57 / 2.48-2.34 (2m, 1H, partially concealed). Additional signals of minor rotamers were also detected.

Example 3.6C

- 5 (7*R*)-11-Chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer)



- 4-Toluenesulfonic acid monohydrate (0.75 g, 3.9 mmol, 1.8 eq.) and lithium iodide (1.46 g, 10.9 mmol, 5.0 eq.) were added at RT to a solution of (7*R*)-11-chloro-2-methoxy-7-(trifluoromethyl)-7,8-dihydro-6*H*-[3]benzoxocino[2,1-*c*]pyridine (single stereoisomer) (0.75 g, 2.2 mmol) in 1-butanol (40 ml). After stirring at 85°C for 15 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and saturated aqueous solution of sodium carbonate and stirred for 10 min. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate / methanol 5:19:1) to give 0.44 g of the crude product, which was triturated with methanol and stirred for 30 min. The solid was collected by filtration, washed with methanol and dried under air atmosphere. Yield: 0.35 g (48% of theory).

LC-MS (method 9): *R*_t = 1.34 min; MS (ESIpos): *m/z* = 330 [M+H]⁺

- 20 ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 11.55 (s, 1H), 7.54-7.25 (m, 4H), 6.35 (s, 1H), 4.75-4.55 (m, 1H), 4.11-3.78 (m, 1H), 3.12-2.86 (m, 2H), 2.69-2.55 (m, 1H).

¹⁹F-NMR (376 MHz, DMSO-*d*₆): δ [ppm] = -69.67 (s, 3F).

Alternative synthetic route:

- Under argon atmosphere, 4-toluenesulfonic acid monohydrate (97.3 g, 511 mmol, 1.85 eq.) and lithium chloride (58.6 g, 42.4 mmol, 5.0 eq.) were added at RT to a solution of (7*R*)-11-chloro-2-methoxy-7-(trifluoromethyl)-7,8-dihydro-6*H*-[3]benzoxocino[2,1-*c*]pyridine (single stereoisomer) (95.0 g, 276 mmol) in 2-propanol (1.2 l). After stirring under reflux for 16 h, the reaction mixture was cooled to RT and then concentrated under reduced pressure to a volume of about 250 ml. Water (2.0 l) was added to the mixture and the resulting solution was extracted with ethyl acetate (1.5 l and

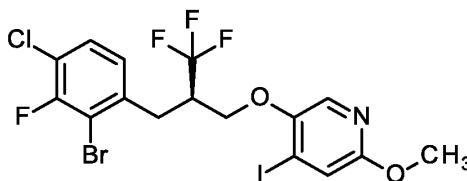
500 ml). The precipitate between the two layers was filtered off under reduced pressure, washed with ethyl acetate (200 ml) and dried under air atmosphere (yield: 53.2 g). After phase separation, the combined organic phases were concentrated under reduced pressure to a remaining volume of about 100 ml. The precipitate was filtered off under reduced pressure, washed with ethyl acetate and dried under air atmosphere (yield: 23.5 g). The combined filtrates were washed with saturated aqueous sodium bicarbonate solution (1.1 l) and the precipitate, formed between the two layers, was filtered off under reduced pressure, washed with ethyl acetate and dried under air atmosphere (yield: 9.2 g). Combined yield: 85.9 g (94% of theory).

LC-MS (method 3): $R_t = 2.54$ min; MS (ESIpos): $m/z = 330$ $[M+H]^+$

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 11.46 (br s, 1H), 7.59 (br s, 1H), 7.50 (br d, 1H), 7.42-7.26 (m, 2H), 6.33 (br s, 1H), 4.64 (br d, 1H), 4.09-3.97 / 3.84 (m / br t, 1H), 3.26-3.14 / 3.08-2.89 (m, 2H), 2.81-2.69 / 2.58-2.51 (2m, 1H, partially concealed). Additional signals of minor rotamers were also detected.

Example 3.7A1

5- $\{(2R)$ -2-[(2-Bromo-4-chloro-3-fluorophenyl)methyl]-3,3,3-trifluoropropoxy}-4-iodo-2-methoxypyridine (single stereoisomer)

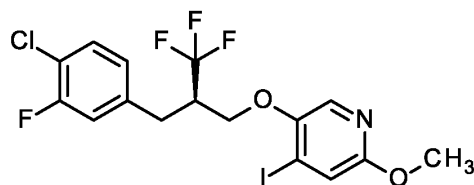


General Method 2 was carried out four times with (2R)-2-[(2-bromo-4-chloro-3-fluorophenyl)methyl]-3,3,3-trifluoropropan-1-ol (single stereoisomer) (920 mg, 2.60 mmol, 1.0 eq.), 4-iodo-6-methoxypyridin-3-ol (850 mg, 3.39 mmol, 1.3 eq.) and (tributylphosphoranylidene)acetonitrile (1.0 ml, 3.9 mmol, 1.5 eq.) in toluene (15 ml) at 120°C including the following variations of the procedure: The crude mixtures of the four reactions were combined, concentrated under reduced pressure and purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 100:0 to 75:25). Yield: 2.71 g (46% of theory).

LC-MS (method 5): $R_t = 1.78$ min; MS (ESIpos): $m/z = 569$ $[M+H]^+$

Example 3.7A2

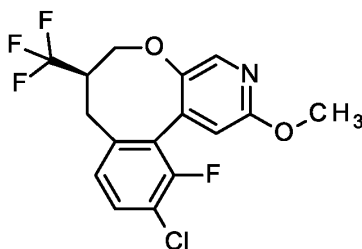
5-[(2R)-2-(4-Chloro-3-fluorobenzyl)-3,3,3-trifluoropropoxy]-4-iodo-2-methoxypyridine (single stereoisomer)



- General Method 2 was carried out six times at 120°C for 3.0 h: one time with (2*R*)-2-[(2-bromo-4-chloro-3-fluorophenyl)methyl]-3,3,3-trifluoropropan-1-ol (single stereoisomer) (50 mg, 189 μmol, 1.0 eq.), 4-iodo-6-methoxypyridin-3-ol (77 mg, 92% purity, 283 μmol, 1.5 eq.) and (tributyl-phosphoranylidene)acetonitrile (74 μl, 283 μmol, 1.5 eq.) in toluene (2.5 ml), four times with (2*R*)-2-[(2-bromo-4-chloro-3-fluorophenyl)methyl]-3,3,3-trifluoropropan-1-ol (single stereoisomer) (360 mg, 1.36 mmol, 1.0 eq.), 4-iodo-6-methoxypyridin-3-ol (408 mg, 92% purity, 1.50 mmol, 1.1 eq.) and (tributyl-phosphoranylidene)acetonitrile (530 μl, 2.0 mmol, 1.5 eq.) in toluene (17 ml) and one time with (2*R*)-2-[(2-bromo-4-chloro-3-fluorophenyl)methyl]-3,3,3-trifluoropropan-1-ol (single stereoisomer) (360 mg, 1.36 mmol, 1.0 eq.), 4-iodo-6-methoxy-pyridin-3-ol (376 mg, 1.49 mmol, 1.5 eq.) and (tributylphosphoranylidene)-acetonitrile (530 μl, 2.0 mmol, 1.5 eq.) in toluene (17 ml) including the following variations of the procedure: The crude mixtures of the six reactions were combined, concentrated under reduced pressure and purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 100:0 to 80:20). Yield: 1.35 g (40% of theory).
- LC-MS (method 4): $R_t = 2.65$ min; MS (ESIpos): $m/z = 490$ $[M+H]^+$

Example 3.7B

(7*R*)-11-Chloro-12-fluoro-2-methoxy-7-(trifluoromethyl)-7,8-dihydro-6*H*-[3]benzoxocino[2,1-*c*]pyridine (single stereoisomer)



- General Method 3a was carried with 5-[(2*R*)-2-[(2-bromo-4-chloro-3-fluorophenyl)methyl]-3,3,3-trifluoropropoxy]-4-iodo-2-methoxypyridine (single stereoisomer) (2.71 g, 4.77 mmol, 1.0 eq.), bis(pinacolato)diboron (1.94 g, 7.63 mmol, 1.6 eq.), palladium(II) acetate (107 mg, 477 μmol, 0.1 eq.), potassium acetate (1.40 g, 14.3 mmol, 3.0 eq.) in *N,N*-dimethylformamide (70 ml) including the following variations of the procedure: After stirring of the reaction mixture at 80°C for 3 days, water was added and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The

crude mixture was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 95:0 to 20:80). Yield: 342 mg (99% purity, 20% of theory) and 1.33g (64% purity, 49% of theory).

LC-MS (method 15): $R_t = 2.03$ min; MS (ESIpos): $m/z = 362$ $[M+H]^+$

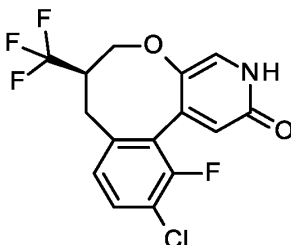
Alternative synthetic route:

- 5 5-[(2*R*)-2-(4-Chloro-3-fluorobenzyl)-3,3,3-trifluoropropoxy]-4-iodo-2-methoxypyridine (single stereoisomer) (1.25 g, 2.50 mmol, 1.0 eq.) and potassium pivalate (1.40 g, 10.0 mmol, 4.0 eq.) were dissolved in *N,N*-dimethylacetamide (100 ml) and argon was passed through the mixture for 10 min. Subsequently, tetrakis(triphenylphosphine)palladium(0) (289 mg, 250 μ mol, 0.1 eq.) was added and the mixture was stirred at 150°C for 2.5 h. The mixture was concentrated under reduced pressure,
- 10 the residue was diluted with water and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 95:5 to 60:40). Yield: 420 mg (43% of theory).

LC-MS (method 5): $R_t = 1.55$ min; MS (ESIpos): $m/z = 362$ $[M+H]^+$

15 **Example 3.7C**

(7*R*)-11-Chloro-12-fluoro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer)

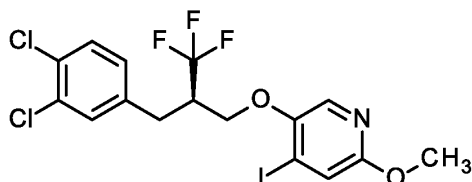


- General Method 4 was carried out with (7*R*)-11-chloro-12-fluoro-2-methoxy-7-(trifluoromethyl)-
- 20 7,8-dihydro-6*H*-[3]benzoxocino[2,1-*c*]pyridine (single stereoisomer) (1.62 g, 71% purity, 3.18 mmol) and sodium iodide (954 mg, 6.37 mmol, 2.0 eq.) in acetic acid (70 ml) at 100°C overnight including the following variations of the procedure: Additional amounts of sodium iodide (954 mg, 6.37 mmol, 2.0 eq.) were added to the reaction mixture and stirring was continued at 100°C for 4 h. The crude mixture was purified by column chromatography (silica gel, eluent: dichloromethane /
- 25 methanol 98:2 to 80:20), followed by additional purification by column chromatography (silica gel, eluent: dichloromethane / methanol 98:2 to 80:20). Yield: 1.11 g (76% purity, 76% of theory).

LC-MS (method 5): $R_t = 1.15$ min; MS (ESIpos): $m/z = 348$ $[M+H]^+$

Example 3.8A

5-[(2*R*)-2-(3,4-Dichlorobenzyl)-3,3,3-trifluoropropoxy]-4-iodo-2-methoxypyridine (single stereoisomer)

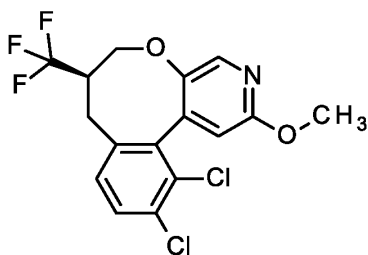


- 5 General Method 2 was carried out four times at 120°C for 6.0 h with (2*R*)-2-(3,4-dichlorobenzyl)-3,3,3-trifluoropropan-1-ol (single stereoisomer) (420 mg, 62% purity, 954 μ mol, 1.0 eq.), 4-iodo-6-methoxypyridin-3-ol (390 mg, 92% purity, 1.43 mmol, 1.5 eq.) and (tributyl-phosphoranylidene)-acetonitrile (500 μ l, 1.9 mmol, 2.0 eq.) in toluene (10 ml) including the following variations of the procedure: The crude mixtures of the four reactions were combined, concentrated under reduced pressure and purified twice by column chromatography (silica gel, eluent first column: cyclohexane / ethyl acetate 100:0 to 85:15, eluent second column: pure dichloromethane). Yield: 0.48 g (25% of theory).

LC-MS (method 4): R_t = 2.72 min; MS (ESIpos): m/z = 506 $[M+H]^+$

Example 3.8B

- 15 (7*R*)-11,12-Dichloro-2-methoxy-7-(trifluoromethyl)-7,8-dihydro-6*H*-[3]benzoxocino[2,1-*c*]pyridine (single stereoisomer)



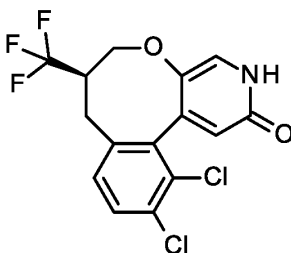
- 5-[(2*R*)-2-(3,4-Dichlorobenzyl)-3,3,3-trifluoropropoxy]-4-iodo-2-methoxypyridine (single stereoisomer) (378 mg, 747 μ mol, 1.0 eq.) and potassium pivalate (1.05 g, 7.47 mmol, 10.0 eq.) were dissolved in *N,N*-dimethylacetamide (25 ml) and argon was passed through the mixture for 10 min. Subsequently, tetrakis(triphenylphosphine)palladium(0) (86.3 mg, 74.7 μ mol, 0.1 eq.) was added and the mixture was stirred at 120°C overnight. The mixture was concentrated under reduced pressure, diluted with water and extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was

purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate 95:5 to 60:40).
Yield: 420 mg (47% purity, 16% of theory).

LC-MS (method 3): $R_t = 4.22$ min; MS (ESIpos): $m/z = 378$ $[M+H]^+$

Example 3.8C

- 5 (7*R*)-11,12-Dichloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer)



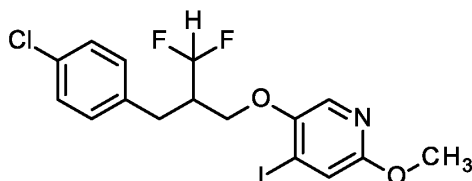
- General Method 4 was carried out with (7*R*)-11,12-dichloro-2-methoxy-7-(trifluoromethyl)-7,8-dihydro-6*H*-[3]benzoxocino[2,1-*c*]pyridine (single stereoisomer) (95.0 mg, 47% purity, 118 μ mol, 10 1.0 eq.) and sodium iodide (88.5 mg, 590 μ mol, 5.0 eq.) in acetic acid (4.0 ml) at 100°C for 2.0 h including the following variations of the procedure: The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 21.0 mg (49% of theory).

LC-MS (method 3): $R_t = 2.73$; MS (ESIpos): $m/z = 364$ $[M+H]^+$

- 15 $^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 7.75-7.69 (m, 2H), 7.41 (d, 1H), 6.41 (s, 1H), 4.62 (dd, 1H), 3.82 (t, 1H), 3.07 (d, 2H), 3.02-2.86 (m, 1H).

Example 3.9A

5-[2-(4-Chlorobenzyl)-3,3-difluoropropoxy]-4-iodo-2-methoxypyridine (racemate)



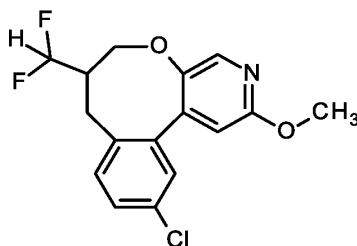
- 20 Under argon atmosphere, a mixture of 2-(4-chlorobenzyl)-3,3-difluoropropan-1-ol (racemate) (3.50 g, 15.9 mmol) and 4-iodo-6-methoxypyridin-3-ol (3.98 g, 15.9 mmol, 1.0 eq.) in toluene (50 ml) was treated with (tributylphosphoranylidene)acetonitrile (1.50 g, 23.8 mmol, 1.5 eq.). The reaction mixture was stirred for 16 h under reflux, cooled to RT and purified by column

chromatography (silica gel, eluent: cyclohexane / ethyl acetate 100:0 to 95:5 to 9:1). Yield: 6.74 g (94% of theory).

LC-MS (method 3): $R_t = 4.48$ min; MS (ESIpos): $m/z = 454$ $[M+H]^+$

Example 3.9B

- 5 11-Chloro-7-(difluoromethyl)-2-methoxy-7,8-dihydro-6H-[3]benzoxocino[2,1-c]pyridine (racemate)

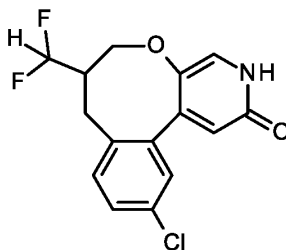


- Under argon atmosphere, a round bottom flask was charged with cesium pivalate (3.48 g, 14.9 mmol, 1.5 eq.) in *N,N*-dimethylacetamide (150 ml) and then the flask was frozen, evacuated and back-filled with argon three times. The mixture was then heated to 150°C. A second round bottom flask was charged with 5-[2-(4-chlorobenzyl)-3,3-difluoropropoxy]-4-iodo-2-methoxypyridine (racemate) (4.5 g, 9.91 mmol) in *N,N*-dimethylacetamide (30 ml) and the flask was frozen, evacuated and back-filled with argon three times. Tetrakis(triphenylphosphine)palladium(0) (1.15 g, 0.99 mmol, 0.10 eq.) was added and the mixture was added *via* pump addition to the preheated potassium pivalate solution at 150°C within 1.0 h. After the addition, the reaction mixture was stirred for another 5.5 h at 150°C. The reaction mixture was diluted with saturated aqueous ammonium chloride solution and extracted with *tert*-butylmethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / toluene 100:0 to 3:1 to 1:1 to 1:3 to 0:100). Yield: 600 mg (17% of theory).

LC-MS (method 3): $R_t = 3.68$ min; MS (ESIpos): $m/z = 326$ $[M+H]^+$

Example 3.9C

- 11-Chloro-7-(difluoromethyl)-7,8-dihydro-3H-[3]benzoxocino[2,1-c]pyridin-2(6H)-one (racemate)

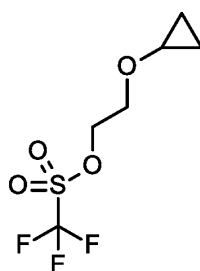


Under argon atmosphere, 4-toluenesulfonic acid monohydrate (596 mg, 3.13 mmol, 1.85 eq.) and lithium chloride (359 mg, 8.47 mmol, 5.0 eq.) were added at RT to a solution of 11-chloro-7-(difluoromethyl)-2-methoxy-7,8-dihydro-6*H*-[3]benzoxocino[2,1-*c*]pyridine (racemate) (600 mg, 1.69 mmol) in 2-propanol (7.1 ml). After stirring under reflux for 16 h, the reaction mixture was cooled to RT and the resulting precipitate was filtered, washed with water and dried. Yield: 515 mg (98% of theory).

LC-MS (method 3): $R_t = 2.26$ min; MS (ESIpos): $m/z = 312$ $[M+H]^+$

Example 4.1A

2-(Cyclopropyloxy)ethyl trifluoromethanesulfonate



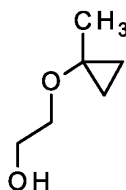
10

2,6-Dimethylpyridine (171 μ l, 1.47 mmol, 1.5 eq.) and trifluoromethanesulfonic anhydride (249 μ l, 1.47 mmol, 1.5 eq.) were added dropwise under argon atmosphere at 0°C to a solution of 2-(cyclopropyloxy)ethan-1-ol (100 mg, 0.98 mmol) in dichloromethane (4 ml). The reaction mixture was stirred at 0°C for 45 min, diluted with *tert*-butyl methyl ether and extracted with a mixture (3:1) of saturated aqueous solution of sodium chloride and aqueous hydrochloric acid (1 N). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used without further purification. Yield: 262 mg.

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 4.44-4.37 (m, 2H), 3.72-3.65 (m, 2H), 3.45-3.38 (m, 1H), 0.55-0.45 (m, 4H).

Example 4.2A

2-[(1-Methylcyclopropyl)oxy]ethan-1-ol



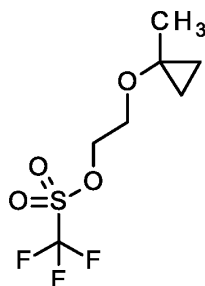
Magnesium turnings (474 mg, 19.5 mmol, 6.5 eq.) were placed into a round-bottom flask and heated, followed by addition of diethyl ether (5 ml) and some iodine. A solution of 1,2-dibromoethane (1.1

ml, 13 mmol) in diethyl ether (5 ml) was added dropwise under reflux. After stirring for additional 5 min, a solution of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (585 mg, 3.00 mmol) in diethyl ether (5 ml) was added dropwise. The reaction mixture was stirred under reflux overnight, cooled to RT, diluted with diethyl ether, quenched cautiously with saturated aqueous solution of ammonium chloride and diluted with ethyl acetate and water. After phase separation, the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used without further purification. Yield: 211 mg (61% of theory).

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 3.70-3.63 (m, 2H), 3.60-3.54 (m, 2H), 1.40 (s, 3H), 0.81-0.75 (m, 2H), 0.45-0.40 (m, 2H).

Example 4.2B

2-[(1-Methylcyclopropyl)oxy]ethyl trifluoromethanesulfonate

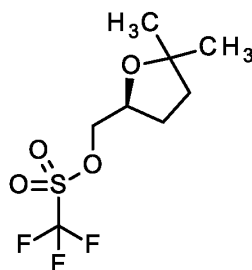


2,6-Dimethylpyridine (317 µl, 2.73 mmol, 1.5 eq.) and trifluoromethanesulfonic anhydride (461 µl, 2.73 mmol, 1.5 eq.) were added dropwise under argon atmosphere at 0°C to a solution of 2-[(1-methylcyclopropyl)oxy]ethan-1-ol (211 mg, 1.82 mmol) in dichloromethane (3 ml). The reaction mixture was stirred at 0°C for 1.5 h, diluted with *tert*-butyl methyl ether and extracted with a mixture (3:1) of saturated aqueous solution of sodium chloride and aqueous hydrochloric acid (1 N). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used without further purification. Yield: 509 mg.

¹H-NMR (600 MHz, CDCl₃): δ [ppm] = 4.58-4.53 (m, 2H), 3.80-3.75 (m, 2H), 1.39 (s, 3H), 0.84-0.78 (m, 2H), 0.46-0.40 (m, 2H).

Example 4.3A

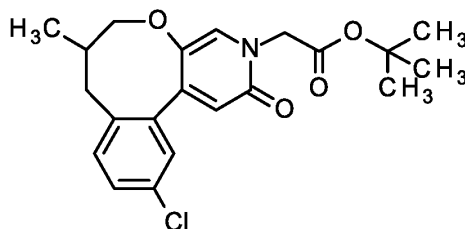
[(2*S*)-5,5-Dimethyloxolan-2-yl]methyl trifluoromethanesulfonate (single stereoisomer)



- 2,6-Dimethylpyridine (161 μ l, 1.38 mmol, 1.5 eq.) and trifluoromethanesulfonic anhydride (234 μ l, 1.38 mmol, 1.5 eq.) were added dropwise under argon atmosphere at 0°C to a solution of [(2*S*)-5,5-dimethyloxolan-2-yl]methanol (single stereoisomer) (120 mg, 0.92 mmol) in dichloromethane (5 ml). The reaction mixture was stirred at 0°C for 45 min, diluted with *tert*-butyl methyl ether and extracted with a mixture (3:1) of saturated aqueous solution of sodium chloride and aqueous hydrochloric acid (1 N). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used without further purification. Yield: 265 mg.
- ¹H-NMR (400 MHz, CDCl₃): δ [ppm] = 4.53-4.46 (m, 1H), 4.44-4.37 (m, 1H), 4.33-4.24 (m, 1H), 2.21-2.10 (m, 1H), 1.92-1.76 (m, 3H), 1.28 (s, 3H), 1.25 (s, 3H).

Example 5.1A

tert-Butyl (11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)acetate (racemate)



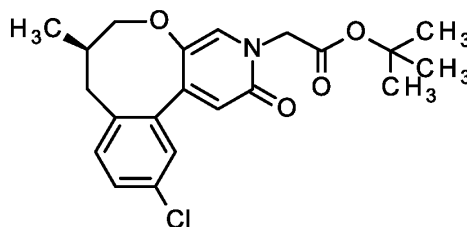
15

- Potassium carbonate (226 mg, 1.63 mmol, 1.5 eq.) was added to a solution of 11-chloro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (racemate) (300 mg, 1.09 mmol) and *tert*-butyl bromoacetate (193 μ l, 255 mg, 1.31 mmol, 1.2 eq.) in *N,N*-dimethylformamide (3.0 ml). The reaction mixture was stirred at 50°C overnight and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 0-95% ethyl acetate / cyclohexane). Yield: 281 mg (66% of theory).

LC-MS (method 4): R_t = 2.10 min; MS (ESIpos): m/z = 390 [M+H]⁺

Example 5.1B

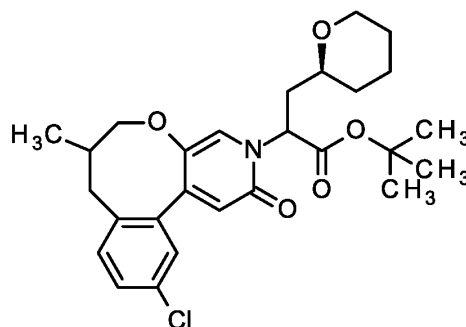
tert-Butyl [(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer)



- 5 Enantiomer separation of 830 mg of *tert*-butyl (11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)acetate (racemate), Example 5.1A gave single stereoisomer 1 (the title compound Example 5.1B) (chiral SFC: $R_t = 0.74$ min, >99% ee): 414 mg, single stereoisomer 2 (chiral SFC: $R_t = 1.39$ min, >99% ee): 413 mg.
- 10 Separation method: SFC: column: Daicel Chiralpak AS-H 5 μ m, 250 mm x 20 mm; eluent: 65% carbon dioxide / 35% methanol; temperature: 40°C; flow rate: 80 ml/min; UV detection: 210 nm.
Analysis method: SFC: column: Daicel Chiralpak AS 5 μ m, 100 mm x 4.6 mm; eluent: 70% carbon dioxide / 30% methanol; temperature: 40°C; flow rate: 3 ml/min; UV detection: 210 nm.
LC-MS (method 4): $R_t = 2.08$ min; MS (ESIpos): $m/z = 390$ $[M+H]^+$
- 15 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 7.74 (s, 1H), 7.47-7.38 (m, 2H), 7.33-7.30 (m, 1H), 6.35 (s, 1H), 4.65-4.50 (m, 2H), 4.48-4.41 (m, 1H), 3.30-3.25 (m, 1H), 2.70 (d, 1H), 2.33-2.24 (m, 1H), 2.09-1.94 (m, 1H), 1.44 (s, 9H), 0.89 (d, 3H). Additional signals of minor rotamers were also detected.

Example 5.2A

- 20 *tert*-Butyl 2-(11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoate (mixture of stereoisomers)

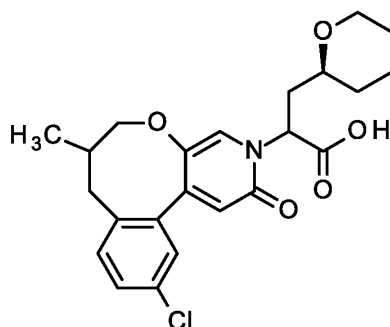


- A solution of sodium bis(trimethylsilyl)amide (0.8 ml, 1 M in tetrahydrofuran, 0.8 mmol, 1.25 eq.) was added under argon atmosphere at -78°C dropwise to a solution of *tert*-butyl (11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)acetate (racemate) (250 mg, 0.641 mmol) in tetrahydrofuran (9.3 ml). After stirring at -78°C for 20 min, (2*S*)-tetrahydro-2*H*-pyran-2-ylmethyl trifluoromethanesulfonate (single stereoisomer) (205 mg, 0.802 mmol, 1.25 eq.) (prepared according to WO 2017/005725, example 3.3D) was added. The resulting reaction mixture was stirred at -78°C for 30 min, then slowly warmed to RT and stirred for 1 h. Glacial acetic acid (55 μl , 58 mg, 0.96 mmol, 1.5 eq.) was added and the reaction mixture was concentrated under reduced pressure.
- The crude product was purified by preparative HPLC (reversed phase, eluent: 10-90% acetonitrile / water with 0.05% formic acid). Yield: 144 mg (46% of theory).

LC-MS (method 1): $R_t = 1.27$ min; MS (ESIpos): $m/z = 488$ $[\text{M}+\text{H}]^+$

Example 5.2B

- 2-(11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoic acid (mixture of stereoisomers)



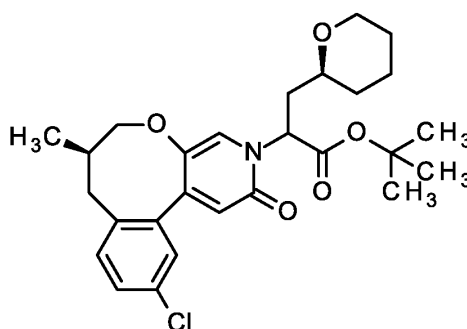
- Trifluoroacetic acid (3.1 ml) was added at RT to a solution of *tert*-butyl 2-(11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoate (mixture of stereoisomers) (140 mg, 0.287 mmol) in dichloromethane (3 ml). The reaction mixture was stirred for 45 min and then concentrated under reduced pressure. The residue was dissolved in toluene and concentrated under reduced pressure. The residue was dissolved in a

mixture of acetonitrile and water and lyophilized. The crude product was used without further purification. Yield: 152 mg.

LC-MS (method 1): $R_t = 1.01$ min; MS (ESIpos): $m/z = 432$ $[M+H]^+$

Example 5.3A

- 5 *tert*-Butyl 2-[(*7R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(*2S*)-tetrahydro-2*H*-pyran-2-yl]propanoate (mixture of two diastereomers)

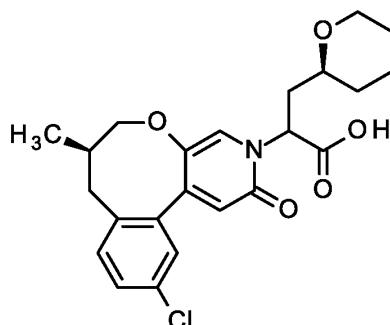


- A solution of sodium bis(trimethylsilyl)amide (0.51 ml, 1 M in tetrahydrofuran, 0.51 mmol, 1.25 eq.) was added dropwise under argon atmosphere at -78°C to a solution of *tert*-butyl [(*7R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer) (158 mg, 0.406 mmol) in tetrahydrofuran (12 ml). After stirring at -78°C for 20 min, a solution of (*2S*)-tetrahydro-2*H*-pyran-2-ylmethyl trifluoromethanesulfonate (single stereoisomer) (130 mg, 0.508 mmol, 1.25 eq.) (prepared according to WO 2017/005725, example 3.3D) in tetrahydrofuran (4 ml) was added. The resulting reaction mixture was stirred at -78°C for 30 min, then slowly warmed to RT and stirred for 1 h. Glacial acetic acid (35 μl , 37 mg, 0.61 mmol, 1.5 eq.) was added and the reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: 0-100% ethyl acetate / cyclohexane). Yield: 112 mg (87% purity, 49% of theory).

LC-MS (method 4): $R_t = 2.47$ min; MS (ESIpos): $m/z = 488$ $[M+H]^+$

20 Example 5.3B

2-[(*7R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(*2S*)-tetrahydro-2*H*-pyran-2-yl]propanoic acid (mixture of two diastereomers)

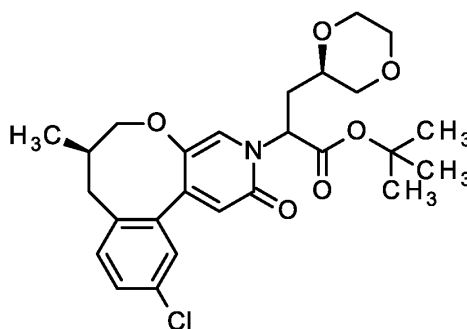


Lithium hydroxide (109 mg, 4.58 mmol, 23 eq.) was added to a solution of *tert*-butyl 2-[(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoate (mixture of two diastereomers) (111 mg, 87% purity, 0.197 mmol) in tetrahydrofuran (4.6 ml) and water (2.3 ml). The resulting reaction mixture was shaken at 40°C for 22 h, then acidified with aqueous hydrochloric acid (1 N) and diluted with ethyl acetate. After phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used without further purification. Yield: 22 mg (85% purity, 22% of theory).

LC-MS (method 4): $R_t = 1.86 / 1.89$ min; MS (ESIpos): $m/z = 432$ $[M+H]^+$

Example 5.4A

tert-Butyl 2-[(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*R*)-1,4-dioxan-2-yl]propanoate (mixture of two diastereomers)



15

A solution of sodium bis(trimethylsilyl)amide (0.80 ml, 1 M in tetrahydrofuran, 0.80 mmol, 1.25 eq.) was added dropwise under argon atmosphere at -78°C to a solution of *tert*-butyl [(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer) (250 mg, 0.641 mmol) in tetrahydrofuran (18 ml). After stirring at -78°C for 20 min, a solution of (2*S*)-1,4-dioxan-2-ylmethyl trifluoromethanesulfonate (single stereoisomer) (201 mg, 0.802 mmol, 1.25 eq.) (prepared according to WO 2017/005725, example 3.5A) in tetrahydrofuran

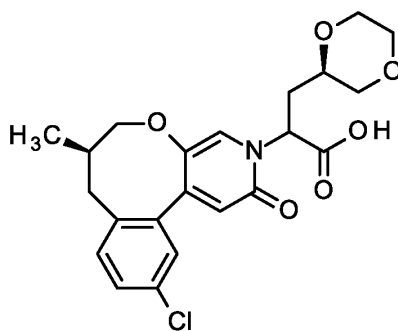
20

(6 ml) was added. The resulting reaction mixture was stirred at -78°C for 30 min, then slowly warmed to RT and stirred for 1 h. Glacial acetic acid (55 µl, 58 mg, 0.96 mmol, 1.5 eq.) was added and the reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent: 0-100% ethyl acetate / cyclohexane). Yield: 150 mg (47% of theory).

LC-MS (method 4): $R_t = 2.18$ min; MS (ESIpos): $m/z = 490$ $[M+H]^+$

Example 5.4B

2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*R*)-1,4-dioxan-2-yl]propanoic acid (mixture of two diastereomers)



10

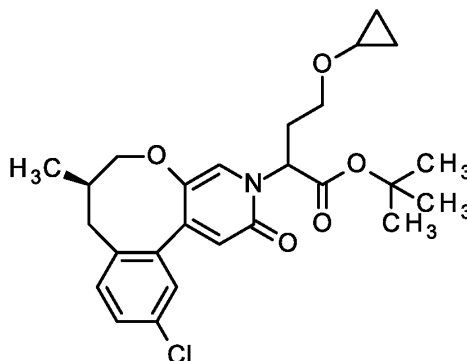
Lithium hydroxide (147 mg, 6.12 mmol, 20 eq.) was added to a solution of *tert*-butyl 2-[(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*R*)-1,4-dioxan-2-yl]propanoate (mixture of two diastereomers) (150 mg, 0.306 mmol) in tetrahydrofuran (6.2 ml) and water (3.1 ml). The resulting reaction mixture was shaken at 40°C overnight, then acidified with aqueous hydrochloric acid (1 N) and diluted with ethyl acetate. After phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The product was dried *in vacuo* and used in the next step without further purification. Yield: 105 mg (78% of theory).

15

LC-MS (method 4): $R_t = 1.61$ min; MS (ESIpos): $m/z = 434$ $[M+H]^+$

Example 5.5A

tert-Butyl 2-[(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclopropyloxy)butanoate (mixture of two diastereomers)

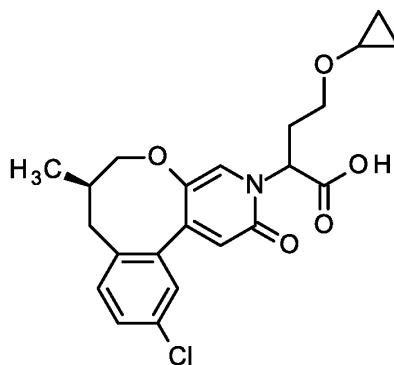


A solution of lithium bis(trimethylsilyl)amide (0.31 ml, 1 M in tetrahydrofuran, 0.31 mmol, 1.2 eq.) was added under argon atmosphere at -78°C to a solution of *tert*-butyl [(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer) (101 mg, 0.26 mmol) in tetrahydrofuran (3 ml). After stirring at -78°C for 15 min, 2-(cyclopropyloxy)ethyl trifluoromethanesulfonate (91 mg, 0.39 mmol, 1.5 eq.) was added dropwise. The resulting reaction mixture was stirred at -78°C for 15 min and then allowed to warm to RT. The reaction mixture was quenched with water. After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 12 mg (10% of theory).

LC-MS (method 4): $R_t = 2.41$ min; MS (ESIpos): $m/z = 474$ $[\text{M}+\text{H}]^+$

Example 5.5B

2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclopropyloxy)butanoic acid (mixture of two diastereomers)



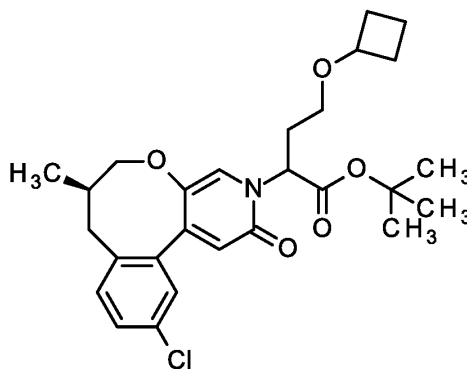
Lithium hydroxide (3 mg, 0.12 mmol, 4.5 eq.) was added at RT to a solution of *tert*-butyl 2-[(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-

(cyclopropyloxy)butanoate (mixture of two diastereomers) (12 mg, 0.03 mmol) in a mixture of tetrahydrofuran and water (3:1, 1 ml). The reaction mixture was stirred at RT overnight and then acidified with aqueous hydrochloric acid (1 N). After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used without further purification. Yield: 9 mg (82% of theory).

LC-MS (method 1): $R_t = 1.01$ min; MS (ESIpos): $m/z = 418$ $[M+H]^+$

Example 5.6A

tert-Butyl 2-[(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclobutyloxy)butanoate (mixture of two diastereomers)

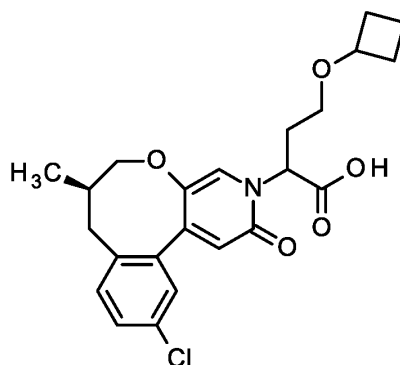


A solution of lithium bis(trimethylsilyl)amide (0.31 ml, 1 M in tetrahydrofuran, 0.31 mmol, 1.2 eq.) was added under argon atmosphere at -78°C to a solution of *tert*-butyl [(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer) (101 mg, 0.26 mmol) in tetrahydrofuran (3 ml). After stirring at -78°C for 15 min, 2-(cyclobutyloxy)ethyl trifluoromethanesulfonate (124 mg, 78% assumed purity of crude product, 0.39 mmol, 1.5 eq.) (prepared according to WO 2016/146606, example 2.2A) was added dropwise. The resulting reaction mixture was stirred at -78°C for 15 min, then allowed to warm to RT and stirred at RT for 3 h. The reaction mixture was quenched with water. After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 80 mg (63% of theory).

LC-MS (method 3): $R_t = 4.46$ min; MS (ESIpos): $m/z = 488$ $[M+H]^+$

Example 5.6B

2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclobutyloxy)butanoic acid (mixture of two diastereomers)

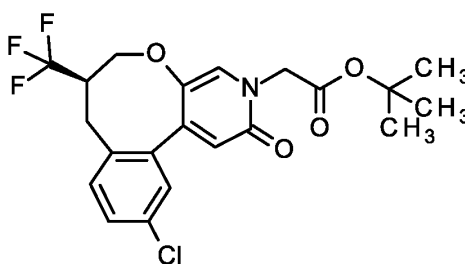


- 5 Trifluoroacetic acid (341 μ l, 4.43 mmol, 20 eq.) was added at 0°C to a solution of *tert*-butyl 2-[(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclobutyloxy)-butanoate (mixture of two diastereomers) (108 mg, 0.22 mmol) in dichloromethane (3 ml). The reaction mixture was stirred for 3.5 h and then concentrated under reduced pressure. The residue was dissolved in toluene and concentrated under reduced pressure. The residue was dissolved in dichloromethane and concentrated under reduced pressure. Yield: 106 mg (83% purity, 92% of theory).

LC-MS (method 4): R_t = 1.96 min; MS (ESIpos): m/z = 432 $[M+H]^+$

Example 5.7A

- 15 *tert*-Butyl [(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer)



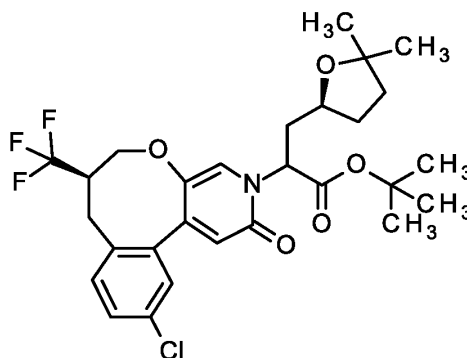
- Potassium carbonate (365 mg, 2.64 mmol, 1.5 eq.) and *tert*-butyl bromoacetate (318 μ l, 420 mg, 2.11 mmol, 1.2 eq.) were added to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (580 mg, 1.76 mmol) in *N,N*-dimethylformamide (8 ml). The reaction mixture was stirred at 100°C for 50 min, cooled to RT and

concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate gradient). Yield: 635 mg (81% of theory).

LC-MS (method 1): $R_t = 1.15$ min; MS (ESIpos): $m/z = 444$ $[M+H]^+$

Example 5.8A

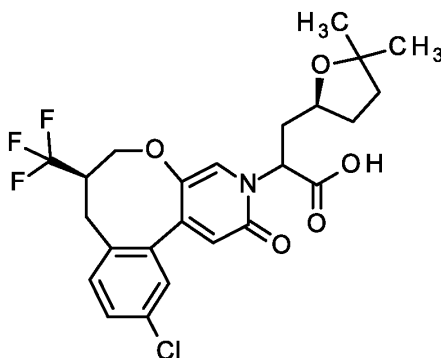
- 5 *tert*-Butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*S*)-5,5-dimethyloxolan-2-yl]propanoate (mixture of two diastereomers)



- A solution of lithium bis(trimethylsilyl)amide (0.27 ml, 1 M in tetrahydrofuran, 0.27 mmol, 1.2 eq.) was added under argon atmosphere at -78°C to a solution of *tert*-butyl [(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer) (100 mg, 0.23 mmol) in tetrahydrofuran (3 ml). After stirring at -78°C for 15 min, [(2*S*)-5,5-dimethyloxolan-2-yl]methyl trifluoromethanesulfonate (single stereoisomer) (100 mg, 0.36 mmol, 1.6 eq.) was added dropwise. The reaction mixture was stirred at -78°C for 45 min, then allowed to warm to 0°C and stirred at 0°C for another 80 min. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride. After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 65 mg (52% of theory).
- 20 LC-MS (method 4): $R_t = 2.55 / 2.58$ min; MS (ESIpos): $m/z = 556$ $[M+H]^+$

Example 5.8B

2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*S*)-5,5-dimethyloxolan-2-yl]propanoic acid (mixture of two diastereomers)

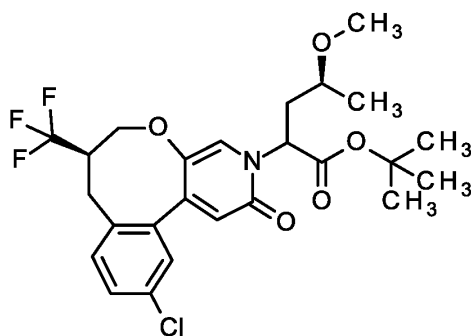


Lithium hydroxide (10 mg, 0.42 mmol, 2.0 eq.) was added at RT to a solution of *tert*-butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*S*)-5,5-dimethyloxolan-2-yl]propanoate (mixture of two diastereomers) (117 mg, 0.21 mmol) in a mixture of tetrahydrofuran and water (3:1, 4 ml). The reaction mixture was stirred at RT overnight and then acidified with aqueous hydrochloric acid (1 N). After removing all volatiles under reduced pressure, the residue was diluted with water. The forming precipitate was filtered, washed with water and dried *in vacuo*. Yield: 98 mg (87% purity, 81% of theory).

LC-MS (method 3): $R_t = 3.56 / 3.61$ min; MS (ESIpos): $m/z = 500$ $[M+H]^+$

10 **Example 5.9A**

tert-Butyl (2*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonoate (mixture of two diastereomers)



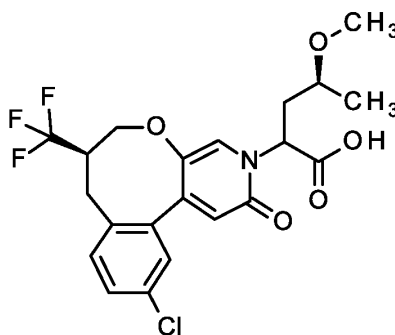
15 A solution of lithium bis(trimethylsilyl)amide (0.46 ml, 1 M in tetrahydrofuran, 0.46 mmol, 1.2 eq.) was added under argon atmosphere at -78°C to a solution of *tert*-butyl [(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer) (170 mg, 0.38 mmol) in tetrahydrofuran (5 ml). After stirring at -78°C for 15 min, (2*S*)-2-methoxypropyl trifluoromethanesulfonate (single stereoisomer) (128 mg, 0.58 mmol, 1.5 eq.)
20 (prepared according to WO 2014/154794, example 28.1A) was added dropwise. The reaction mixture

was stirred at -78°C for 15 min, then allowed to warm to RT and stirred at RT for 1 h. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride. After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification. Yield: 235 mg.

LC-MS (method 4): $R_t = 2.36$ min; MS (ESIpos): $m/z = 516$ $[M+H]^+$

Example 5.9B

(2*ξ*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonic acid (mixture of two diastereomers)

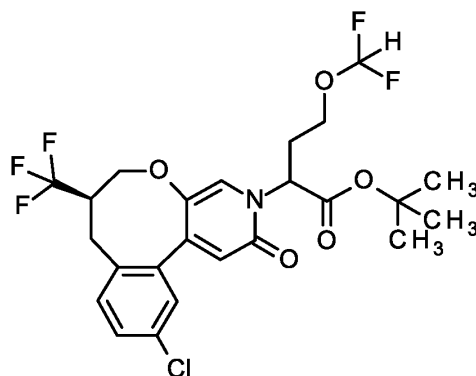


Trifluoroacetic acid (0.60 ml, 7.74 mmol, 20.0 eq.) was added at RT to a solution of *tert*-butyl (2*ξ*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentionate (mixture of two diastereomers) (235 mg, 85% assumed purity of crude product, 0.39 mmol) in dichloromethane (5 ml). The reaction mixture was stirred at RT for 4.5 h, concentrated under reduced pressure and coevaporated two times with dichloromethane. The crude product was used without further purification. Yield: 255 mg (86% purity).

LC-MS (method 4): $R_t = 1.82 / 1.84$ min; MS (ESIpos): $m/z = 460$ $[M+H]^+$

Example 5.10A

tert-Butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)butanoate (mixture of two diastereomers)

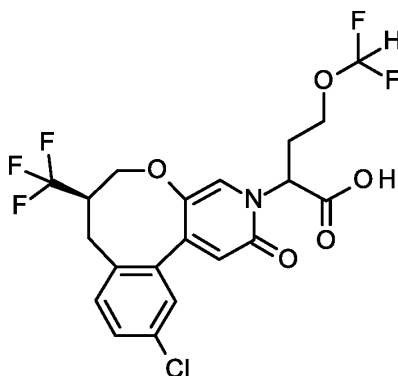


- 1,1,3,3-Tetramethylguanidine (149 μ l, 1.19 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (132 mg, 0.40 mmol) in 2-propanol / acetone (4:1, 1.75 ml). The mixture was stirred at RT for 15 min, followed by addition of *tert*-butyl 2-bromo-4-(difluoromethoxy)butanoate (racemate) (157 mg, 80% purity, 0.44 mmol, 1.1 eq.) and of further 2-propanol / acetone (4.1, 1.75 ml). The reaction mixture was stirred at RT for 3 days, pooled with a preceding, analogously performed test campaign using (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (28 mg, 0.09 mmol) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate gradient). Yield: 188 mg (73% of theory for both reaction campaigns).

LC-MS (method 4): R_t = 2.43 min; MS (ESIpos): m/z = 538 $[M+H]^+$

Example 5.10B

- 2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)butanoic acid (mixture of two diastereomers)



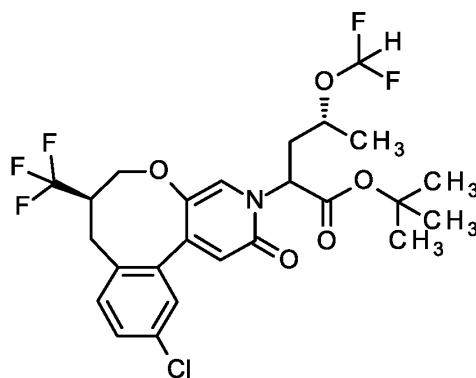
Lithium hydroxide (17 mg, 0.70 mmol, 2.0 eq.) was added at RT to a solution of *tert*-butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-

(difluoro-methoxy)butanoate (mixture of two diastereomers) (188 mg, 0.35 mmol) in a mixture of tetrahydrofuran and water (3:1, 7 ml). The reaction mixture was stirred at RT overnight and then acidified with aqueous hydrochloric acid (1 N). After removing all volatiles under reduced pressure, the residue was diluted with water. The forming precipitate was filtered, washed with water and dried *in vacuo*. Yield: 140 mg (83% of theory).

LC-MS (method 1): $R_t = 0.96$ min; MS (ESIpos): $m/z = 482$ $[M+H]^+$

Example 5.11A

tert-Butyl (2*ξ*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-(difluoromethyl)-*D*-glycero-pentanoate (mixture of two diastereomers)

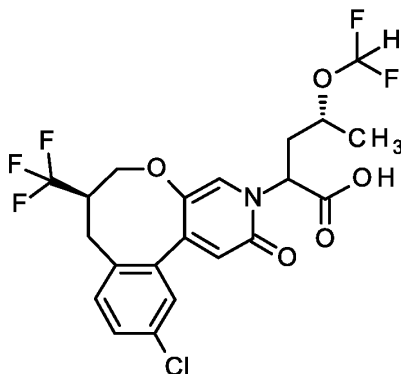


1,1,3,3-Tetramethylguanidine (205 μ l, 1.63 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (181 mg, 0.55 mmol) in 2-propanol / acetone (4:1, 2.5 ml). The mixture was stirred at RT for 15 min, followed by addition of *tert*-butyl (4*R*)-2-bromo-4-(difluoromethoxy)-pentanoate (mixture of two diastereomers) (182 mg, 0.60 mmol, 1.1 eq.) and of further 2-propanol / acetone (4:1, 2.5 ml). The reaction mixture was stirred at RT for 2 days and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate gradient). Yield: 224 mg (75% of theory).

LC-MS (method 1): $R_t = 1.23$ min; MS (ESIpos): $m/z = 552$ $[M+H]^+$

Example 5.11B

(2*ξ*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-(difluoromethyl)-*D*-glycero-pentonic acid (mixture of two diastereomers)

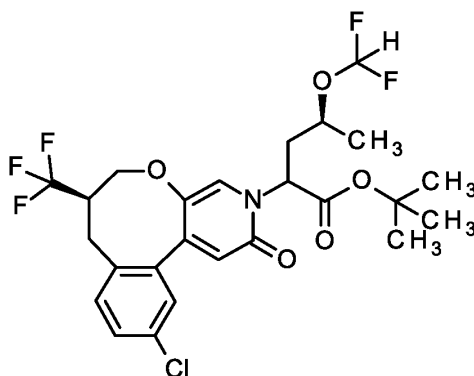


Lithium hydroxide (19 mg, 0.80 mmol, 2.0 eq.) was added at RT to a solution of *tert*-butyl (2*ξ*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-(difluoromethyl)-*D*-glycero-pentonate (mixture of two diastereomers) (220 mg, 0.40 mmol) in a mixture of tetrahydrofuran and water (3:1, 5 ml). The reaction mixture was stirred at RT overnight and then acidified with aqueous hydrochloric acid (1 N). After removing all volatiles under reduced pressure, the residue was diluted with water. The forming precipitate was filtered, washed with water and dried *in vacuo*. Yield: 176 mg (89% of theory).

LC-MS (method 4): $R_t = 2.04$ min; MS (ESIpos): $m/z = 496$ $[M+H]^+$

10 Example 5.12A

tert-Butyl (2*ξ*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-(difluoromethyl)-*L*-glycero-pentonate (mixture of two diastereomers)



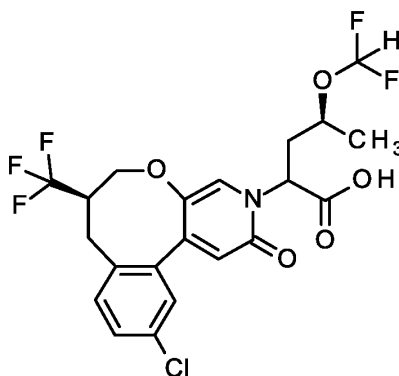
1,1,3,3-Tetramethylguanidine (151 μ l, 1.20 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (133 mg, 0.40 mmol) in 2-propanol / acetone (4:1, 2.5 ml). The mixture was stirred at RT for 15 min, followed by addition of *tert*-butyl (4*S*)-2-bromo-4-(difluoromethoxy)-pentanoate (mixture of two diastereomers) (138 mg, 0.44 mmol, 1.1 eq.) and of

further 2-propanol / acetone (4:1, 2.5 ml). The reaction mixture was stirred at RT for 3 days and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 128 mg (58% of theory).

LC-MS (method 1): $R_t = 1.23$ min; MS (ESIpos): $m/z = 552$ $[M+H]^+$

5 Example 5.12B

(2*ξ*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-(difluoromethyl)-*L*-glycero-pentonic acid (mixture of two diastereomers)

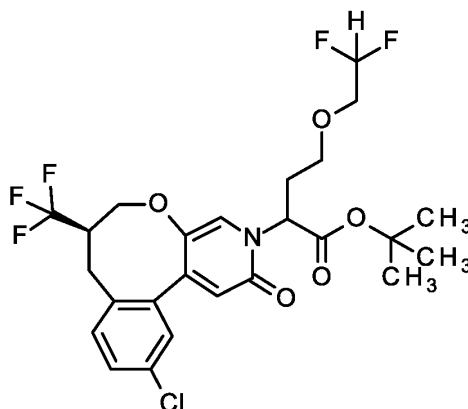


- 10 Lithium hydroxide (11 mg, 0.46 mmol, 2.0 eq.) was added at RT to a solution of *tert*-butyl (2*ξ*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-(difluoromethyl)-*L*-glycero-pentionate (mixture of two diastereomers) (128 mg, 0.23 mmol) in a mixture of tetrahydrofuran and water (3:1, 5 ml). The reaction mixture was stirred at RT overnight and then acidified with aqueous hydrochloric acid (1 N). After removing all
- 15 volatiles under reduced pressure, the residue was diluted with water. The forming precipitate was filtered, washed with water and dried *in vacuo*. Yield: 93 mg (89% purity, 72% of theory).

LC-MS (method 4): $R_t = 1.95$ min; MS (ESIpos): $m/z = 496$ $[M+H]^+$

Example 5.13A

- tert*-Butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(2,2-difluoroethoxy)butanoate (mixture of two diastereomers)
- 20

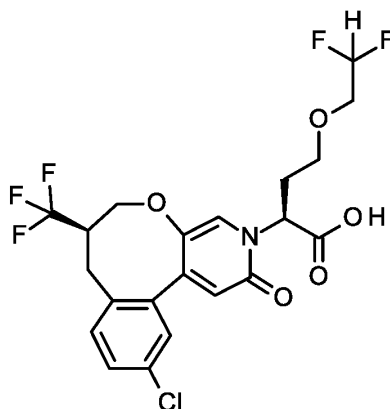


- A solution of lithium bis(trimethylsilyl)amide (0.41 ml, 1 M in tetrahydrofuran, 0.41 mmol, 1.2 eq.) was added under argon atmosphere at -78°C to a solution of *tert*-butyl [(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer) (150 mg, 0.34 mmol) in tetrahydrofuran (5 ml). After stirring at -78°C for 15 min, 2-(2,2-difluoroethoxy)ethyl trifluoromethanesulfonate (131 mg, 0.51 mmol, 1.5 eq.) (prepared according to WO 2016/046164, example 24.1A) was added dropwise. The reaction mixture was stirred at -78°C for 30 min and then allowed to warm to 0°C . The reaction mixture was quenched with saturated aqueous solution of ammonium chloride. After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate gradient). Yield: 126 mg (66% of theory).

LC-MS (method 1): $R_t = 1.21$ min; MS (ESIpos): $m/z = 552$ $[\text{M}+\text{H}]^+$

15 **Example 5.13B**

2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(2,2-difluoroethoxy)butanoic acid (mixture of two diastereomers)

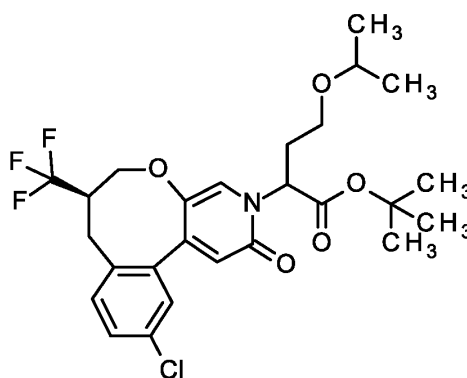


Lithium hydroxide (11 mg, 0.44 mmol, 2.0 eq.) was added at RT to a solution of *tert*-butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(2,2-difluoroethoxy)butanoate (mixture of two diastereomers) (125 mg, 0.22 mmol) in a mixture of tetrahydrofuran and water (3:1, 5 ml). The reaction mixture was stirred at RT overnight, then
5 acidified with aqueous hydrochloric acid (1 N) and diluted with water. After removing all volatiles under reduced pressure, the forming precipitate was filtered, washed with water and dried *in vacuo*. Yield: 85 mg (78% of theory).

LC-MS (method 4): $R_t = 1.85$ min; MS (ESIpos): $m/z = 496$ $[M+H]^+$

Example 5.14A

10 *tert*-Butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(propan-2-yl)oxy]butanoate (mixture of two diastereomers)

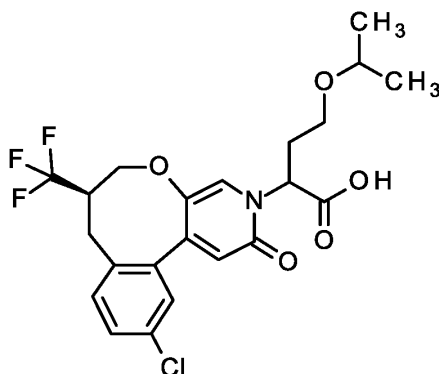


A solution of lithium bis(trimethylsilyl)amide (0.46 ml, 1 M in tetrahydrofuran, 0.46 mmol, 1.2 eq.) was added under argon atmosphere at -78°C to a solution of *tert*-butyl [(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer) (170 mg, 0.38 mmol) in tetrahydrofuran (5 ml). After stirring at -78°C for 15 min, 2-[(propan-2-yl)oxy]ethyl trifluoromethanesulfonate (136 mg, 0.58 mmol, 1.5 eq.) (prepared according to WO 2016/146606, example 2.1A) was added dropwise. The resulting reaction mixture was stirred at -78°C for 15 min, then allowed to warm to RT and stirred at RT for 1.5 h. The reaction mixture
20 was quenched with saturated aqueous solution of ammonium chloride. After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification. Yield: 260 mg.

25 LC-MS (method 1): $R_t = 1.29$ min; MS (ESIpos): $m/z = 530$ $[M+H]^+$.

Example 5.14B

2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(propan-2-yl)oxy]butanoic acid (mixture of two diastereomers)

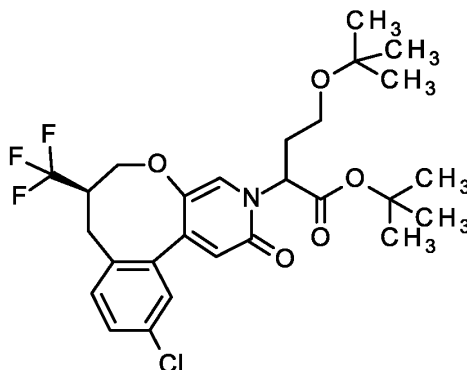


- 5 Lithium hydroxide (19 mg, 0.79 mmol, 2.0 eq.) was added at RT to a solution of *tert*-butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(propan-2-yl)oxy]butanoate (mixture of two diastereomers) (260 mg, 80% assumed purity of crude product, 0.39 mmol) in a mixture of tetrahydrofuran and water (3:1, 8 ml). The reaction mixture was stirred at RT overnight, then acidified with aqueous hydrochloric acid (1 N) and diluted with water.
- 10 After removing all volatiles under reduced pressure, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used without further purification. Yield: 166 mg (92% purity, 82% of theory).

LC-MS (method 4): $R_t = 1.97$ min; MS (ESIpos): $m/z = 474$ $[M+H]^+$

Example 5.15A

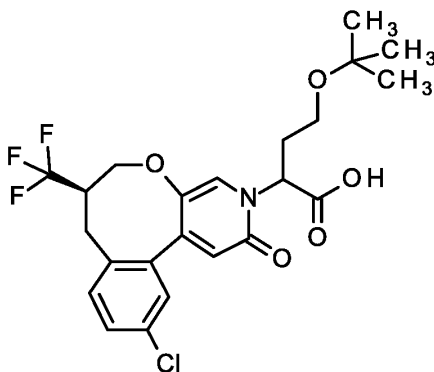
tert-Butyl 4-*tert*-butoxy-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoate (mixture of two diastereomers)



- A solution of lithium bis(trimethylsilyl)amide (0.41 ml, 1 M in tetrahydrofuran, 0.41 mmol, 1.2 eq.) was added under argon atmosphere at -78°C to a solution of *tert*-butyl [(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer) (150 mg, 0.34 mmol) in tetrahydrofuran (5 ml). After stirring at -78°C for 15 min, 2-*tert*-butoxyethyl trifluoromethanesulfonate (190 mg, 80% assumed purity of crude product, 0.61 mmol, 1.8 eq.) (prepared according to WO 2016/146606, example 2.3A) was added dropwise. The reaction mixture was stirred at -78°C for 15 min, then allowed to warm to RT and stirred at RT for 20 min. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride. After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane and filtered. The filtrate was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate gradient), the precipitate was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient), and both batches were combined. Yield: 81 mg (44% of theory).
- LC-MS (method 4): $R_t = 2.56$ min; MS (ESIpos): $m/z = 544$ $[\text{M}+\text{H}]^+$

Example 5.15B

4-*tert*-Butoxy-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoic acid (mixture of two diastereomers)

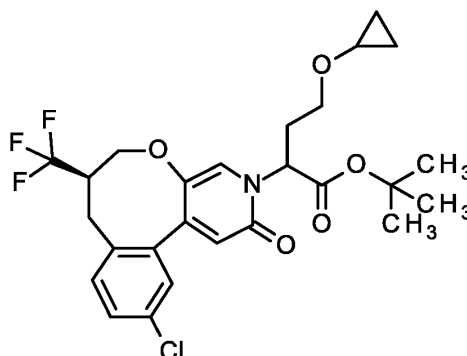


- Lithium hydroxide (7 mg, 0.29 mmol, 2.0 eq.) was added at RT to a solution of *tert*-butyl 4-*tert*-butoxy-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoate (mixture of two diastereomers) (80 mg, 0.15 mmol) in a mixture of tetrahydrofuran and water (3:1, 4 ml). The reaction mixture was stirred at RT overnight, then acidified with aqueous hydrochloric acid (1 N) and diluted with water. After removing all volatiles under reduced pressure, the aqueous phase was cooled in an ice bath. The forming precipitate was filtered, washed with water and dried *in vacuo*. Yield: 182 mg (72% of theory).

LC-MS (method 4): $R_t = 2.06$ min; MS (ESIpos): $m/z = 488$ $[\text{M}+\text{H}]^+$

Example 5.16A

tert-Butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclopropyloxy)butanoate (mixture of two diastereomers)

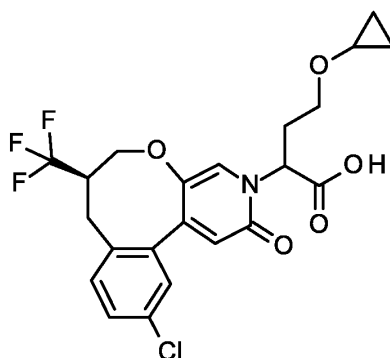


- 5 A solution of lithium bis(trimethylsilyl)amide (0.41 ml, 1 M in tetrahydrofuran, 0.41 mmol, 1.2 eq.) was added under argon atmosphere at -78°C to a solution of *tert*-butyl [(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer) (150 mg, 0.34 mmol) in tetrahydrofuran (5 ml). After stirring at -78°C for 15 min,
- 10 2-(cyclopropyloxy)ethyl trifluoromethanesulfonate (127 mg, 0.54 mmol, 1.6 eq.) was added dropwise. The reaction mixture was stirred at -78°C for 30 min and then allowed to warm to RT. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride. After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography
- 15 (silica gel, eluent: cyclohexane / ethyl acetate gradient). Yield: 94 mg (53% of theory).

LC-MS (method 3): $R_t = 4.34$ min; MS (ESIpos): $m/z = 528$ $[M+H]^+$

Example 5.16B

2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclopropyloxy)butanoic acid (mixture of two diastereomers)

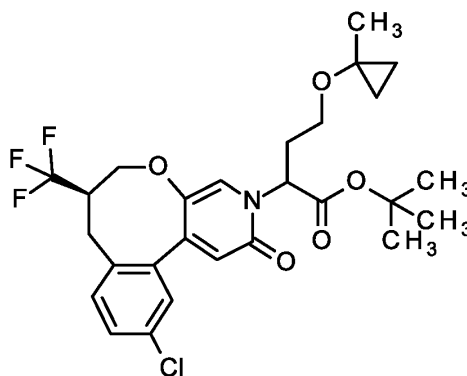


Lithium hydroxide (9 mg, 0.36 mmol, 2.0 eq.) was added at RT to a solution of *tert*-butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclopropyloxy)butanoate (mixture of two diastereomers) (94 mg, 0.18 mmol) in a mixture of tetrahydrofuran and water (3:1, 5 ml). The reaction mixture was stirred at RT for 2 days, then acidified with aqueous hydrochloric acid (1 N) and diluted with water. After removing all volatiles under reduced pressure, the forming precipitate was filtered, washed with water and dried *in vacuo*. Yield: 66 mg (79% of theory).

LC-MS (method 4): $R_t = 1.91$ min; MS (ESIpos): $m/z = 472$ $[M+H]^+$

10 Example 5.17A

tert-Butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclopropyl)oxy]butanoate (mixture of two diastereomers)

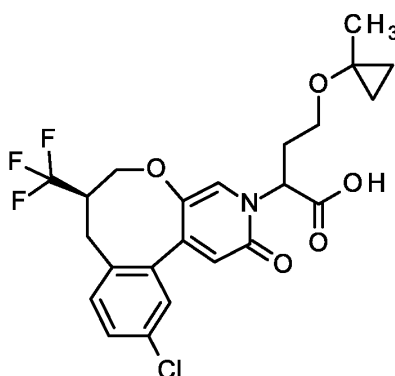


A solution of lithium bis(trimethylsilyl)amide (0.84 ml, 1 M in tetrahydrofuran, 0.84 mmol, 1.2 eq.) was added under argon atmosphere at -78°C to a solution of *tert*-butyl [(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer) (310 mg, 0.70 mmol) in tetrahydrofuran (10 ml). After stirring at -78°C for 15 min, 2-[(1-methylcyclopropyl)oxy]ethyl trifluoromethanesulfonate (260 mg, 1.05 mmol, 1.5 eq.) was added dropwise. The reaction mixture was stirred at -78°C for 15 min, then allowed to warm to RT and

- stirred at RT for 2 h. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride. After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was combined with crude product from a preceding, analogously performed test campaign using 30 mg (0.07 mmol) of *tert*-butyl [(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer) and purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate gradient). Yield: 260 mg (67% of theory over both batches).
- 10 LC-MS (method 4): $R_t = 2.51$ min; MS (ESIpos): $m/z = 542$ $[M+H]^+$

Example 5.17B

2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclopropyl)oxy]butanoic acid (mixture of two diastereomers)

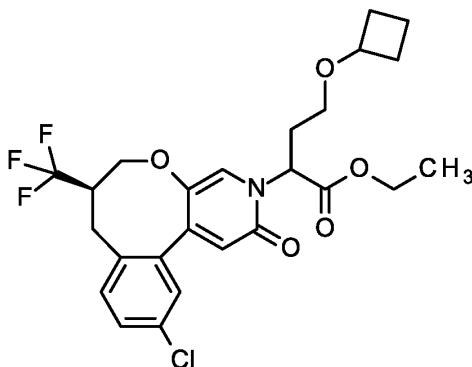


- 15 Lithium hydroxide (23 mg, 0.94 mmol, 2.0 eq.) was added at RT to a solution of *tert*-butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclopropyl)oxy]butanoate (mixture of two diastereomers) (260 mg, 0.47 mmol) in a mixture of tetrahydrofuran and water (3:1, 5 ml). The reaction mixture was stirred at RT for 26 h, then acidified with aqueous hydrochloric acid (1 N) and diluted with water. After removing all
- 20 volatiles under reduced pressure, the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used without further purification. Yield: 182 mg (93% purity, 74% of theory).

LC-MS (method 4): $R_t = 2.02$ min; MS (ESIpos): $m/z = 486$ $[M+H]^+$

Example 5.18A

Ethyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclobutyloxy)butanoate (mixture of two diastereomers)

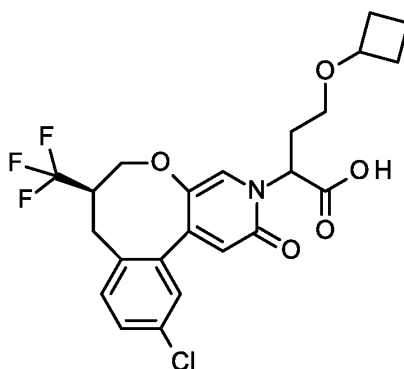


- 5 General Method 7 was carried out with (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (99.5 mg, 302 μ mol, 1.0 eq.), ethyl 2-bromo-4-(cyclobutyloxy)butanoate (racemate) (120 mg, 75% purity, 453 μ mol, 1.125 eq.) and 1,1,3,3-tetramethylguanidine (110 μ l, 910 μ mol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 3.75 ml) including the following variations of the procedure: After stirring for 3 days, additional
- 10 amounts of 1,1,3,3-tetramethylguanidine (100 μ l, 800 μ mol, 2.65 eq.) were added and the mixture was stirred overnight. The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 80:20 to 5:95). Yield: 85 mg (54% of theory).

LC-MS (method 1): R_t = 1.22 min; MS (ESIpos): m/z = 514 $[M+H]^+$

Example 5.18B

- 15 2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclobutyloxy)butanoic acid (mixture of two diastereomers)

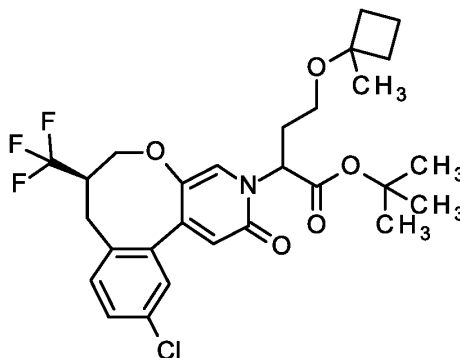


General Method 10 was carried out with ethyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclobutylloxy)butanoate (mixture of two diastereomers) (85.0 mg, 165 μ mol, 1.0 eq.) and lithium hydroxide (19.8 mg, 827 μ mol, 5.0 eq.) in a mixture of ethanol / tetrahydrofuran (2:1, 3 ml). Yield: 76.2 mg (95% of theory).

- 5 LC-MS (method 1): R_t = 1.06 min; MS (ESIpos): m/z = 486 $[M+H]^+$

Example 5.19A

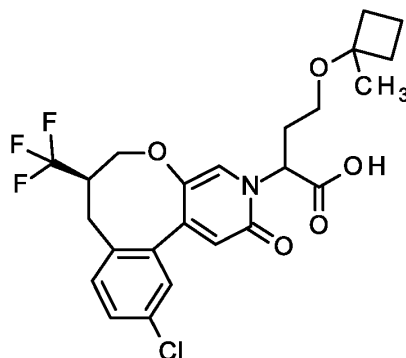
tert-Butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclobutyl)oxy]butanoate (mixture of two diastereomers)



- 10 General Method 9 was carried out with *tert*-butyl [(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]acetate (single stereoisomer) (150 mg, 338 μ mol), 2-[(1-methylcyclobutyl)oxy]ethyl trifluoromethanesulfonate (148 mg, 90% purity, 507 μ mol, 1.5 eq., preparation according to WO 2017/037051, example 3.10C) and lithium bis(trimethylsilyl)amide (410 μ l, 1.0 M, 410 μ mol, 1.2 eq.) in tetrahydrofuran (6.1 ml) including the
- 15 following variations of the procedure: The reaction mixture was worked up by addition of saturated aqueous ammonium chloride solution, water and ethyl acetate, extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 80:20 to 5:95). Yield: 49.7 mg (27% of theory).
- 20 LC-MS (method 1): R_t = 1.38 min; MS (ESIpos): m/z = 556 $[M+H]^+$

Example 5.19B

2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclobutyl)oxy]butanoic acid (mixture of two diastereomers)

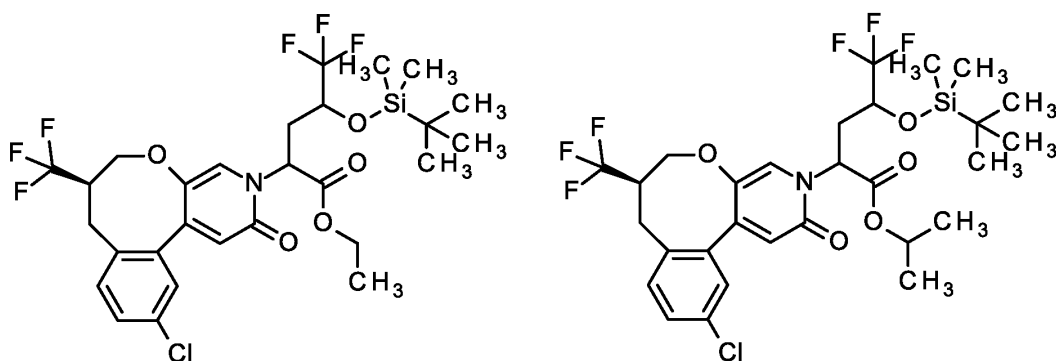


General Method 10 was carried out with *tert*-butyl 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclobutyl)oxy]butanoate (mixture of two diastereomers) (49.5 mg, 89.0 μ mol, 1.0 eq.) and lithium hydroxide (10.7 mg, 445 μ mol, 5.0 eq.) in a mixture of ethanol / tetrahydrofuran (2:1, 3 ml). Yield: 50.0 mg (quantitative of theory).

LC-MS (method 1): R_t = 1.10 min; MS (ESIpos): m/z = 500 $[M+H]^+$

Example 5.20A

Mixture of ethyl 4-*O*-[*tert*-butyl(dimethyl)silyl]-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-5,5,5-trifluoropentanoate (mixture of stereoisomers) and isopropyl 4-*O*-[*tert*-butyl(dimethyl)silyl]-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-5,5,5-trifluoropentanoate (mixture of stereoisomers)



General Method 7 was carried out with (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (250 mg, 758 μ mol, 1.0 eq.), ethyl 2-bromo-4-[[*tert*-butyl(dimethyl)silyl]oxy]-5,5,5-trifluoropentanoate (mixture of stereoisomers) (519 mg, 69% purity, 910 μ mol, 1.2 eq.) and 1,1,3,3-tetramethylguanidine (270 μ l, 2.1 mmol, 2.8 eq.) in a mixture of 2-propanol / acetone (4:1, 8.5 ml) including the following variations of the procedure:

The mixture was stirred at RT for 3 h and at 50°C overnight and then used in the subsequent reaction without further purification as a mixture (due to partial transesterification during the reaction) of

- ethyl 4-*O*-[*tert*-butyl(dimethyl)silyl]-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-5,5,5-trifluoropentionate (mixture of stereoisomers):

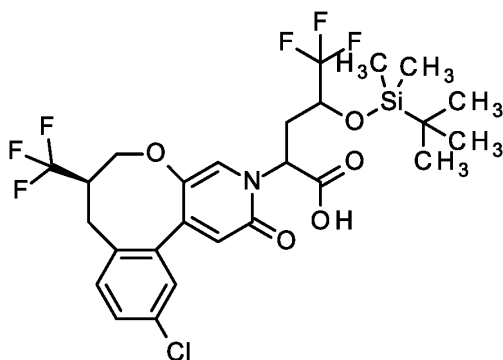
LC-MS (method 1): $R_t = 1.65 / 1.64 / 1.63$ min; MS (ESIpos): $m/z = 642$ $[M+H]^+$

and isopropyl 4-*O*-[*tert*-butyl(dimethyl)silyl]-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-5,5,5-trifluoropentionate (mixture of stereoisomers):

- 10 LC-MS (method 1): $R_t = 1.53$; MS (ESIpos): $m/z = 656$ $[M+H]^+$

Example 5.20B

4-*O*-[*tert*-Butyl(dimethyl)silyl]-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-5,5,5-trifluoro-*D*-erythro-pentonic acid (mixture of stereoisomers)



15

General Method 10 was carried out with a mixture of ethyl 4-*O*-[*tert*-butyl(dimethyl)silyl]-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-5,5,5-trifluoropentionate (mixture of stereoisomers) and isopropyl 4-*O*-[*tert*-butyl(dimethyl)silyl]-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-5,5,5-trifluoropentionate (mixture of stereoisomers) (combined 350 mg, 545 μ mol, 1.0 eq.) and lithium hydroxide (131 mg, 5.45 mmol, 10.0 eq.) including the following variations of the procedure: the crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95) leading to two separated mixtures of diastereomers.

- 25 Diastereomeric mixture 1 (desired product): 109 mg (33% of theory):

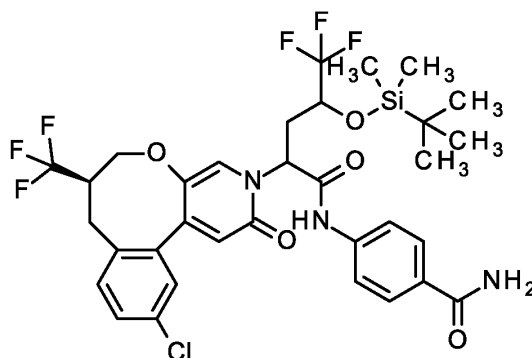
LC-MS (method 3): $R_t = 4.71 / 4.73$ min ; MS (ESIpos): $m/z = 614$ $[M+H]^+$ and

Diastereomeric mixture 2: 50.0 mg (15% of theory):

LC-MS (method 3): $R_t = 5.24 / 5.28 / 5.35$ min ; MS (ESIpos): $m/z = 614 [M+H]^+$

Example 5.20C

- 4-[(4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-5,5,5-trifluoropentanoyl)amino]benzamide
(mixture of stereoisomers)

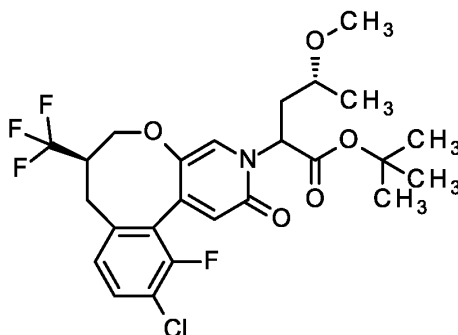


- To a solution of 4-*O*-[*tert*-butyl(dimethyl)silyl]-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-5,5,5-trifluoropentonic acid (diastereomeric mixture 1) (15.0 mg, 24.4 μ mol, 1.0 eq.) in dichloromethane (1.0 ml) was added 1-chloro-*N,N*,2-trimethylprop-1-en-1-amine (4.2 mg, 31.8 μ mol, 1.3 eq.) and the resulting mixture was stirred for 10 min before 4-aminobenzamide (4.3 mg, 31.8 μ mol, 1.3 eq.) was added and stirring was continued at RT for 3 h. The same procedure was repeated with 4-*O*-[*tert*-butyl(dimethyl)silyl]-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-5,5,5-trifluoropentonic acid (diastereomeric mixture 1) (60.0 mg, 97.7 μ mol, 1.0 eq.), 1-chloro-*N,N*,2-trimethylprop-1-en-1-amine (17 μ l, 17.0 mg, 130 μ mol, 1.3 eq.) and 4-aminobenzamide (20.0 mg, 147 μ mol, 1.5 eq.) in dichloromethane (4.0 ml). The two reaction mixtures were then combined, diluted with dichloromethane, subsequently washed with a saturated aqueous solution of ammonium chloride and a saturated aqueous solution of sodium bicarbonate. The organic phase was then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mixture was used in the subsequent step without further purification. Yield: 88.0 mg (57% purity, 70% of theory).

LC-MS (method 3): $R_t = 4.70$ min; MS (ESIpos): $m/z = 732 [M+H]^+$

Example 5.21A

- tert*-Butyl (2*ξ*)-2-[(7*R*)-11-chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*D*-glycero-pentionate (mixture of two diastereomers)

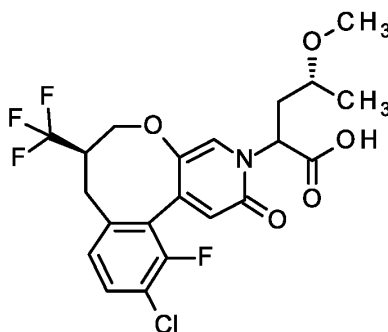


General Method 7 was carried two times with (7*R*)-11-chloro-12-fluoro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (130 mg, 76% purity, 284 μ mol, 1.0 eq.), *tert*-butyl (4*R*)-2-bromo-4-methoxypentanoate (mixture of two diastereomers) (98.2 mg, 85% purity, 313 μ mol, 1.1 eq.) and 1,1,3,3-tetramethylguanidine (107 μ l, 852 μ mol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 4.5 ml) and, in a second batch, (7*R*)-11-chloro-12-fluoro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (100 mg, 76% purity, 219 μ mol, 1.0 eq.), *tert*-butyl (4*R*)-2-bromo-4-methoxypentanoate (mixture of two diastereomers) (75.6 mg, 85% purity, 240 μ mol, 1.1 eq.) and 1,1,3,3-tetramethylguanidine (82 μ l, 660 μ mol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 3.5 ml) including the following variations of the procedure: The crude mixtures of the two reactions were combined and purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 80:20 to 5:95). Yield: 196 mg (74% of theory).

LC-MS (method 1): R_t = 1.25 min; MS (ESIpos): m/z = 534 $[M+H]^+$

15 **Example 5.21B**

(2*ξ*)-2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*D*-glycero-pentonic acid (mixture of two diastereomers)



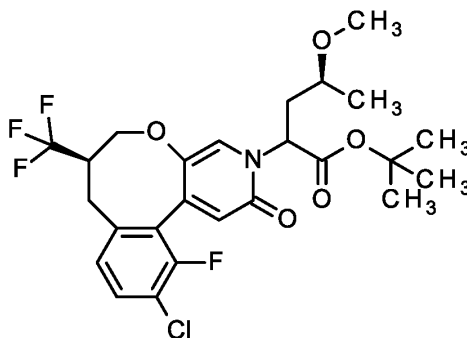
20 General Method 10 was carried out with *tert*-butyl (2*ξ*)-2-[(7*R*)-11-chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-

methyl-*D*-glycero-pentionate (mixture of two diastereomers) (192 mg, 345 μ mol, 1.0 eq.) and lithium hydroxide (41.3 mg, 1.73 mmol, 5.0 eq.) in a mixture of tetrahydrofuran / water (2:1, 13 ml) at 40°C. Yield: 152 mg (92% of theory).

LC-MS (method 3): R_t = 3.10 / 3.13 min; MS (ESIpos): m/z = 478 [M+H]⁺

5 Example 5.22A

tert-Butyl (2 ξ)-2-[(7*R*)-11-chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentionate (mixture of two diastereomers)

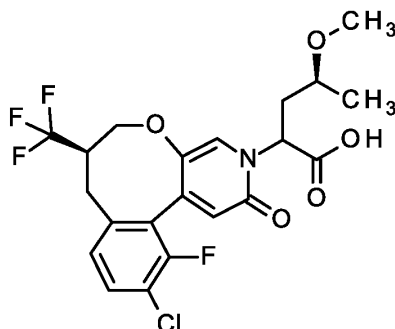


- 10 General Method 7 was carried out with (7*R*)-11-chloro-12-fluoro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (250 mg, 76% purity, 546 μ mol, 1.0 eq.), *tert*-butyl (4*S*)-2-bromo-4-methoxypentanoate (mixture of two diastereomers) (161 mg, 601 μ mol, 1.1 eq.) and 1,1,3,3-tetramethylguanidine (210 μ l, 1.6 mmol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 5 ml) including the following variations of the procedure: The crude mixture
- 15 was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 80:20 to 5:95). Yield: 155 mg (53% of theory).

LC-MS (method 1): R_t = 1.24 min; MS (ESIpos): m/z = 534 [M+H]⁺

Example 5.22B

- (2 ξ)-2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonic acid (mixture of two diastereomers)
- 20

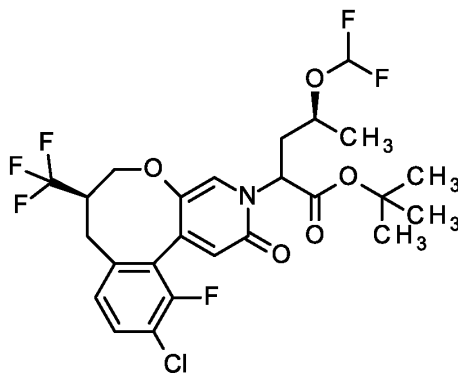


General Method 10 was carried out with *tert*-butyl (2*ξ*)-2-[(7*R*)-11-chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentionate (mixture of two diastereomers) (155 mg, 290 μ mol, 1.0 eq.) and lithium hydroxide (34.8 mg, 1.45 mmol, 5.0 eq.) in a mixture of tetrahydrofuran / water (2:1, 4.5 ml). Yield: 185 mg (quantitative of theory).

LC-MS (method 1): R_t = 0.97 min; MS (ESIpos): m/z = 478 $[M+H]^+$

Example 5.23A

tert-Butyl (2*ξ*)-2-[(7*R*)-11-chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-(difluoromethyl)-*L*-glycero-pentionate (mixture of two diastereomers)

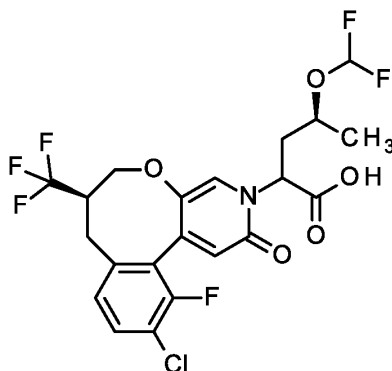


General Method 7 was carried out with (7*R*)-11-chloro-12-fluoro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (120 mg, 76% purity, 262 μ mol, 1.0 eq.), *tert*-butyl (4*S*)-2-bromo-4-(difluoromethoxy)pentanoate (mixture of two diastereomers) (95.4 mg, 315 μ mol, 1.2 eq.) and 1,1,3,3-tetramethylguanidine (99 μ l, 790 μ mol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 2.4 ml) including the following variations of the procedure: The reaction mixture was stirred for 4 days and the crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 80:20 to 5:95). Yield: 85.0 mg (53% of theory).

LC-MS (method 3): $R_t = 4.29$ min; MS (ESIpos): $m/z = 570$ $[M+H]^+$

Example 5.23B

(2*ξ*)-2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-
[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-(difluoromethyl)-*L*-glycero-pentonic acid
(mixture of two diastereomers)

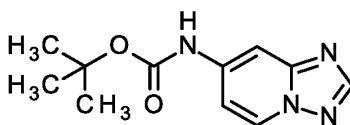


General Method 10 was carried out with *tert*-butyl (2*ξ*)-2-[(7*R*)-11-chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-(difluoromethyl)-*L*-glycero-pentionate (mixture of two diastereomers) (83.0 mg, 94% purity, 137
μmol, 1.0 eq.) and lithium hydroxide (16.4 mg, 684 μmol, 5.0 eq.) in a mixture of tetrahydrofuran /
water (3:1, 4 ml). Yield: 116 mg (99% of theory).

LC-MS (method 1): $R_t = 1.01$ min; MS (ESIpos): $m/z = 514$ $[M+H]^+$

Example 6.1A

tert-Butyl [1,2,4]triazolo[1,5-*a*]pyridin-7-ylcarbamate



15

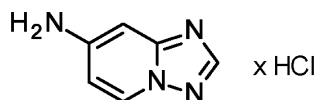
A mixture of 7-bromo[1,2,4]triazolo[1,5-*a*]pyridine (18.5 g, 93.4 mmol, 1.0 eq.), *tert*-butyl carbamate (16.42 g, 140.1 mmol, 1.5 eq.), palladium(II) acetate (2.10 g, 9.3 mmol, 0.1 eq.), 2-dicyclohexyl-phosphino-2',4',6'-triisopropyl-1,1'-biphenyl (13.36 g, 28.0 mmol, 0.3 eq.) and caesium carbonate (60.88 g, 186.8 mmol, 2.0 eq.) in 1,4-dioxane (930 ml) was purged with nitrogen gas for
10 min. The reaction mixture was heated to 100°C for 15 h, cooled to RT and filtered through Celite®. The filtrate was concentrated. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 1:3). Yield: 17.0 g (77% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 9.99 (s, 1H), 8.77 (d, 1H), 8.30 (s, 1H), 7.87 (s, 1H),

7.19-7.12 (m, 1H), 1.49 (s, 9H).

Example 6.1B

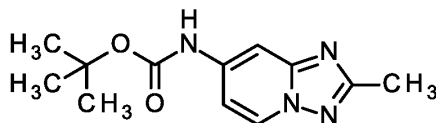
[1,2,4]Triazolo[1,5-a]pyridin-7-amine hydrochloride



- 5 Hydrogen chloride solution (362.8 ml, 4 M in 1,4-dioxane) was added to a stirred solution of *tert*-butyl [1,2,4]triazolo[1,5-a]pyridin-7-ylcarbamate (17.00 g, 72.6 mmol) in dichloromethane (1 l). The reaction mixture was stirred at RT for 15 h and diluted with diethyl ether. The precipitate was collected by filtration, washed with diethyl ether and dried under reduced pressure. Yield: 10.45 g (84% of theory).
- 10 ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 8.97-8.90 (m, 1H), 8.67 (d, 1H), 7.40 (br s, 2H), 6.90-6.81 (m, 1H), 6.73-6.68 (m, 1H).

Example 6.2A

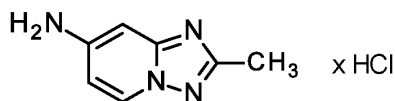
tert-Butyl (2-methyl[1,2,4]triazolo[1,5-a]pyridin-7-yl)carbamate



- 15 A mixture of 7-bromo-2-methyl[1,2,4]triazolo[1,5-a]pyridine (8.00 g, 37.7 mmol, 1.0 eq.), *tert*-butyl carbamate (6.63 g, 56.6 mmol, 1.5 eq.), palladium(II) acetate (0.85 g, 3.8 mmol, 0.1 eq.), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (5.40 g, 11.3 mmol, 0.3 eq.) and caesium carbonate (24.58 g, 75.4 mmol, 2.0 eq.) in 1,4-dioxane (400 ml) was purged with nitrogen for 5 min. The reaction mixture was stirred at 100°C for 15 h, cooled to RT and filtered through Celite®. The
- 20 filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 2:3). Yield: 5.50 g (58% of theory).
- ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 9.92 (s, 1H), 8.63 (d, 1H), 7.74 (s, 1H), 7.12-7.03 (m, 1H), 2.37 (s, 3H), 1.49 (s, 9H).

Example 6.2B

- 25 2-Methyl[1,2,4]triazolo[1,5-a]pyridin-7-amine hydrochloride



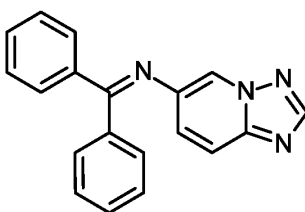
Hydrogen chloride solution (125 ml, 4 M in 1,4-dioxane) was added to a solution of *tert*-butyl (2-methyl[1,2,4]triazolo[1,5-a]pyridin-7-yl)carbamate (6.20 g, 25.0 mmol) in dichloromethane (125 ml). The reaction mixture was stirred at RT for 15 h and diluted with diethyl ether. The precipitate was collected by filtration, washed with diethyl ether and dried under reduced pressure.

5 Yield: 3.69 g (78% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 8.58 (d, 1H), 7.45 (br s, 2H), 6.82 (dd, 1H), 6.66 (d, 1H), 2.49 (s, 3H).

Example 6.3A

1,1-Diphenyl-*N*-([1,2,4]triazolo[1,5-a]pyridin-6-yl)methanimine



10

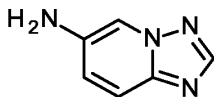
A mixture of 6-bromo[1,2,4]triazolo[1,5-a]pyridine (3.00 g, 15.2 mmol), 1,1-diphenylmethanimine (5.49 g, 30.3 mmol, 2.0 eq.), tris(dibenzylideneacetone)dipalladium (1.11 g, 1.2 mmol, 0.08 eq.), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (1.89 g, 3.0 mmol, 0.2 eq.) and sodium *tert*-butoxide (4.37 g, 45.5 mmol, 3.0 eq.) in toluene (100 ml) was heated at 80°C under nitrogen atmosphere overnight. The reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was poured into water and extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 3:1). Yield: 3.00 g (64% of theory).

15

20 ¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 8.34 (d, 1H), 7.74-7.41 (m, 6H), 7.38-7.13 (m, 6H).

Example 6.3B

[1,2,4]Triazolo[1,5-a]pyridin-6-amine



Aqueous hydrochloric acid (50 ml, 2 N, 101 mmol, 10 eq.) was added to a solution of 1,1-diphenyl-*N*-([1,2,4]triazolo[1,5-a]pyridin-6-yl)methanimine (3.00 g, 10.1 mmol) in tetrahydrofuran (100 ml). The reaction mixture was stirred at RT for 2 h and washed with ethyl acetate. The aqueous phase was adjusted to neutral with aqueous solution of sodium hydroxide (0.1 M) and concentrated under

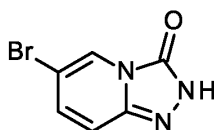
25

reduced pressure. The residue was purified by column chromatography (reversed phase, eluent: water / acetonitrile: 10% acetonitrile to 35% acetonitrile in 15 min, flow rate: 80 ml/min). Yield: 1.10 g (81% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 8.17 (s, 1H), 8.03 (d, 1H), 7.56 (d, 1H), 7.20 (d, 1H),
5 5.25 (br s, 2H).

Example 6.4A

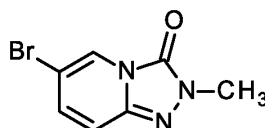
6-Bromo[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one



5-Bromo-2-hydrazinopyridine (15.00 g, 79.78 mmol, 1.0 eq.) was added in several portions over 0.5
10 h at 0°C to a solution of bis(trichloromethyl) carbonate (71.02 g, 239.3 mmol, 3.0 eq.) in tetrahydrofuran (1 l). After stirring for 15 h at RT, the reaction mixture was diluted with water, adjusted to pH 8 with sodium carbonate and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. Yield: 11.30 g (62% of theory).
15 ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 12.60 (s, 1H), 8.06 (t, 1H), 7.25-7.19 (m, 2H).

Example 6.4B

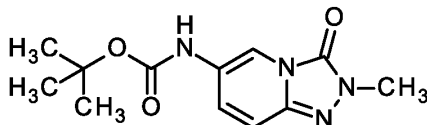
6-Bromo-2-methyl[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one



Iodomethane (5.73 g, 40.4 mmol, 1.2 eq.) was added dropwise at RT to a mixture of 6-
20 bromo[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one (7.20 g, 33.6 mmol, 1.0 eq.) and caesium carbonate (12.06 g, 37.0 mmol, 1.1 eq.) in *N,N*-dimethylformamide (144 ml). After stirring for 2 h, the reaction mixture was concentrated under reduced pressure. The residual mixture was diluted with water and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified
25 by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 1:1). Yield: 7.10 g (92% of theory).
¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 8.13-8.09 (m, 1H), 7.28 (dd, 1H), 7.22 (dd, 1H), 3.52 (s, 3H).

Example 6.4C

tert-Butyl (2-methyl-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-a]pyridin-6-yl)carbamate

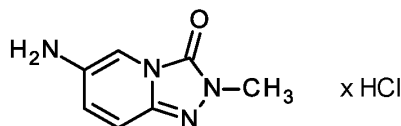


- A mixture of 6-bromo-2-methyl[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one (3.00 g, 13.2 mmol, 1.0 eq.),
 5 *tert*-butyl carbamate (2.31 g, 19.7 mmol, 1.5 eq.), tris(dibenzylideneacetone)dipalladium chloroform complex (0.68 g, 0.7 mmol, 0.05 eq.), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (1.14 g, 2.0 mmol, 0.15 eq.) and caesium carbonate (8.57 g, 26.3 mmol, 2.0 eq.) in 1,4-dioxane (130 ml) was purged with nitrogen for 5 minutes. The reaction was stirred at 110°C for 4 h, cooled to RT and filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was
 10 purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 1:4). Yield: 3.00 g (82% of theory).

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 9.43 (br s, 1H), 8.08 (br s, 1H), 7.20 (dd, 1H), 7.13 (dd, 1H), 3.48 (s, 3H), 1.44 (s, 9H).

Example 6.4D

- 15 6-Amino-2-methyl[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one hydrochloride

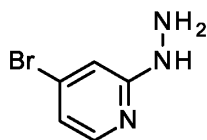


- Hydrogen chloride solution (100 ml, 4 M in 1,4-dioxane) was added to a solution of *tert*-butyl (2-methyl-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-a]pyridin-6-yl)carbamate (6.50 g, 22.4 mmol) in dichloromethane (100 ml). The reaction mixture was stirred for 6 h at RT and diluted with
 20 dichloromethane. The precipitate was collected by filtration, washed with acetonitrile and dried *in vacuo*. Yield: 3.26 g (70% of theory).

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 9.05 (br s, 3H), 7.71 (s, 1H), 7.27 (dd, 1H), 7.09 (dd, 1H), 3.50 (s, 3H).

Example 6.5A

- 25 4-Bromo-2-hydrazinopyridine

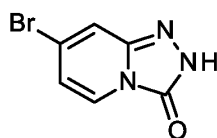


Hydrazine hydrate (80.0 g, 80% in water, 1.3 mol, 15.0 eq.) was added to a solution of 4-bromo-2-fluoropyridine (15.0 g, 85.2 mmol) in ethanol (200 ml). The reaction mixture was stirred at RT for 15 h and concentrated under reduced pressure. The residual mixture was diluted with water and
5 extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. Yield: 15.0 g (93% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 7.85 (d, 1H), 7.72 (s, 1H), 6.93 (d, 1H), 6.72-6.70 (m, 1H), 4.21 (s, 2H).

Example 6.5B

10 7-Bromo[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one

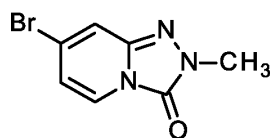


4-Bromo-2-hydrazinopyridine (10.0 g, 53.2 mmol) was added in several portions over 0.5 h at 0°C to a solution of 1,1'-carbonyldiimidazole (17.25 g, 106.4 mmol, 2.0 eq.) in tetrahydrofuran (600 ml). After stirring for 15 h at RT, the reaction mixture was diluted with saturated sodium bicarbonate
15 solution and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: dichloromethane / methanol 50:1). Yield: 7.3 g (63% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 12.55 (s, 1H), 7.79-7.76 (m, 1H), 7.63 (d, 1H), 6.68-6.66
20 (m, 1H).

Example 6.5C

7-Bromo-2-methyl[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one



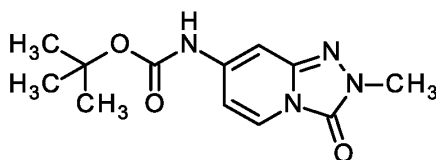
Iodomethane (4.77 g, 33.6 mmol, 1.2 eq.) was added dropwise at RT to a mixture of 7-bromo[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (6.00 g, 28.0 mmol) and caesium carbonate (13.70 g,
25

42.0 mmol, 1.5 eq.) in *N,N*-dimethylformamide (100 ml). After stirring for 3 h at RT, the reaction mixture was concentrated under reduced pressure. The residual mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: petroleum ether / ethyl acetate 1:1). Yield: 3.60 g (56% of theory).

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 7.83-7.80 (m, 1H), 7.66-7.65 (m, 1H), 6.73-6.70 (m, 1H), 3.52 (s, 3H).

Example 6.5D

tert-Butyl (2-methyl-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)carbamate

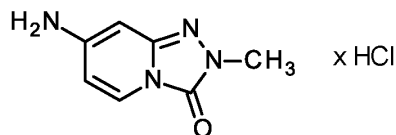


tert-Butyl carbamate (2.77 g, 23.7 mmol, 1.5 eq.), tris(dibenzylideneacetone)dipalladium chloroform complex (0.82 g, 0.8 mmol, 0.05 eq.), 9,9-dimethyl-4,5-bis(diphenylphosphino)-xanthene (1.37 g, 2.4 mmol, 0.15 eq.) and caesium carbonate (10.29 g, 31.6 mmol, 2.0 eq.) were added to a solution of 7-bromo-2-methyl[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one (3.60 g, 15.8 mmol) in 1,4-dioxane (72 ml). The resulting mixture was purged with nitrogen for 5 minutes, stirred at 110°C for 4 h, cooled to RT and filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was purified by chromatography (silica gel, eluent: petroleum ether / ethyl acetate 1:4). Yield: 3.10 g (68% of theory).

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 9.82 (m, 1H), 7.79-7.76 (m, 1H), 7.28-7.27 (m, 1H), 6.58-6.55 (m, 1H), 3.45 (s, 3H), 1.48 (s, 9H).

Example 6.5E

7-Amino-2-methyl[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochloride



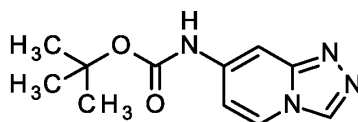
Hydrogen chloride solution (100 ml, 4 M in 1,4-dioxane) was added to a solution of *tert*-butyl (2-methyl-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)carbamate (5.70 g, 19.8 mmol) in dichloromethane (100 ml). The reaction mixture was stirred for 6 h at RT and diluted with

dichloromethane. The precipitate was collected by filtration, washed with acetonitrile and dried *in vacuo*. Yield: 3.06 g (76% of theory).

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 7.59-7.56 (m, 1H), 6.28-6.25 (m, 2H), 6.20-6.17 (m, 2H), 5.76 (d, 1H), 3.36 (s, 3H).

5 Example 6.6A

tert-Butyl [1,2,4]triazolo[4,3-*a*]pyridin-7-ylcarbamate

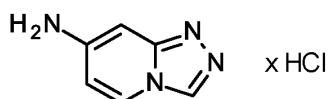


tert-Butyl carbamate (8.87 g, 75.7 mmol, 3.0 eq.), tris(dibenzylideneacetone)dipalladium chloroform complex (2.61 g, 2.5 mmol, 0.1 eq.), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (4.38 g, 7.6 mmol, 0.3 eq.) and caesium carbonate (16.4 g, 50.5 mmol, 2.0 eq.) were added to a solution of 7-bromo[1,2,4]triazolo[4,3-*a*]pyridine (5.00 g, 25.2 mmol) in 1,4-dioxane (250 ml). The resulting mixture was purged with nitrogen for 5 minutes, stirred at 110°C for 4 h, cooled to RT and filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was purified by chromatography (silica gel, eluent: petroleum ether / ethyl acetate 1:9). Yield: 3.50 g (49% of theory).

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 9.88 (s, 1H), 9.06 (s, 1H), 8.42 (d, 1H), 7.80 (s, 1H), 6.97-6.94 (m, 1H), 1.51 (s, 9H).

Example 6.6B

[1,2,4]Triazolo[4,3-*a*]pyridin-7-amine hydrochloride

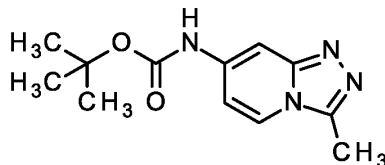


20

Hydrogen chloride solution (107 ml, 4 M in 1,4-dioxane) was added to a stirred solution of *tert*-butyl [1,2,4]triazolo[4,3-*a*]pyridin-7-ylcarbamate (5.00 g, 21.3 mmol) in dichloromethane (120 ml). The reaction mixture was stirred for 15 h at RT and diluted with dichloromethane. The precipitate was collected by filtration, washed with dichloromethane and dried *in vacuo*. The crude product was purified by flash chromatography (330 g C18-bonded silica gel, 100% water). Yield: 2.40 g (58% of theory).

¹H-NMR (300 MHz, DMSO-*d*₆): δ [ppm] = 9.15 (s, 1H), 8.47-8.44 (m, 1H), 7.62 (s, 2H), 6.92-6.70 (m, 1H), 6.58 (d, 1H).

25

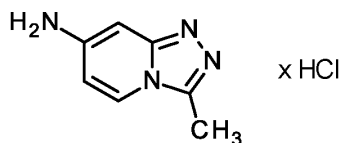
Example 6.7A*tert*-Butyl (3-methyl[1,2,4]triazolo[4,3-a]pyridin-7-yl)carbamate

A mixture of 7-bromo-3-methyl[1,2,4]triazolo[4,3-a]pyridine (210 mg, 0.99 mmol), *tert*-butyl carbamate (174 mg, 1.49 mmol, 1.5 eq.), palladium(II) acetate (22 mg, 0.1 mmol, 0.1 eq.), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (142 mg, 0.3 mmol, 0.3 eq.) and caesium carbonate (647 mg, 1.98 mmol, 2.0 eq.) in 1,4-dioxane (10 ml) was stirred at 100°C overnight. Tris(dibenzylideneacetone)dipalladium (18 mg, 0.02 mmol, 0.02 eq.) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (46 mg, 0.08 mmol, 0.08 eq.) were added. The reaction mixture was stirred at 100°C for additional 3 h, cooled to RT and filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 72 mg (29% of theory).

LC-MS (method 4): $R_t = 0.86$ min; MS (ESIpos): $m/z = 249$ $[M+H]^+$

Example 6.7B

3-Methyl[1,2,4]triazolo[4,3-a]pyridin-7-amine hydrochloride

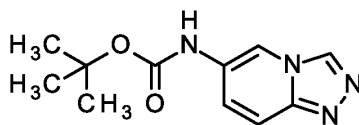


A solution of *tert*-butyl (3-methyl[1,2,4]triazolo[4,3-a]pyridin-7-yl)carbamate (72 mg, 0.29 mmol) in hydrogen chloride solution (1.44 ml, 4 M in 1,4-dioxane, 5.77 mmol, 20 eq.) was stirred at RT overnight. Additional hydrogen chloride solution (1.44 ml, 4 M in 1,4-dioxane, 5.77 mmol, 20 eq.) was added. The reaction mixture was stirred again at RT overnight, concentrated *in vacuo*, coevaporated two times with dichloromethane and used in the subsequent reaction without further purification. Yield: 59 mg (quantitative of theory).

LC-MS (method 15): $R_t = 0.43$ min; MS (ESIpos): $m/z = 149$ $[M+H]^+$

¹H-NMR (500 MHz, DMSO-*d*₆): δ [ppm] = 8.37 (d, 1H), 7.55 (br s, 2H), 6.89 (dd, 1H), 6.53 (d, 1H), 2.61 (s, 3H).

Example 6.8A*tert*-Butyl [1,2,4]triazolo[4,3-a]pyridin-6-ylcarbamate



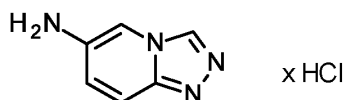
A mixture of 6-bromo[1,2,4]triazolo[4,3-a]pyridine (1.00 g, 5.05 mmol), *tert*-butyl carbamate (887 mg, 7.58 mmol, 1.5 eq.), tris(dibenzylideneacetone)dipalladium (93 mg, 0.10 mmol, 0.02 eq.), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (234 mg, 0.40 mmol, 0.08 eq.) and caesium carbonate (3.29 g, 10.10 mmol, 2.0 eq.) in 1,4-dioxane (20 ml) was stirred at 100°C overnight. Tris(dibenzylideneacetone)dipalladium (46 mg, 0.05 mmol, 0.01 eq.) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (117 mg, 0.20 mmol, 0.04 eq.) were added. The reaction mixture was stirred again at 100°C overnight, cooled to RT and filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: dichloromethane / methanol gradient). Yield: 167 mg (14% of theory).

LC-MS (method 4): $R_t = 1.09$ min; MS (ESIpos): $m/z = 235$ $[M+H]^+$

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 9.68 (br s, 1H), 9.23 (d, 1H), 8.97 (br s, 1H), 7.73 (d, 1H), 7.26 (dd, 1H), 1.50 (s, 9H).

Example 6.8B

[1,2,4]Triazolo[4,3-a]pyridin-6-amine hydrochloride



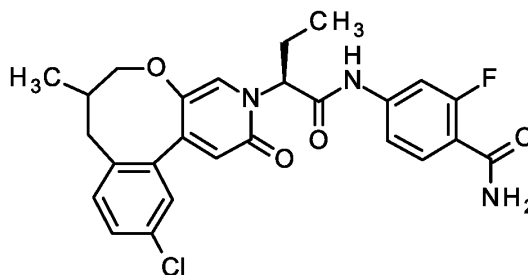
A solution of *tert*-butyl [1,2,4]triazolo[4,3-a]pyridin-6-ylcarbamate (180 mg, 0.75 mmol) in hydrogen chloride solution (3.77 ml, 4 M in 1,4-dioxane, 15.09 mmol, 20 eq.) was stirred at RT overnight, concentrated *in vacuo*, coevaporated two times with dichloromethane and used in the subsequent reaction without further purification. Yield: 171 mg (80% purity).

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 9.53 (s, 1H), 8.00 (d, 1H), 7.90 (d, 1H), 7.66 (dd, 1H), 6.0 (br s, 3H).

Working examples

Example 1

4-{[(2*S*)-2-(11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)butanoyl]amino}-2-fluorobenzamide (mixture of two diastereomers)



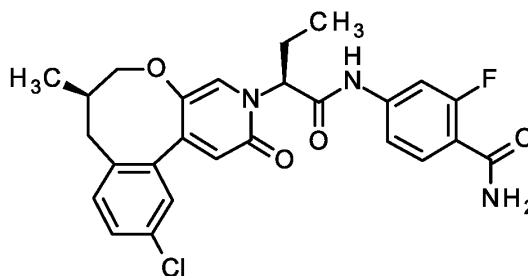
1,1,3,3-Tetramethylguanidine (52 μ l, 0.42 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of 11-chloro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (racemate) (40 mg, 0.14 mmol) in 2-propanol / acetone (4:1, 0.5 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-[(2*R*)-2-bromobutanoyl]amino}-2-fluorobenzamide (single stereoisomer) (63 mg, 0.21 mmol, 1.5 eq.) and further 2-propanol / acetone (4:1, 0.6 ml). The reaction mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (column: Chromatorex C18 10 μ m, 125 mm x 30 mm; eluent: acetonitrile / 0.05% formic acid; gradient: 0-3 min 10% acetonitrile, to 35 min 90% acetonitrile and further 3 min 90% acetonitrile). Yield: 58 mg (83% of theory).

LC-MS (method 4): R_t = 1.88 min; MS (ESIpos): m/z = 498 $[M+H]^+$

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.91-10.81 (m, 1H), 7.83-7.75 (m, 1H), 7.73-7.62 (m, 2H), 7.59-7.48 (m, 2H), 7.48-7.30 (m, 4H), 6.42-6.32 (m, 1H), 5.61-5.51 (m, 1H), 4.54-4.44 / 4.34-4.25 / 3.91-3.81 / 3.39-3.26 (4m, 2H, partially concealed), 2.91-2.80 / 2.75-2.60 (2m, 1H), 2.35-2.25 / 2.22-1.95 (2m, 4H), 0.98-0.83 (m, 6H). Additional signals of minor rotamers were also detected.

Example 2

4-({(2*S*)-2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoyl]amino}-2-fluorobenzamide (single stereoisomer)



Diastereomer separation of 58 mg of 4-[(2*S*)-2-[(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoyl]amino}-2-fluorobenzamide (mixture of two diastereomers), Example 1 gave

single stereoisomer 1 (chiral SFC: R_t = 0.97 min, >99% de): 20 mg,

single stereoisomer 2 (chiral SFC: R_t = 1.98 min, >99% de): 21 mg.

Separation method: SFC: column: Daicel Chiralpak AD, 250 mm x 20 mm; eluent: 72% carbon dioxide / 28% 2-propanol; temperature: 40°C; flow rate: 80 ml/min; UV detection: 210 nm.

Analysis method: SFC: column: Daicel Chiralpak AD, 50 mm x 4.6 mm; eluent: 70% carbon dioxide / 30% 2-propanol; temperature: 40°C; flow rate: 3 ml/min; UV detection: 210 nm.

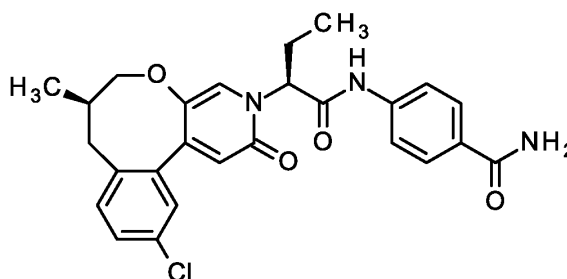
20 mg of single stereoisomer 1 were further purified by preparative HPLC (column: Chromatorex C18 10 μ m, 125 mm x 30 mm; eluent: acetonitrile / 0.05% formic acid; gradient: 0-3 min 10% acetonitrile, to 35 min 90% acetonitrile and further 3 min 90% acetonitrile) to give 18 mg of the title compound Example 2.

10 LC-MS (method 4): R_t = 1.88 min; MS (ESIpos): m/z = 498 $[M+H]^+$

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.90-10.82 (m, 1H), 7.78 (s, 1H), 7.70 (t, 1H), 7.68-7.61 (m, 1H), 7.58-7.49 (m, 2H), 7.48-7.36 (m, 3H), 7.36-7.30 (m, 1H), 6.41-6.32 (m, 1H), 5.60-5.52 (m, 1H), 4.54-4.46 / 4.32-4.25 / 3.90-3.83 / 3.3-3.24 (4m, 2H, partially concealed), 2.90-2.81 / 2.76-2.62 (2m, 1H, partially concealed), 2.34-2.26 / 2.22-1.96 (2m, 4H), 0.97-0.83 (m, 6H). Additional
15 signals of minor rotamers were also detected.

Example 3

4-({(2*S*)-2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoyl}amino)benzamide (single stereoisomer)



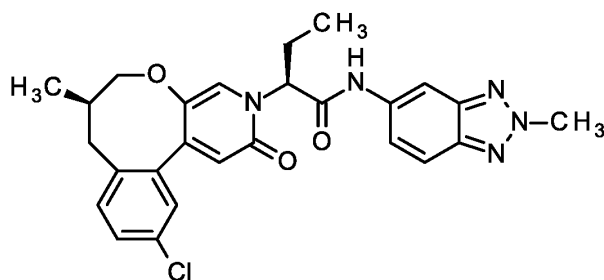
20 1,1,3,3-Tetramethylguanidine (38 μ l, 0.30 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (32 mg, 86% purity, 0.10 mmol) in 2-propanol / acetone (4:1, 1.25 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-({(2*R*)-2-bromobutanoyl}amino)benzamide (single stereoisomer) (31 mg, 0.11 mmol, 1.1 eq.). The reaction
25 mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 26 mg (54% of theory).

LC-MS (method 4): R_t = 1.79 min; MS (ESIpos): m/z = 480 $[M+H]^+$

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 10.69 (br s, 1H), 7.92-7.77 (m, 4H), 7.73-7.63 (m, 2H), 7.50-7.30 (m, 3H), 7.30-7.20 (m, 1H), 6.42-6.32 (m, 1H), 5.66-5.55 (m, 1H), 4.55-4.45 / 4.33-4.24 / 3.90-3.82 / 3.3-3.23 (4m, 2H, partially concealed), 2.91-2.81 / 2.76-2.63 (2m, 1H), 2.35-2.25 / 2.22-1.96 (2m, 4H), 0.98-0.83 (m, 6H). Additional signals of minor rotamers were also detected.

5 Example 4

(2*S*)-2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-*N*-(2-methyl-2*H*-benzotriazol-5-yl)butanamide (single stereoisomer)



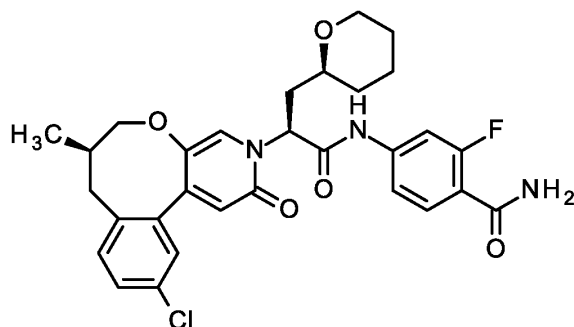
1,1,3,3-Tetramethylguanidine (38 µl, 0.30 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (32 mg, 86% purity, 0.10 mmol) in 2-propanol / acetone (4:1, 1.25 ml). The mixture was stirred at RT for 15 min, followed by addition of (2*R*)-2-bromo-*N*-(2-methyl-2*H*-benzotriazol-5-yl)butanamide (single stereoisomer) (31 mg, 0.10 mmol, 1.0 eq.). The reaction mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 38 mg (77% of theory).

LC-MS (method 4): *R*_t = 2.06 min; MS (ESIpos): *m/z* = 492 [M+H]⁺

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 10.76-10.69 (m, 1H), 8.38-8.33 (m, 1H), 7.89 (d, 1H), 7.85-7.80 (m, 1H), 7.51-7.31 (m, 4H), 6.42-6.33 (m, 1H), 5.68-5.60 (m, 1H), 4.54-4.48 / 4.32-4.27 / 3.91-3.84 / 3.37-3.3 (4m, 2H, partially concealed), 4.45 (s, 3H), 2.89-2.82 / 2.75-2.64 (2m, 1H), 2.35-2.27 / 2.23-1.98 (2m, 4H), 0.98-0.84 (m, 6H). Additional signals of minor rotamers were also detected.

Example 5

4-({(2*S*)-2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)-2-fluorobenzamide (single stereoisomer)



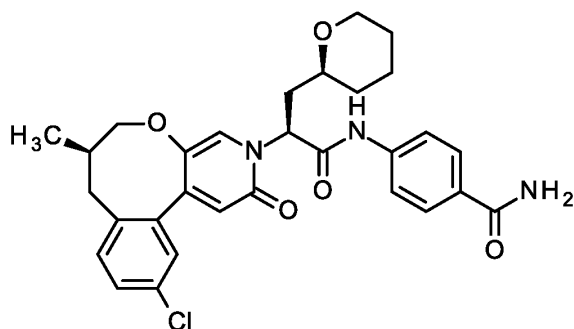
1,1,3,3-Tetramethylguanidine (38 μ l, 0.30 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (32 mg, 86% purity, 0.10 mmol) in 2-propanol / acetone (4:1, 1.25 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-({(2*R*)-2-bromo-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)-2-fluorobenzamide (single stereoisomer) (37 mg, 0.10 mmol, 1.0 eq.). The reaction mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 27 mg (47% of theory).

10 LC-MS (method 4): R_t = 2.05 min; MS (ESIpos): m/z = 568 $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.85-10.66 (m, 1H), 7.84-7.76 (m, 1H), 7.72-7.62 (m, 2H), 7.58-7.48 (m, 2H), 7.48-7.37 (m, 3H), 7.36-7.29 (m, 1H), 6.38-6.30 (m, 1H), 5.81-5.65 (m, 1H), 4.54-4.44 / 4.31-4.23 / 3.92-3.79 / 3.3-3.16 (4m, 5H, partially concealed), 2.90-2.80 / 2.75-2.65 (2m, 1H), 2.35-2.19 / 2.17-1.95 (2m, 4H), 1.82-1.70 (m, 1H), 1.67-1.57 (m, 1H), 1.49-1.34 (m, 3H), 1.33-1.20 (m, 1H), 0.96-0.82 (m, 3H). Additional signals of minor rotamers were also detected.

Example 6

4-({(2*S*)-2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)benzamide (single stereoisomer)



20 General Method 7 was carried out with (7*R*)-11-chloro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (50.0 mg, 181 μ mol, 1.0 eq.), 4-

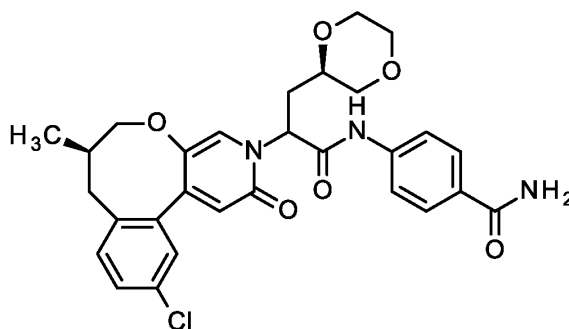
((2*R*)-2-bromo-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)benzamide (single stereoisomer) (96.6 mg, 272 μ mol, 1.5 eq.) and 1,1,3,3-tetramethylguanidine (68 μ l, 540 μ mol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 2.6 ml). The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 80:20 to 1:99). Yield: 50.0 mg (50% of theory).

LC-MS (method 1): R_t = 1.04 min; MS (ESIpos): m/z = 550 $[M+H]^+$

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.70 / 10.63 (2s, 1H), 7.90 (br s, 1H), 7.87-7.80 (m, 3H), 7.73-7.66 (m, 2H), 7.49-7.38 (m, 2H), 7.35-7.31 (m, 1H), 7.29 (br s, 1H), 6.37 / 6.32 (2s, 1H), 5.81 / 5.75 (2t, 1H), 4.54-4.44 (m, 1H), 3.91-3.80 (m, 1H), 3.31-3.18 (m, 3H), 2.70 (d, 1H), 2.36-2.17 (m, 2H), 2.17-2.07 (m, 1H), 2.06-1.95 (m, 1H), 1.80-1.71 (m, 1H), 1.67-1.56 (m, 1H), 1.46-1.34 (m, 3H), 1.32-1.17 (m, 1H), 0.91 / 0.86 (2d, 3H). Additional signals of minor rotamers were also detected.

Example 7

4-{2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*R*)-1,4-dioxan-2-yl]propanamido}benzamide (mixture of two diastereomers)



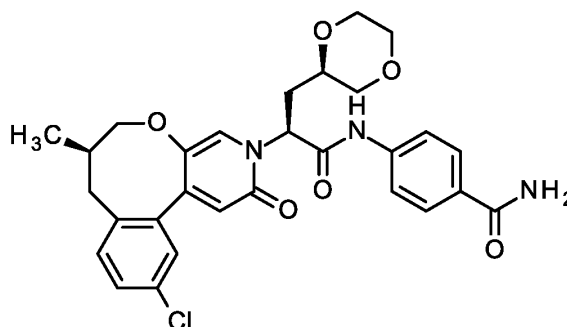
2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*R*)-1,4-dioxan-2-yl]propanoic acid (mixture of two diastereomers) (51 mg, 0.12 mmol) and 4-aminobenzamide (24 mg, 0.18 mmol, 1.5 eq.) were reacted according to General Method 11. Yield: 57 mg (86% of theory).

LC-MS (method 4): R_t = 1.65 / 1.68 min; MS (ESIpos): m/z = 552 $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.73-10.56 (m, 1H), 7.91-7.77 (m, 4H), 7.73-7.64 (m, 2H), 7.48-7.30 (m, 3H), 7.29-7.20 (m, 1H), 6.40-6.31 (m, 1H), 5.81-5.66 (m, 1H), 4.53-4.44 / 4.34-4.24 / 3.92-3.81 / 3.40-3.19 (4m, 3H, partially concealed), 3.77-3.57 (m, 3H), 3.55-3.40 (m, 3H), 2.90-2.82 / 2.76-2.65 (2m, 1H), 2.35-1.95 (m, 4H), 0.96-0.83 (m, 3H). Additional signals of minor rotamers were also detected.

Example 8

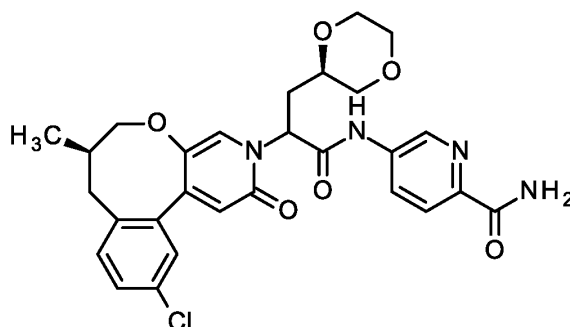
4-({(2*S*)-2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*R*)-1,4-dioxan-2-yl]propanoyl}amino)benzamide (single stereoisomer)



- 5 Diastereomer separation of 50 mg of 4-{{2-[(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*R*)-1,4-dioxan-2-yl]propanamido}benzamide (mixture of two diastereomers), Example 7 gave
- single stereoisomer 1 (chiral HPLC: $R_t = 3.58$ min, 99% de): 18 mg,
- single stereoisomer 2 (chiral HPLC: $R_t = 4.60$ min, 99% de): 37 mg.
- 10 Separation method: HPLC: column: Daicel Chiralcel OX-H 5 μm , 250 mm x 20 mm; eluent: 50% *n*-heptane / 50% ethanol; temperature: 40°C; flow rate: 15 ml/min; UV detection: 210 nm.
- Analysis method: HPLC: column: Daicel Chiralpak OX-3 3 μm , 50 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% ethanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.
- 18 mg of single stereoisomer 1 were further purified by preparative HPLC (reversed phase, eluent: acetonitrile / 0.05% formic acid gradient) to give 15 mg of the title compound Example 8.
- 15 LC-MS (method 4): $R_t = 1.69$ min; MS (ESIpos): $m/z = 552$ $[\text{M}+\text{H}]^+$
- $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.69-10.55 (m, 1H), 7.91-7.76 (m, 4H), 7.72-7.66 (m, 2H), 7.48-7.38 / 7.36-7.30 (2m, 3H), 7.29-7.22 (m, 1H), 6.40-6.32 (m, 1H), 5.82-5.66 (m, 1H), 4.53-4.46 / 4.30-4.23 / 3.92-3.86 / 3.37-3.22 (4m, 3H, partially concealed), 3.77-3.65 (m, 2H), 3.65-3.59 (m, 1H), 3.55-3.42 (m, 3H), 2.90-2.81 / 2.73-2.65 (2m, 1H), 2.33-2.26 / 2.26-2.17 (2m, 2H), 2.15-1.95 (m, 2H), 0.94-0.83 (m, 3H). Additional signals of minor rotamers were also detected.

Example 9

5-{2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*R*)-1,4-dioxan-2-yl]propanamido}pyridine-2-carboxamide (mixture of two diastereomers)



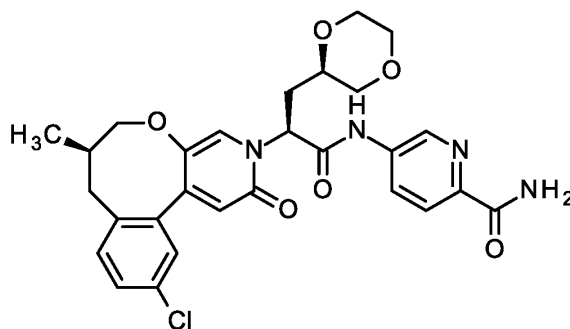
2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*R*)-1,4-dioxan-2-yl]propanoic acid (mixture of two diastereomers) (51 mg, 0.12 mmol) and 5-aminopyridine-2-carboxamide (24 mg, 0.18 mmol, 1.5 eq.) (prepared according to WO 2017/005725, example 1.3B) were reacted according to General Method 11. Yield: 50 mg (75% of theory).

LC-MS (method 4): $R_t = 1.69 / 1.72$ min; MS (ESIpos): $m/z = 553$ $[M+H]^+$

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.99-10.75 (m, 1H), 8.89-8.80 (m, 1H), 8.27-8.15 (m, 1H), 8.05-7.97 (m, 2H), 7.88-7.76 (m, 1H), 7.56-7.49 (m, 1H), 7.49-7.29 (m, 3H), 6.41-6.32 (m, 1H), 5.83-5.62 (m, 1H), 4.53-4.45 / 4.34-4.24 / 3.92-3.81 / 3.39-3.21 (4m, 3H, partially concealed), 3.78-3.57 (m, 3H), 3.55-3.41 (m, 3H), 2.90-2.81 / 2.76-2.65 (2m, 1H), 2.38-1.96 (m, 4H), 0.96-0.83 (m, 3H). Additional signals of minor rotamers were also detected.

Example 10

5-({(2*S*)-2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*R*)-1,4-dioxan-2-yl]propanoyl}amino)pyridine-2-carboxamide (single stereoisomer)



15

Diastereomer separation of 45 mg of 5-{{2-[(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*R*)-1,4-dioxan-2-yl]propanamido}pyridine-2-carboxamide (mixture of two diastereomers), Example 9 gave

single stereoisomer 1 (chiral HPLC: $R_t = 3.36$ min, 97% de): 14 mg,

20 single stereoisomer 2 (chiral HPLC: $R_t = 5.43$ min, 93% de): 24 mg.

Separation method: HPLC: column: Daicel Chiralpak ID 5 μm , 250 mm x 20 mm; eluent: 25% *n*-heptane / 75% ethanol; temperature: 50°C; flow rate: 15 ml/min; UV detection: 210 nm.

Analysis method: HPLC: column: Daicel Chiralpak OX-3 3 μm , 50 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% ethanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.

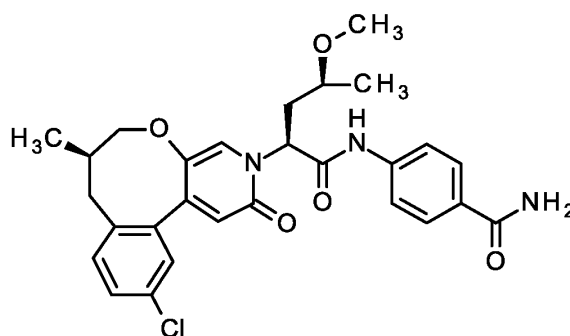
- 5 14 mg of single stereoisomer 1 were further purified by preparative HPLC (reversed phase, eluent: acetonitrile / 0.05% formic acid gradient) to give 9 mg of the title compound Example 10.

LC-MS (method 4): $R_t = 1.72$ min; MS (ESIpos): $m/z = 553$ $[\text{M}+\text{H}]^+$

- $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.96-10.76 (m, 1H), 8.90-8.80 (m, 1H), 8.27-8.17 (m, 1H), 8.05-7.98 (m, 2H), 7.86-7.77 (m, 1H), 7.55-7.50 (m, 1H), 7.48-7.30 (m, 3H), 6.40-6.32 (m, 1H),
 10 5.83-5.76 / 5.68-5.62 (2m, 1H), 4.53-4.46 / 4.30-4.23 / 3.93-3.85 / 3.39-3.23 (4m, 3H, partially concealed), 3.78-3.65 (m, 2H), 3.65-3.59 (m, 1H), 3.55-3.42 (m, 3H), 2.89-2.81 / 2.74-2.65 (2m, 1H), 2.33-2.22 (m, 2H), 2.17-1.95 (m, 2H), 0.94-0.83 (m, 3H). Additional signals of minor rotamers were also detected.

Example 11

- 15 4-({(2*S*,4*S*)-2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (single stereoisomer)



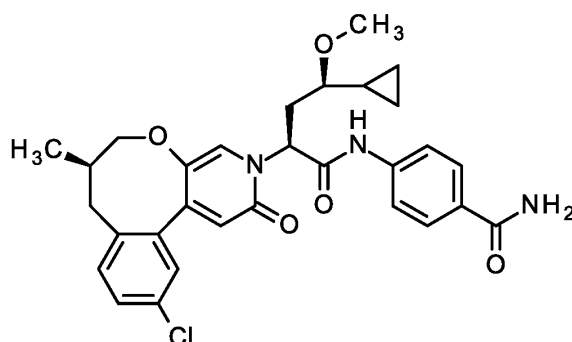
- 1,1,3,3-Tetramethylguanidine (22 μl , 178 μmol , 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (17 mg, 59 μmol) in 2-propanol / acetone (4:1, 0.6 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-({(2*R*,4*S*)-2-bromo-4-methoxypentanoyl}amino)benzamide (single stereoisomer) (22 mg, 65 μmol , 1.1 eq.) and of further 2-propanol / acetone (4:1, 0.6 ml). The reaction mixture was stirred at RT for 2 days and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent:
 20 acetonitrile / water gradient). Yield: 22 mg (69% of theory).
 25

LC-MS (method 1): $R_t = 0.97$ min; MS (ESIpos): $m/z = 524$ $[\text{M}+\text{H}]^+$

¹H-NMR (500 MHz, DMSO-*d*₆): δ [ppm] = 10.66 (br s, 1H), 7.92-7.80 (m, 4H), 7.75-7.66 (m, 2H), 7.49-7.29 (m, 3H), 7.25 (br s, 1H), 6.40-6.31 (m, 1H), 5.87-5.76 (m, 1H), 4.54-4.44 / 4.31-4.24 / 3.90-3.82 / 3.3-3.20 (4m, 2H, partially concealed), 3.20-3.10 (m, 3H), 2.90-2.80 / 2.75-2.64 (2m, 2H), 2.34-2.13 / 2.10-1.96 (2m, 4H), 1.16 (d, 3H), 0.97-0.82 (m, 3H). Additional signals of minor rotamers were also detected.

Example 12

4-({(2*S*,4*R*)-2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-cyclopropyl-4-methoxybutanoyl}amino)benzamide (single stereoisomer)



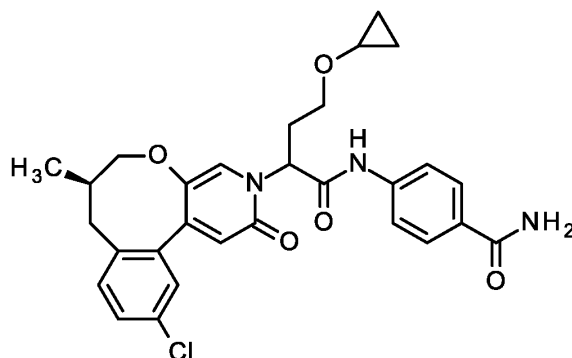
1,1,3,3-Tetramethylguanidine (19 µl, 149 µmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (14 mg, 50 µmol) in 2-propanol / acetone (4:1, 0.5 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-{{(2*R*,4*R*)-2-bromo-4-cyclopropyl-4-methoxybutanoyl}-amino}benzamide (single stereoisomer) (19 mg, 55 µmol, 1.1 eq.) and of further 2-propanol / acetone (4:1, 0.5 ml). The reaction mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 16 mg (59% of theory).

LC-MS (method 4): *R*_t = 1.95 min; MS (ESIpos): *m/z* = 550 [M+H]⁺

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 10.69-10.54 (m, 1H), 7.90-7.74 (m, 4H), 7.73-7.66 (m, 2H), 7.48-7.28 (m, 3H), 7.22 (br s, 1H), 6.38-6.30 (m, 1H), 5.88-5.75 (m, 1H), 4.54-4.45 / 4.33-4.26 / 3.36-3.76 / 3.3-3.26 (4m, 2H, partially concealed), 3.23 / 3.21 (2s, 3H), 2.89-2.81 / 2.79-2.67 (2m, 1H), 2.45-2.21 (m, 4H), 2.11-1.97 (m, 1H), 0.96-0.77 (m, 4H), 0.63-0.51 (m, 1H), 0.45-0.33 (m, 2H), 0.10-0.0 (m, 1H). Additional signals of minor rotamers were also detected.

Example 13

4-{2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclopropyloxy)butanamido}benzamide (mixture of two diastereomers)



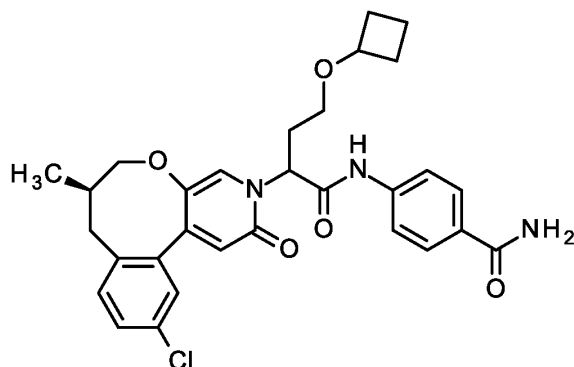
4-Aminobenzamide (3 mg, 25 μ mol, 1.2 eq.), pyridine (2 μ l, 25 μ mol, 1.2 eq.) and T3P (19 μ l, 50% solution in ethyl acetate, 31 μ mol, 1.5 eq.) were added under argon atmosphere at RT to a solution of 2-[(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclo-propyloxy)butanoic acid (mixture of two diastereomers) (9 mg, 21 μ mol) in tetrahydrofuran (1 ml). The reaction mixture was stirred at RT for 1.5 h before water was added. After phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 5 mg (44% of theory).

LC-MS (method 4): R_t = 1.90 min; MS (ESIpos): m/z = 536 $[M+H]^+$

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.73-10.61 (m, 1H), 7.91-7.76 (m, 4H), 7.73-7.64 (m, 2H), 7.49-7.21 (m, 4H), 6.41-6.31 (m, 1H), 5.78-5.69 (m, 1H), 4.54-4.45 / 4.32-4.26 / 3.91-3.84 / 3.58-3.06 (4m, 4H, partially concealed), 2.91-2.82 / 2.77-2.69 (2m, 1H), 2.4-2.26 (m, 4H, partially concealed), 2.11-1.97 (m, 1H), 0.97-0.85 (m, 3H), 0.45-0.28 (m, 4H). Additional signals of minor rotamers were also detected.

Example 14

4-{[2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclobutyloxy)butanoyl]amino}benzamide (mixture of two diastereomers)



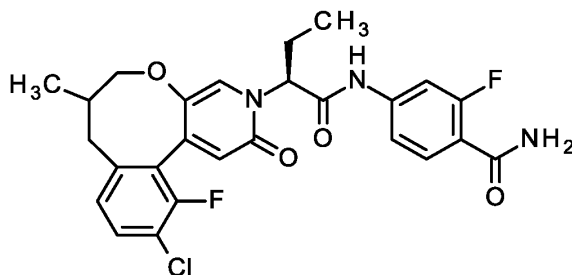
4-Aminobenzamide (42 mg, 0.31 mmol, 1.5 eq.) and *N,N*-diisopropylethylamine (107 μ l, 0.61 mmol, 3.0 eq.) were added at RT to a solution of 2-[(7*R*)-11-chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclobutyloxy)butanoic acid (mixture of two diastereomers) (106 mg, 83% purity, 0.20 mmol) in *N,N*-dimethylformamide (1 ml). A solution of HATU (116 mg, 0.31 mmol, 1.5 eq.) in *N,N*-dimethylformamide (2 ml) was added dropwise and the reaction mixture stirred at RT for 2 days. Additional HATU (39 mg, 0.10 mmol, 0.5 eq.) and *N,N*-diisopropylethylamine (36 μ l, 0.20 mmol, 1.0 eq.) were added. The reaction mixture was stirred for 3 h before water was added. After addition of ethyl acetate and phase separation, the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 31 mg (27% of theory).

LC-MS (method 4): R_t = 1.99 min; MS (ESIpos): m/z = 550 $[M+H]^+$

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.75-10.60 (m, 1H), 7.93-7.77 (m, 4H), 7.74-7.65 (m, 2H), 7.49-7.20 (m, 4H), 6.41-6.31 (m, 1H), 5.81-5.71 (m, 1H), 4.53-4.44 / 4.32-4.25 / 3.89-3.78 / 3.39-3.17 (4m, 5H, partially concealed), 2.89-2.81 / 2.75-2.68 (2m, 1H), 2.41-2.24 (m, 3H), 2.12-1.96 (m, 3H), 1.30-1.49 / 1.47-1.35 (2m, 4H), 0.96-0.83 (m, 3H). Additional signals of minor rotamers were also detected.

Example 15

4-[(2*S*)-2-(11-Chloro-12-fluoro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)butanoyl]amino}-2-fluorobenzamide (mixture of two diastereomers)

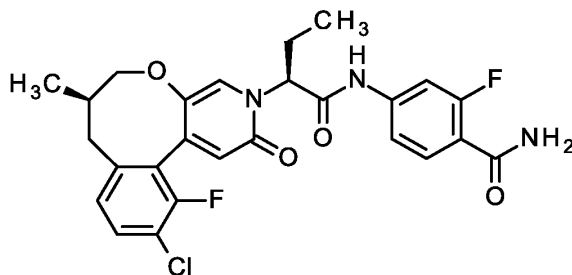


General Method 7 was carried out with 11-chloro-12-fluoro-7-methyl-7,8-dihydro-3H-[3]benzoxocino[2,1-c]pyridin-2(6H)-one (racemate) (30.0 mg, 92% purity, 94.0 μmol , 1.0 eq.), 4-
 5 {[(2R)-2-bromobutanoyl]amino}-2-fluorobenzamide (single stereoisomer) (42.7 mg, 141 μmol , 1.5 eq.) and 1,1,3,3-tetramethylguanidine (35 μl , 280 μmol , 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 1.0 ml) including the following variations of the procedure: The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 35.0 mg (72% of theory).

LC-MS (method 3): $R_t = 3.09 / 3.16$ min; MS (ESIpos): $m/z = 516$ $[\text{M}+\text{H}]^+$

10 **Example 16**

4-({(2S)-2-[(7R)-11-Chloro-12-fluoro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3H-[3]benzoxocino[2,1-c]pyridin-3-yl]butanoyl}amino)-2-fluorobenzamide (single stereoisomer)



Diastereomer separation of 30 mg of 4-[(2S)-2-(11-chloro-12-fluoro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3H-[3]benzoxocino[2,1-c]pyridin-3-yl)butanoyl]amino}-2-fluorobenzamide (mixture of
 15 two diastereomers), Example 15 gave

single stereoisomer 1 (the title compound 16) (chiral HPLC: $R_t = 11.5$ min, >98% de): 11.0 mg (23% of theory),

single stereoisomer 2 (chiral HPLC: $R_t = 15.3$ min): 11.0 mg.

20 Separation method: HPLC: column: Daicel Chiralpak IA 5 μm , 250 mm x 20 mm; eluent: ethanol; temperature: 20°C; flow rate: 7 ml/min; UV detection: 240 nm.

Analysis method: HPLC: column: Daicel Chiralpak IA 5 μm , 250 mm x 4.6 mm; eluent: ethanol;

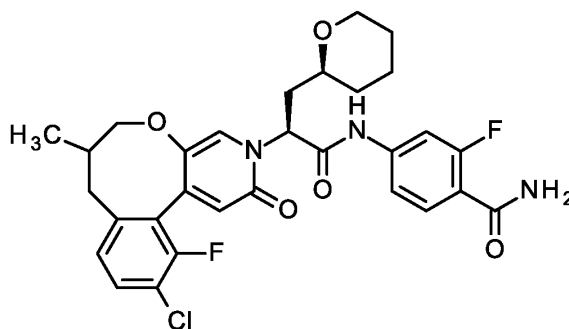
temperature: 20°C; flow rate: 0.4 ml/min; UV detection: 240 nm.

LC-MS (method 3): $R_t = 3.36$ min; MS (ESIpos): $m/z = 516$ $[M+H]^+$

1H -NMR (400 MHz, DMSO- d_6): δ [ppm] = 10.89 / 10.86 (2s, 1H), 7.89 (s, 1H), 7.73-7.57 (m, 3H), 7.56-7.51 (m, 2H), 7.43-7.37 (m, 1H), 7.30 / 7.22 (2d, 1H), 6.49 / 6.45 (2d, 1H), 5.66-5.50 (m, 1H),
 5 4.50 (dd, 1H), 3.33-3.27 (m, 1H), 2.77 (d, 1H), 2.32-2.24 (m, 1H), 2.31-1.99 (m, 3H), 0.96-0.82 (m, 6H). Additional signals of minor rotamers were also detected.

Example 17

4-({(2*S*)-2-(11-Chloro-12-fluoro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-
 c]pyridin-3-yl)-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)-2-fluorobenzamide (mixture
 10 of two diastereomers)

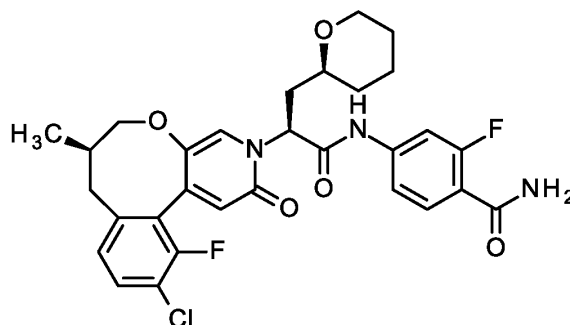


General Method 7 was carried out with 11-chloro-12-fluoro-7-methyl-7,8-dihydro-3*H*-
 [3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (racemate) (50.0 mg, 92% purity, 157 μ mol, 1.0 eq.), 4-
 ({(2*R*)-2-bromo-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)-2-fluorobenzamide (single
 15 stereoisomer) (87.7 mg, 235 μ mol, 1.5 eq.) and 1,1,3,3-tetramethylguanidine (59 μ l, 470 μ mol, 3.0
 eq.) in a mixture of 2-propanol / acetone (4:1, 1.5 ml) including the following variations of the
 procedure: The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with
 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 65.0 mg (71% of theory).

LC-MS (method 4): $R_t = 2.00$ min; MS (ESIpos): $m/z = 586$ $[M+H]^+$

20 Example 18

4-({(2*S*)-2-[(7*R*)-11-Chloro-12-fluoro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-
 c]pyridin-3-yl]-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)-2-fluorobenzamide (single
 stereoisomer)



Diastereomer separation of 60 mg of 4-({(2*S*)-2-(11-chloro-12-fluoro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)-2-fluorobenzamide (mixture of two diastereomers), Example 17 gave

- 5 single stereoisomer 1 (the title compound 18) (chiral HPLC: $R_t = 36.3$ min, >98% de): 12.0 mg (13% of theory),

single stereoisomer 2 (chiral HPLC: $R_t = 48.6$ min): 15.0 mg.

Separation method: HPLC: column: two coupled Daicel Chiralpak OD-H 5 μ m, 250 mm x 20 mm; eluent: 90% *n*-heptane / 5% 2-propanol / 5% ethanol; temperature: 20°C; flow rate: 8.0 ml/min; UV

- 10 detection: 240 nm.

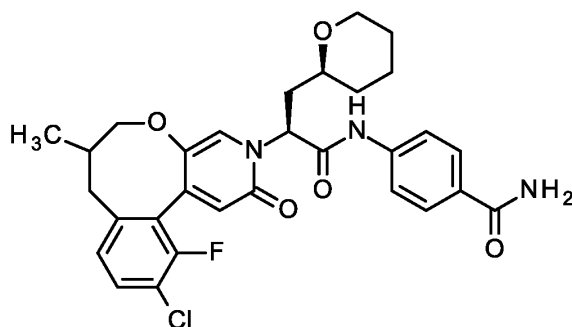
Analysis method: HPLC: column: two coupled Daicel Chiralpak OD-H 5 μ m, 250 mm x 4.6 mm; eluent: 90% *n*-heptane / 5% methanol / 5% ethanol; temperature: 20°C; flow rate: 1.0 ml/min; UV detection: 240 nm.

LC-MS (method 3): $R_t = 3.71$ min; MS (ESIpos): $m/z = 586$ $[M+H]^+$

- 15 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.84 / 10.75 (2s, 1H), 7.90 / 7.87 (2s, 1H), 7.74-7.57 (m, 3H), 7.56-7.50 (m, 2H), 7.47-7.42 (m, 1H), 7.29 (d, 1H), 6.49-6.41 (m, 1H), 5.79 / 5.72 (2t, 1H), 4.49 (dd, 1H), 3.85-3.79 (m, 1H), 3.29-3.21 (m, 2H), 2.75 (d, 1H), 2.33-2.21 (m, 2H), 2.20-1.95 (m, 2H), 1.81-1.70 (m, 1H), 1.61 (d, 1H), 1.48-1.39 (m, 3H), 1.32-1.21 (m, 2H), 0.90 / 0.84 (2t, 3H). Additional signals of minor rotamers were also detected.

20 **Example 19**

4-({(2*S*)-2-(11-Chloro-12-fluoro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)benzamide (mixture of two diastereomers)

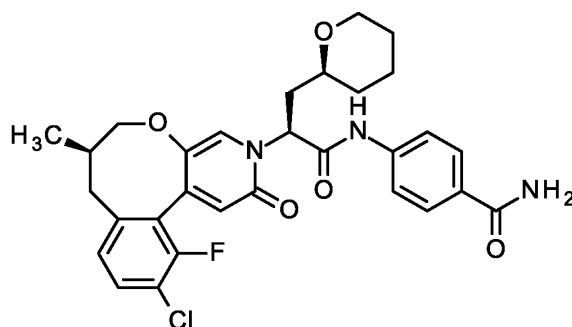


- General Method 7 was carried out with 11-chloro-12-fluoro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (racemate) (50.0 mg, 92% purity, 157 μ mol, 1.0 eq.), 4-((*(2R)*)-2-bromo-3-[(*(2S)*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)benzamide (single stereoisomer) (83.4 mg, 235 μ mol, 1.5 eq.) and 1,1,3,3-tetramethylguanidine (59 μ l, 470 μ mol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 1.5 ml) including the following variations of the procedure: The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 57 mg (64% of theory).

LC-MS (method 3): R_t = 3.36 / 3.42 min; MS (ESIpos): m/z = 568 $[M+H]^+$

10 Example 20

4-((*(2S)*)-2-[(*(7R)*)-11-Chloro-12-fluoro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(*(2S)*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)benzamide (single stereoisomer)



- 15 Diastereomer separation of 55 mg of 4-((*(2S)*)-2-(11-chloro-12-fluoro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)-3-[(*(2S)*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)-benzamide (mixture of two diastereomers), Example 19 gave single stereoisomer 1 (the title compound 20) (chiral HPLC: R_t = 43.7 min, >95% de): 11.0 mg (11% of theory),
- 20 single stereoisomer 2 (chiral HPLC: R_t = 62.6 min): 13.0 mg.

Separation method: HPLC: column: two coupled Daicel Chiralpak OD-H 5 μ m, 250 mm x 20 mm; eluent: 90% *n*-heptane / 5% 2-propanol / 5% ethanol; temperature: 20°C; flow rate: 15 ml/min; UV detection: 240 nm.

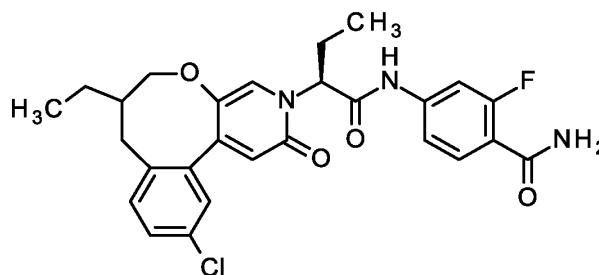
Analysis method: HPLC: column: two coupled Daicel Chiralpak OD-H 5 μ m, 250 mm x 4.6 mm; 5 eluent: 90% *n*-heptane / 5% 2-propanol / 5% ethanol; temperature: 20°C; flow rate: 1.0 ml/min; UV detection: 240 nm.

LC-MS (method 3): R_t = 3.50 min; MS (ESIpos): m/z = 568 $[M+H]^+$

1H -NMR (400 MHz, DMSO- d_6): δ [ppm] = 10.68 / 10.61 (2s, 1H), 7.93-7.80 (m, 4H), 7.74-7.67 (m, 2H), 7.62-7.57 (m, 1H), 7.33-7.19 (m, 2H), 6.49-6.41 (m, 1H), 5.82 / 5.77 (2t, 1H), 4.51-4.47 (m, 10 1H), 3.85-3.79 (m, 1H), 3.29-3.21 (m, 2H), 2.75 (d, 1H), 2.33-2.24 (m, 2H), 2.25-2.17 (m, 1H), 2.14-1.99 (m, 1H), 1.81-1.70 (m, 1H), 1.62 (d, 1H), 1.49-1.35 (m, 3H), 1.35-1.14 (m, 2H), 0.91 / 0.84 (2t, 3H). Additional signals of minor rotamers were also detected.

Example 21

4-{[(2*S*)-2-(11-Chloro-7-ethyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)butanoyl]amino}-2-fluorobenzamide (mixture of two diastereomers) 15

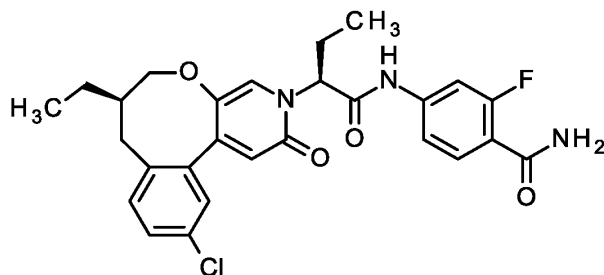


General Method 7 was carried out with 11-chloro-7-ethyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (racemate) (25.0 mg, 78% purity, 67.3 μ mol, 1.0 eq.), 4-{[(2*R*)-2-bromobutanoyl]amino}-2-fluorobenzamide (single stereoisomer) (40.8 mg, 135 μ mol, 2.0 eq.) and 20 1,1,3,3-tetramethylguanidine (25 μ l, 200 μ mol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 0.9 ml) including the following variations of the procedure: The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 42.0 mg (quantitative of theory).

LC-MS (method 1): R_t = 1.09 min; MS (ESIpos): m/z = 512 $[M+H]^+$

Example 22

4-({(2*S*)-2-[(7*R*)-11-Chloro-7-ethyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoyl}amino)-2-fluorobenzamide (single stereoisomer)



Diastereomer separation of 37 mg of 4-[(2*S*)-2-(11-chloro-7-ethyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)butanoyl]amino}-2-fluorobenzamide (mixture of two diastereomers), Example 21 gave

- 5 single stereoisomer 1 (the title compound 22) (chiral HPLC: $R_t = 1.26$ min, 99% de): 10.8 mg (31% of theory),

single stereoisomer 2 (chiral HPLC: $R_t = 2.70$ min): 10.2 mg.

Separation method: HPLC: column: Daicel Chiralpak ID 5 μ m, 250 mm x 20 mm; eluent: 50% *n*-heptane / 50% ethanol; temperature: 40°C; flow rate: 20 ml/min; UV detection: 220 nm.

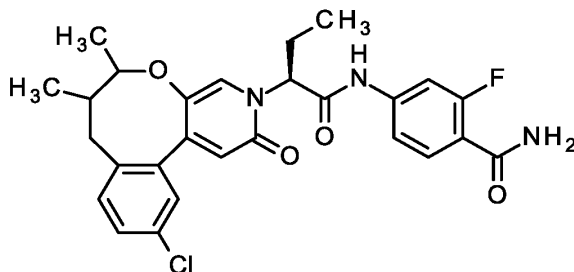
- 10 Analysis method: HPLC: column: Daicel Chiralpak ID-3 3 μ m, 50 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% ethanol; flow rate: 1.0 ml/min; UV detection: 220 nm.

LC-MS (method 3): $R_t = 3.57$ min; MS (ESIpos): $m/z = 512$ $[M+H]^+$

- $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.87 / 10.84 (2s, 1H), 7.78 (s, 1H), 7.73-7.62 (m, 2H), 7.58-7.50 (m, 2H), 7.49-7.44 (m, 1H), 7.42-7.32 (m, 3H), 6.39 / 6.34 (2s, 1H), 5.61-5.52 (m, 1H),
15 4.58-4.47 (m, 1H), 3.45-3.35 (m, 1H), 2.77 (br d, 1H), 2.28-2.02 (m, 3H), 1.86-1.68 (m, 1H), 1.36-1.16 (m, 2H), 0.99 (t, 3H), 0.89 (t, 3H). Additional signals of minor rotamers were also detected.

Example 23

4-[(2*S*)-2-(11-Chloro-6,7-dimethyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)butanoyl]amino}-2-fluorobenzamide (mixture of stereoisomers)



20

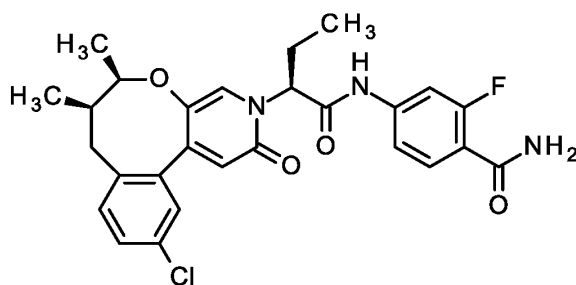
General Method 7 was carried out with 11-chloro-6,7-dimethyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (mixture of stereoisomers) (65.0 mg, 224 μ mol, 1.0 eq.), 4-[(2*R*)-2-

bromobutanoyl]amino}-2-fluorobenzamide (single stereoisomer) (68.0 mg, 224 μ mol, 1.0 eq.) and 1,1,3,3-tetramethylguanidine (84 μ l, 670 μ mol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 3.75 ml) including the following variations of the procedure: After stirring overnight, additional amounts of 4-{(2*R*)-2-bromobutanoyl]amino}-2-fluorobenzamide (single stereoisomer) (20.4 mg, 67.2 μ mol, 0.3 eq.) and 1,1,3,3-tetramethylguanidine (21 μ l, 168 μ mol, 0.75 eq.) were added and stirring was continued at RT for 3 h. The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 80:20 to 5:95). Yield: 55.0 mg (48% of theory).

LC-MS (method 1): R_t = 1.03 / 1.05 min; MS (ESIpos): m/z = 512 $[M+H]^+$

10 Example 24

4-{(2*S*)-2-[(6*R*,7*R*)-11-Chloro-6,7-dimethyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoyl]amino)-2-fluorobenzamide (single stereoisomer)



15 Stereoisomer separation of 50 mg of 4-{(2*S*)-2-[(11-chloro-6,7-dimethyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoyl]amino}-2-fluorobenzamide (mixture of stereoisomers), Example 23 gave

single stereoisomer 1 (the title compound 24) (chiral HPLC: R_t = 5.25 min, 99% de): 5.60 mg (5% of theory),

20 single stereoisomer 2 (chiral HPLC: R_t = 6.01 min): 1.70 mg,

single stereoisomer 3 (chiral HPLC: R_t = 7.18 min): 17.3 mg,

single stereoisomer 4 (chiral HPLC: R_t = 8.65 min): 18.3 mg.

Separation method: HPLC: column: Daicel Chiralpak IF 5 μ m, 250 mm x 20 mm; eluent: 60% *n*-heptane / 40% ethanol; temperature: 40°C; flow rate: 15 ml/min; UV detection: 220 nm.

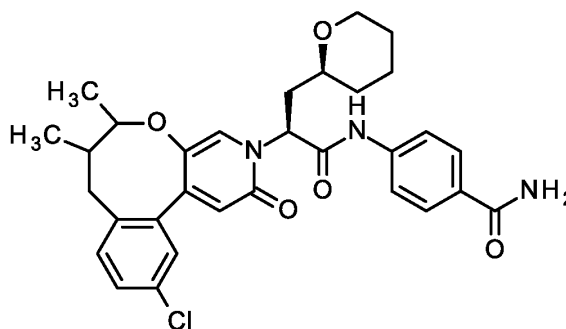
25 Analysis method: HPLC: column: Daicel Chiralpak IF 5 μ m, 250 mm x 4.6 mm; eluent: 60% *iso*-hexane / 40% ethanol; flow rate: 1.0 ml/min; UV detection: 220 nm.

LC-MS (method 1): R_t = 1.07 min; MS (ESIpos): m/z = 512 $[M+H]^+$

¹H-NMR (500 MHz, DMSO-*d*₆): δ [ppm] = 10.82 (s, 1H), 7.77 (s, 1H), 7.73-7.60 (m, 2H), 7.57-7.47 (m, 2H), 7.46-7.38 (m, 3H), 7.37-7.30 (m, 1H), 6.40 / 6.35 (2s, 1H), 5.59 (dd, 1H), 3.58-3.45 (m, 1H), 2.70-2.59 (m, 1H), 2.44-2.33 (m, 1H), 2.23-2.03 (m, 2H), 1.78-1.62 (m, 1H), 1.38 / 1.32 (2d, 3H), 1.01 (d, 3H), 0.89 / 0.77 (2t, 3H). Additional signals of minor rotamers were also detected.

5 Example 25

4-({(2*S*)-2-(11-Chloro-6,7-dimethyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)benzamide (mixture of stereoisomers)

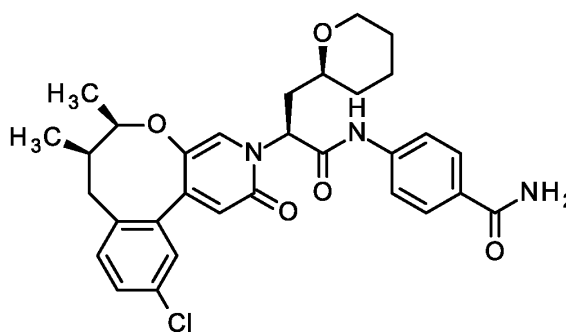


General Method 7 was carried out with 11-chloro-6,7-dimethyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (mixture of stereoisomers) (25.0 mg, 86.3 μ mol, 1.0 eq.), 4-({(2*R*)-2-bromo-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)benzamide (single stereoisomer) (46.0 mg, 129 μ mol, 1.5 eq.) and 1,1,3,3-tetramethylguanidine (32 μ l, 260 μ mol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 0.5 ml) and the crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 80:20 to 5:95). Yield: 38.7 mg (79% of theory).

LC-MS (method 4): R_t = 2.02 min; MS (ESIpos): m/z = 564 [M+H]⁺

Example 26

4-({(2*S*)-2-[(6*R*,7*R*)-11-Chloro-6,7-dimethyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)benzamide (single stereoisomer)



Stereoisomer separation of 35 mg of 4-((2*S*)-2-(11-chloro-6,7-dimethyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl)amino)benzamide (mixture of stereoisomers), Example 25 gave

single stereoisomer 1 (the title compound 26) (chiral HPLC: $R_t = 6.41$ min, 99% de): 6.0 mg (12% of theory),

single stereoisomer 2 (chiral HPLC: $R_t = 9.80$ min): 7.0 mg,

mixture of stereoisomers (chiral HPLC: $R_t = 6.43 / 8.10$ min): 3.0 mg.

Separation method: HPLC: column: Daicel Chiralpak IE 5 μm , 250 mm x 20 mm; eluent: 50% *n*-heptane / 50% ethanol; temperature: 40°C; flow rate: 15 ml/min; UV detection: 220 nm.

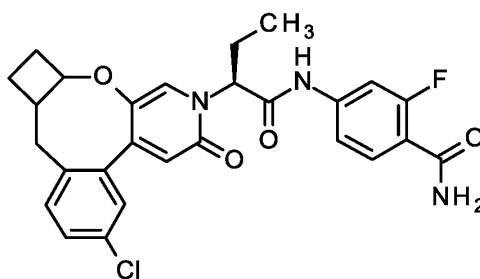
10 Analysis method: HPLC: column: Daicel Chiralpak IE 5 μm , 250 mm x 4.6 mm; eluent: 50% *iso*-hexane / 50% ethanol; flow rate: 1.0 ml/min; UV detection: 220 nm.

LC-MS (method 1): $R_t = 1.07$ min; MS (ESIpos): $m/z = 564$ $[\text{M}+\text{H}]^+$

$^1\text{H-NMR}$ (500 MHz, CDCl_3): δ [ppm] = 9.80 (s, 1H), 7.84-7.75 (m, 2H), 7.74-7.65 (m, 2H), 7.36-7.31 (m, 2H), 7.23-7.17 (m, 2H), 6.56 (s, 1H), 5.93 (dd, 1H), 6.20-5.57 (m, 2H), 4.09-3.94 (m, 1H),
15 3.60-3.50 (m, 1H), 3.45-3.36 (m, 2H), 2.63-2.46 (m, 3H), 1.97-1.47 (m, 8H), 1.40 (d, 3H), 1.00 (d, 3H). Additional signals of minor rotamers were also detected.

Example 27

4-{[(2*S*)-2-(*cis*-6-Chloro-3-oxo-3,9,9a,10,11,11a-hexahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-*c*]pyridin-2-yl)butanoyl]amino}-2-fluorobenzamide (mixture of two diastereomers)



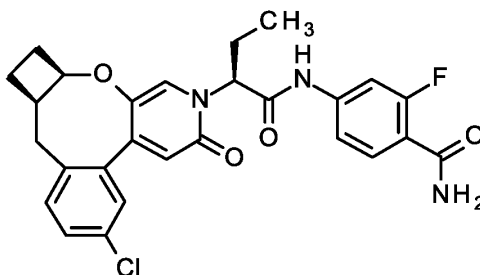
20

1,1,3,3-Tetramethylguanidine (46 μl , 0.37 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of *cis*-6-chloro-9a,10,11,11a-tetrahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-*c*]pyridin-3(9*H*)-one (racemate) (35 mg, 0.12 mmol) in 2-propanol / acetone (4:1, 3.75 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-{[(2*R*)-2-bromobutanoyl]amino}-2-fluorobenzamide (single stereoisomer) (55 mg, 0.18 mmol, 1.5 eq.). The reaction mixture was stirred
25 at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 43 mg (69% of theory).

LC-MS (method 4): $R_t = 1.93$ min; MS (ESIpos): $m/z = 510$ $[M+H]^+$

Example 28

4-({(2*S*)-2-[(9*aR*,11*aR*)-6-Chloro-3-oxo-3,9,9*a*,10,11,11*a*-hexahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-*c*]pyridin-2-yl]butanoyl}amino)-2-fluorobenzamide (single stereoisomer)



5

Diastereomer and atropisomer separation of 32 mg of 4-[(2*S*)-2-(*cis*-6-chloro-3-oxo-3,9,9*a*,10,11,11*a*-hexahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-*c*]pyridin-2-yl)butanoyl]amino}-2-fluorobenzamide (mixture of two diastereomers), Example 27 gave

single stereoisomer 1 (the title compound Example 28), (chiral HPLC: $R_t = 2.81$ min, >99% de): 5
10 mg,

single stereoisomer 2 (chiral HPLC: $R_t = 3.37$ min): 4 mg,

single stereoisomer 3 (chiral HPLC: $R_t = 4.57$ min): 5 mg,

single stereoisomer 4 (chiral HPLC: $R_t = 5.35$ min): 3 mg.

Separation method: HPLC: column: Daicel Chiralpak ID 5 μ m, 250 mm x 20 mm; eluent: 50%
15 *n*-heptane / 50% ethanol; temperature: 30°C; flow rate: 20 ml/min; UV detection: 265 nm.

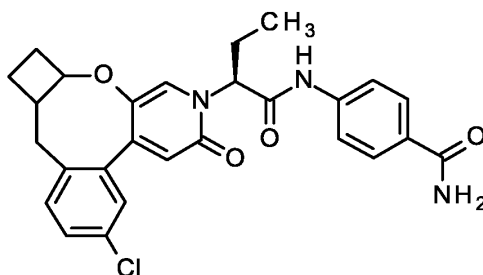
Analysis method: HPLC: column: Daicel Chiralpak ID 5 μ m, 250 mm x 4.6 mm; eluent: 50%
n-heptane / 50% ethanol; temperature: 50°C; flow rate: 1 ml/min; UV detection: 220 nm.

LC-MS (method 4): $R_t = 1.91$ min; MS (ESIpos): $m/z = 510$ $[M+H]^+$

1 H-NMR (500 MHz, DMSO- d_6): δ [ppm] = 10.93-10.74 (m, 1H), 7.70 (br t, 1H), 7.64 (br d, 1H),
20 7.53 (br d, 2H), 7.48-7.38 (m, 4H), 7.36 (br s, 1H), 6.39 (s, 1H), 5.66-5.53 (m, 1H), 4.65-4.56 (m,
1H), 2.78-2.65 (m, 2H), 2.65-2.54 (m, 2H), 2.21-1.99 (m, 3H), 1.82-1.69 (m, 1H), 1.40-1.20 (m, 1H),
0.92-0.83 (m, 3H).

Example 29

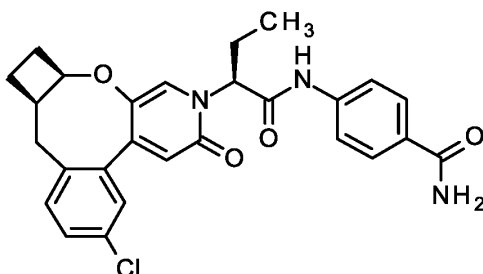
4-({(2*S*)-2-[*cis*-6-Chloro-3-oxo-3,9,9*a*,10,11,11*a*-hexahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-
25 *c*]pyridin-2-yl]butanoyl}amino)-benzamide (mixture of two diastereomers)



- 1,1,3,3-Tetramethylguanidine (66 μ l, 0.53 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of *cis*-6-chloro-9a,10,11,11a-tetrahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-c]pyridin-3(9*H*)-one (racemate) (51 mg, 0.18 mmol) in 2-propanol / acetone (4:1, 5.5 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-{(2*R*)-2-bromobutanoyl}amino}benzamide (single stereoisomer) (76 mg, 0.27 mmol, 1.5 eq.). The reaction mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 39 mg (43% of theory).
- 10 LC-MS (method 4): R_t = 1.81 min; MS (ESIpos): m/z = 492 $[M+H]^+$

Example 30

4-({(2*S*)-2-[(9*aR*,11*aR*)-6-Chloro-3-oxo-3,9,9a,10,11,11a-hexahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-c]pyridin-2-yl]butanoyl}amino)benzamide (single stereoisomer)



- 15 Diastereomer and atropisomer separation of 35 mg of 4-({(2*S*)-2-[(*cis*-6-chloro-3-oxo-3,9,9a,10,11,11a-hexahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-c]pyridin-2-yl]butanoyl}amino)benzamide (mixture of two diastereomers), Example 29 gave
- single stereoisomer 1 (the title compound Example 30) (chiral HPLC: R_t = 7.09 min, >99% de): 5 mg,
- 20 single stereoisomer 4 (chiral HPLC: R_t = 8.30 min): 3 mg,
- single stereoisomer 3 (chiral HPLC: R_t = 10.81 min): 1 mg,
- single stereoisomer 2 (chiral HPLC: R_t = 12.50 min): 9 mg.

Separation method: HPLC: column: Daicel Chiralpak IE 5 μm , 250 mm x 20 mm; eluent: 50% *n*-heptane / 50% ethanol; temperature: 60°C; flow rate: 15 ml/min; UV detection: 220 nm.

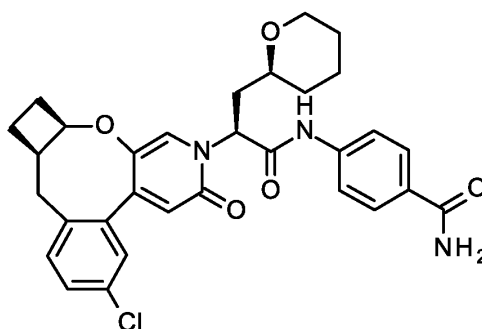
Analysis method: HPLC: column: Daicel Chiralpak IE 5 μm , 250 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% ethanol; temperature: 50°C; flow rate: 1 ml/min; UV detection: 220 nm.

- 5 LC-MS (method 4): R_t = 1.83 min; MS (ESIpos): m/z = 492 $[\text{M}+\text{H}]^+$

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.72-10.63 (m, 1H), 7.94-7.81 (m, 3H), 7.67 (d, 2H), 7.49-7.33 (m, 4H), 7.26 (br s, 1H), 6.38 (s, 1H), 5.70-5.58 (m, 1H), 4.64-4.57 (m, 1H), 2.79-2.66 (m, 2H), 2.63-2.56 (m, 2H), 2.21-2.01 (m, 3H), 1.81-1.65 (m, 1H), 1.37-1.21 (m, 1H), 0.89 (t, 3H).

Example 31

- 10 4-({(2*S*)-2-[(9*aR*,11*aR*)-6-Chloro-3-oxo-3,9,9*a*,10,11,11*a*-hexahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-*c*]pyridin-2-yl]-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)benzamide (single stereoisomer)



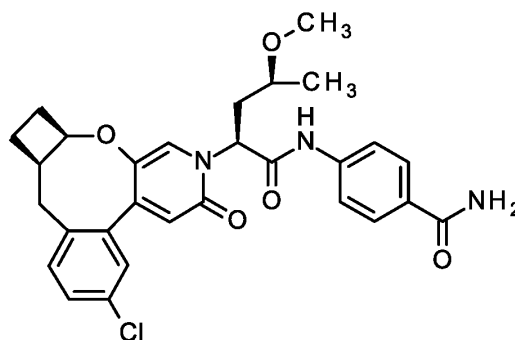
- 15 to a solution of (9*aR*,11*aR*)-6-chloro-9*a*,10,11,11*a*-tetrahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-*c*]pyridin-3(9*H*)-one (single stereoisomer) (25 mg, 0.09 mmol) in 2-propanol / acetone (4:1, 2.7 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-({(2*R*)-2-bromo-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)benzamide (single stereoisomer) (46 mg, 0.13 mmol, 1.5 eq.). The reaction mixture was stirred at RT overnight, at 40°C
- 20 for further 22 h and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 30 mg (61% of theory).

LC-MS (method 4): R_t = 1.99 min; MS (ESIpos): m/z = 562 $[\text{M}+\text{H}]^+$

- $^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.75-10.57 (m, 1H), 7.92-7.78 (m, 3H), 7.70 (d, 2H), 7.54-7.30 (m, 4H), 7.26 (br s, 1H), 6.37 (s, 1H), 5.81 (br t, 1H), 4.60 (q, 1H), 3.85 (br d, 1H), 3.3-3.16 (m, 2H, partially concealed), 2.82-2.63 (m, 2H), 2.63-2.5 (m, 2H, partially concealed), 2.30-2.01 (m, 3H), 1.94-1.57 (m, 3H), 1.48-1.20 (m, 5H). Additional signals of minor rotamers were also detected.
- 25

Example 32

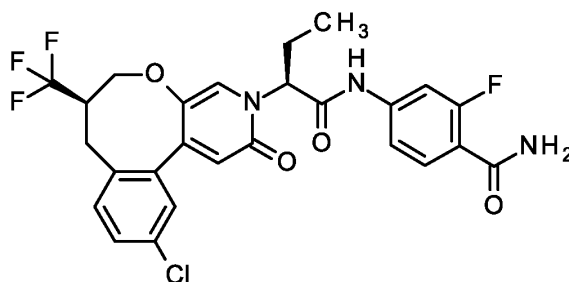
4-({(2*S*,4*S*)-2-[(9*aR*,11*aR*)-6-Chloro-3-oxo-3,9,9*a*,10,11,11*a*-hexahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-*c*]pyridin-2-yl]-4-methoxypentanoyl}amino)benzamide (single stereoisomer)



- 5 1,1,3,3-Tetramethylguanidine (21 μ l, 0.17 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (9*aR*,11*aR*)-6-chloro-9*a*,10,11,11*a*-tetrahydro-2*H*-cyclobuta[4,5][3]benzoxocino[2,1-*c*]pyridin-3(9*H*)-one (single stereoisomer) (16 mg, 0.06 mmol) in 2-propanol / acetone (4:1, 0.6 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-[(2*R*,4*S*)-2-bromo-4-methoxypentanoyl]amino}benzamide (single stereoisomer) (18 mg, 0.06
- 10 mmol, 1.0 eq.) and 2-propanol / acetone (4:1, 0.6 ml). The reaction mixture was stirred at RT for 3 days, followed by the addition of 1,1,3,3-tetramethylguanidine (7 μ l, 0.06 mmol, 1.0 eq.), stirred at RT for 1 additional day and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 19 mg (61% of theory).
- 15 LC-MS (method 4): R_t = 1.86 min; MS (ESIpos): m/z = 536 $[M+H]^+$
- $^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.74-10.58 (m, 1H), 7.88-7.80 (m, 3H), 7.77-7.66 (m, 2H), 7.56-7.31 (m, 3H), 7.23 (br s, 1H), 6.40-6.35 (m, 1H), 5.84 (br t, 1H), 4.60 (q, 1H), 3.3-3.20 (m, 2H, partially concealed), 3.17 / 3.15 (2s, 3H), 2.79-2.66 (m, 2H), 2.64-2.56 (m, 2H), 2.32-2.04 (m, 3H), 1.82-1.66 (m, 1H), 1.40-1.22 (m, 1H), 1.19-1.10 (m, 3H). Additional signals of minor rotamers
- 20 were also detected.

Example 33

4-({(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoyl}amino)-2-fluorobenzamide (single stereoisomer)



- 1,1,3,3-Tetramethylguanidine (75 μ l, 0.60 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (69 mg, 0.20 mmol) in 2-propanol / acetone (4:1, 1.05 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-{{(2*R*)-2-bromobutanoyl}amino}-2-fluorobenzamide (single stereoisomer) (79 mg, 0.26 mmol, 1.3 eq.) and of further 2-propanol / acetone (4:1, 1.05 ml). The reaction mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was suspended in a mixture of *N,N*-dimethylformamide / acetonitrile / water. Material not dissolved was filtered and dried *in vacuo*. Yield: 52 mg (47% of theory).
- The filtrate was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 40 mg (36% of theory).

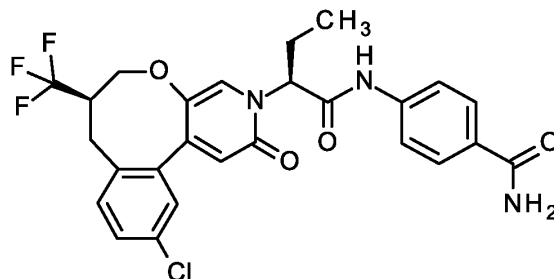
52 mg-batch: LC-MS (method 4): R_t = 1.93 min; MS (ESIpos): m/z = 552 $[M+H]^+$

40 mg-batch: LC-MS (method 1): R_t = 1.04 min; MS (ESIpos): m/z = 552 $[M+H]^+$

- 40 mg-batch: $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.93-10.77 (m, 1H), 8.00-7.90 (m, 1H), 7.69 (t, 1H), 7.64 (dd, 1H), 7.59-7.47 (m, 3H), 7.47-7.32 (m, 3H), 6.47-6.35 (m, 1H), 5.56 (dd, 1H), 4.80-4.64 (m, 1H), 4.12-3.99 / 3.85-3.72 (2m, 1H), 3.27-3.19 / 3.15-2.99 (2m, 2H), 2.85-2.75 / 2.61-2.5 (2m, 1H, partially concealed), 2.25-2.08 (m, 2H), 0.99-0.84 (m, 3H). Additional signals of minor rotamers were also detected.

Example 34

- 4-({(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoyl}amino)benzamide (single stereoisomer)



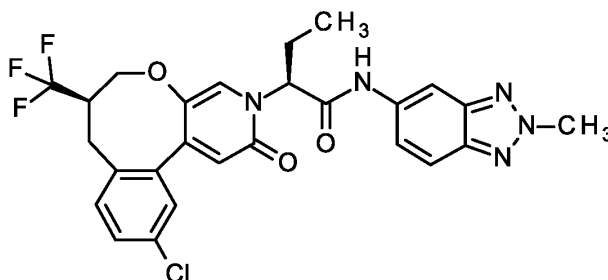
1,1,3,3-Tetramethylguanidine (38 μ l, 0.30 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (34 mg, 0.10 mmol) in 2-propanol / acetone (3:1, 0.8 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-{[(2*R*)-2-bromobutanoyl]amino}benzamide (single stereoisomer) (31 mg, 0.11 mmol, 1.1 eq.) and of further 2-propanol / acetone (3:1, 0.8 ml). The reaction mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 41 mg (76% of theory).

LC-MS (method 4): R_t = 1.85 min; MS (ESIpos): m/z = 534 [M+H]⁺

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 10.74-10.62 (m, 1H), 8.00-7.92 (m, 1H), 7.91-7.81 (m, 3H), 7.68 (d, 2H), 7.56-7.32 (m, 3H), 7.30-7.19 (m, 1H), 6.47-6.34 (m, 1H), 5.60 (dd, 1H), 4.82-4.65 (m, 1H), 4.12-4.00 / 3.92-3.72 (2m, 1H), 3.3-3.19 / 3.16-2.96 (2m, 2H), 2.85-2.75 / 2.62-2.5 (2m, 1H, partially concealed), 2.25-2.08 (m, 2H), 0.99-0.83 (m, 3H). Additional signals of minor rotamers were also detected.

Example 35

(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-*N*-(2-methyl-2*H*-benzotriazol-5-yl)butanamide (single stereoisomer)



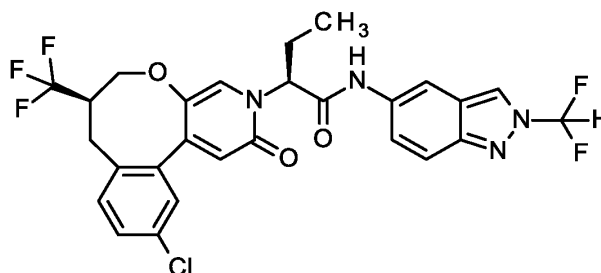
1,1,3,3-Tetramethylguanidine (38 μ l, 0.30 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (34 mg, 0.10 mmol) in 2-propanol / acetone (3:1, 0.8 ml). The mixture was stirred at RT for 15 min, followed by addition of (2*R*)-2-bromo-*N*-(2-methyl-2*H*-benzotriazol-5-yl)butanamide (single stereoisomer) (34 mg, 0.11 mmol, 1.1 eq.) and of further 2-propanol / acetone (3:1, 0.8 ml). The reaction mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 33 mg (60% of theory).

LC-MS (method 4): R_t = 2.06 min; MS (ESIpos): m/z = 546 [M+H]⁺

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 10.77-10.66 (m, 1H), 8.37-8.31 (m, 1H), 8.05-7.96 (m, 1H), 7.89 (d, 1H), 7.57-7.32 (m, 4H), 6.48-6.35 (m, 1H), 5.63 (dd, 1H), 4.81-4.66 (m, 1H), 4.45 (s, 3H), 4.10-4.02 / 3.85-3.76 (2m, 1H), 3.14-2.96 (m, 2H), 2.64-2.52 (m, 1H, partially concealed), 2.26-2.08 (m, 2H), 0.99-0.84 (m, 3H). Additional signals of minor rotamers were also detected.

5 **Example 36**

(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-*N*-[2-(difluoromethyl)-2*H*-indazol-5-yl]butanamide (single stereoisomer)



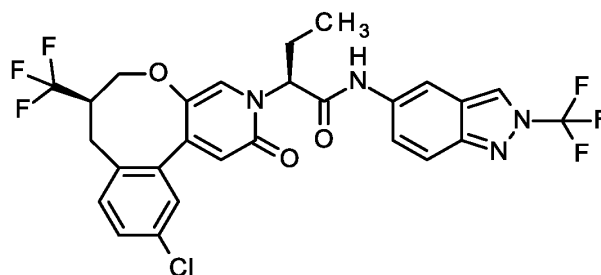
General Method 7 was carried out with (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (33.9 mg, 103 μmol, 1.0 eq.), (2*R*)-2-bromo-*N*-[2-(difluoromethyl)-2*H*-indazol-5-yl]butanamide (single stereoisomer) (57.0 mg, 90% purity, 154 μmol, 1.5 eq.) and 1,1,3,3-tetramethylguanidine (37 μl, 290 μmol, 2.84 eq.) in a mixture of 2-propanol / acetone (4:1, 1.25 ml) including the following variations of the procedure: After stirring of the reaction mixture at RT overnight, further amounts of 1,1,3,3-tetramethylguanidine (19 μl, 150 μmol, 1.5 eq.) were added and the mixture was stirred again overnight. The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 1:95). Yield: 23.0 mg (38% of theory).

LC-MS (method 3): *R*_t = 3.80 min; MS (ESIpos): *m/z* = 581 [M+H]⁺

¹H-NMR (500 MHz, DMSO-*d*₆): δ [ppm] = 10.61 / 10.57 (2br s, 1H), 8.80 (s, 1H), 8.33-8.23 (m, 1H), 8.22 / 8.10 (2s, 1H), 8.04-7.94 (m, 1H), 7.72 (d, 1H), 7.57-7.47 (m, 1H), 7.49-7.35 (m, 3H), 6.44 / 6.39 (2s, 1H), 5.72-5.52 (m, 1H), 4.85-4.64 (m, 1H), 3.88 / 3.79 (2t, 1H), 3.27-2.93 (m, 2H), 2.63-2.53 (m, 1H), 2.24-2.15 (m, 1H), 2.15-2.03 (m, 1H), 0.94 / 0.91 (2t, 3H). Additional signals of minor rotamers were also detected.

Example 37

(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-*N*-[2-(trifluoromethyl)-2*H*-indazol-5-yl]butanamide (single stereoisomer)



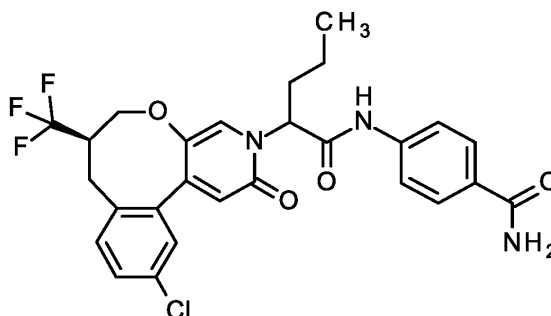
General Method 7 was carried out with (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (71.7 mg, 217 μ mol, 1.0 eq.), (2*R*)-2-bromo-*N*-[2-(trifluoromethyl)-2*H*-indazol-5-yl]butanamide (single stereoisomer) (177 mg, 86% purity, 435 μ mol, 2.0 eq.) and 1,1,3,3-tetramethylguanidine (77 μ l, 620 μ mol, 2.83 eq.) in a mixture of 2-propanol / acetone (4:1, 3.8 ml) including the following variations of the procedure: After stirring of the reaction mixture at RT overnight, further amounts of 1,1,3,3-tetramethylguanidine (41 μ l, 330 μ mol, 1.5 eq.) were added and the mixture was stirred again overnight. The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 1:95). Yield: 86.0 mg (66% of theory).

LC-MS (method 3): R_t = 4.13 min; MS (ESIpos): m/z = 599 $[M+H]^+$

1H -NMR (500 MHz, DMSO- d_6): δ [ppm] = 10.67 / 10.63 (2s, 1H), 9.07 / 9.06 (2s, 1H), 8.30 / 8.27 (2s, 1H), 7.99 / 7.96 (2s, 1H), 7.75 (d, 1H), 7.57-7.30 (m, 4H), 6.44 / 6.38 (2s, 1H), 5.67-5.57 (m, 1H), 4.81-4.64 (m, 1H), 3.79 (t, 1H), 3.17-2.92 (m, 2H), 2.60-2.52 (m, 1H), 2.26-2.14 (m, 1H), 2.14-2.03 (m, 1H), 0.94 / 0.91 (2t, 3H). Additional signals of minor rotamers were also detected.

Example 38

4-({2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]pentanoyl}amino)benzamide (mixture of two diastereomers)



1,1,3,3-Tetramethylguanidine (35 μ l, 0.28 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (31 mg, 0.09 mmol) in 2-propanol / acetone (3:1, 0.8 ml). The

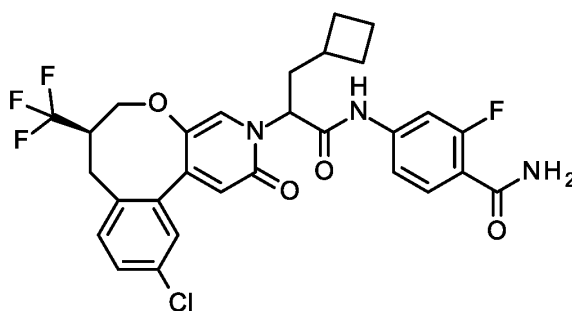
mixture was stirred at RT for 15 min, followed by addition of 4-[(2-bromopentanoyl)amino]benzamide (racemate) (33 mg, 92% purity, 0.10 mmol, 1.1 eq.) and of further 2-propanol / acetone (3:1, 0.8 ml). The reaction mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 37 mg (73% of theory).

LC-MS (method 4): $R_t = 1.92$ min; MS (ESIpos): $m/z = 548$ $[M+H]^+$

1H -NMR (400 MHz, DMSO- d_6): δ [ppm] = 10.76-10.65 (m, 1H), 7.99 (d, 1H), 7.90-7.80 (m, 3H), 7.68 (d, 2H), 7.57-7.32 (m, 3H), 7.30-7.20 (m, 1H), 6.46-6.35 (m, 1H), 5.75-5.63 (m, 1H), 4.81-4.66 (m, 1H), 4.10-3.73 (m, 1H), 3.28-2.98 (m, 2H), 2.62-2.5 (m, 1H, partially concealed), 2.21-2.02 (m, 2H), 1.43-1.19 (m, 2H), 0.94 (t, 3H). Additional signals of minor rotamers were also detected.

Example 39

4-{2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-cyclobutylpropanamido}-2-fluorobenzamide (mixture of two diastereomers)

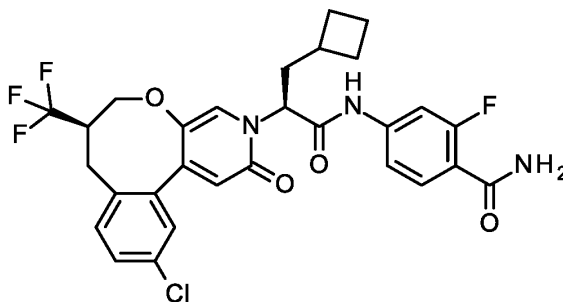


General Method 7 was carried out with (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benz-oxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (29.0 mg, 78% purity, 68.5 μ mol, 1.0 eq.), 4-(2-bromo-3-cyclobutylpropanamido)-2-fluorobenzamide (racemate) (31.0 mg, 91% purity, 82.2 μ mol, 1.2 eq.), and 1,1,3,3-tetramethylguanidine (26 μ l, 210 μ mol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 1.25 ml) including the following variations of the procedure: The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 20.0 mg (49% of theory).

LC-MS (method 3): $R_t = 3.89 / 3.94$ min; MS (ESIpos): $m/z = 592$ $[M+H]^+$

Example 40

4-({(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-cyclobutylpropanoyl}amino)-2-fluorobenzamide (single stereoisomer)



Diastereomer separation of 15 mg of 4-{2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-cyclobutylpropanamido}-2-fluorobenzamide (mixture of two diastereomers), Example 39 gave

- 5 single stereoisomer 1 (the title compound 40) (chiral HPLC: R_t = 4.66 min, 99% de): 6.5mg (14% of theory),

single stereoisomer 2 (chiral HPLC: R_t = 7.07 min): 8.8 mg.

Separation method: HPLC: column: Daicel Chiralpak ID 5 μ m, 250 mm x 20 mm; eluent: 55% *n*-heptane / 45% 2-propanol; temperature: 40°C; flow rate: 20 ml/min; UV detection: 220 nm.

- 10 Analysis method: HPLC: column: Daicel Chiralpak ID 5 μ m, 250 mm x 4.6 mm; eluent: 55% *iso*-hexane / 45% 2-propanol; flow rate: 1.0 ml/min; UV detection: 220 nm.

LC-MS (method 5): R_t = 1.45 min; MS (ESI^{neg}): m/z = 590 [M-H]⁻

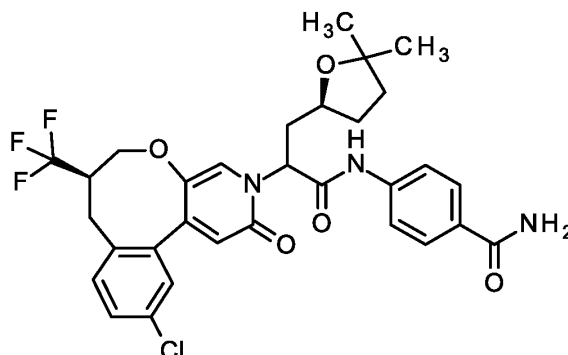
¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 10.87 / 10.80 (2s, 1H), 7.96 (s, 1H), 7.72-7.67 (m, 1H), 7.67-7.62 (m, 1H), 7.57-7.35 (m, 6H), 6.41 / 6.37 (2s, 1H), 5.66-5.54 (m, 1H), 4.81-4.62 (m, 1H),

- 15 3.78 (t, 1H), 3.07 (br d, 2H), 2.60-2.55 (m, 1H), 2.27-2.15 (m, 3H), 2.02-1.88 (m, 2H), 1.84-1.73 (m, 3H), 1.67-1.58 (m, 1H). Additional signals of minor rotamers were also detected.

Example 41

4-{2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*S*)-5,5-dimethyltetrahydrofuran-2-yl]propanamido}benzamide (mixture of two

- 20 diastereomers)



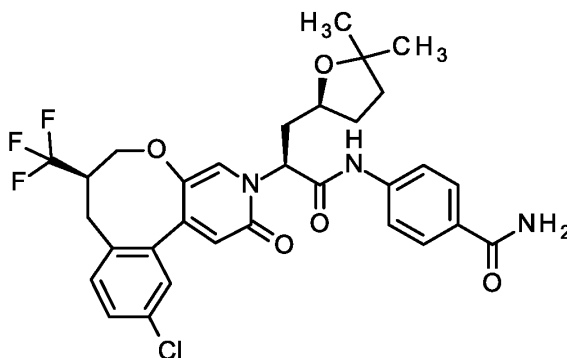
2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*S*)-5,5-dimethyloxolan-2-yl]propanoic acid (mixture of two diastereomers) (98 mg, 87% purity, 0.17 mmol), pyridine (15 μ l, 0.19 mmol, 1.1 eq.) and T3P (152 μ l, 50% solution in ethyl acetate, 0.26 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of 4-aminobenzamide (26 mg, 0.19 mmol, 1.1 eq.) in tetrahydrofuran (5 ml). The reaction mixture was stirred at RT for 1.5 h and put into iced water. After phase separation, the organic phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 67 mg (64% of theory).

LC-MS (method 1): $R_t = 1.08$ min; MS (ESIpos): $m/z = 618$ $[M+H]^+$

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.72-10.52 (m, 1H), 8.02-7.95 (m, 1H), 7.87 (br s, 1H), 7.84 (d, 2H), 7.69 (d, 2H), 7.56-7.31 (m, 3H), 7.25 (br s, 1H), 6.44-6.32 (m, 1H), 5.85-5.60 (m, 1H), 4.80-4.64 (m, 1H), 4.09-3.70 (m, 2H), 3.14-2.99 (m, 2H), 2.79-2.70 / 2.60-2.5 (2m, 1H, partially concealed), 2.42-2.19 (m, 2H), 2.04-1.94 (m, 1H), 1.74-1.55 (m, 3H), 1.15 / 1.09 (2s, 6H). Additional signals of minor rotamers were also detected.

Example 42

4-({(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*S*)-5,5-dimethyloxolan-2-yl]propanoyl}amino)benzamide (single stereoisomer)



Diastereomer separation of 64 mg of 4-{2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*S*)-5,5-dimethyltetrahydrofuran-2-yl]propanamido}-benzamide (mixture of two diastereomers), Example 41 gave

- 5 single stereoisomer 1 (the title compound Example 42) (chiral HPLC: $R_t = 2.50$ min, >99% de): 47 mg,

single stereoisomer 2 (chiral HPLC: $R_t = 3.90$ min, >99% de): 10 mg.

Separation method: HPLC: column: Daicel Chiralpak OZ-H 5 μm , 250 mm x 20 mm; eluent: 70% *n*-heptane / 30% ethanol; temperature: 40°C; flow rate: 25 ml/min; UV detection: 220 nm.

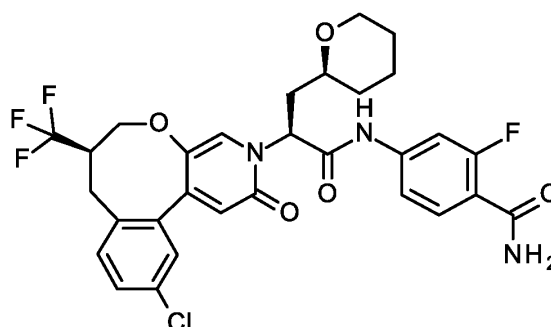
- 10 Analysis method: HPLC: column: Daicel Chiralpak OZ-3 3 μm , 50 mm x 4.6 mm; eluent: 80% *n*-hexane / 20% ethanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.

- ¹H-NMR (500 MHz, DMSO-*d*₆): δ [ppm] = 10.72-10.50 (m, 1H), 7.97 (s, 1H), 7.91-7.80 (m, 3H), 7.68 (d, 2H), 7.57-7.32 (m, 3H), 7.24 (br s, 1H), 6.45-6.32 (m, 1H), 5.78-5.60 (m, 1H), 4.81-4.64 (m, 1H), 4.09-3.71 (m, 2H), 3.14-2.99 (m, 2H), 2.81-2.69 / 2.60-2.5 (2m, 1H, partially concealed), 2.42-2.18 (m, 2H), 2.04-1.93 (m, 1H), 1.75-1.55 (m, 3H), 1.15 / 1.09 (2s, 6H). Additional signals of minor rotamers were also detected.
- 15

Example 43

4-({(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)-2-fluorobenzamide (single

- 20 stereoisomer)



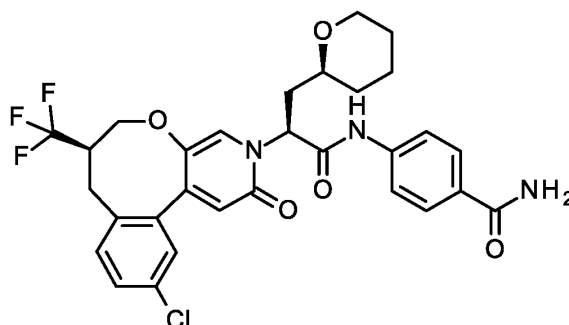
1,1,3,3-Tetramethylguanidine (45 μ l, 0.36 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (40 mg, 0.12 mmol) in 2-propanol / acetone (3:1, 0.8 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-({(2*R*)-2-bromo-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)-2-fluorobenzamide (single stereoisomer) (49 mg, 0.13 mmol, 1.1 eq.) and of further 2-propanol / acetone (3:1, 0.8 ml). The reaction mixture was stirred at RT overnight. Further 1,1,3,3-Tetramethylguanidine (15 μ l, 0.12 mmol, 1.0 eq.) was added. The reaction mixture was stirred for 4 h and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 41 mg (55% of theory).

LC-MS (method 4): R_t = 2.08 min; MS (ESIpos): m/z = 622 $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.89-10.62 (m, 1H), 8.03-7.87 (m, 1H), 7.72-7.60 (m, 2H), 7.59-7.32 (m, 6H), 6.44-6.32 (m, 1H), 5.82-5.61 (m, 1H), 4.80-4.64 (m, 1H), 4.13-4.00 / 3.91-3.72 (2m, 2H), 3.3-3.18 (m, 2H, partially concealed), 3.18-2.97 (m, 2H), 2.62-2.5 (m, 1H, partially concealed), 2.31-2.08 (m, 2H), 1.83-1.70 (m, 1H), 1.67-1.56 (m, 1H), 1.49-1.19 (m, 4H). Additional signals of minor rotamers were also detected.

Example 44

4-({(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl}amino)benzamide (single stereoisomer)



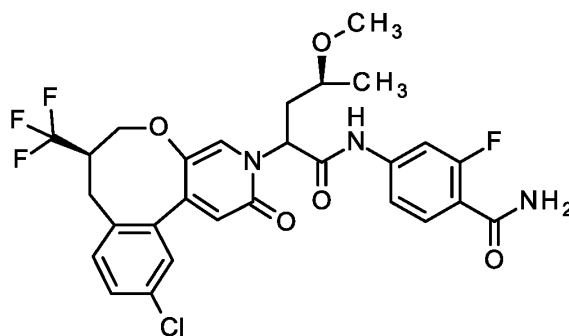
1,1,3,3-Tetramethylguanidine (75 μ l, 0.60 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (69 mg, 0.20 mmol) in 2-propanol / acetone (4:1, 2.5 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-((2*R*)-2-bromo-3-[(2*S*)-tetrahydro-2*H*-pyran-2-yl]propanoyl)amino)benzamide (single stereoisomer) (78 mg, 0.22 mmol, 1.1 eq.) and of further 2-propanol / acetone (4:1, 2.5 ml). The reaction mixture was stirred at RT for 4 days and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 77 mg (64% of theory).

LC-MS (method 4): R_t = 1.97 min; MS (ESIpos): m/z = 604 $[M+H]^+$

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.72-10.52 (m, 1H), 8.05-7.80 (m, 4H), 7.73-7.66 (m, 2H), 7.56-7.32 (m, 3H), 7.31-7.22 (m, 1H), 6.45-6.32 (m, 1H), 5.85-5.66 (m, 1H), 4.79-4.66 (m, 1H), 4.10-4.01 / 3.90-3.73 (2m, 2H), 3.3-3.20 (m, 2H), 3.17-2.98 (m, 2H), 2.62-2.5 (m, 1H, partially concealed), 2.32-2.10 (m, 2H), 1.81-1.71 (m, 1H), 1.67-1.57 (m, 1H), 1.48-1.20 (m, 4H). Additional signals of minor rotamers were also detected.

Example 45

4-((4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl)amino)-2-fluorobenzamide (mixture of two diastereomers)



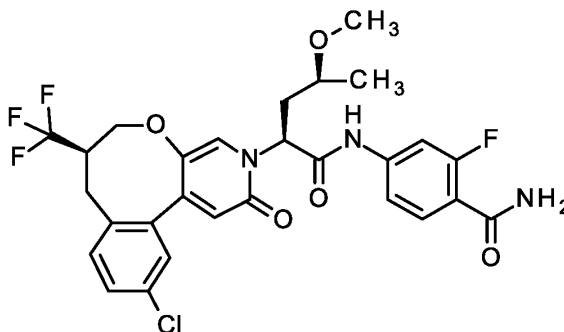
4-Amino-2-fluorobenzamide (38 mg, 0.25 mmol, 1.1 eq.), *N,N*-diisopropylethylamine (97 μ l, 0.56 mmol, 2.5 eq.) and a solution of HATU (110 mg, 0.29 mmol, 1.3 eq.) in *N,N*-dimethylformamide (2 ml) were added under argon atmosphere at RT to a solution of (2*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonic acid (mixture of two diastereomers) (128 mg, 80% assumed purity of crude product, 0.22 mmol) in *N,N*-dimethylformamide (4 ml). The reaction mixture was stirred at RT for 5.5 h and concentrated under reduced pressure. The residue was crystallized with water, filtered, washed with water and dried *in vacuo*. This residue was dissolved in dichloromethane and purified by column chromatography (silica gel, eluent: dichloromethane / methanol gradient). Yield: 52 mg (39% of theory).

LC-MS (method 4): R_t = 1.95 min; MS (ESIpos): m/z = 596 $[M+H]^+$

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.92-10.73 (m, 1H), 8.06-7.97 (m, 1H), 7.72-7.61 (m, 2H), 7.59-7.33 (m, 6H), 6.46-6.34 (m, 1H), 5.84-5.71 (m, 1H), 4.79-4.66 (m, 1H), 4.08-3.95 / 3.92-3.74 (2m, 1H), 3.3-3.00 (m, 6H, partially concealed), 2.83-2.74 / 2.62-2.5 (2m, 1H, partially concealed), 2.40-2.16 (m, 2H), 1.19-1.08 (m, 3H). Additional signals of minor rotamers were also detected.

Example 46

4-({(2*S*,4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)-2-fluorobenzamide (single stereoisomer)



Diastereomer separation of 50 mg of 4-({(4*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)-2-fluorobenzamide (mixture of two diastereomers), Example 45 gave

single stereoisomer 1 (the title compound Example 46) (chiral SFC: R_t = 0.61 min, >99% de): 17 mg,

single stereoisomer 2 (chiral SFC: R_t = 0.86 min, >99% de): 21 mg.

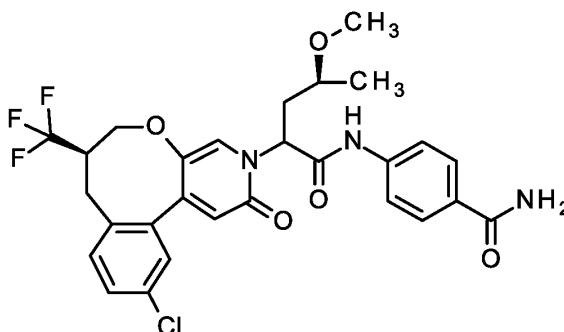
Separation method: SFC: column: Daicel Chiralpak IG 5 μm , 250 mm x 20 mm; eluent: 70% carbon dioxide / 30% methanol; temperature: 40°C; flow rate: 80 ml/min; UV detection: 210 nm.

Analysis method: SFC: column: Daicel Chiralpak IG 3 μm , 50 mm x 4.6 mm; eluent: 70% carbon dioxide / 30% 2-propanol; temperature: 40°C; flow rate: 3 ml/min; UV detection: 220 nm.

- 5 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.92-10.71 (m, 1H), 8.05-7.96 (m, 1H), 7.73-7.60 (m, 2H), 7.58-7.32 (m, 6H), 6.46-6.33 (m, 1H), 5.84-5.68 (m, 1H), 4.80-4.64 (m, 1H), 4.10-3.97 / 3.84-3.72 (2m, 1H), 3.3-2.98 (m, 6H, partially concealed), 2.84-2.73 / 2.63-2.5 (2m, 1H, partially concealed), 2.31-2.16 (m, 2H), 1.15 (d, 3H). Additional signals of minor rotamers were also detected.

Example 47

- 10 4-({(4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (mixture of two diastereomers)

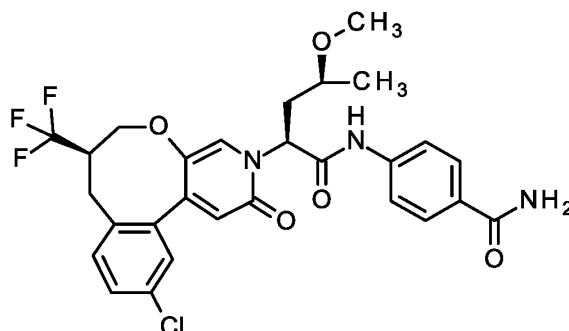


- 4-Aminobenzamide (33 mg, 0.25 mmol, 1.1 eq.), *N,N*-diisopropylethylamine (97 μl , 0.56 mmol, 2.5 eq.) and a solution of HATU (110 mg, 0.29 mmol, 1.3 eq.) in *N,N*-dimethylformamide (2 ml) were added under argon atmosphere at RT to a solution of (2*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonic acid (mixture of two diastereomers) (128 mg, 80% assumed purity of crude product, 0.22 mmol) in *N,N*-dimethylformamide (4 ml). The reaction mixture was stirred at RT for 2 h and concentrated under reduced pressure. The residue was crystallized with water, filtered, washed with water and dried *in vacuo*. This residue was purified by column chromatography (silica gel, eluent: cyclohexane / ethyl acetate gradient). Yield: two batches isolated, 67 mg and 16 mg (64% of theory for both batches together).

67 mg-batch: LC-MS (method 4): R_t = 1.88 min; MS (ESIpos): m/z = 578 $[\text{M}+\text{H}]^+$

Example 48

- 25 4-({(2*S*,4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (single stereoisomer)



Diastereomer separation of 82 mg of 4-({(4*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (mixture of two diastereomers), Example 47 gave

- 5 single stereoisomer 1 (the title compound Example 48) (chiral SFC: $R_t = 4.44$ min, >99% de): 19 mg,

single stereoisomer 2 (chiral SFC: $R_t = 6.31$ min, >99% de): 22 mg.

Separation method: SFC: column: Daicel Chiralpak IE 5 μm , 250 mm x 20 mm; eluent: 65% carbon dioxide / 35% methanol; temperature: 40°C; flow rate: 80 ml/min; UV detection: 210 nm.

- 10 Analysis method: SFC: column: Daicel Chiralpak IE, 50 mm x 4.6 mm; eluent: 70% carbon dioxide / 30% methanol; temperature: 40°C; flow rate: 3 ml/min; UV detection: 210 nm.

- $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.75-10.58 (m, 1H), 8.05-7.97 (m, 1H), 7.91-7.79 (m, 3H), 7.70 (d, 2H), 7.57-7.32 (m, 3H), 7.25 (br s, 1H), 6.46-6.33 (m, 1H), 5.86-5.73 (m, 1H), 4.80-4.64 (m, 1H), 4.10-3.95 / 3.84-3.71 (2m, 1H), 3.3-2.97 (m, 6H, partially concealed), 2.85-2.73 / 2.63-2.5 (2m, 1H, partially concealed), 2.30-2.15 (m, 2H), 1.16 (d, 3H). Additional signals of minor rotamers were also detected.

Alternative synthetic route:

- 1,1,3,3-Tetramethylguanidine (93 μl , 0.74 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (82 mg, 0.25 mmol) in 2-propanol / acetone (4:1, 2 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-{{(2*R*,4*S*)-2-bromo-4-methoxypentanoyl}amino}benzamide (single stereoisomer) (90 mg, 0.27 mmol, 1.1 eq.) and of further 2-propanol / acetone (4:1, 2 ml). The reaction mixture was stirred at RT for 5 days and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, 20 eluent: acetonitrile / water gradient). Yield: 106 mg (74% of theory).

LC-MS (method 1): $R_t = 1.00$ min; MS (ESIpos): $m/z = 578$ $[\text{M}+\text{H}]^+$

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 10.75-10.56 (m, 1H), 8.07-7.97 (m, 1H), 7.92-7.80 (m, 3H), 7.70 (d, 2H), 7.57-7.32 (m, 3H), 7.25 (br s, 1H), 6.46-6.33 (m, 1H), 5.88-5.73 (m, 1H), 4.81-4.64 (m, 1H), 4.10-3.97 / 3.92-3.72 (2m, 1H), 3.3-2.97 (m, 6H, partially concealed), 2.87-2.73 / 2.63-2.5 (2m, 1H, partially concealed), 2.30-2.15 (m, 2H), 1.16 (d, 3H). Additional signals of minor rotamers were also detected.

Further alternative synthetic route:

1,1,3,3-Tetramethylguanidine (2.19 ml, 17.5 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (2.00 g, 96% purity, 5.82 mmol) in 2-propanol / acetone (4:1, 136 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-{[(2*R*,4*S*)-2-bromo-4-methoxypentanoyl]amino}benzamide (single stereoisomer) (3.26 g, 9.90 mmol, 1.7 eq.). The reaction mixture was stirred at RT for 3 days and then poured into 0.05 N aqueous hydrogen chloride solution (700 ml). After extraction with ethyl acetate (2 x 100 ml), the combined organic phases were washed with saturated aqueous sodium chloride solution (100 ml), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (Biotage Isolera, 100 g SNAP-Ultra cartridge, eluent: dichloromethane (5 cv), dichloromethane / acetonitrile 75:25, 50:50, 25:75 (5 cv each), acetonitrile (20 cv) to yield two fractions. Yield: 2.00 g (59% of theory, >98% de), 1.00 g (29% of theory, >49% de).

Chiral SFC: *R*_t = 4.03 min, >98% de

Analysis method: SFC: column: Chiralcel AZ-3, 3 μm, 100 mm x 4.6 mm, eluent: isocratic 80% carbon dioxide / 20% isopropanol, 10 min, temperature: 40°C; flow rate: 3.0 ml/min; UV detection: 210 nm, backpressure: 130 bar.

Further alternative synthetic route:

1,1,3,3-Tetramethylguanidine (68.5 ml, 546 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (60.0 g, 182 mmol) in 2-propanol / acetone (4:1, 2.1 l). The mixture was stirred at RT for 15 min, followed by addition of 4-{[(2*R*,4*S*)-2-bromo-4-methoxypentanoyl]amino}benzamide (single stereoisomer) (89.9 g, 273 mmol, 1.5 eq.). The reaction mixture was stirred at RT for 3 days and then neutralized with acidic acid (31.3 ml, 546 mmol, 3.0 eq.). The reaction was concentrated to 1/4 of the original volume and then poured into 0.02 N aqueous hydrogen chloride solution (4.5 l). The precipitate was filtered off under reduced pressure, washed with water and dried under air atmosphere (yield: 119 g). The crude material was purified via SFC to obtain the product as single stereoisomer. Yield: 77.8 g (73% of theory, >99% de).

Separation method: SFC: column: Chiralpak AZ 20 μm, 350 mm x 50 mm, eluent: isocratic 70% carbon dioxide / 30% isopropanol, 4 min, temperature: 30°C; flow rate: 300 ml/min; UV detection:

210 nm; backpressure: 100 bar.

Chiral SFC: $R_t = 1.39$ min, >99% de

Analysis method: SFC: column: Chiralcel AZ-3, 3 μm , 100 mm x 4.6 mm, eluent: isocratic 70% carbon dioxide / 30% isopropanol, 10 min, temperature: 40°C; flow rate: 3.0 ml/min; UV detection:

5 210 nm, backpressure: 130 bar.

Chiral HPLC: $R_t = 3.15$ min, >99% de

Analysis method: HPLC: column: Chiralcel OZ-3, 3 μm , 50 mm x 4,6 mm, eluent: isocratic 80% heptane / 20% ethanol, 10 min, temperature: 50°C; flow rate: 1.0 ml/min; UV detection: 210 nm.

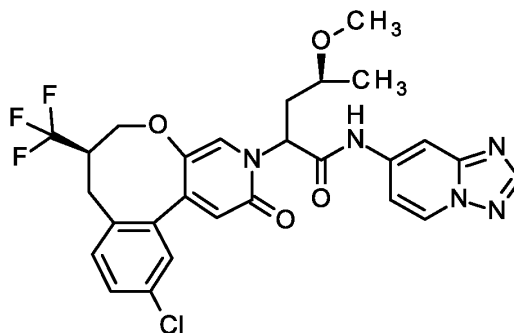
LC-MS (method 3): $R_t = 3.12$ min; MS (ESIpos): $m/z = 578$ $[\text{M}+\text{H}]^+$

10 ^1H -NMR (600 MHz, $\text{DMSO}-d_6$): δ [ppm] = 10.70-10.53 (m, 1H), 8.05-7.94 (m, 1H), 7.85 (br d, 3H), 7.70 (d, 2H), 7.58-7.32 (m, 3H), 7.21 (br s, 1H), 6.48-6.31 (m, 1H), 5.91-5.71 (m, 1H), 4.83-4.64 (m, 1H), 4.09-3.97 / 3.87-3.68 (2m, 1H), 3.39-2.99 (m, 6H, partially concealed), 2.85-2.74 / 2.65-2.50 (2m, 1H, partially concealed), 2.34-2.15 (m, 2H), 1.16 (d, 3H). Additional signals of minor rotamers were also detected.

15 ^{13}C -NMR (126 MHz, $\text{DMSO}-d_6$): δ [ppm] = 168.03 (s, 1C), 167.17 (s, 1C), 159.71 (s, 1C), 146.90 (s, 1C), 140.97 (2 overlapped s, 2C), 136.48 (s, 1C), 135.92 (s, 1C), 131.89 (s, 1C), 131.62 (d, 1CH), 129.74 (d, 1CH), 129.33 (overlapped d, 1CH), 129.33 (overlapped s, 1C), 128.27 (d, 2CH), 128.02 (d, 1CH), 126.24 [s, 1CF_3 ($J = 280.8$ Hz)], 118.78 (d, 2CH), 116.67 (d, 1CH), 75.08 (t, 1CH_2), 73.54 (d, 1CH), 55.45 (q, $1\text{CH}_3\text{O}$), 55.37 (d, 1CH), 44.23 (d, 1CH), 37.33 (t, 1CH_2), 29.72 (t, 1CH_2), 18.55 (q, 1CH_3).

Example 49

(4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-([1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pentanamide (mixture of two diastereomers)



[1,2,4]Triazolo[1,5-a]pyridin-7-amine hydrochloride (23 mg, 0.13 mmol, 1.1 eq.), pyridine (28 μ l, 0.35 mmol, 3.0 eq.) and T3P (102 μ l, 50% solution in ethyl acetate, 0.17 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of (2*ξ*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-

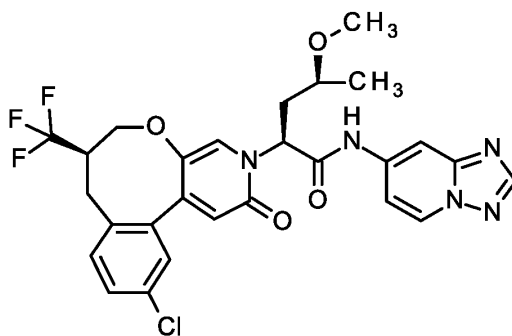
5 pentonic acid (mixture of two diastereomers) (57 mg, 93% purity, 0.12 mmol) in tetrahydrofuran (4 ml). The reaction mixture was stirred at RT overnight before all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 44 mg (66% of theory).

LC-MS (method 1): R_t = 0.99 min; MS (ESIpos): m/z = 576 $[M+H]^+$

10 1H -NMR (600 MHz, $DMSO-d_6$): δ [ppm] = 11.06-10.87 (m, 1H), 8.87 (d, 1H), 8.39 / 8.38 (2s, 1H), 8.22-8.16 (m, 1H), 8.09-7.91 (m, 1H), 7.56-7.29 (m, 4H), 6.46-6.36 (m, 1H), 5.87-5.74 (m, 1H), 4.80-4.69 (m, 1H), 4.11-3.75 (m, 1H), 3.3-2.98 (m, 3H, partially concealed), 3.19 / 3.12 (2s, 3H), 2.84-2.72 / 2.60-2.46 (2m, 1H, partially concealed), 2.43-2.20 (m, 2H), 1.20-1.11 (m, 3H). Additional signals of minor rotamers were also detected.

15 **Example 50**

(2*S*,4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-([1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pentanamide (single stereoisomer)



Diastereomer separation of 41 mg of (4*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-([1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pentanamide (mixture of two diastereomers), Example 49 gave

20 single stereoisomer 1 (the title compound Example 50) (chiral HPLC: R_t = 2.31 min, 99% de): 10 mg,

single stereoisomer 2 (chiral HPLC: R_t = 3.41 min, 99% de): 21 mg.

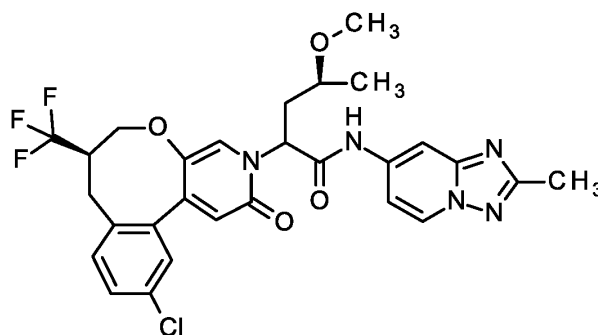
25 Separation method: HPLC: column: Daicel Chiralpak IC 5 μ m, 250 mm x 20 mm; eluent: 60% *n*-heptane / 40% 2-propanol; temperature: 40°C; flow rate: 20 ml/min; UV detection: 220 nm.

Analysis method: HPLC: column: Daicel Chiralpak IC 3 μ m, 50 mm x 4.6 mm; eluent: 60% *iso*-heptane / 40% ethanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 11.09-10.88 (m, 1H), 8.87 (d, 1H), 8.39 (s, 1H), 8.23-8.17 (m, 1H), 8.08-7.99 (m, 1H), 7.57-7.30 (m, 4H), 6.47-6.35 (m, 1H), 5.89-5.72 (m, 1H), 4.82-4.66 (m, 1H), 4.13-3.98 / 3.82-3.74 (2m, 1H), 3.3-2.97 (m, 3H, partially concealed), 3.19 (s, 3H), 2.85-2.73 / 2.63-2.5 (2m, 1H, partially concealed), 2.32-2.20 (m, 2H), 1.17 (d, 3H). Additional signals of minor rotamers were also detected.

Example 51

(4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-(2-methyl[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pentanamide (mixture of two diastereomers)



2-Methyl[1,2,4]triazolo[1,5-*a*]pyridin-7-amine hydrochloride (24 mg, 0.13 mmol, 1.1 eq.), pyridine (10 μ l, 0.13 mmol, 1.1 eq.) and T3P (102 μ l, 50% solution in ethyl acetate, 0.17 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of (2*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonic acid (mixture of two diastereomers) (57 mg, 93% purity, 0.12 mmol) in tetrahydrofuran (4 ml). The reaction mixture was stirred at RT for 1 h before all volatiles were removed under reduced pressure. The residue was dissolved in pyridine (1 ml). T3P (68 μ l, 50% solution in ethyl acetate, 0.12 mmol, 1.0 eq.) was added under argon atmosphere at RT. The reaction mixture was stirred at RT for 1 h, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 43 mg (63% of theory).

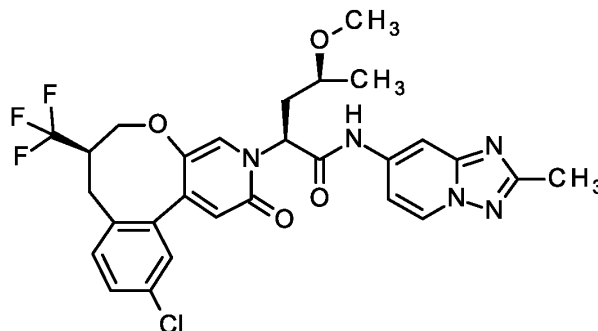
LC-MS (method 1): R_t = 0.99 min; MS (ESIpos): m/z = 590 [M+H]⁺

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 11.01-10.82 (m, 1H), 8.73 (d, 1H), 8.09-7.90 (m, 2H), 7.56-7.32 (m, 3H), 7.28-7.19 (m, 1H), 6.46-6.34 (m, 1H), 5.86-5.72 (m, 1H), 4.80-4.67 (m, 1H), 4.08-3.75 (m, 1H), 3.25-3.00 (m, 3H), 3.18 / 3.11 (2s, 3H), 2.84-2.73 / 2.59-2.46 (2m, 1H, partially

concealed), 2.44-2.20 (m, 2H), 2.42 / 2.41 (2s, 3H), 1.19-1.12 (m, 3H). Additional signals of minor rotamers were also detected.

Example 52

(2*S*,4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-
5 c]pyridin-3-yl]-4-methoxy-*N*-(2-methyl[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pentanamide (single stereoisomer)



Diastereomer separation of 40 mg of (4*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-(2-methyl[1,2,4]triazolo[1,5-
10 a]pyridin-7-yl)pentanamide (mixture of two diastereomers), Example 51 gave
single stereoisomer 1 (the title compound Example 52) (chiral HPLC: R_t = 1.64 min, 99% de): 11 mg,
single stereoisomer 2 (chiral HPLC: R_t = 2.51 min, 99% de): 25 mg.

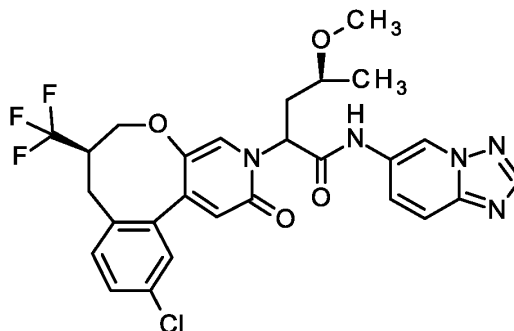
Separation method: HPLC: column: Daicel Chiralpak IC 5 μ m, 250 mm x 20 mm; eluent: 50%
15 *n*-heptane / 50% 2-propanol; temperature: 40°C; flow rate: 20 ml/min; UV detection: 220 nm.

Analysis method: HPLC: column: Daicel Chiralpak IC 3 μ m, 50 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% 2-propanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 11.02-10.82 (m, 1H), 8.74 (d, 1H), 8.10-7.99 (m, 2H), 7.57-7.31 (m, 3H), 7.29-7.21 (m, 1H), 6.46-6.34 (m, 1H), 5.89-5.69 (m, 1H), 4.81-4.66 (m, 1H),
20 4.12-3.94 / 3.87-3.74 (2m, 1H), 3.3-2.98 (m, 3H, partially concealed), 3.18 (s, 3H), 2.84-2.74 / 2.63-2.5 (2m, 1H, partially concealed), 2.42 (s, 3H), 2.31-2.20 (m, 2H), 1.19-1.12 (m, 3H). Additional signals of minor rotamers were also detected.

Example 53

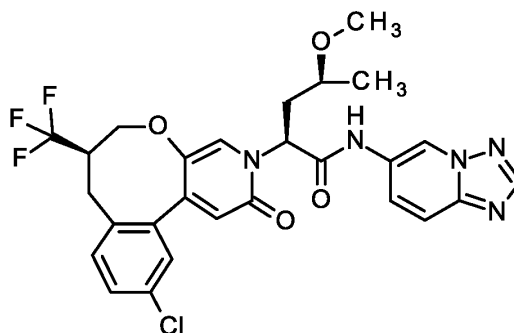
(4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-
25 c]pyridin-3-yl]-4-methoxy-*N*-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)pentanamide (mixture of two diastereomers)



- [1,2,4]Triazolo[1,5-a]pyridin-6-amine (17 mg, 0.13 mmol, 1.1 eq.), *N,N*-diisopropylethylamine (51 μ l, 0.29 mmol, 2.5 eq.) and a solution of HATU (53 mg, 0.14 mmol, 1.2 eq.) in *N,N*-dimethylformamide (1 ml) were added under argon atmosphere at RT to a solution of (2*S*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonic acid (mixture of two diastereomers) (57 mg, 93% purity, 0.12 mmol) in *N,N*-dimethylformamide (3 ml). The reaction mixture was stirred at RT for 30 min and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 49 mg (72% of theory).
- 10 LC-MS (method 4): R_t = 1.92 / 1.93 min; MS (ESIpos): m/z = 576 $[M+H]^+$
- $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.95-10.75 (m, 1H), 9.42 (s, 1H), 8.46 / 8.44 (2s, 1H), 8.09-7.92 (m, 1H), 7.86 (d, 1H), 7.76-7.68 (m, 1H), 7.56-7.32 (m, 3H), 6.47-6.35 (m, 1H), 5.89-5.74 (m, 1H), 4.80-4.65 (m, 1H), 4.14-3.74 (m, 1H), 3.3-2.98 (m, 3H, partially concealed), 3.19 / 3.12 (2s, 3H), 2.85-2.73 / 2.64-2.5 (2m, 1H, partially concealed), 2.45-2.18 (m, 2H), 1.21-1.11 (m, 3H).
- 15 Additional signals of minor rotamers were also detected.

Example 54

(2*S*,4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)pentanamide (single stereoisomer)



Diastereomer separation of 45 mg of (4*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)pentanamide (mixture of two diastereomers), Example 53 gave

single stereoisomer 1 (the title compound Example 54) (chiral HPLC: R_t = 2.38 min, 99% de): 16 mg,

single stereoisomer 2 (chiral HPLC: R_t = 3.25 min, 99% de): 22 mg.

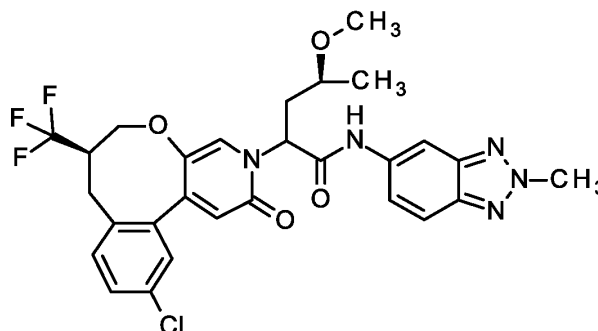
Separation method: HPLC: column: Daicel Chiralpak IE 3 μ m, 50 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% 2-propanol; temperature: 60°C; flow rate: 25 ml/min; UV detection: 220 nm.

Analysis method: HPLC: column: Daicel Chiralpak IE 3 μ m, 50 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% 2-propanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 10.97-10.73 (m, 1H), 9.43 (s, 1H), 8.46 (s, 1H), 8.04 (br s, 1H), 7.86 (d, 1H), 7.73 (dd, 1H), 7.57-7.33 (m, 3H), 6.48-6.35 (m, 1H), 5.90-5.73 (m, 1H), 4.82-4.65 (m, 1H), 4.14-3.99 / 3.87-3.72 (2m, 1H), 3.3-2.97 (m, 3H, partially concealed), 3.19 (s, 3H), 2.86-2.73 / 2.64-2.5 (2m, 1H, partially concealed), 2.32-2.15 (m, 2H), 1.16 (d, 3H). Additional signals of minor rotamers were also detected.

Example 55

(4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-(2-methyl-2*H*-benzotriazol-5-yl)pentanamide (mixture of two diastereomers)



20

2-Methyl-2*H*-benzotriazol-5-amine (19 mg, 0.13 mmol, 1.1 eq.), pyridine (11 μ l, 0.13 mmol, 1.1 eq.) and T3P (104 μ l, 50% solution in ethyl acetate, 0.18 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of (2*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonic acid (mixture of two diastereomers) (57 mg, 95% purity, 0.12 mmol) in tetrahydrofuran (4 ml). The reaction mixture was stirred at RT for 30 min before all volatiles were removed under reduced

25

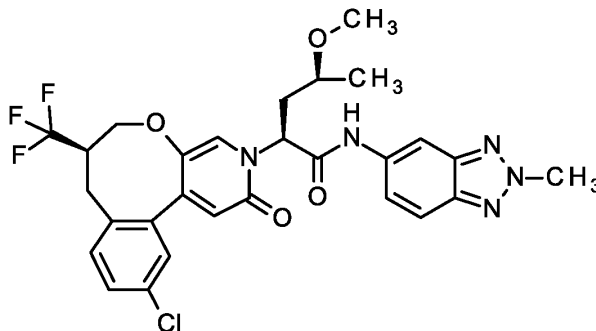
pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 58 mg (80% of theory).

LC-MS (method 4): $R_t = 2.10 / 2.12$ min; MS (ESIpos): $m/z = 590$ $[M+H]^+$

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.75-10.59 (m, 1H), 8.36-8.30 (m, 1H), 8.10-7.93 (m, 1H), 7.90-7.84 (m, 1H), 7.58-7.32 (m, 4H), 6.46-6.34 (m, 1H), 5.91-5.79 (m, 1H), 4.80-4.66 (m, 1H), 4.45 / 4.45 (2s, 3H), 4.08-3.75 (m, 1H), 3.25-2.99 (m, 3H), 3.19 / 3.12 (2s, 3H), 2.84-2.73 / 2.61-2.5 (2m, 1H, partially concealed), 2.43-2.19 (m, 2H), 1.20-1.11 (m, 3H). Additional signals of minor rotamers were also detected.

Example 56

(2*S*,4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-(2-methyl-2*H*-benzotriazol-5-yl)pentanamide (single stereoisomer)



Diastereomer separation of 55 mg of (4*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-(2-methyl-2*H*-benzotriazol-5-yl)pentanamide (mixture of two diastereomers), Example 55 gave

single stereoisomer 1 (the title compound Example 56) (chiral HPLC: $R_t = 1.18$ min, 99% de): 14 mg,

single stereoisomer 2 (chiral HPLC: $R_t = 1.76$ min, 99% de): 29 mg.

Separation method: HPLC: column: Daicel Chiralpak IC 3 μm , 50 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% 2-propanol; temperature: 60°C; flow rate: 20 ml/min; UV detection: 220 nm.

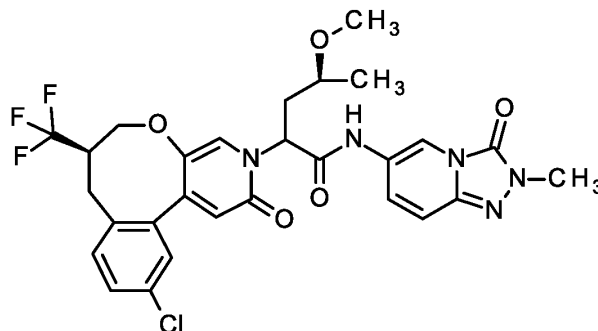
Analysis method: HPLC: column: Daicel Chiralpak IC 3 μm , 50 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% 2-propanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.77-10.60 (m, 1H), 8.33 (br s, 1H), 8.05 (br s, 1H), 7.88 (d, 1H), 7.58-7.30 (m, 4H), 6.46-6.34 (m, 1H), 5.91-5.77 (m, 1H), 4.81-4.65 (m, 1H), 4.45 (s, 3H), 4.12-3.97 / 3.87-3.72 (2m, 1H), 3.3-2.97 (m, 3H, partially concealed), 3.19 (s, 3H), 2.86-2.73 /

2.64-2.5 (2m, 1H, partially concealed), 2.35-2.18 (m, 2H), 1.16 (d, 3H). Additional signals of minor rotamers were also detected.

Example 57

(4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-
5 c]pyridin-3-yl]-4-methoxy-*N*-(2-methyl-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-*a*]pyridin-6-yl)pentanamide (mixture of two diastereomers)



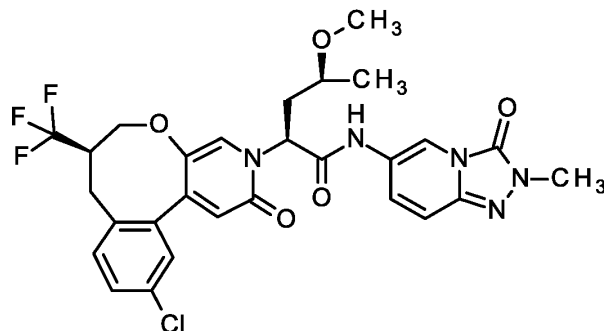
6-Amino-2-methyl[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrogen chloride (26 mg, 0.13 mmol, 1.1 eq.), pyridine (28 µl, 0.35 mmol, 3.0 eq.) and T3P (102 µl, 50% solution in ethyl acetate, 0.17
10 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of (2*ξ*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonic acid (mixture of two diastereomers) (57 mg, 93% purity, 0.12 mmol) in tetrahydrofuran (4 ml). The reaction mixture was stirred at RT for 3 days and filtered through Celite®. The filtrate removed under reduced pressure. The residue was purified by preparative HPLC
15 (reversed phase, eluent: acetonitrile / water gradient). Yield: 57 mg (81% of theory).

LC-MS (method 4): $R_t = 1.88$ min; MS (ESIpos): $m/z = 606$ $[M+H]^+$

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 10.65-10.48 (m, 1H), 8.54-8.41 (m, 1H), 8.06-7.90 (m, 1H), 7.56-7.33 (m, 3H), 7.31-7.24 (m, 2H), 6.46-6.34 (m, 1H), 5.87-5.70 (m, 1H), 4.79-4.66 (m, 1H), 4.08-3.74 (m, 1H), 3.53 / 3.53 (2s, 3H), 3.3-2.98 (m, 3H, partially concealed), 3.18 / 3.12 (2s, 3H),
20 2.85-2.71 / 2.60-2.5 (2m, 1H, partially concealed), 2.40-2.14 (m, 2H), 1.18-1.10 (m, 3H). Additional signals of minor rotamers were also detected.

Example 58

(2*S*,4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-
c]pyridin-3-yl]-4-methoxy-*N*-(2-methyl-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-*a*]pyridin-6-
25 yl)pentanamide (single stereoisomer)



Diastereomer separation of 54 mg of (4*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-(2-methyl-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-*a*]pyridin-6-yl)pentanamide (mixture of two diastereomers), Example 57
 5 gave

single stereoisomer 1 (the title compound Example 58) (chiral HPLC: $R_t = 6.45$ min, >99% de): 17 mg,

single stereoisomer 2 (chiral HPLC: $R_t = 10.03$ min, >99% de): 32 mg.

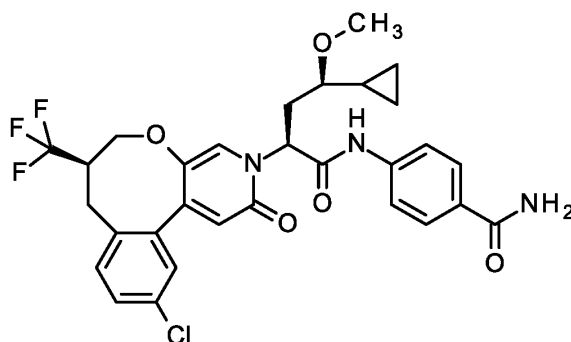
Separation method: HPLC: column: Daicel Chiralcel OX-H 5 μm , 250 mm x 20 mm; eluent: 60%
 10 *n*-heptane / 40% ethanol; temperature: 40°C; flow rate: 20 ml/min; UV detection: 220 nm.

Analysis method: HPLC: column: Daicel Chiralcel OX-H 5 μm , 250 mm x 4.6 mm; eluent: 60%
iso-hexane / 40% ethanol; temperature: 30°C; flow rate: 1 ml/min; UV detection: 220 nm.

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 10.66-10.46 (m, 1H), 8.46 (s, 1H), 8.04-7.94 (m, 1H), 7.56-7.32 (m, 3H), 7.31-7.25 (m, 2H), 6.46-6.33 (m, 1H), 5.83-5.69 (m, 1H), 4.79-4.65 (m, 1H),
 15 4.10-3.98 / 3.83-3.74 (2m, 1H), 3.53 (s, 3H), 3.3-2.99 (m, 3H, partially concealed), 3.18 (s, 3H), 2.85-2.73 / 2.63-2.5 (2m, 1H, partially concealed), 2.27-2.14 (m, 2H), 1.15 (m, 3H). Additional signals of minor rotamers were also detected.

Example 59

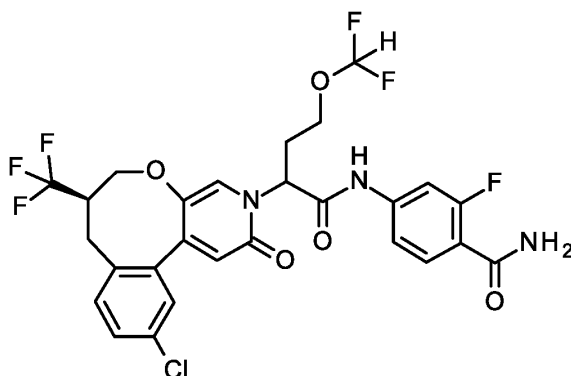
4-({(2*S*,4*R*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-
 20 [3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-cyclopropyl-4-methoxybutanoyl}amino)benzamide (single stereoisomer)



- 1,1,3,3-Tetramethylguanidine (30 μ l, 0.24 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (27 mg, 0.08 mmol) in 2-propanol / acetone (4:1, 1.0 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-[(2*R*,4*R*)-2-bromo-4-cyclopropyl-4-methoxybutanoyl]-amino}-benzamide (single stereoisomer) (31 mg, 0.09 mmol, 1.1 eq.) and of further 2-propanol / acetone (4:1, 1.0 ml). The reaction mixture was stirred at RT for 7 days and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 28 mg (58% of theory).
- LC-MS (method 16): R_t = 4.51 min; MS (ESIpos): m/z = 604 $[M+H]^+$
- $^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.76-10.47 (m, 1H), 8.11-7.93 (m, 1H), 7.92-7.78 (m, 3H), 7.70 (d, 2H), 7.58-7.31 (m, 3H), 7.22 (br s, 1H), 6.46-6.32 (m, 1H), 5.91-5.73 (m, 1H), 4.81-4.65 (m, 1H), 4.11-4.00 / 3.84-3.71 (2m, 1H), 3.29-3.17 (m, 3H), 3.13-2.96 (m, 2H), 2.82-2.72 / 2.63-2.5 (2m, 2H, partially concealed), 2.44-2.20 (m, 2H), 0.90-0.77 (m, 1H), 0.63-0.52 (m, 1H), 0.46-0.27 (m, 2H), 0.11-0.0 (m, 1H). Additional signals of minor rotamers were also detected.

Example 60

4-{2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)butanamido}-2-fluorobenzamide (mixture of two diastereomers)



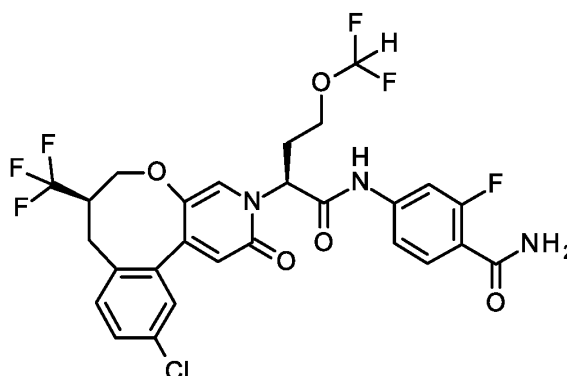
2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)butanoic acid (mixture of two diastereomers) (63 mg, 0.13 mmol), pyridine (12 μ l, 0.14 mmol, 1.1 eq.) and T3P (114 μ l, 50% solution in ethyl acetate, 0.20 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of 4-amino-2-fluorobenzamide (22 mg, 0.14 mmol, 1.1 eq.) in tetrahydrofuran (4 ml). The reaction mixture was stirred at RT for 0.5 h and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 74 mg (92% of theory).

LC-MS (method 4): R_t = 1.94 min; MS (ESIpos): m/z = 618 $[M+H]^+$

1H -NMR (600 MHz, DMSO- d_6): δ [ppm] = 10.94-10.63 (m, 1H), 8.03-7.91 (m, 1H), 7.73-7.60 (m, 2H), 7.59-7.32 (m, 6H), 6.64 / 6.63 (2t, 1H), 6.47-6.35 (m, 1H), 5.81-5.58 (m, 1H), 4.78-4.63 (m, 1H), 4.17-3.73 (m, 3H), 3.28-2.96 (m, 2H), 2.84-2.72 / 2.64-2.4 (2m, 3H, partially concealed). Additional signals of minor rotamers were also detected.

Example 61

4-{[(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)butanoyl]amino}-2-fluorobenzamide (single stereoisomer)



Diastereomer separation of 72 mg of 4-{2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)butanamido}-2-fluorobenzamide (mixture of two diastereomers), Example 60 gave

single stereoisomer 1 (the title compound Example 61) (chiral SFC: R_t = 1.41 min, >99% de): 26 mg,

single stereoisomer 2 (chiral SFC: R_t = 2.01 min, 95% de): 23 mg.

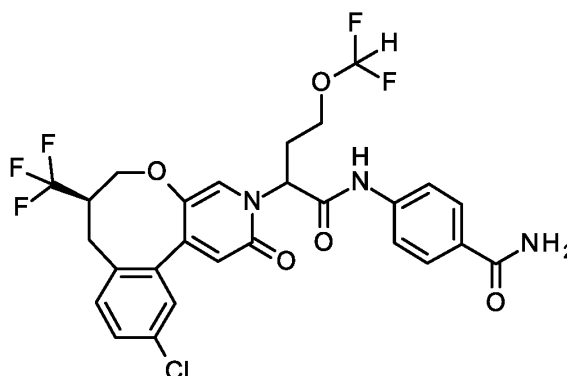
Separation method: SFC: column: Daicel Chiralpak ID 5 μ m, 250 mm x 20 mm; eluent: 82% carbon dioxide / 18% methanol; temperature: 40°C; flow rate: 80 ml/min; UV detection: 210 nm.

Analysis method: SFC: column: Daicel Chiralpak ID, 50 mm x 4.6 mm; eluent: 80% carbon dioxide / 20% methanol; temperature: 40°C; flow rate: 3 ml/min; UV detection: 210 nm.

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 10.93-10.63 (m, 1H), 7.96 (br s, 1H), 7.74-7.32 (m, 8H), 6.63 (t, 1H), 6.46-6.33 (m, 1H), 5.82-5.56 (m, 1H), 4.81-4.62 (m, 1H), 4.18-3.71 (m, 3H), 3.16-2.96 (m, 2H), 2.86-2.74 / 2.65-2.4 (2m, 3H, partially concealed). Additional signals of minor rotamers were also detected.

5 **Example 62**

4-{2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)butanamido}benzamide (mixture of two diastereomers)



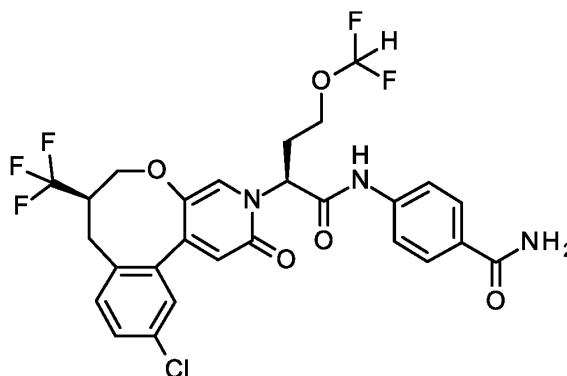
2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)butanoic acid (mixture of two diastereomers) (77 mg, 0.16 mmol), pyridine (14 μ l, 0.18 mmol, 1.1 eq.) and T3P (140 μ l, 50% solution in ethyl acetate, 0.24 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of 4-aminobenzamide (24 mg, 0.18 mmol, 1.1 eq.) in tetrahydrofuran (5 ml). The reaction mixture was stirred at RT for 0.5 h and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 83 mg (84% of theory).

LC-MS (method 4): R_t = 1.87 min; MS (ESIpos): m/z = 600 $[M+H]^+$

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 10.77-10.51 (m, 1H), 8.04-7.93 (m, 1H), 7.92-7.81 (m, 3H), 7.68 (d, 2H), 7.57-7.32 (m, 3H), 7.26 (br s, 1H), 6.64 / 6.62 (2t, 1H), 6.46-6.34 (m, 1H), 5.84-5.63 (m, 1H), 4.79-4.64 (m, 1H), 4.13-3.73 (m, 3H), 3.28-2.97 (m, 2H), 2.84-2.72 / 2.63-2.4 (2m, 3H, partially concealed). Additional signals of minor rotamers were also detected.

Example 63

4-{[(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)butanoyl]amino}benzamide (single stereoisomer)



Diastereomer separation of 80 mg of 4-{2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)butanamido}benzamide (mixture of two diastereomers), Example 62 gave

- 5 single stereoisomer 1 (the title compound Example 63) (chiral HPLC: $R_t = 1.41$ min, >99% de): 20 mg,

single stereoisomer 2 (chiral HPLC: $R_t = 1.74$ min, >99% de): 17 mg.

Separation method: HPLC: column: Daicel Chiralpak ID 5 μm , 250 mm x 20 mm; eluent: 70% *n*-heptane / 30% ethanol; temperature: 40°C; flow rate: 20 ml/min; UV detection: 220 nm.

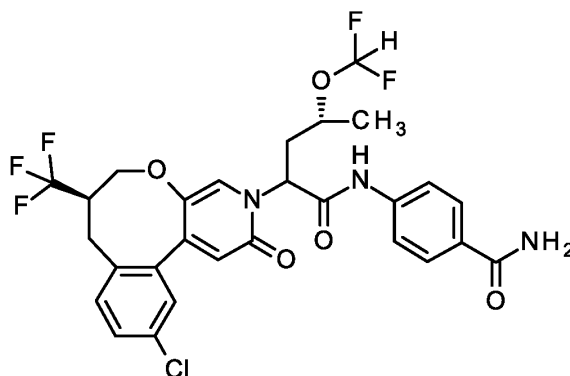
- 10 Analysis method: HPLC: column: Daicel Chiralpak ID-3 3 μm , 50 mm x 4.6 mm; eluent: 70% *n*-hexane / 30% ethanol; temperature: 30°C; flow rate: 1 ml/min; UV detection: 220 nm.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.77-10.48 (m, 1H), 7.97 (br s, 1H), 7.92-7.80 (m, 3H), 7.68 (d, 2H), 7.59-7.31 (m, 3H), 7.25 (br s, 1H), 6.64 (t, 1H), 6.48-6.34 (m, 1H), 5.85-5.61 (m, 1H), 4.82-4.61 (m, 1H), 4.15-3.69 (m, 3H), 3.17-2.96 (m, 2H), 2.86-2.73 / 2.65-2.4 (2m, 3H, partially

- 15 concealed). Additional signals of minor rotamers were also detected.

Example 64

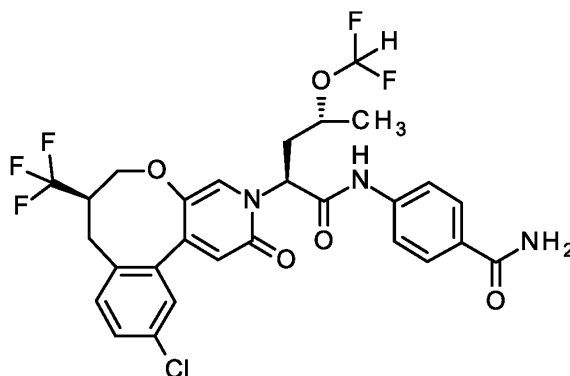
4-{[(4*R*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)pentanoyl]amino}benzamide (mixture of two diastereomers)



- (2*ξ*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-c]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-(difluoromethyl)-*D*-glycero-pentonic acid (mixture of two diastereomers) (99 mg, 0.20 mmol), pyridine (18 μ l, 0.22 mmol, 1.1 eq.) and T3P (175 μ l, 50% solution in ethyl acetate, 0.30 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of 4-aminobenzamide (30 mg, 0.22 mmol, 1.1 eq.) in tetrahydrofuran (4 ml). The reaction mixture was stirred at RT for 0.5 h and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 101 mg (82% of theory).
- 10 LC-MS (method 4): R_t = 1.93 min; MS (ESIpos): m/z = 614 $[M+H]^+$
- 1H -NMR (400 MHz, DMSO- d_6): δ [ppm] = 10.82-10.56 (m, 1H), 8.05-7.93 (m, 1H), 7.92-7.80 (m, 3H), 7.72-7.63 (m, 2H), 7.58-7.32 (m, 3H), 7.25 (br s, 1H), 6.62 / 6.59 (2t, 1H), 6.47-6.33 (m, 1H), 5.90-5.67 (m, 1H), 4.81-4.64 (m, 1H), 4.20-3.99 / 3.92-3.72 (2m, 2H), 3.16-2.97 (m, 2H), 2.84-2.70 / 2.65-2.5 (2m, 1H, partially concealed), 2.5-2.28 (m, 2H, partially concealed), 1.36-1.25 (m, 3H).
- 15 Additional signals of minor rotamers were also detected.

Example 65

4-{[(2*S*,4*R*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-c]pyridin-3-yl]-4-(difluoromethoxy)pentanoyl]amino}benzamide (single stereoisomer)



Diastereomer separation of 99 mg of 4-{[(4*R*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-

(difluoromethoxy)pentanoyl]amino}benzamide (mixture of two diastereomers), Example 64 gave

- 5 single stereoisomer 1 (the title compound Example 65) (chiral HPLC: R_t = 4.38 min, 99% de): 58 mg,

single stereoisomer 2 (chiral HPLC: R_t = 6.11 min, 99% de): 25 mg.

Separation method: HPLC: column: Daicel Chiralpak OZ-H 5 μ m, 250 mm x 20 mm; eluent: 55% *n*-heptane / 45% ethanol; temperature: 55°C; flow rate: 15 ml/min; UV detection: 220 nm.

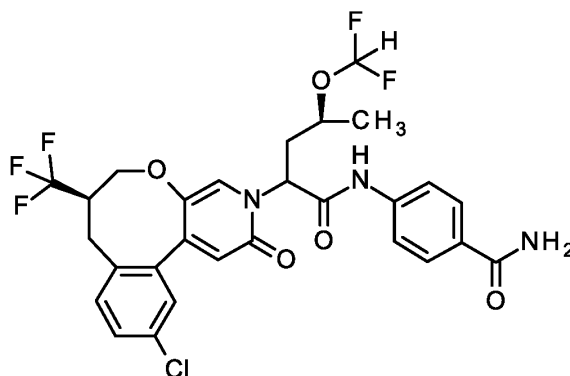
- 10 Analysis method: HPLC: column: Daicel Chiralpak OZ-H 5 μ m, 250 mm x 4.6 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 50°C; flow rate: 1 ml/min; UV detection: 220 nm.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.80-10.57 (m, 1H), 7.97 (br s, 1H), 7.91-7.80 (m, 3H), 7.68 (d, 2H), 7.58-7.32 (m, 3H), 7.24 (br s, 1H), 6.59 (t, 1H), 6.47-6.33 (m, 1H), 5.86-5.68 (m, 1H), 4.81-4.63 (m, 1H), 4.23-3.99 / 3.85-3.72 (2m, 2H), 3.17-2.97 (m, 2H), 2.83-2.73 / 2.65-2.5 (2m, 1H,

- 15 partially concealed), 2.5-2.29 (m, 2H, partially concealed), 1.30 (d, 3H). Additional signals of minor rotamers were also detected.

Example 66

4-{[(4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)pentanoyl]amino}benzamide (mixture of two diastereomers)



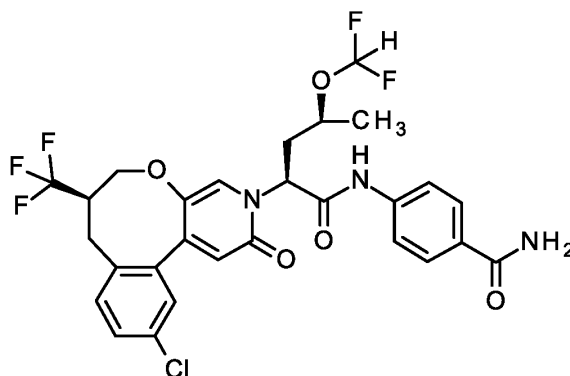
(2*ξ*)-2-[(*7R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-c]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-(difluoromethyl)-*L*-glycero-pentonic acid (mixture of two diastereomers) (93 mg, 89% purity, 0.17 mmol), pyridine (15 μ l, 0.18 mmol, 1.1 eq.) and T3P (146 μ l, 50% solution in ethyl acetate, 0.25 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of 4-aminobenzamide (25 mg, 0.18 mmol, 1.1 eq.) in tetrahydrofuran (3.6 ml). The reaction mixture was stirred at RT for 0.5 h and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 89 mg (87% of theory).

LC-MS (method 4): R_t = 1.97 min; MS (ESI^{neg}): m/z = 612 [$M-H$]⁻

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 10.81-10.53 (m, 1H), 8.07-7.94 (m, 1H), 7.92-7.80 (m, 3H), 7.72-7.64 (m, 2H), 7.57-7.31 (m, 3H), 7.26 (br s, 1H), 6.64 / 6.59 (2t, 1H), 6.45-6.35 (m, 1H), 5.88-5.70 (m, 1H), 4.80-4.65 (m, 1H), 4.25-3.73 (m, 2H), 3.13-2.96 (m, 2H), 2.83-2.72 / 2.64-2.5 (2m, 1H), 2.5-2.30 (m, 2H, partially concealed), 1.36-1.25 (m, 3H). Additional signals of minor rotamers were also detected.

Example 67

4-{[(2*S*,4*S*)-2-[(*7R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-c]pyridin-3-yl]-4-(difluoromethoxy)pentanoyl]amino}benzamide (single stereoisomer)



Diastereomer separation of 89 mg of 4-{[(4*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-

(difluoromethoxy)pentanoyl]amino}benzamide (mixture of two diastereomers), Example 66 gave

- 5 single stereoisomer 1 (the title compound Example 67) (chiral HPLC: R_t = 4.18 min, 99% de): 29 mg,

single stereoisomer 2 (chiral HPLC: R_t = 4.85 min, 99% de): 44 mg.

Separation method: HPLC: column: Daicel Chiralpak ID 5 μ m, 250 mm x 20 mm; eluent: 50% *n*-heptane / 50% ethanol; temperature: 30°C; flow rate: 15 ml/min; UV detection: 220 nm.

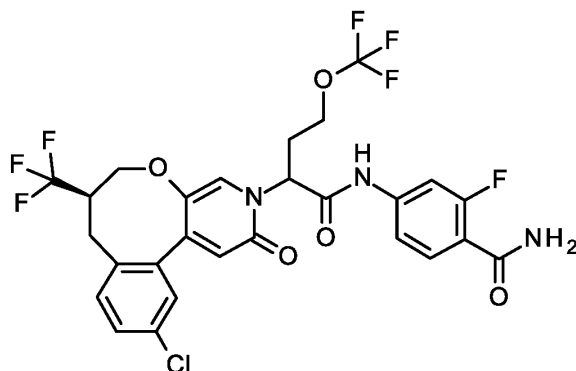
- 10 Analysis method: HPLC: column: Daicel Chiralpak ID 5 μ m, 250 mm x 4.6 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 30°C; flow rate: 1 ml/min; UV detection: 220 nm.

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 10.75-10.50 (m, 1H), 7.98 (br s, 1H), 7.92-7.80 (m, 3H), 7.67 (d, 2H), 7.57-7.31 (m, 3H), 7.25 (br s, 1H), 6.64 (t, 1H), 6.47-6.35 (m, 1H), 5.89-5.70 (m, 1H), 4.80-4.64 (m, 1H), 4.27-4.15 (m, 1H), 4.11-3.98 / 3.84-3.71 (2m, 1H), 3.16-2.96 (m, 2H), 2.85-2.72 / 2.64-2.5 (2m, 1H), 2.5-2.30 (m, 2H, partially concealed), 1.31 (d, 3H). Additional signals of minor rotamers were also detected.

Example 68

4-{2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(trifluoromethoxy)butanamido}-2-fluorobenzamide (mixture of two diastereomers)

20



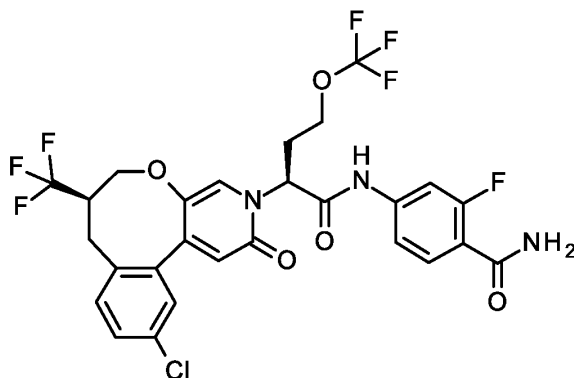
4-Amino-2-fluorobenzamide (12 mg, 76 μmol , 1.1 eq.), *N,N*-diisopropylethylamine (30 μl , 170 μmol , 2.5 eq.) and a solution of HATU (34 mg, 89 μmol , 1.3 eq.) in *N,N*-dimethylformamide (1.0 ml) were added under argon atmosphere at RT to a solution of 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(trifluoromethoxy)butanoic acid (mixture of two diastereomers) (35 mg, 69 μmol) in *N,N*-dimethylformamide (3.0 ml). The reaction mixture was stirred at RT for 1.5 h, followed by addition of further 4-amino-2-fluorobenzamide (3 mg, 21 μmol , 0.3 eq.), *N,N*-diisopropylethylamine (6 μl , 34 μmol , 0.5 eq.) and HATU (13 mg, 34 μmol , 0.5 eq.). The reaction mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 35 mg (80% of theory).

LC-MS (method 1): R_t = 1.08 min; MS (ESIpos): m/z = 636 $[\text{M}+\text{H}]^+$

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.94-10.86 / 10.65-10.59 (2m, 1H), 8.01 (d, 1H), 7.72-7.60 (m, 2H), 7.60-7.46 (m, 3H), 7.46-7.33 (m, 3H), 6.47-6.36 (m, 1H), 5.87-5.79 / 5.63-5.54 (2m, 1H), 4.79-4.64 (m, 1H), 4.24-4.16 (m, 1H), 4.16-4.01 / 3.94-3.73 (2m, 2H), 3.15-3.00 (m, 2H), 2.64-2.5 (m, 3H, partially concealed). Additional signals of minor rotamers were also detected.

Example 69

4-[(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(trifluoromethoxy)butanoyl]amino}-2-fluorobenzamide (single stereoisomer)



Diastereomer separation of 24 mg of 4-{2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(trifluoromethoxy)butanamido}-2-fluorobenzamide (mixture of two diastereomers), Example 68 gave

- 5 single stereoisomer 1 (the title compound Example 69) (chiral HPLC: R_t = 1.55 min, 94% de): 13 mg,

single stereoisomer 2 (chiral HPLC: R_t = 2.31 min, 99% de): 9 mg.

Separation method: HPLC: column: Daicel Chiralpak ID 5 μ m, 250 mm x 20 mm; eluent: 80% *n*-heptane / 20% ethanol; temperature: 40°C; flow rate: 20 ml/min; UV detection: 210 nm.

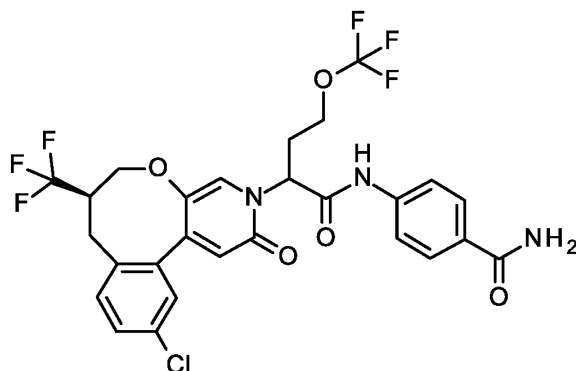
- 10 Analysis method: HPLC: column: Daicel Chiralpak ID-3 3 μ m, 50 mm x 4.6 mm; eluent: 80% *iso*-hexane / 20% ethanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.94-10.86 / 10.67-10.58 (m / br s, 1H), 7.99 (s, 1H), 7.73-7.60 (m, 2H), 7.60-7.46 (m, 3H), 7.46-7.23 (m, 3H), 6.48-6.36 (m, 1H), 5.86-5.78 / 5.64-5.54 (2m, 1H), 4.80-4.63 (m, 1H), 4.24-4.16 (m, 1H), 4.15-4.00 / 3.82-3.72 (2m, 2H), 3.15-2.98 (m, 2H),

- 15 2.67-2.5 (m, 3H, partially concealed). Additional signals of minor rotamers were also detected.

Example 70

4-{2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(trifluoromethoxy)butanamido}benzamide (mixture of two diastereomers)



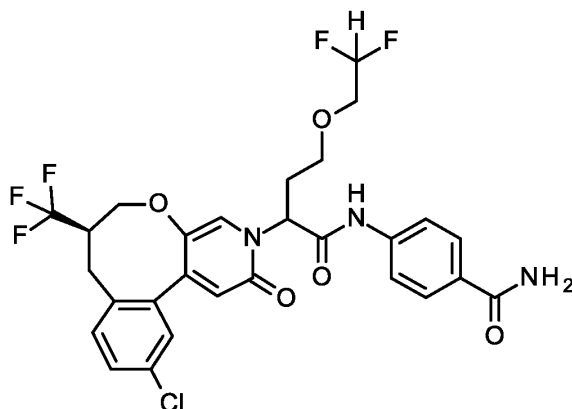
4-Aminobenzamide (9 mg, 63 μ mol, 1.1 eq.), *N,N*-diisopropylethylamine (25 μ l, 140 μ mol, 2.5 eq.) and a solution of HATU (28 mg, 74 μ mol, 1.3 eq.) in *N,N*-dimethylformamide (1.0 ml) were added under argon atmosphere at RT to a solution of 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(trifluoromethoxy)butanoic acid (mixture of two diastereomers) (29 mg, 57 μ mol) in *N,N*-dimethylformamide (2.0 ml). The reaction mixture was stirred at RT for 4 h, followed by addition of further 4-aminobenzamide (4 mg, 28 μ mol, 0.5 eq.), *N,N*-diisopropylethylamine (5 μ l, 28 μ mol, 0.5 eq.) and HATU (11 mg, 28 μ mol, 0.5 eq.). The reaction mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 20 mg (56% of theory).

LC-MS (method 3): R_t = 3.46 min; MS (ESIpos): m/z = 618 $[M+H]^+$

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.76-10.70 / 10.54-10.47 (2m, 1H), 8.01 (d, 1H), 7.91-7.81 (m, 3H), 7.67 (d, 2H), 7.56-7.46 (m, 1H), 7.46-7.32 (m, 2H), 7.30-7.20 (m, 1H), 6.47-6.36 (m, 1H), 5.90-5.79 / 5.70-5.60 (2m, 1H), 4.80-4.65 (m, 1H), 4.23-4.15 (m, 1H), 4.15-3.96 / 3.94-3.71 (2m, 2H), 3.13-2.98 (m, 2H), 2.72-2.52 (m, 3H, partially concealed). Additional signals of minor rotamers were also detected.

Example 71

4-{[2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(2,2-difluoroethoxy)butanoyl]amino}benzamide (mixture of two diastereomers)



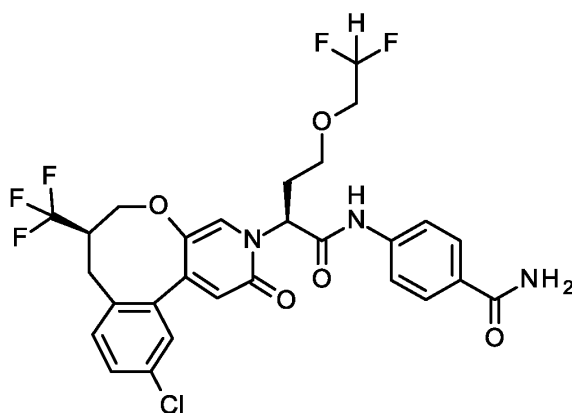
- 2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(2,2-difluoroethoxy)butanoic acid (mixture of two diastereomers) (85 mg, 0.17 mmol), pyridine (15 μ l, 0.19 mmol, 1.1 eq.) and T3P (150 μ l, 50% solution in ethyl acetate, 0.26 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of 4-aminobenzamide (26 mg, 0.19 mmol, 1.1 eq.) in tetrahydrofuran (5 ml). The reaction mixture was stirred at RT for 2.5 h before water was added. The forming precipitate was filtered, washed with water and dried *in vacuo*. Yield: 91 mg (86% of theory).

LC-MS (method 3): R_t = 3.37 min; MS (ESIpos): m/z = 614 $[M+H]^+$

- ¹H-NMR (500 MHz, DMSO- d_6): δ [ppm] = 10.74-10.55 (m, 1H), 8.03-7.93 (m, 1H), 7.91-7.79 (m, 3H), 7.68 (d, 2H), 7.56-7.32 (m, 3H), 7.26 (br s, 1H), 6.45-6.32 (m, 1H), 6.21-5.90 (m, 1H), 5.80-5.67 (m, 1H), 4.79-4.64 (m, 1H), 4.12-3.46 (m, 5H), 3.15-2.95 (m, 2H), 2.87-2.71 / 2.65-2.5 (m, 1H, partially concealed), 2.48-2.32 (m, 2H). Additional signals of minor rotamers were also detected.

Example 72

- 4-{[(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(2,2-difluoroethoxy)butanoyl]amino}benzamide (single stereoisomer)



Diastereomer separation of 89 mg of 4-{2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(2,2-difluoroethoxy)butanoyl]amino}benzamide (mixture of two diastereomers), Example 71 gave

single stereoisomer 1 (chiral HPLC: R_t = 6.40 min, 99% de): 36 mg,

- 5 single stereoisomer 2 (the title compound Example 72) (chiral HPLC: R_t = 8.95 min, 99% de): 35 mg.

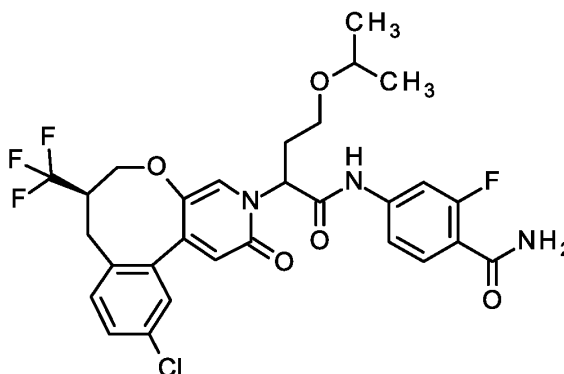
Separation method: HPLC: column: Daicel Chiralpak IG 5 μ m, 250 mm x 20 mm; eluent: 40% *n*-heptane / 60% ethanol; temperature: 60°C; flow rate: 15 ml/min; UV detection: 220 nm.

- Analysis method: HPLC: column: Daicel Chiralpak IG 5 μ m, 250 mm x 4.6 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 60°C; flow rate: 1 ml/min; UV detection: 220 nm.

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 10.73-10.52 (m, 1H), 7.98 (br s, 1H), 7.91-7.80 (m, 3H), 7.68 (d, 2H), 7.56-7.33 (m, 3H), 7.25 (br s, 1H), 6.46-6.33 (m, 1H), 6.07 (tt, 1H), 5.80-5.67 (m, 1H), 4.80-4.64 (m, 1H), 4.13-3.43 (m, 5H), 3.16-2.95 (m, 2H), 2.87-2.76 / 2.64-2.5 (2m, 1H, partially concealed), 2.48-2.34 (m, 2H). Additional signals of minor rotamers were also detected.

15 **Example 73**

4-({2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(propan-2-yl)oxy]butanoyl}amino)-2-fluorobenzamide (mixture of two diastereomers)



- 20 4-Amino-2-fluorobenzamide (27 mg, 0.17 mmol, 1.1 eq.), *N,N*-diisopropylethylamine (68 μ l, 0.39 mmol, 2.5 eq.) and a solution of HATU (78 mg, 0.20 mmol, 1.3 eq.) in *N,N*-dimethylformamide (1 ml) were added under argon atmosphere at RT to a solution of 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(propan-2-yl)oxy]butanoic acid (mixture of two diastereomers) (81 mg, 92% purity, 0.16 mmol) in *N,N*-
25 dimethylformamide (4 ml). The reaction mixture was stirred at RT for 3 h and concentrated under

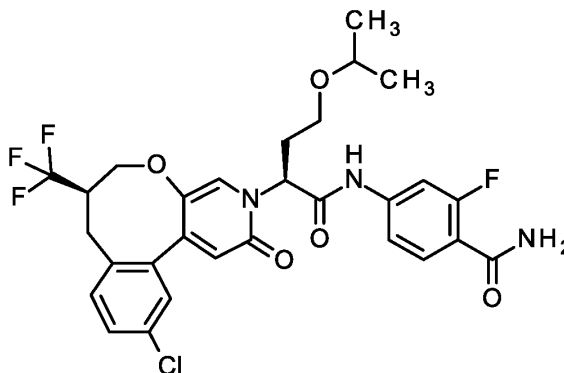
reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 64 mg (66% of theory).

LC-MS (method 4): $R_t = 2.05$ min; MS (ESIpos): $m/z = 610$ $[M+H]^+$

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.92-10.67 (m, 1H), 8.04-7.93 (m, 1H), 7.72-7.61 (m, 2H), 7.60-7.30 (m, 6H), 6.46-6.33 (m, 1H), 5.79-5.64 (m, 1H), 4.79-4.64 (m, 1H), 4.10-3.94 / 3.92-3.72 (2m, 1H), 3.53-3.38 (m, 2H), 3.15-2.98 (m, 2H), 2.81-2.69 / 2.63-2.4 (2m, 1H, partially concealed), 2.43-2.25 (m, 2H), 1.05-0.90 (m, 6H). Additional signals of minor rotamers were also detected.

Example 74

10 4-({(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(propan-2-yl)oxy]butanoyl}amino)-2-fluorobenzamide (single stereoisomer)



Diastereomer separation of 60 mg of 4-({(2*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(propan-2-yl)oxy]butanoyl}amino)-2-fluorobenzamide (mixture of two diastereomers), Example 73 gave

single stereoisomer 1 (the title compound Example 74) (chiral HPLC: $R_t = 1.29$ min, >99% de): 16 mg,

single stereoisomer 2 (chiral HPLC: $R_t = 2.03$ min, >99% de): 14 mg.

Separation method: HPLC: column: Daicel Chiralpak ID 5 μm , 250 mm x 20 mm; eluent: 70% *n*-heptane / 30% ethanol; temperature: 40°C; flow rate: 20 ml/min; UV detection: 220 nm.

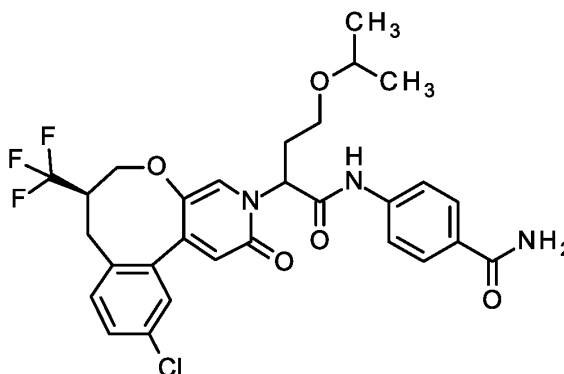
Analysis method: HPLC: column: Daicel Chiralpak ID 3 μm , 50 mm x 4.6 mm; eluent: 70% *n*-heptane / 30% ethanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.87-10.67 (m, 1H), 7.97 (s, 1H), 7.75-7.60 (m, 2H), 7.58-7.31 (m, 6H), 6.47-6.32 (m, 1H), 5.81-5.63 (m, 1H), 4.81-4.62 (m, 1H), 4.13-3.99 / 3.83-3.70

(2m, 1H), 3.55-3.39 (m, 2H), 3.16-2.97 (m, 2H), 2.82-2.69 / 2.63-2.4 (2m, 1H, partially concealed), 2.43-2.25 (m, 2H), 1.05-0.93 (m, 6H). Additional signals of minor rotamers were also detected.

Example 75

4-((2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-
5 c]pyridin-3-yl]-4-[(propan-2-yl)oxy]butanoyl}amino)benzamide (mixture of two diastereomers)



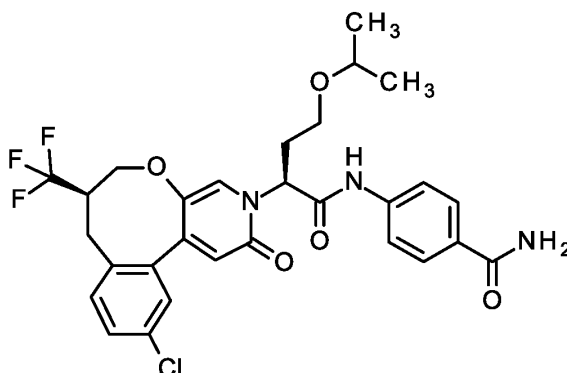
4-Aminobenzamide (24 mg, 0.17 mmol, 1.1 eq.), *N,N*-diisopropylethylamine (68 μ l, 0.39 mmol, 2.5 eq.) and a solution of HATU (78 mg, 0.20 mmol, 1.3 eq.) in *N,N*-dimethylformamide (1 ml) were added under argon atmosphere at RT to a solution of 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-
10 2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(propan-2-yl)oxy]butanoic acid (mixture of two diastereomers) (81 mg, 92% purity, 0.16 mmol) in *N,N*-dimethylformamide (4 ml). The reaction mixture was stirred at RT for 2 h and concentrated under reduced pressure. The residue was crystallized with water, filtered, washed with water and dissolved in acetonitrile. This solution was used in purification by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient).
15 Yield: 55 mg (59% of theory).

LC-MS (method 4): R_t = 1.98 min; MS (ESIpos): m/z = 592 $[M+H]^+$

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.75-10.55 (m, 1H), 8.05-7.94 (m, 1H), 7.88 (br s, 1H), 7.85 (d, 2H), 7.70 (d, 2H), 7.57-7.32 (m, 3H), 7.27 (br s, 1H), 6.45-6.33 (m, 1H), 5.82-5.69 (m, 1H), 4.80-4.65 (m, 1H), 4.10-3.95 / 3.92-3.72 (2m, 1H), 3.54-3.39 (m, 2H), 3.16-2.97 (m, 2H), 2.80-2.70
20 / 2.62-2.45 (2m, 1H, partially concealed), 2.44-2.26 (m, 2H), 1.05-0.91 (m, 6H). Additional signals of minor rotamers were also detected.

Example 76

4-((2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-
c]pyridin-3-yl]-4-[(propan-2-yl)oxy]butanoyl}amino)benzamide (single stereoisomer)



Diastereomer separation of 55 mg of 4-({2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(propan-2-yl)oxy]butanoyl}amino)benzamide (mixture of two diastereomers), Example 75 gave

- 5 single stereoisomer 1 (the title compound Example 76) (chiral SFC: R_t = 4.13 min, >99% de): 19 mg,

single stereoisomer 2 (chiral SFC: R_t = 6.13 min, >99% de): 15 mg.

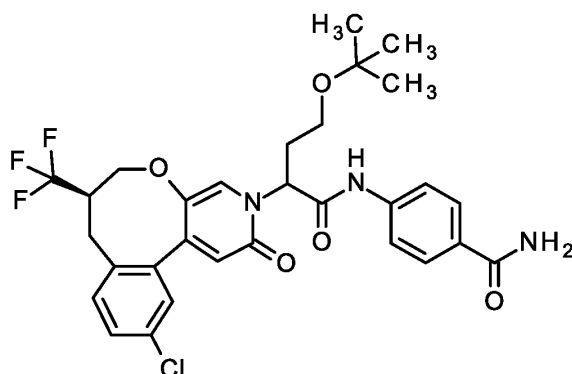
Separation method: SFC: column: Daicel Chiralpak IE 5 μ m, 250 mm x 20 mm; eluent: 74% carbon dioxide / 26% methanol; temperature: 40°C; flow rate: 80 ml/min; UV detection: 210 nm.

- 10 Analysis method: SFC: column: Daicel Chiralpak IE, 50 mm x 4.6 mm; eluent: 70% carbon dioxide / 30% methanol; temperature: 40°C; flow rate: 3 ml/min; UV detection: 220 nm.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.72-10.53 (m, 1H), 7.97 (s, 1H), 7.92-7.79 (m, 3H), 7.69 (d, 2H), 7.57-7.33 (m, 3H), 7.24 (br s, 1H), 6.46-6.33 (m, 1H), 5.80-5.68 (m, 1H), 4.81-4.64 (m, 1H), 4.12-3.99 / 3.84-3.71 (2m, 1H), 3.54-3.39 (m, 2H), 3.15-2.97 (m, 2H), 2.80-2.71 / 2.64-2.5 (2m, 1H, partially concealed), 2.44-2.25 (m, 2H), 1.06-0.94 (m, 6H). Additional signals of minor rotamers were also detected.

Example 77

4-({4-*tert*-Butoxy-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoyl}amino)benzamide (mixture of two diastereomers)



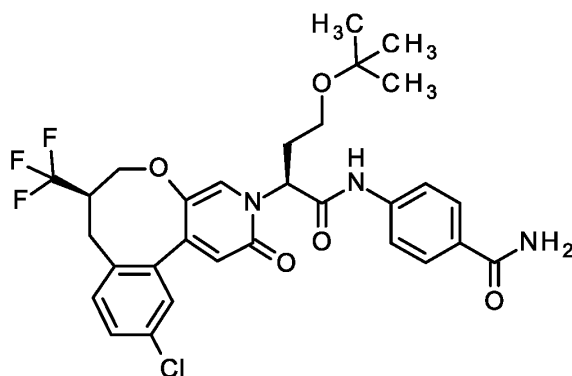
- 4-*tert*-Butoxy-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-
[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoic acid (mixture of two diastereomers) (53 mg, 0.11
mmol), pyridine (9 μ l, 0.12 mmol, 1.1 eq.) and T3P (92 μ l, 50% solution in ethyl acetate, 0.16 mmol,
5 1.5 eq.) were added under argon atmosphere at RT to a solution of 4-aminobenzamide (16 mg, 0.12
mmol, 1.1 eq.) in tetrahydrofuran (3 ml). The reaction mixture was stirred at RT for 2.5 h before
water was added. The forming precipitate was filtered, washed with water and dried *in vacuo*. Yield:
51 mg (80% of theory).

LC-MS (method 3): R_t = 3.62 min; MS (ESIpos): m/z = 606 $[M+H]^+$

- 10 $^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.75-10.55 (m, 1H), 8.02 / 7.97 (2s, 1H), 7.86 (br s,
1H), 7.85 (d, 2H), 7.70 (d, 2H), 7.57-7.31 (m, 3H), 7.25 (br s, 1H), 6.46-6.33 (m, 1H), 5.83-5.70 (m,
1H), 4.79-4.66 (m, 1H), 4.09-3.94 / 3.91-3.72 (2m, 1H), 3.63-3.57 / 3.47-3.3 (2m, 2H, partially
concealed), 3.15-3.01 (m, 2H), 2.76-2.67 / 2.62-2.5 (2m, 1H, partially concealed), 2.42-2.25 (m, 2H),
1.04 / 1.01 (2s, 9H). Additional signals of minor rotamers were also detected.

15 **Example 78**

4-({(2*S*)-4-*tert*-Butoxy-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-
[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoyl}amino)benzamide (single stereoisomer)



Diastereomer separation of 50 mg of 4-({4-*tert*-butoxy-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoyl}amino)benzamide (mixture of two diastereomers), Example 77 gave

single stereoisomer 1 (the title compound Example 78) (chiral HPLC: R_t = 1.18 min, >99% de): 18 mg,

single stereoisomer 2 (chiral HPLC: R_t = 1.71 min, 99% de): 17 mg.

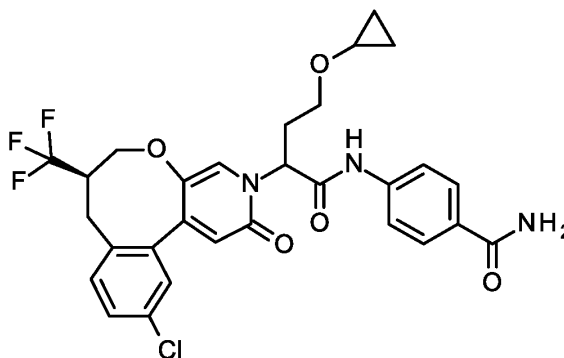
Separation method: HPLC: column: Daicel Chiralpak ID 5 μ m, 250 mm x 20 mm; eluent: 70% *n*-heptane / 30% ethanol; temperature: 40°C; flow rate: 25 ml/min; UV detection: 220 nm.

Analysis method: HPLC: column: Daicel Chiralpak ID 3 μ m, 50 mm x 4.6 mm; eluent: 70% *n*-hexane / 30% ethanol; temperature: 30°C; flow rate: 1 ml/min; UV detection: 220 nm.

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 10.70-10.55 (m, 1H), 7.97 (s, 1H), 7.89-7.81 (m, 3H), 7.70 (d, 2H), 7.57-7.31 (m, 3H), 7.24 (br s, 1H), 6.45-6.34 (m, 1H), 5.83-5.70 (m, 1H), 4.80-4.66 (m, 1H), 4.09-3.96 / 3.85-3.72 (2m, 1H), 3.48-3.3 (m, 2H, partially concealed), 3.15-3.00 (m, 2H), 2.76-2.67 / 2.62-2.5 (2m, 1H, partially concealed), 2.40-2.26 (m, 2H), 1.04 (s, 9H). Additional signals of minor rotamers were also detected.

Example 79

4-{[2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclopropyloxy)butanoyl]amino}benzamide (mixture of two diastereomers)



2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclopropyloxy)butanoic acid (mixture of two diastereomers) (66 mg, 0.14 mmol), pyridine (12 μ l, 0.15 mmol, 1.1 eq.) and T3P (123 μ l, 50% solution in ethyl acetate, 0.21 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of 4-aminobenzamide (21 mg, 0.15 mmol, 1.1 eq.) in tetrahydrofuran (3 ml). The reaction mixture was stirred at RT for 2.5 h before water was added. The forming precipitate was filtered, washed with water and dried *in vacuo*. Yield: 33 mg (40% of theory).

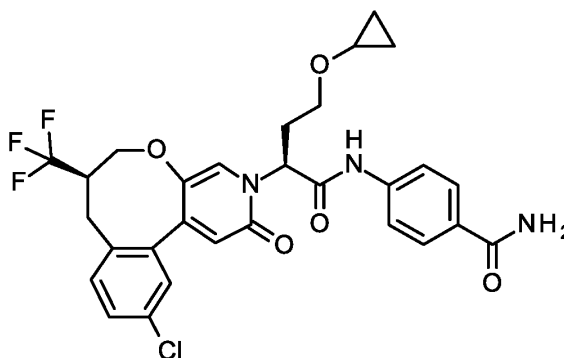
The combined filtrates were extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Yield: 24 mg (28% of theory).

24 mg-batch: LC-MS (method 4): $R_t = 1.93$ min; MS (ESIpos): $m/z = 590$ $[M+H]^+$

- 5 33 mg-batch: $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.74-10.57 (m, 1H), 8.04-7.93 (m, 1H), 7.87 (br s, 1H), 7.85 (d, 2H), 7.69 (d, 2H), 7.57-7.32 (m, 3H), 7.26 (br s, 1H), 6.46-6.33 (m, 1H), 5.80-5.66 (m, 1H), 4.80-4.66 (m, 1H), 4.10-3.95 / 3.93-3.72 (2m, 1H), 3.57-3.3 (m, 2H, partially concealed), 3.27-3.20 (m, 1H), 3.14-2.99 (m, 2H), 2.82-2.71 / 2.63-2.5 (2m, 1H, partially concealed), 2.44-2.25 (m, 2H), 0.45-0.23 (m, 4H). Additional signals of minor rotamers were also detected.

10 **Example 80**

4-{[(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclopropyloxy)butanoyl]amino}benzamide (single stereoisomer)



- Diastereomer separation of 55 mg of 4-{[2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclopropyloxy)butanoyl]amino}benzamide (mixture of two diastereomers), Example 79 gave

single stereoisomer 1 (chiral HPLC: $R_t = 7.13$ min, 99% de): 24 mg,

single stereoisomer 2 (the title compound Example 80) (chiral HPLC: $R_t = 11.69$ min, 99% de): 26 mg.

- 20 Separation method: HPLC: column: Daicel Chiralpak IG 5 μm , 250 mm x 20 mm; eluent: 40% *n*-heptane / 60% ethanol; temperature: 60°C; flow rate: 15 ml/min; UV detection: 220 nm.

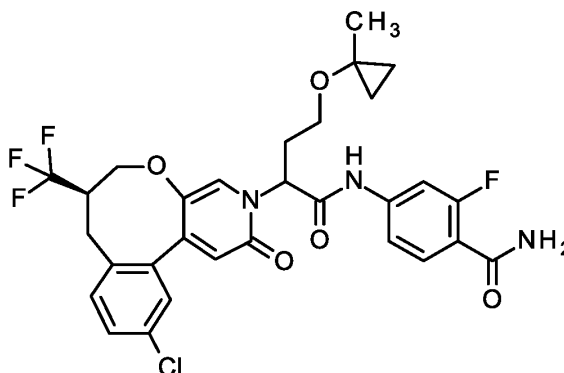
Analysis method: HPLC: column: Daicel Chiralpak IG 5 μm , 250 mm x 4.6 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 60°C; flow rate: 1 ml/min; UV detection: 220 nm.

- $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.72-10.55 (m, 1H), 7.97 (br s, 1H), 7.91-7.80 (m, 3H), 7.68 (d, 2H), 7.57-7.33 (m, 3H), 7.24 (br s, 1H), 6.46-6.33 (m, 1H), 5.80-5.66 (m, 1H), 4.81-4.65 (m, 1H), 4.10-3.99 / 3.83-3.72 (2m, 1H), 3.58-3.3 (m, 2H, partially concealed), 3.27-3.20 (m, 1H), 3.14-

2.99 (m, 2H), 2.82-2.74 / 2.63-2.5 (2m, 1H, partially concealed), 2.44-2.25 (m, 2H), 0.46-0.29 (m, 4H). Additional signals of minor rotamers were also detected.

Example 81

4-({2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-
5 c]pyridin-3-yl]-4-[(1-methylcyclopropyl)oxy]butanoyl}amino)-2-fluorobenzamide (mixture of two diastereomers)



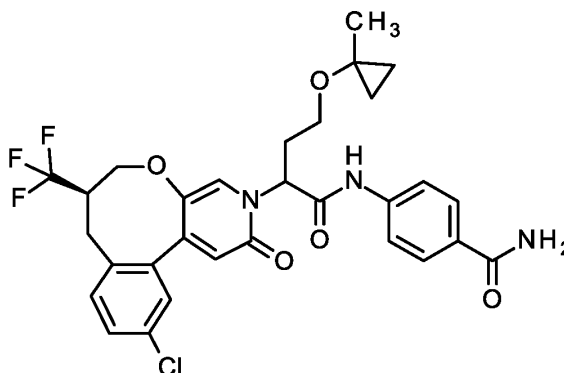
4-Amino-2-fluorobenzamide (15 mg, 0.10 mmol, 1.1 eq.), *N,N*-diisopropylethylamine (38 μ l, 0.22 mmol, 2.5 eq.) and a solution of HATU (43 mg, 0.11 mmol, 1.3 eq.) in *N,N*-dimethylformamide (1 ml) were added under argon atmosphere at RT to a solution of 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-
10 c]pyridin-3-yl]-4-[(1-methylcyclopropyl)-oxy]butanoic acid (mixture of two diastereomers) (45 mg, 93% purity, 0.09 mmol) in *N,N*-dimethylformamide (2 ml). After stirring at RT for 4.5 h, additionally 4-amino-2-fluorobenzamide (7 mg, 0.04 mmol, 0.5 eq.) and HATU (16 mg, 0.04 mmol, 0.5 eq.) were added.
15 The reaction mixture was stirred for 2 days and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 10 mg (19% of theory).

LC-MS (method 4): R_t = 2.10 min; MS (ESIpos): m/z = 622 $[M+H]^+$

1H -NMR (600 MHz, DMSO- d_6): δ [ppm] = 10.90-10.70 (m, 1H), 8.01 / 7.96 (2s, 1H), 7.72-7.61 (m, 2H), 7.59-7.47 (m, 3H), 7.46-7.33 (m, 3H), 6.46-6.33 (m, 1H), 5.76-5.63 (m, 1H), 4.78-4.66 (m, 1H), 4.10-3.94 / 3.91-3.73 (2m, 1H), 3.57-3.45 (m, 1H), 3.15-3.01 (m, 2H), 2.80-2.70 / 2.62-2.5 (2m, 1H, partially concealed), 2.41-2.27 (m, 2H), 1.27-1.16 (m, 3H), 0.64-0.56 (m, 1H), 0.54-0.38 (m, 1H), 0.35-0.22 (m, 2H). One proton is concealed. Additional signals of minor rotamers were also detected.

Example 82

4-({2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclopropyl)oxy]butanoyl}amino)benzamide (mixture of two diastereomers)



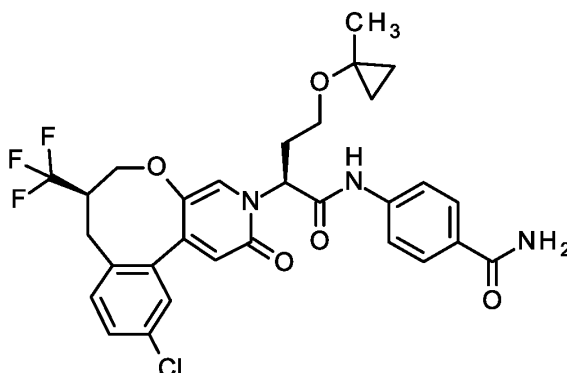
5
4-Aminobenzamide (39 mg, 0.29 mmol, 1.1 eq.), *N,N*-diisopropylethylamine (113 μ l, 0.65 mmol, 2.5 eq.) and a solution of HATU (129 mg, 0.34 mmol, 1.3 eq.) in *N,N*-dimethylformamide (1 ml) were added under argon atmosphere at RT to a solution of 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclopropyl)oxy]butanoic acid (mixture of two diastereomers) (136 mg, 93% purity, 0.26 mmol) in *N,N*-dimethylformamide (4 ml). The reaction mixture was stirred at RT for 3 h and concentrated under reduced pressure at 50°C water bath temperature. The residue was crystallized with water, filtered, washed with water and dried *in vacuo*. This residue was purified by column chromatography (silica gel, eluent: dichloromethane / methanol gradient). Yield: two batches
10
15 isolated, 83 mg and 48 mg (82% of theory for both batches together).

both batches: LC-MS (method 4): $R_t = 2.03$ min; MS (ESIpos): $m/z = 604$ $[M+H]^+$

48mg-batch: $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.72-10.56 (m, 1H), 8.01 / 7.96 (2s, 1H), 7.86 (br s, 1H), 7.84 (d, 2H), 7.69 (d, 2H), 7.56-7.33 (m, 3H), 7.25 (br s, 1H), 6.46-6.34 (m, 1H), 5.78-5.66 (m, 1H), 4.80-4.66 (m, 1H), 4.09-3.96 / 3.92-3.72 (2m, 1H), 3.66-3.45 (m, 1H), 3.3-3.20 (m, 1H, partially concealed), 3.17-3.01 (m, 2H), 2.78-2.71 / 2.60-2.5 (2m, 1H, partially concealed), 2.42-2.25 (m, 2H), 1.29-1.18 (m, 3H), 0.66-0.56 (m, 1H), 0.54-0.39 (m, 1H), 0.36-0.22 (m, 2H). Additional signals of minor rotamers were also detected.

Example 83

4-({2-[(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclopropyl)oxy]butanoyl}amino)benzamide (single stereoisomer)
25



Diastereomer separation of 122 mg of 4-({2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclopropyl)oxy]butanoyl}amino)-benzamide (mixture of two diastereomers), Example 82 gave

- 5 single stereoisomer 1 (the title compound Example 83) (chiral HPLC: R_t = 2.49 min, 99% de): 75 mg,

single stereoisomer 2 (chiral HPLC: R_t = 3.43 min, 98% de): 45 mg.

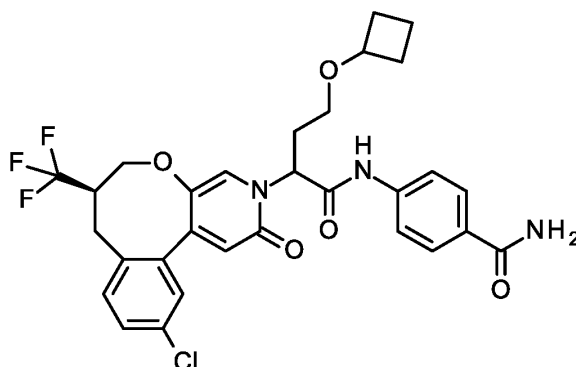
Separation method: HPLC: column: Daicel Chiralpak OZ-H 5 μ m, 250 mm x 20 mm; eluent: 50% *n*-heptane / 50% ethanol; temperature: 40°C; flow rate: 25 ml/min; UV detection: 220 nm.

- 10 Analysis method: HPLC: column: Daicel Chiralpak OZ-H 3 μ m, 50 mm x 4.6 mm; eluent: 50% *iso*-hexane / 50% ethanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.71-10.55 (m, 1H), 7.96 (s, 1H), 7.90-7.80 (m, 3H), 7.69 (d, 2H), 7.57-7.33 (m, 3H), 7.24 (br s, 1H), 6.46-6.33 (m, 1H), 5.79-5.66 (m, 1H), 4.80-4.65 (m, 1H), 4.10-4.00 / 3.83-3.72 (2m, 1H), 3.67-3.44 (m, 1H), 3.37-3.3 (m, 1H, partially concealed), 3.18-3.00 (m, 2H), 2.79-2.69 / 2.63-2.5 (2m, 1H, partially concealed), 2.89-2.25 (m, 2H), 1.28-1.18 (m, 3H), 0.66-0.58 (m, 1H), 0.55-0.44 (m, 1H), 0.37-0.25 (m, 2H). Additional signals of minor rotamers were also detected.

Example 84

- 4-{{2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-
20 c]pyridin-3-yl]-4-(cyclobutyloxy)butanamido}benzamide (mixture of two diastereomers)

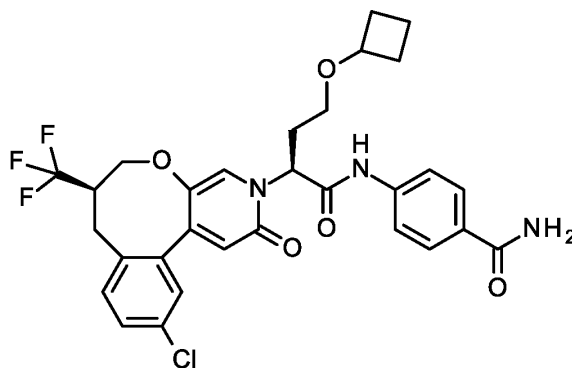


General Method 11 was carried out with 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclobutyloxy)butanoic acid (mixture of two diastereomers) (8.0 mg, 16 μ mol, 1.0 eq.), 4-aminobenzamide (3.36 mg, 25 μ mol, 1.5 eq.) and T3P (39 μ l, 50% solution in ethyl acetate, 66 μ mol, 4.0 eq.) in pyridine (0.5 ml) including the following variations of the procedure: The reaction mixture was stirred at 50°C for 2 h, concentrated under reduced pressure and purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 80:20 to 5:95). Yield: 2.3 mg (22% of theory).

LC-MS (method 3): R_t = 3.58 min; MS (ESIpos): m/z = 604 $[M+H]^+$

10 **Example 85**

4-{[(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclobutyloxy)butanoyl]amino}benzamide (single stereoisomer)



General Method 11 was carried out two times: the first time with 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclobutyloxy)butanoic acid (mixture of two diastereomers) (74.0 mg, 152 μ mol, 1.0 eq.), 4-aminobenzamide (31.1 mg, 228 μ mol, 1.5 eq.) and T3P (360 μ l, 50% solution in ethyl acetate, 610 μ mol, 4.0 eq.) in pyridine (4.6 ml) and the second time with 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-

- (cyclobutyloxy)butanoic acid (mixture of two diastereomers) (30.0 mg, 62 μmol , 1.0 eq.), 4-aminobenzamide (12.6 mg, 93 μmol , 1.5 eq.) and T3P (147 μl , 50% solution in ethyl acetate, 247 μmol , 4.0 eq.) in pyridine (1.9 ml) including the following variations of the procedure: The reaction mixtures were stirred for 4 h at 50°C, concentrated under reduced pressure and purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 80:20 to 5:95). The two product batches were combined and 50 mg of 4-{2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(cyclobutyloxy)butanamido}benzamide (mixture of two diastereomers) were further purified by diastereomer separation to provide:
- single stereoisomer 1 (the title compound 85) (chiral HPLC: R_t = 1.00 min, 92% de): 12.8 mg (10% of theory),

single stereoisomer 2 (chiral HPLC: R_t = 1.03 min): 13.2 mg.

Separation method: HPLC: column: Daicel Chiralpak IF 5 μm , 250 mm x 20 mm; eluent: 40% *n*-heptane / 60% ethanol; temperature: 40°C; flow rate: 20 ml/min; UV detection: 220 nm.

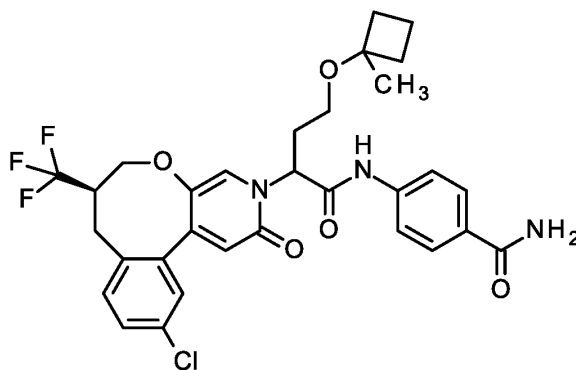
- Analysis method: HPLC: column: Daicel Chiraltek IC 3 μm , 50 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% ethanol; flow rate: 1.0 ml/min; UV detection: 220 nm.

LC-MS (method 1): R_t = 1.11 min; MS (ESIpos): m/z = 604 $[\text{M}+\text{H}]^+$

- $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.73 (s, 1H), 8.03 (s, 1H), 7.90-7.80 (m, 3H), 7.73-7.60 (m, 2H), 7.53 (br d, 1H), 7.47-7.33 (m, 2H), 7.24 (br s, 1H), 6.44 / 6.40 (2s, 1H), 5.84-5.78 (m, 1H), 4.77-4.69 (m, 1H), 3.86 (t, 1H), 3.27-3.14 (m, 1H), 3.14-2.99 (m, 2H), 2.48-2.34 (m, 2H), 2.13-1.90 (m, 1H), 1.85-1.72 (m, 1H), 1.72-1.58 (m, 2H), 1.57-1.38 (m, 2H), 1.30-1.14 (m, 3H). Additional signals of minor rotamers were also detected.

Example 86

- 4-{2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclobutyl)oxy]butanamido}benzamide (mixture of two diastereomers)

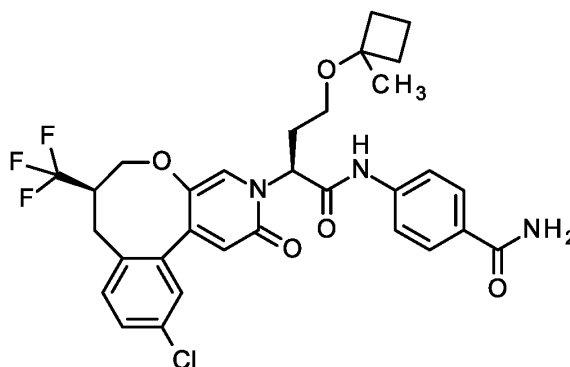


General Method 11 was carried out with 2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclobutyl)oxy]butanoic acid (mixture of two diastereomers) (44.5 mg, 89.0 μ mol, 1.0 eq.), 4-aminobenzamide (18.2 mg, 134 μ mol, 1.5 eq.) and T3P (210 μ l, 50% solution in ethyl acetate, 360 μ mol, 4.0 eq.) in pyridine (2.7 ml) including the following variations of the procedure: The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 80:20 to 5:95). Yield: 35 mg (64% of theory).

LC-MS (method 1): R_t = 1.12 min; MS (ESIpos): m/z = 618 $[M+H]^+$

Example 87

4-({(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclobutyl)oxy]butanoyl}amino)benzamide (single stereoisomer)



Diastereomer separation of 28 mg of 4-{{2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-[(1-methylcyclobutyl)oxy]butanamido}benzamide (mixture of two diastereomers), Example 86 gave single stereoisomer 1 (the title compound 87) (chiral HPLC: R_t = 5.44 min, 99% de): 10.6 mg (19% of theory),

single stereoisomer 2 (chiral HPLC: R_t = 6.52 min): 6.2 mg.

Separation method: HPLC: column: Daicel Chiralpak IE 5 μ m, 250 mm x 20 mm; eluent: 50% *n*-heptane / 50% 2-propanol; temperature: 40°C; flow rate: 15 ml/min; UV detection: 235 nm.

Analysis method: HPLC: column: Daicel Chiraltek IE 5 μ m, 250 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% 2-propanol; flow rate: 1.0 ml/min; UV detection: 220 nm.

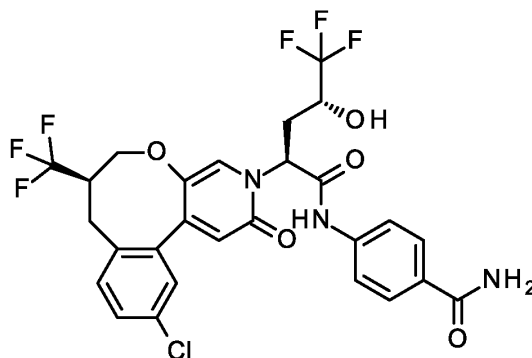
LC-MS (method 1): R_t = 1.08 min; MS (ESIpos): m/z = 618 $[M+H]^+$

1 H-NMR (500 MHz, DMSO- d_6): δ [ppm] = 10.70 / 10.62 (2br s, 1H), 7.98 (br s, 1H), 7.84 (br d, 3H), 7.70 (br d, 2H), 7.52 (br s, 1H), 7.48-7.32 (m, 2H), 7.24 (br s, 1H), 6.44 / 6.40 (2s, 1H), 5.84-5.72 (m, 1H), 4.82-4.64 (m, 1H), 3.82-3.72 (m, 1H), 3.23-3.17 (m, 1H), 3.13-3.02 (m, 2H), 2.61-2.24 (m,

1H), 2.04-1.92 (m, 1H), 1.90-1.80 (m, 1H), 1.77-1.29 (m, 6H), 1.28-1.21 (m, 1H), 1.18 (s, 3H). Additional signals of minor rotamers were also detected.

Example 88

- 4-({(2*S*,4*R*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-
5 [3]benzoxocino[2,1-*c*]pyridin-3-yl]-5,5,5-trifluoro-4-hydroxypentanoyl}amino)benzamide (single stereoisomer)



- To a solution of 4-[(4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-5,5,5-
10 trifluoropentanoyl)amino]benzamide (mixture of two diastereomers) (87.0 mg, 57% purity, 67.7 μmol, 1.0 eq.) in tetrahydrofuran (4.0 ml) was added a solution of tetra-*n*-butylammoniumfluoride (200 μl, 1.0 M in tetrahydrofuran, 200 μmol, 3.0 eq.) at RT. The mixture was stirred for 3 h and then concentrated under reduced pressure and further purified by diastereomer separation to provide:

- single stereoisomer 1 (LC-MS (method 5): $R_t = 1.27$ min): 2.4 mg
15 single stereoisomer 2 (the title compound 88) (LC-MS (method 5): $R_t = 1.28$ min, 99% de): 2.1 mg (5% of theory).

Separation method: HPLC: column: Phenomenex Kinetex C18 5 μm, 100 x 30 mm; eluent: 80% water with 2.0% formic acid / 20% acetonitrile; temperature: RT; flow rate: 80 ml/min; UV detection: 220 nm.

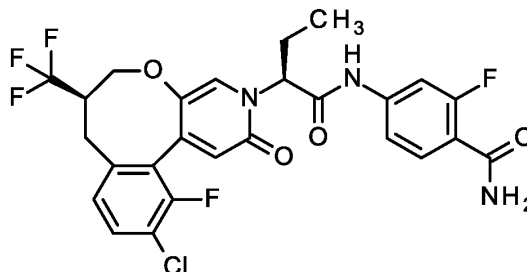
- 20 Analysis method: LC-MS: method 5

LC-MS (method 5): $R_t = 1.28$ min; MS (ESI^{neg}): $m/z = 616$ [M-H]⁻

- ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 10.63 (br s, 1H), 7.93 (s, 1H), 7.89-7.81 (m, 3H), 7.68 (d, 2H), 7.59-7.46 (m, 1H), 7.46-7.34 (m, 2H), 7.26 (br s, 1H), 6.52-6.34 (m, 2H), 5.86-5.66 (m, 1H), 4.75-4.62 (m, 1H), 4.18-4.04 (m, 1H), 4.03-3.87 (m, 1H), 3.18-2.96 (m, 2H), 2.71-2.49 (m, 2H),
25 2.25-2.09 (m, 1H). Additional signals of minor rotamers were also detected.

Example 89

4-({(2*S*)-2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoyl}amino)-2-fluorobenzamide (single stereoisomer)



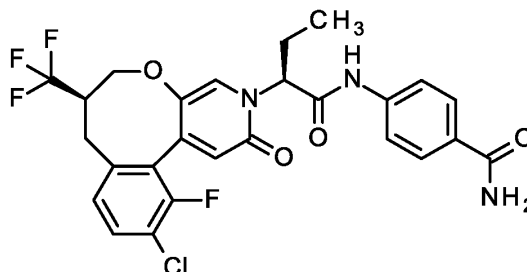
- 5 General Method 7 was carried out with (7*R*)-11-chloro-12-fluoro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (60.0 mg, 76% purity, 131 μ mol, 1.0 eq.), 4-{{(2*R*)-2-bromobutanoyl}amino}-2-fluorobenzamide (single stereoisomer) (47.7 mg, 157 μ mol, 1.2 eq.) and 1,1,3,3-tetramethylguanidine (49 μ l, 390 μ mol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 1.2 ml) including the following variations of the procedure: The crude
10 mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 34.0 mg (41% of theory).

LC-MS (method 1): R_t = 1.69 min; MS (ESIpos): m/z = 570 $[M+H]^+$

- $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.90 / 10.83 (2s, 1H), 8.06 / 8.02 (2s, 1H), 7.74-7.59 (m, 3H), 7.58-7.47 (m, 2H), 7.44-7.36 (m, 1H), 7.34-7.28 (m, 1H), 6.55 / 6.49 (2d, 1H), 5.60-5.50
15 (m, 1H), 4.79-4.67 (m, 1H), 3.86 / 3.78 (2t, 1H), 3.19-2.97 (m, 2H), 2.60-2.46 (m, 1H), 2.25-2.04 (m, 2H), 0.94-0.91 (2t, 3H). Additional signals of minor rotamers were also detected.

Example 90

4-({(2*S*)-2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]butanoyl}amino)benzamide (single stereoisomer)



20

General Method 7 was carried out with (7*R*)-11-chloro-12-fluoro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (60.0 mg, 76% purity, 131 μ mol,

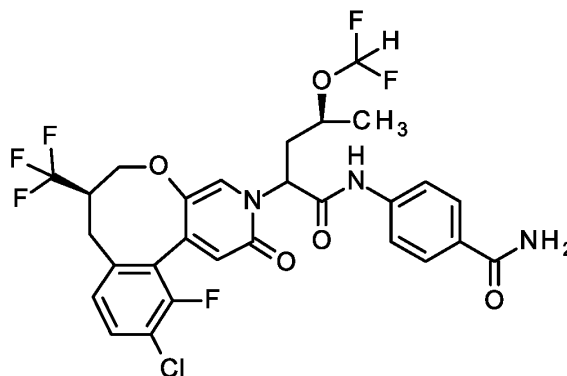
1.0 eq.), 4-[(2*R*)-2-bromobutanoyl]amino}benzamide (single stereoisomer) (44.9 mg, 157 μ mol, 1.2 eq.) and 1,1,3,3-tetramethylguanidine (49 μ l, 390 μ mol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 1.2 ml) including the following variations of the procedure: The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 42.0 mg (57% of theory).

LC-MS (method 3): R_t = 3.22 min; MS (ESIpos): m/z = 552 $[M+H]^+$

1H -NMR (400 MHz, DMSO- d_6): δ [ppm] = 10.73 / 10.67 (2s, 1H), 8.07 / 8.03 (2s, 1H), 7.93-7.79 (m, 3H), 7.74-7.60 (m, 3H), 7.31 (d, 1H), 7.27-7.18 (m, 1H), 6.54 / 6.48 (2d, 1H), 5.64-5.55 (m, 1H), 4.79-4.67 (m, 1H), 3.78 (t, 1H), 3.30-3.24 (m, 1H), 3.16-2.96 (m, 2H), 2.24-2.05 (m, 2H), 0.97-0.86 (m, 3H). Additional signals of minor rotamers were also detected.

Example 91

4-[(4*S*)-2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)pentanoyl]amino}benzamide (mixture of two diastereomers)



15

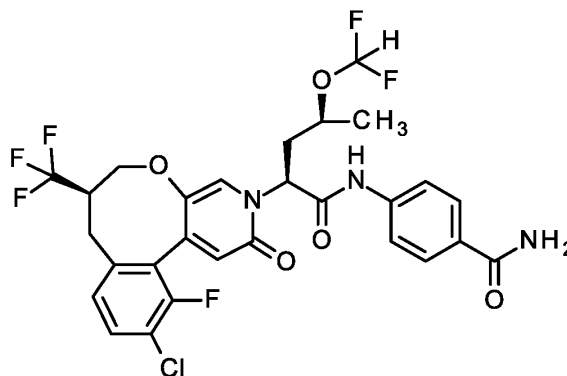
(2*S*)-2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-(difluoromethyl)-*L*-glycero-pentonic acid (mixture of two diastereomers) (116 mg, 60% purity, 135 μ mol, 1.0 eq.) was dissolved in dichloromethane (5.0 ml), 1-chloro-*N,N*,2-trimethylprop-1-en-1-amine (23 μ l, 180 μ mol, 1.3 eq.) was added and the reaction mixture was stirred for 10 min. Then 4-aminobenzamide (24.0 mg, 176 μ mol, 1.3 eq.) was added and the reaction mixture was stirred for 3 h. All volatiles were removed under reduced pressure and the residue was dissolved in *N,N*-dimethylformamide (4.0 ml). Then HATU (77.3 mg, 203 μ mol, 1.5 eq.) and *N,N*-diisopropylethylamine (71 μ l, 410 μ mol, 3.0 eq.) were added and the mixture was stirred at RT overnight and at 50°C for 1 h. The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 43.0 mg (49% of theory).

20

LC-MS (method 3): R_t = 3.40 min; MS (ESIpos): m/z = 632 $[M+H]^+$

Example 92

4-{[(2*S*,4*S*)-2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)pentanoyl]amino}benzamide (single stereoisomer)



5 Diastereomer separation of 37 mg of 4-{[(4*S*)-2-[(7*R*)-11-chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-(difluoromethoxy)pentanoyl]amino}-benzamide (mixture of two diastereomers), Example 91 gave single stereoisomer 1 (the title compound 92) (chiral HPLC: $R_t = 7.95$ min, 97% de): 9.0 mg (10% of theory),

single stereoisomer 2 (chiral HPLC: $R_t = 10.31$ min): 22.0 mg.

Separation method: HPLC: column: Daicel Chiralpak ID 5 μm , 250 mm x 20 mm; eluent: 80% *n*-heptane / 20% ethanol; temperature: RT; flow rate: 15 ml/min; UV detection: 220 nm.

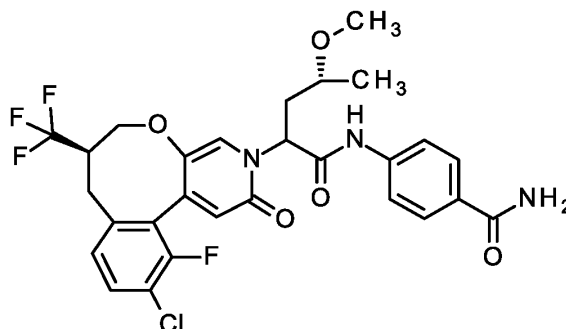
15 Analysis method: HPLC: column: Daicel Chiralpak ID 5 μm , 250 mm x 4.6 mm; eluent: 80% *iso*-hexane / 20% ethanol; temperature: 50°C, flow rate: 1.0 ml/min; UV detection: 220 nm.

LC-MS (method 1): $R_t = 1.04$ min; MS (ESIpos): $m/z = 632$ $[\text{M}+\text{H}]^+$

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.73 / 10.56 (2s, 1H), 8.08 / 8.04 (2s, 1H), 7.92-7.79 (m, 3H), 7.74-7.60 (m, 3H), 7.35-7.27 (m, 1H), 7.27-7.18 (m, 1H), 6.80-6.77 / 6.66-6.60 (2m, 1H), 6.56-6.47 (m, 1H), 5.85 / 5.77 (dd, 1H), 4.78-4.67 (m, 1H), 4.30-4.13 (m, 1H), 3.85-3.71 (m, 1H), 20 3.14-2.90 (m, 2H), 2.68-2.53 (m, 1H), 2.48-2.33 (m, 2H), 1.38-1.09 (m, 3H). Additional signals of minor rotamers were also detected.

Example 93

4-({(4*R*)-2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (mixture of two diastereomers)

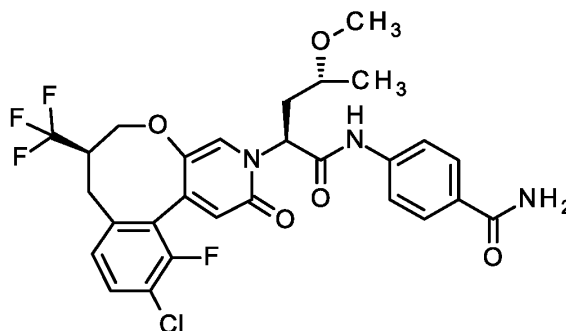


- (2*ξ*)-2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*D*-glycero-pentonic acid (mixture of two diastereomers) (90.0 mg, 188 μ mol, 1.0 eq.) was dissolved in dichloromethane (5.0 ml), 1-chloro-*N,N*,2-trimethylprop-1-en-1-amine (32 μ l, 240 μ mol, 1.3 eq.) was added and the reaction mixture was stirred for 10 min. Then 4-aminobenzamide (33.3 mg, 245 μ mol, 1.3 eq.) was added and the reaction mixture was stirred overnight. All volatiles were removed under reduced pressure and General Method 11 was carried out with the residue using T3P (170 μ l, 50% solution in ethyl acetate, 280 μ mol, 1.5 eq.), pyridine (18 μ l, 226 μ mol, 1.2 eq.) in tetrahydrofuran (4.0 ml). The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 58.0 mg (49% of theory).

LC-MS (method 3): R_t = 3.24 min; MS (ESIpos): m/z = 596 $[M+H]^+$

Example 94

- 4-({(2*S*,4*R*)-2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (single stereoisomer)



- Diastereomer separation of 52 mg of 4-({(4*R*)-2-[(7*R*)-11-chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (mixture of two diastereomers), Example 93 gave single stereoisomer 1 (the title compound 94) (chiral HPLC: R_t = 3.39 min, >99% de): 13.1 mg (12% of theory),

single stereoisomer 2 (chiral HPLC: R_t = 6.91 min): 15.9 mg.

Separation method: HPLC: column: Daicel OZ 5 μ m, 250 mm x 20 mm; eluent: 50% *n*-heptane / 50% 2-propanol; temperature: RT; flow rate: 20 ml/min; UV detection: 220 nm.

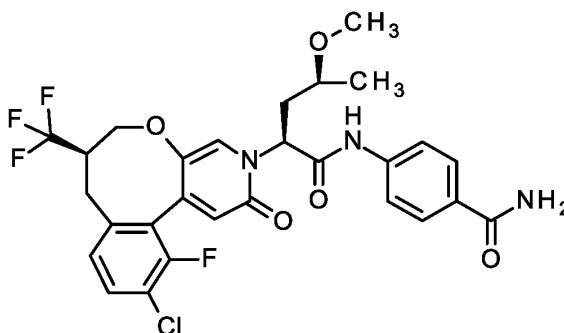
Analysis method: HPLC: column: Daicel Chiralpak OX-3 3 μ m, 50 mm x 4.6 mm; eluent: 80%
5 *n*-heptane / 20% ethanol; flow rate: 1.0 ml/min; UV detection: 220 nm.

LC-MS (method 5): R_t = 1.30 min; MS (ESI^{neg}): m/z = 594 [M-H]⁻

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 10.72 / 10.62 (2s, 1H), 8.08 / 8.07 (2s, 1H), 7.90-7.81
(m, 3H), 7.73-7.60 (m, 3H), 7.31 (d, 1H), 7.27-7.20 (m, 1H), 6.53 / 6.47 (2d, 1H), 5.86 / 5.80 (2dd,
1H), 4.80-4.67 (m, 1H), 3.77 (t, 1H), 3.20-3.04 (m, 6H), 2.62-2.55 (m, 1H), 2.38-2.19 (m, 2H), 1.20-
10 1.08 (m, 3H). Additional signals of minor rotamers were also detected.

Example 95

4-({(2*S*,4*S*)-2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-
[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (single stereoisomer)



15 General Method 11 was carried out with (2*S*)-2-[(7*R*)-11-chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonic acid (mixture of two diastereomers) (139 mg, 290 μ mol, 1.0 eq.), 4-aminobenzamide (51.3 mg, 377 μ mol, 1.3 eq.), T3P (259 μ l, 50% solution in ethyl acetate, 435 μ mol, 1.5 eq.) and pyridine (28 μ l, 350 μ mol, 1.2 eq.) in tetrahydrofuran (8.0 ml) at RT including the
20 following variations of the procedure: After 3 h, additional amounts of 4-aminobenzamide (11.8 mg, 87 μ mol, 0.3 eq.), pyridine (8.2 μ l, 102 μ mol, 0.35 eq.) and T3P (48 μ l, 50% solution in ethyl acetate, 81 μ mol, 0.28 eq.) were added and stirring was continued overnight. The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95).

25 Diastereomer separation of 13 mg of 4-({(4*S*)-2-[(7*R*)-11-chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (mixture of two diastereomers) gave

single stereoisomer 1 (the title compound 95) (chiral HPLC: R_t = 5.81 min, 99% de): 5.2 mg (3% of theory),

single stereoisomer 2 (chiral HPLC: R_t = 8.47 min): 1.6 mg.

Separation method: HPLC: column: Daicel Chiralpak ID 5 μ m, 250 mm x 20 mm; eluent: 80%
5 *n*-heptane / 20% ethanol; temperature: 40°C; flow rate: 25 ml/min; UV detection: 265 nm.

Analysis method: HPLC: column: Daicel Chiraltek ID 3 μ m, 250 mm x 4.6 mm; eluent: 80%
n-heptane / 20% ethanol; flow rate: 1.0 ml/min; UV detection: 220 nm.

LC-MS (method 3): R_t = 1.29 min; MS (ESI^{neg}): m/z = 594 [M-H]⁻

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 9.75 / 9.63 (2br s, 1H), 7.80 (br d, 2H), 7.74-7.67 (m, 2H),
10 7.60 / 7.59 (2s, 1H), 7.48-7.41 (m, 1H), 7.08 (d, 1H), 6.66 (d, 1H), 5.93 (br dd, 1H), 6.20-5.58 (m,
2H), 4.75 (dd, 1H), 3.78 (t, 1H), 3.53-3.43 (m, 1H), 3.37-3.27 (m, 3H), 3.06 (br d, 1H), 2.79-2.68
(m, 1H), 2.65-2.53 (m, 2H), 1.97-1.89 (m, 1H), 1.27 (d, 3H). Additional signals of minor rotamers
were also detected.

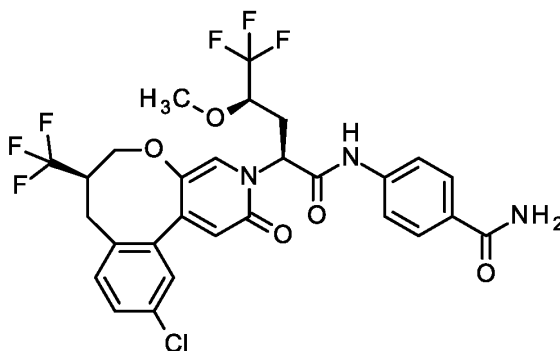
Alternatively, General Method 7 was carried out with (7*R*)-11-chloro-12-fluoro-7-(trifluoromethyl)-
15 7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (43.0 mg, 124 μ mol,
1.0 eq.), 4-{[(2*R*,4*S*)-2-bromo-4-methoxypentanoyl]amino}benzamide (single stereoisomer)
(44.9 mg, 124 μ mol, 1.0 eq.) and 1,1,3,3-tetramethylguanidine (47 μ l, 371 μ mol, 3.0 eq.) in a mixture
of 2-propanol / acetone (4:1, 2.0 ml) including the following variations of the procedure: The crude
mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid /
20 acetonitrile 80:20 to 5:95). Yield: 42.0 mg (57% of theory).

LC-MS (method 1): R_t = 0.98 min; MS (ESI^{pos}): m/z = 596 [M+H]⁺

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 9.77 (br s, 1H), 7.80 (br d, 2H), 7.74-7.67 (m, 2H), 7.61 (s,
1H), 7.48-7.41 (m, 1H), 7.08 (d, 1H), 6.66 (d, 1H), 5.93 (br dd, 1H), 6.20-5.63 (m, 2H), 4.75 (dd,
1H), 3.78 (t, 1H), 3.53-3.44 (m, 1H), 3.37-3.27 (m, 3H), 3.06 (br d, 1H), 2.80-2.68 (m, 1H), 2.65-
25 2.53 (m, 2H), 1.97-1.89 (m, 1H), 1.27 (d, 3H). Additional signals of minor rotamers were also
detected.

Example 96

4-({(2*S*,4*R*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-
[3]benzoxocino[2,1-*c*]pyridin-3-yl]-5,5,5-trifluoro-4-methoxypentanoyl}amino)benzamide (single
30 stereoisomer)



General Method 7 was carried out with (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (15.0 mg, 45.5 μ mol, 1.0 eq.), 4-{[(2*R*,4*R*)-2-bromo-5,5,5-trifluoro-4-methoxypentanoyl]amino}benzamide (single stereoisomer) (20.9 mg, 54.6 μ mol, 1.2 eq.) and 1,1,3,3-tetramethylguanidine (17 μ l, 140 μ mol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 0.8 ml) including the following variations of the procedure: The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Due to epimerization, a mixture of stereoisomers was obtained (d.r. 3.6:1). Yield: 16.0 mg (55% of theory).

LC-MS (method 3): R_t = 3.62 / 3.67 min; MS (ESIpos): m/z = 632 $[M+H]^+$

Stereoisomer separation of 16.0 mg of this epimerized mixture provides:

single stereoisomer 1 (chiral HPLC: R_t = 1.25 min): 2.5 mg,

single stereoisomer 2 (the title compound 96) (chiral HPLC: R_t = 2.59 min, 99% de): 6.5 mg (23% of theory).

Separation method: HPLC: column: Daicel Chiralpak IE 5 μ m, 250 mm x 20 mm; eluent: 50% *n*-heptane / 50% ethanol; temperature: 40°C; flow rate: 20 ml/min; UV detection: 210 nm.

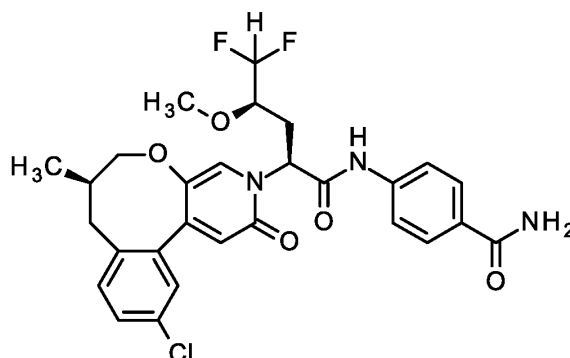
Analysis method: HPLC: column: Daicel Chiralpak IE-3 3 μ m, 50 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% ethanol; flow rate: 1.0 ml/min; UV detection: 220 nm.

LC-MS (method 3): R_t = 3.51; MS (ESIpos): m/z = 632 $[M+H]^+$

¹H-NMR (500 MHz, DMSO-*d*₆): δ [ppm] = 10.69 / 10.48 (2br s, 1H), 8.00 (br s, 1H), 7.93-7.81 (m, 3H), 7.69 (br d, 2H), 7.58-7.44 (m, 1H), 7.44-7.33 (m, 2H), 7.26 (br s, 1H), 6.45 / 6.40 (2br s, 1H), 5.90 / 5.76 (2br s, 1H), 4.79-4.65 (m, 1H), 4.13-3.92 (m, 1H), 3.86-3.71 (m, 1H), 3.40 (s, 3H), 3.06 (br d, 2H), 2.69-2.54 (m, 2H), 2.38-2.16 (m, 1H). Additional signals of minor rotamers were also detected.

Example 97

4-({(2*S*,4*R*)-2-[(7*R*)-11-Chloro-7-methyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-5,5-difluoro-4-methoxypentanoyl}amino)benzamide (single stereoisomer)



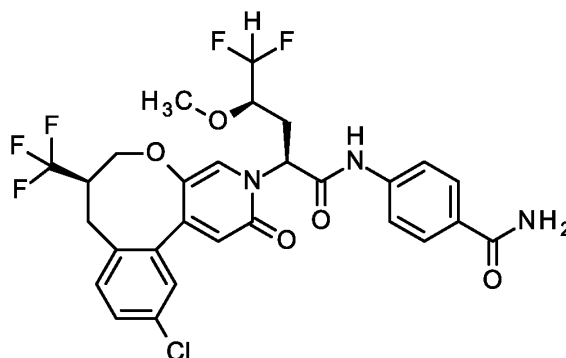
- 5 1,1,3,3-Tetramethylguanidine (19 μ l, 0.15 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-methyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (14 mg, 0.05 mmol) in 2-propanol / acetone (4:1, 0.5 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-{{(2*R*,4*R*)-2-bromo-5,5-difluoro-4-methoxypentanoyl}amino}benzamide (single stereoisomer) (21 mg, 0.06 mmol, 1.1 eq.) and further
- 10 2-propanol / acetone (4:1, 0.5 ml). The reaction mixture was stirred at RT for 7 days and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 22 mg (79% of theory).

LC-MS (method 4): R_t = 1.86 min; MS (ESIpos): m/z = 560 $[M+H]^+$

- ¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 10.84-10.46 (br s, 1H), 7.90-7.77 (m, 4H), 7.73-7.66 (m, 2H), 7.48-7.38 (m, 2H), 7.37-7.28 (m, 1H), 7.23 (br s, 1H), 6.43-6.34 (m, 1H), 6.25-6.00 (m, 1H),
- 15 5.91-5.76 (m, 1H), 4.52-4.45 / 4.32-4.24 / 3.91-3.81 / 3.59-3.47 (4m, 2H), 3.33 (s, 3H), 2.89-2.82 / 2.75-2.64 (2m, 2H), 2.47-2.15 (m, 2H), 2.14-1.96 (m, 2H), 0.95-0.83 (m, 3H). Additional signals of minor rotamers were also detected.

Example 98

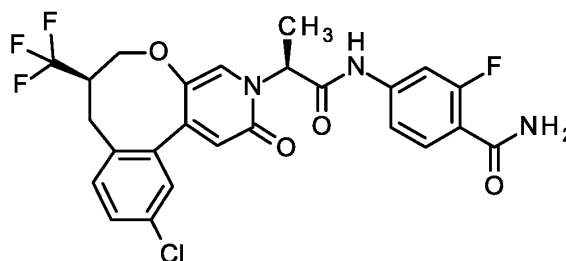
- 20 4-({(2*S*,4*R*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-5,5-difluoro-4-methoxypentanoyl}amino)benzamide (single stereoisomer)



- 1,1,3,3-Tetramethylguanidine (30 μ l, 0.24 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (26 mg, 0.08 mmol) in 2-propanol / acetone (4:1, 1.0 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-{[(2*R*,4*R*)-2-bromo-5,5-difluoro-4-methoxypentanoyl]amino}benzamide (single stereoisomer) (33 mg, 0.09 mmol, 1.1 eq.) and further 2-propanol / acetone (4:1, 1.0 ml). The reaction mixture was stirred at RT for 2 days and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 36 mg (73% of theory).
- 10 LC-MS (method 1): R_t = 1.00 min; MS (ESIpos): m/z = 614 $[M+H]^+$
- $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.89-10.38 (m, 1H), 8.07-7.92 (m, 1H), 7.91-7.80 (m, 3H), 7.73-7.65 (m, 2H), 7.56-7.32 (m, 3H), 7.25 (br s, 1H), 6.50-6.36 (m, 1H), 6.26-6.00 (m, 1H), 5.92-5.71 (m, 1H), 4.80-4.64 / 4.11-3.97 / 3.92-3.84 / 3.82-3.72 / 3.64-3.49 / 3.3-3.18 (6m, 3H, partially concealed), 3.33 (s, 3H), 3.14-2.98 (m, 2H), 2.84-2.74 / 2.65-2.55 (2m, 1H), 2.5-2.40 / 2.38-2.26 / 2.22-2.08 (3m, 2H, partially concealed). Additional signals of minor rotamers were also detected.
- 15

Example 99

4-({(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]propanoyl}amino)-2-fluorobenzamide (single stereoisomer)



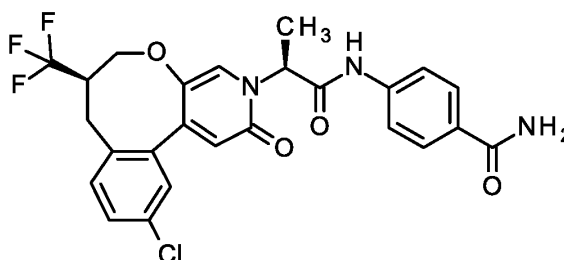
1,1,3,3-Tetramethylguanidine (22 μ l, 0.18 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (20 mg, 0.06 mmol) in 2-propanol / acetone (4:1, 1.0 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-{[(2*R*)-2-bromopropanoyl]amino}-
5 2-fluorobenzamide (single stereoisomer) (19 mg, 0.07 mmol, 1.1 eq.) and of further 2-propanol / acetone (4:1, 1.0 ml). The reaction mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 27 mg (85% of theory).

LC-MS (method 4): R_t = 1.82 min; MS (ESIpos): m/z = 538 $[M+H]^+$

10 $^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.92-10.36 (br s, 1H), 7.97-7.88 (m, 1H), 7.73-7.66 (m, 1H), 7.66-7.60 (m, 1H), 7.56-7.32 (m, 6H), 6.45-6.32 (m, 1H), 5.57-5.47 (m, 1H), 4.78-4.64 (m, 1H), 4.15-4.05 / 3.98-3.77 (2m, 1H), 3.13-2.95 (m, 2H), 2.84-2.73 / 2.60-2.5 (2m, 1H, partially concealed), 1.75-1.64 (m, 3H). Additional signals of minor rotamers were also detected.

Example 100

15 4-({(2*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]propanoyl}amino)benzamide (single stereoisomer)



1,1,3,3-Tetramethylguanidine (23 μ l, 0.18 mmol, 3.0 eq.) was added under argon atmosphere at RT to a solution of (7*R*)-11-chloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (20 mg, 0.06 mmol) in 2-propanol / acetone (4:1, 1.0 ml). The mixture was stirred at RT for 15 min, followed by addition of 4-{[(2*R*)-2-bromopropanoyl]amino}benzamide (single stereoisomer) (18 mg, 0.07 mmol, 1.1 eq.) and of further 2-propanol / acetone (4:1, 1.0 ml). The reaction mixture was stirred at RT overnight and concentrated under reduced pressure. The residue was purified by preparative HPLC (reversed phase, eluent:
25 acetonitrile / water gradient). Yield: 21 mg (68% of theory).

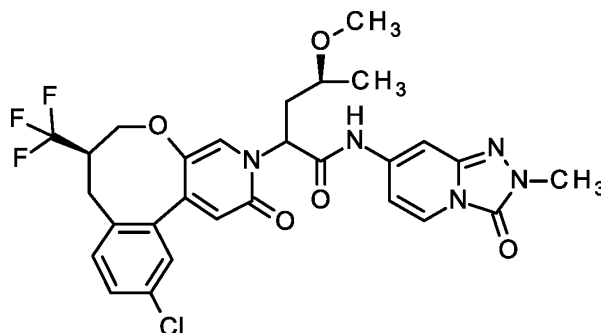
LC-MS (method 4): R_t = 1.75 min; MS (ESIpos): m/z = 520 $[M+H]^+$

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.64-10.54 (m, 1H), 7.97-7.90 (m, 1H), 7.90-7.82 (m, 3H), 7.67 (d, 2H), 7.57-7.38 (m, 3H), 7.24 (br s, 1H), 6.44-6.35 (m, 1H), 5.61-5.52 (m, 1H), 4.80-

4.64 / 4.16-4.04 / 3.88-3.76 (3m, 2H), 3.14-2.99 (m, 2H), 2.84-2.74 / 2.64-2.5 (2m, 1H, partially concealed), 1.75-1.64 (m, 3H). Additional signals of minor rotamers were also detected.

Example 101

- 5 (4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]-pyridin-3-yl]-4-methoxy-*N*-(2-methyl-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)-pentanamide (mixture of two diastereomers)



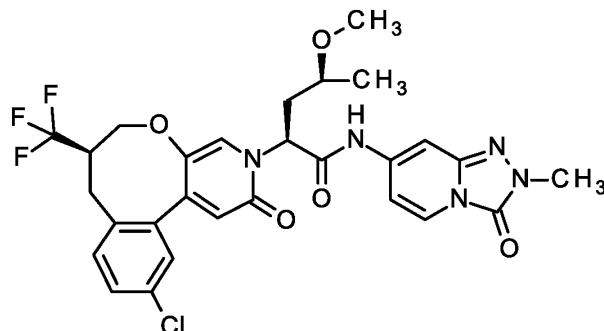
- 10 7-Amino-2-methyl[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochloride (25 mg, 0.12 mmol, 1.1 eq.), pyridine (27 μ l, 0.34 mmol, 3.0 eq.) and T3P (98 μ l, 50% solution in ethyl acetate, 0.17 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of (2*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonic acid (mixture of two diastereomers) (55 mg, 93% purity, 0.11 mmol) in tetrahydrofuran (4 ml). The reaction mixture was stirred at RT for 45 min and concentrated *in vacuo*. The residue was purified by preparative HPLC (reversed phase, eluent: 15 acetonitrile / water gradient). Yield: 59 mg (87% of theory).

LC-MS (method 1): R_t = 0.99 min; MS (ESIpos): m/z = 606 $[M+H]^+$

- 20 $^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.83-10.66 (m, 1H), 8.06-7.96 (m, 1H), 7.86-7.80 (m, 1H), 7.64-7.59 (m, 1H), 7.56-7.32 (m, 3H), 6.75-6.65 (m, 1H), 6.45-6.35 (m, 1H), 5.82-5.67 (m, 1H), 4.78-4.66 (m, 1H), 4.08-3.74 (m, 1H), 3.48 / 3.48 (2s, 3H), 3.3-3.30 (m, 3H, partially concealed), 3.18 / 3.11 (2s, 3H), 2.84-2.71 / 2.60-2.5 (2m, 1H, partially concealed), 2.41-2.17 (m, 2H), 1.18-1.10 (m, 3H). Additional signals of minor rotamers were also detected.

Example 102

- 25 (2*S*,4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-(2-methyl-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)-pentanamide (single stereoisomer)



Diastereomer separation of 56 mg of (4*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-(2-methyl-3-oxo-2,3-dihydro[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)pentanamide (mixture of two diastereomers), Example 101
 5 gave

single stereoisomer 1 (the title compound Example 102) (chiral HPLC: R_t = 8.43 min, >99% de): 16 mg,

single stereoisomer 2 (chiral HPLC: R_t = 10.76 min, >99% de): 30 mg.

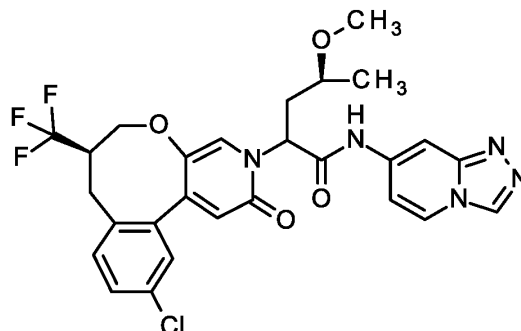
Separation method: HPLC: column: Daicel Chiralcel OX-H 5 μ m, 250 mm x 20 mm; eluent: 70%
 10 *n*-heptane / 30% ethanol; temperature: 40°C; flow rate: 20 ml/min; UV detection: 220 nm.

Analysis method: HPLC: column: Daicel Chiralcel OX-H 5 μ m, 250 mm x 4.6 mm; eluent: 70%
iso-hexane / 30% ethanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.

¹H-NMR (600 MHz, DMSO-*d*₆): δ [ppm] = 10.89-10.71 (m, 1H), 8.06-7.98 (m, 1H), 7.89-7.83 (m, 1H), 7.68-7.61 (m, 1H), 7.57-7.32 (m, 3H), 6.74-6.67 (m, 1H), 6.46-6.35 (m, 1H), 5.83-5.66 (m, 1H),
 15 4.79-4.66 (m, 1H), 4.08-3.98 / 3.83-3.74 (2m, 1H), 3.48 (s, 3H), 3.30-2.98 (m, 3H), 3.17 (s, 3H), 2.82-2.76 / 2.60-2.5 (2m, 1H, partially concealed), 2.34-2.18 (m, 2H), 1.15 (d, 3H). Additional signals of minor rotamers were also detected.

Example 103

(4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]-
 20 pyridin-3-yl]-4-methoxy-*N*-([1,2,4]triazolo[4,3-*a*]pyridin-7-yl)pentanamide (mixture of two diastereomers)



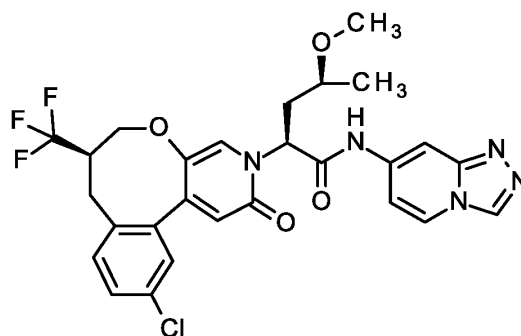
[1,2,4]Triazolo[4,3-a]pyridin-7-amine hydrochloride (22 mg, 0.13 mmol, 1.1 eq.), pyridine (28 μ l, 0.35 mmol, 3.0 eq.) and T3P (102 μ l, 50% solution in ethyl acetate, 0.17 mmol, 1.5 eq.) were added under argon atmosphere at RT to a solution of (2*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonic acid (mixture of two diastereomers) (57 mg, 94% purity, 0.12 mmol) in tetrahydrofuran (4 ml). The reaction mixture was stirred at RT overnight. Further [1,2,4]triazolo[4,3-a]pyridin-7-amine hydrochloride (10 mg, 0.06 mmol, 0.5 eq.), pyridine (9 μ l, 0.12 mmol, 1.0 eq.) and T3P (102 μ l, 50% solution in ethyl acetate, 0.17 mmol, 1.5 eq.) were added. The reaction mixture was stirred at RT for additional 3 days and concentrated *in vacuo*. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 31 mg (46% of theory).

LC-MS (method 4): R_t = 1.76 min; MS (ESIpos): m/z = 576 $[M+H]^+$

$^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.95-10.77 (m, 1H), 9.14/9.14 (2s, 1H), 8.53-8.47 (m, 1H), 8.17-8.10 (m, 1H), 8.08-8.00 (m, 1H), 7.62-7.32 (m, 3H), 7.14-7.05 (m, 1H), 6.46-6.30 (m, 1H), 5.87-5.73 (m, 1H), 4.80-4.60 (m, 1H), 4.10-3.76 (m, 1H), 3.3-2.95 (m, 3H, partially concealed), 3.19 / 3.11 (2s, 3H), 2.84-2.72 / 2.60-2.46 (2m, 1H, partially concealed), 2.43-2.20 (m, 2H), 1.20-1.11 (m, 3H). Additional signals of minor rotamers were also detected.

Example 104

(2*S*,4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-([1,2,4]triazolo[4,3-a]pyridin-7-yl)pentanamide (single stereoisomer)



Diastereomer separation of 29 mg of (4*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-([1,2,4]triazolo[4,3-*a*]pyridin-7-yl)pentanamide (mixture of two diastereomers), Example 103 gave

single stereoisomer 1 (the title compound Example 104) (chiral HPLC: R_t = 3.11 min, 96% de): 4 mg,

5 single stereoisomer 2 (chiral HPLC: R_t = 4.15 min, 97% de): 8 mg.

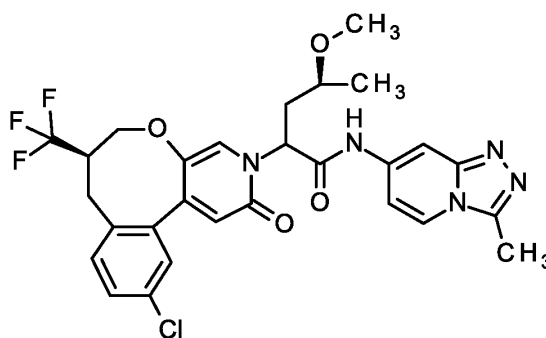
Separation method: HPLC: column: Daicel Chiralcel OZ-H 5 μ m, 250 mm x 20 mm; eluent: 80% *n*-heptane / 20% ethanol; temperature: 50°C; flow rate: 30 ml/min; UV detection: 220 nm.

Analysis method: HPLC: column: Daicel Chiralcel OZ-H 3 μ m, 50 mm x 4.6 mm; eluent: 70% *n*-heptane / 30% ethanol; temperature: 40°C; flow rate: 1 ml/min; UV detection: 220 nm.

10 ¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 11.23-11.00 (m, 1H), 9.33 (br s, 1H), 8.69-8.59 (m, 1H), 8.30-8.22 (m, 1H), 8.08-7.97 (m, 1H), 7.57-7.33 (m, 3H), 7.32-7.22 (m, 1H), 6.48-6.33 (m, 1H), 5.86-5.67 (m, 1H), 4.83-4.63 (m, 1H), 4.15-3.76 (m, 1H), 3.3-2.90 (m, 3H, partially concealed), 3.18 (s, 3H), 2.86-2.74 / 2.61-2.5 (2m, 1H, partially concealed), 2.31-2.21 (m, 2H), 1.17 (m, 3H). Additional signals of minor rotamers were also detected.

15 **Example 105**

(4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-(3-methyl[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)pentanamide (mixture of two diastereomers)



20 *N,N*-Diisopropylethylamine (54 μ l, 0.31 mmol, 3.5 eq.) and a solution of HATU (51 mg, 0.13 mmol, 1.5 eq.) in *N,N*-dimethylformamide (1 ml) were added under argon atmosphere at RT to a solution of (2*S*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonic acid (mixture of two diastereomers) (44 mg, 93% purity, 0.09 mmol) and 3-methyl[1,2,4]triazolo[4,3-*a*]pyridin-7-amine hydrochloride

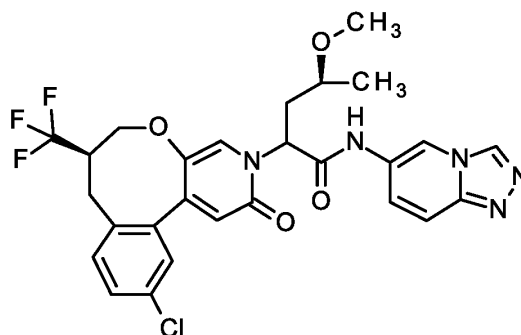
25 (21 mg, 0.11 mmol, 1.2 eq.) in *N,N*-dimethylformamide (4 ml). The reaction mixture was stirred at RT for 4 days. Further 3-methyl[1,2,4]triazolo[4,3-*a*]pyridin-7-amine hydrochloride (10 mg, 0.05 mmol, 0.6 eq.), *N,N*-diisopropylethylamine (22 μ l, 0.13 mmol, 1.4 eq.) and HATU (27 mg,

0.05 mmol, 0.8 eq.) were added. The reaction mixture was stirred at RT overnight and concentrated *in vacuo*. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 11 mg (21% of theory).

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 10.92-10.72 (m, 1H), 8.30 (d, 1H), 8.10-7.98 (m, 2H), 7.57-7.32 (m, 3H), 7.12-7.03 (m, 1H), 6.47-6.35 (m, 1H), 5.82-5.71 (m, 1H), 4.81-4.67 (m, 1H), 4.10-3.75 (m, 1H), 3.3-3.00 (m, 3H), 3.18 / 3.11 (2s, 3H), 2.85-2.73 / 2.65-2.5 (2m, 1H, partially concealed), 2.45-2.18 (m, 2H), 2.42 / 2.41 (2s, 3H), 1.21-1.10 (m, 3H). Additional signals of minor rotamers were also detected.

Example 106

(4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-*N*-([1,2,4]triazolo[4,3-*a*]pyridin-6-yl)pentanamide (mixture of two diastereomers)



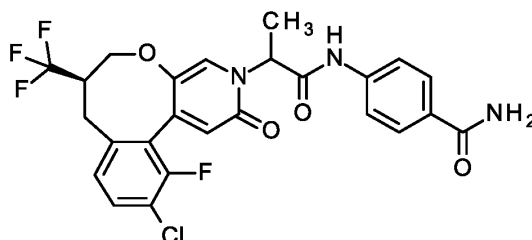
N,N-Diisopropylethylamine (30 µl, 0.17 mmol, 4.0 eq.) and a solution of HATU (20 mg, 0.05 mmol, 1.2 eq.) in *N,N*-dimethylformamide (1 ml) were added under argon atmosphere at RT to a solution of (2*ξ*)-2-[(7*R*)-11-chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-2,3,5-trideoxy-4-*O*-methyl-*L*-glycero-pentonic acid (mixture of two diastereomers) (20 mg, 0.04 mmol) and [1,2,4]triazolo[4,3-*a*]pyridin-6-amine hydrochloride (10 mg, 80% purity, 0.05 mmol, 1.1 eq.) in *N,N*-dimethylformamide (1 ml). The reaction mixture was stirred at RT for 1 h and concentrated *in vacuo*. The residue was purified by preparative HPLC (reversed phase, eluent: acetonitrile / water gradient). Yield: 14 mg (58% of theory).

LC-MS (method 1): *R*_t = 0.93 min; MS (ESIpos): *m/z* = 576 [M+H]⁺

¹H-NMR (400 MHz, DMSO-*d*₆): δ [ppm] = 10.84-10.67 (m, 1H), 9.33-9.20 (m, 2H), 8.08-7.95 (m, 1H), 7.79 (d, 1H), 7.57-7.33 (m, 4H), 6.47-6.35 (m, 1H), 5.89-5.75 (m, 1H), 4.81-4.66 (m, 1H), 4.12-3.71 (m, 1H), 3.3-2.98 (m, 3H, partially concealed), 3.19 / 3.12 (2s, 3H), 2.85-2.72 / 2.64-2.5 (2m, 1H, partially concealed), 2.43-2.17 (m, 2H), 1.21-1.10 (m, 3H). Additional signals of minor rotamers were also detected.

Example 107

4-{2-[(7*R*)-11-Chloro-12-fluoro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]propanamido}benzamide (mixture of two diastereomers)



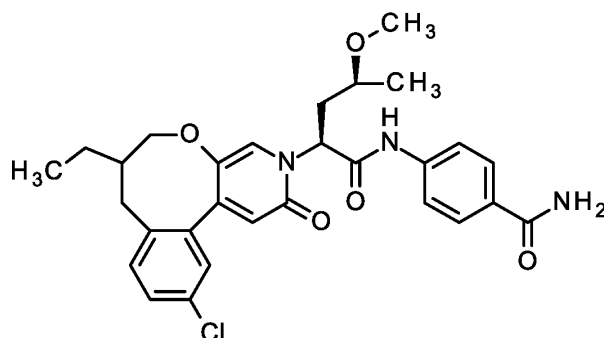
- 5 General Method 7 was carried out with (7*R*)-11-chloro-12-fluoro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (35.0 mg, 95% purity, 95.6 μ mol, 1.0 eq.), 4-[(2*R*)-2-bromopropanoyl]amino}benzamide (single stereoisomer) (31.1 mg, 115 μ mol, 1.2 eq.), 1,1,3,3-tetramethylguanidine (36 μ l, 290 μ mol, 3.0 eq.) in a mixture of isopropanol / acetone (4:1, 1.4 ml) overnight including the following variations of the procedure: The crude mixture was
- 10 purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 80:20 to 5:95). Yield: 41.0 mg (80% of theory, mixture of two diastereomers due to epimerization).

LC-MS (method 3): R_t = 2.78 min; MS (ESIpos): m/z = 538 $[M+H]^+$

- $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.65 / 10.58 (2s, 1H), 8.05 / 8.03 (2s, 1H), 7.90-7.81 (m, 3H), 7.71-7.60 (m, 3H), 7.35-7.28 (m, 1H), 7.24 (br s, 1H), 6.53 / 6.51 (2d, 1H), 5.62-5.52 (m, 1H), 4.77-4.65 (m, 1H), 3.93 / 3.81 (2dd, 1H), 3.17-2.98 (m, 2H), 2.67-2.56 (m, 1H), 1.73 / 1.71 (2d, 3H).
- 15

Example 108

4-{[(2*S*,4*S*)-2-(11-Chloro-7-ethyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)-4-methoxypentanoyl]amino}benzamide (mixture of two diastereomers)



20

General Method 7 was carried out with 11-chloro-7-ethyl-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (racemate) (47.0 mg, 66% purity, 107 μ mol, 1.0 eq.), 4-[(2*R*,4*S*)-2-bromo-4-

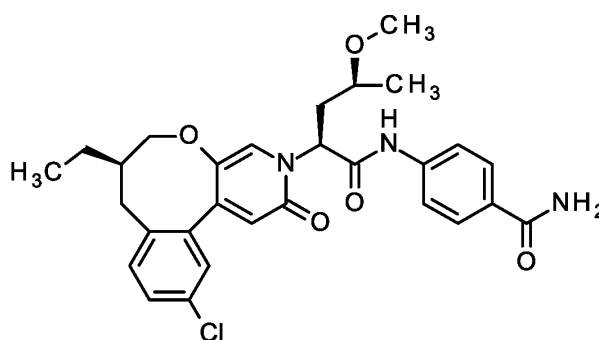
methoxypentanoyl]amino}benzamide (single stereoisomer) (32.5 mg, 98.9 μ mol, 1.2 eq.), 1,1,3,3-tetramethylguanidine (40 μ l, 320 μ mol, 3.0 eq.) in a mixture of isopropanol / acetone (4:1, 1.6 ml) overnight including the following variations of the procedure: The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95).

5 Yield: 37.0 mg (64% of theory).

LC-MS (method 1): R_t = 1.01 min; MS (ESIpos): m/z = 538 $[M+H]^+$

Example 109

4-({(2*S*,4*S*)-2-[(7*R*)-11-Chloro-7-ethyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (single stereoisomer)



10

Stereoisomer separation of 37 mg of 4-{{(2*S*,4*S*)-2-[(11-chloro-7-ethyl-2-oxo-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl)-4-methoxypentanoyl]amino}benzamide (mixture of two diastereomers), Example 108 provided:

single stereoisomer 1 (chiral HPLC: R_t = 2.89 min): 7.5 mg,

15 single stereoisomer 2 (the title compound Example 109) (chiral HPLC: R_t = 3.90 min): 6.0 mg (10% of theory, 99% de).

Separation method: column: Daicel Chiralpak IC 3 μ m, 50 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% ethanol; temperature: 30°C; flow rate: 10 ml/min; UV detection: 220 nm.

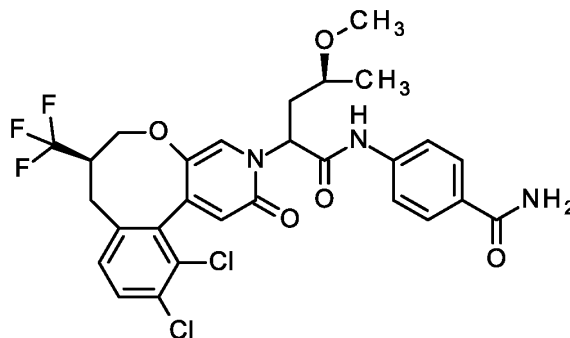
20 Analysis method: column: Daicel Chiralpak IC 3 μ m, 50 mm x 4.6 mm; eluent: 50% *n*-heptane / 50% ethanol; temperature: 30°C; flow rate: 10 ml/min; UV detection: 220 nm.

LC-MS (method 1): R_t = 1.01 min; MS (ESIpos): m/z = 538 $[M+H]^+$

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.69/ 10.65 (2s, 1H), 7.90-7.80 (m, 4H), 7.70 (d, 2H), 7.46 (d, 1H), 7.40-7.30 (m, 2H), 7.25 (br s, 1H), 6.38 / 6.33 (s, 1H), 5.80 (dd, 1H), 4.53 (dd, 1H), 4.37-4.30 / 3.48-3.35 (2m, 1H), 3.28-3.19 (m, 1H), 3.17 (s, 3H), 2.75 (d, 1H), 2.30-2.12 (m, 3H),
25 1.84-1.67 (m, 1H), 1.35-1.21 (m, 2H), 1.16 (d, 3H), 1.06 / 0.98 (2t, 3H).

Example 110

4-({(4*S*)-2-[(7*R*)-11,12-Dichloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (mixture of stereoisomers)

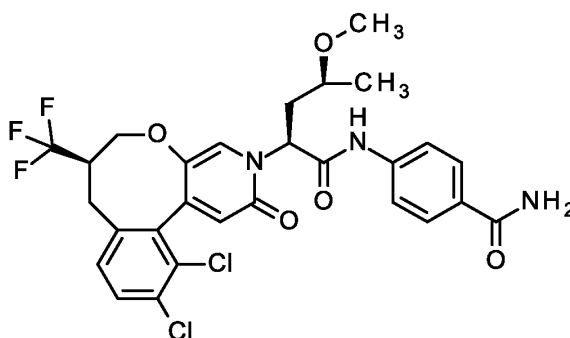


- 5 General Method 7 was carried out with (7*R*)-11,12-dichloro-7-(trifluoromethyl)-7,8-dihydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (single stereoisomer) (20.0 mg, 54.9 μ mol, 1.0 eq.), 4-{{(2*R*,4*S*)-2-bromo-4-methoxypentanoyl}amino}benzamide (single stereoisomer) (21.7 mg, 65.9 μ mol, 1.2 eq.), 1,1,3,3-tetramethylguanidine (21 μ l, 160 μ mol, 3.0 eq.) in a mixture of isopropanol / acetone (4:1, 0.8 ml) overnight including the following variations of the procedure:
- 10 The crude mixture was purified by preparative HPLC (reversed phase, eluent: water with 0.05% formic acid / acetonitrile 90:10 to 5:95). Yield: 37.0 mg (64% of theory).

LC-MS (method 3): R_t = 3.26 / 3.33 min; MS (ESIpos): m/z = 612 $[M+H]^+$

Example 111

- 4-({(2*S*,4*S*)-2-[(7*R*)-11,12-Dichloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (single stereoisomer)
- 15



Stereoisomer separation of 22.9 mg of 4-({(4*S*)-2-[(7*R*)-11,12-dichloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (mixture of stereoisomers), Example 110 provides:

single stereoisomer 1 (the title compound Example 111) (chiral HPLC: $R_t = 1.99$ min): 3.7 mg (11% of theory, 99% de),

single stereoisomer 2 (chiral HPLC: $R_t = 2.96$ min): 1.8 mg.

Separation method: column: Daicel Chiralpak IB 5 μm , 250 mm x 20 mm; eluent: 80% *n*-heptane /
5 20% ethanol; temperature: 30°C; flow rate: 20 ml/min; UV detection: 220 nm.

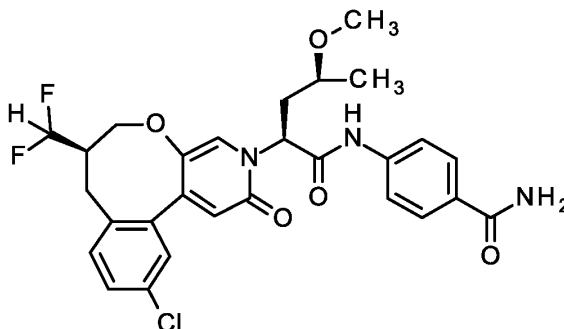
Analysis method: column: Daicel Chiralpak IB 3 μm , 50 mm x 4.6 mm; eluent: 80% *n*-heptane /
20% ethanol; temperature: 30°C; flow rate: 1.0 ml/min; UV detection: 220 nm.

LC-MS (method 3): $R_t = 3.33$ min; MS (ESIpos): $m/z = 612$ $[\text{M}+\text{H}]^+$

^1H -NMR (500 MHz, $\text{DMSO}-d_6$): δ [ppm] = 10.62 (s, 1H), 8.11 (s, 1H), 7.89-7.81 (m, 3H), 7.75-7.67
10 (m, 3H), 7.43 (d, 1H), 7.25 (br s, 1H), 6.48 (s, 1H), 5.83 (s, 1H), 4.78-4.65 (m, 1H), 3.76 (s, 1H),
3.29-3.24 (m, 1H), 3.16 (s, 3H), 3.13-3.00 (m, 2H), 2.63-2.54 (m, 1H), 2.28-2.19 (m, 2H), 1.15 (d,
3H).

Example 112

4-({(2*S*,4*S*)-2-[(7*R*)-11-Chloro-7-(difluoromethyl)-2-oxo-2,6,7,8-tetrahydro-3*H*-
15 [3]benzoxocino[2,1-*c*]pyridin-3-yl]-4-methoxypentanoyl}amino)benzamide (single stereoisomer)



General Method 7 was carried out with 11-chloro-7-(difluoromethyl)-7,8-dihydro-3*H*-
[3]benzoxocino[2,1-*c*]pyridin-2(6*H*)-one (racemate) (550 mg, 1.76 mmol), 4-({(2*R*,4*S*)-2-bromo-4-
methoxypentanoyl}amino)benzamide (single stereoisomer) (987 mg, 3.0 mmol, 1.7 eq.) and 1,1,3,3-
20 tetramethylguanidine (0.66 ml, 5.29 mmol, 3.0 eq.) in a mixture of 2-propanol / acetone (4:1, 20 ml)
for 16 h including the following variations of the procedure: The crude mixture was treated with
acetic acid (0.3 ml, 5.29 mmol, 3.0 eq.), concentrated under reduced pressure to 1/3 of the original
volume, treated with 0.02 N aqueous hydrochloric acid (43 ml) and stirred for 0.5 h. The resulting
precipitate was filtered, washed with water and dried.

25 Diastereomer separation of 1.32 g of the crude product gave:

single stereoisomer 1 (the title compound Example 112) (chiral SFC: $R_t = 4.53$ min, >99% de): 309 mg (88% purity, 22% of theory),

single stereoisomer 2 (chiral SFC: $R_t = 7.21$ min, >99% de): 246 mg (19% of theory).

5 Separation method: SFC: column: Daicel Chiralpak IE 5 μm , 250 mm x 20 mm; eluent: 58% carbon dioxide / 42% ethanol; temperature: 40°C; flow rate: 85 ml/min; UV detection: 210 nm.

Analysis method: SFC: column: Daicel Chiralpak IE 3 μm , 100 mm x 4.6 mm; eluent: 70% carbon dioxide / 30% ethanol; temperature: 40°C; flow rate: 3 ml/min; UV detection: 210 nm.

LC-MS (method 4): $R_t = 1.76$ min; MS (ESIpos): $m/z = 560$ $[\text{M}+\text{H}]^+$

10 $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ [ppm] = 10.70 / 10.65 (2s, 1H), 7.97 (s, 1H), 7.85 (br d, 3H), 7.70 (br d, 2H), 7.53-7.44 (m, 1H), 7.44-7.31 (m, 2H), 7.25 (br s, 1H), 6.40 / 6.39 (2s, 1H), 6.34-6.06 (m, 1H), 5.86-5.75 (m, 1H), 4.76-4.58 (2m, 1H), 3.72 (t, 1H), 3.28-3.19 (m, 2H), 3.17 (s, 3H), 2.96 (d, 1H), 2.43-2.34 (m, 1H), 2.29-2.15 (m, 2H), 1.15 (br d, 3H). Additional signals of minor rotamers were also detected.

B) Assessment of physiological efficacy

The suitability of the compounds according to the invention for treating thromboembolic disorders can be demonstrated in the following assay systems:

a) Test descriptions (*in vitro*)5 **a.1) Measurement of FXIa inhibition**

The factor XIa inhibition of the substances according to the invention is determined using a biochemical test system which utilizes the reaction of a peptidic factor XIa substrate to determine the enzymatic activity of human factor XIa. Here, factor XIa cleaves from the peptidic factor XIa substrate the C-terminal aminomethylcoumarin (AMC), the fluorescence of which is measured. The
10 determinations are carried out in microtitre plates.

Test substances are dissolved in dimethyl sulfoxide and serially diluted in dimethyl sulfoxide (3000 μM to 0.0078 μM ; resulting final concentrations in the test: 50 μM to 0.00013 μM). In each case 1 μl of the diluted substance solutions is placed into the wells of white microtitre plates from Greiner (384 wells). 20 μl of assay buffer (50 mM of Tris/HCl pH 7.4; 100 mM of sodium chloride; 5 mM
15 of calcium chloride; 0.1% of bovine serum albumin) and 20 μl of factor XIa from Kordia (0.45 nM in assay buffer) are then added successively. After 15 min of incubation, the enzyme reaction is started by addition of 20 μl of the factor XIa substrate Boc-Glu(OBzl)-Ala-Arg-AMC dissolved in assay buffer (10 μM in assay buffer) from Bachem, the mixture is incubated at room temperature (22°C) for 30 min and fluorescence is then measured (excitation: 360 nm, emission: 460 nm). The
20 measured emissions of the test batches with test substance are compared to those of control batches without test substance (only dimethyl sulfoxide instead of test substance in dimethyl sulfoxide), and IC_{50} values are calculated from the concentration/activity relationships. Activity data from this test are listed in Table A below (some as mean values from multiple independent individual determinations):

25 **Table A**

Example No.	IC_{50} [nM]		Example No.	IC_{50} [nM]
1	36		2	25
3	11		4	66
5	3.5		6	2.0
7	2.3		8	0.8
9	4.5		10	1.4
11	2.8		12	3.4
13	6.2		14	14

Example No.	IC ₅₀ [nM]		Example No.	IC ₅₀ [nM]
15	50		16	11
17	13		18	3.4
19	3.0		20	1.7
21	81		22	44
23	480		24	81
25	10		26	6.9
27	44		28	15
29	13		30	5.9
31	1.2		32	1.8
33	20		34	7.6
35	55		36	20
37	42		38	32
39	100		40	38
41	14		42	9.8
43	5.8		44	1.8
45	19		46	3.8
47	6.8		48	1.3
49	17		50	5.5
51	10		52	3.5
53	25		54	5.6
55	26		56	8.5
57	45		58	13
59	6.2		60	10
61	4.7		62	5.9
63	0.9		64	100
65	13		66	4.1
67	2.8		68	34
69	25		70	13
71	28		72	6.6
73	31		74	8.1

Example No.	IC ₅₀ [nM]		Example No.	IC ₅₀ [nM]
75	4.4		76	2.7
77	5.4		78	2.7
79	6.5		80	3.0
81	11		82	7.4
83	4.9		84	8.9
85	5.4		86	6.5
87	3.1		88	8.3
89	8.9		90	3.0
91	15		92	4.5
93	9.1		94	4.7
95	1.7		96	2.5
97	3.2		98	1.8
99	13		100	4.7
101	42		102	11
103	15		104	14
105	14		106	17
107	6.2		108	7.4
109	5.4		110	21
111	19		112	1.5

a.2) Determination of the selectivity

To demonstrate the selectivity of the substances with respect to FXIa inhibition, the test substances are examined for their potential to inhibit other human serine proteases, such as factor Xa, trypsin and plasmin. To determine the enzymatic activity of factor Xa (1.3 nmol/l from Kordia), trypsin (83 mU/ml from Sigma) and plasmin (0.1 µg/ml from Kordia), these enzymes are dissolved (50 mmol/l of Tris buffer [C,C,C-tris(hydroxymethyl)aminomethane], 100 mmol/l of NaCl, 0.1% BSA [bovine serum albumin], 5 mmol/l of calcium chloride, pH 7.4) and incubated for 15 min with test substance in various concentrations in dimethyl sulfoxide and also with dimethyl sulfoxide without test substance. The enzymatic reaction is then started by addition of the appropriate substrates (5 µmol/l of Boc-Ile-Glu-Gly-Arg-AMC from Bachem for factor Xa and trypsin, 50 µmol/l of MeOSuc-Ala-Phe-Lys-AMC from Bachem for plasmin). After an incubation time of 30 min at 22°C, fluorescence is measured (excitation: 360 nm, emission: 460 nm). The measured emissions of the test mixtures

with test substance are compared to the control mixtures without test substance (only dimethyl sulfoxide instead of test substance in dimethyl sulfoxide) and IC_{50} values are calculated from the concentration/activity relationships.

a.3) Thrombin generation assay (thrombogram)

- 5 The effect of the test substances in the thrombin generation assay according to Hemker is determined in vitro in human plasma (Octaplas® from Octapharma).

In the thrombin generation assay according to Hemker, the activity of thrombin plasma is determined by measuring the fluorescent cleavage products of the substrate I-1140 (Z-Gly-Gly-Arg-AMC, Bachem). The reactions are carried out in the presence of varying concentrations of test substance or
10 the corresponding solvent. To start the reaction, reagents from Thrombinscope (30 pM to 0.1 pM recombinant tissue factor, 24 μ M phospholipids in HEPES) are used. In addition, a thrombin calibrator from Thrombinscope is used, of which the amidolytic activity is required for calculating the thrombin activity in a sample containing an unknown amount of thrombin. The test is carried out according to the manufacturer's instructions (Thrombinscope BV): 4 μ l of test substance or of the
15 solvent, 76 μ l of plasma and 20 μ l of PPP reagent or thrombin calibrator are incubated at 37°C for 5 min. After addition of 20 μ l of 2.5 mM thrombin substrate in 20 mM Hepes, 60 mg/ml of BSA, 102 mM of calcium chloride, the thrombin generation is measured every 20 s over a period of 120 min. Measurement is carried out using a fluorometer (Fluoroskan Ascent) from Thermo Electron fitted with a 390/460 nm filter pair and a dispenser.

20 Using the Thrombinscope software, the thrombogram is calculated and represented graphically. The following parameters are calculated: lag time, time to peak, peak, ETP (endogenous thrombin potential) and start tail.

a.4) Determination of anticoagulatory activity

The anticoagulatory activity of the test substances is determined in vitro in human plasma and rat
25 plasma. Fresh whole blood is drawn directly into a mixing ratio of sodium citrate/blood of 1:9 using a 0.11 molar sodium citrate solution as receiver. Immediately after the blood has been drawn, it is mixed thoroughly and centrifuged at about 4000 g for 15 minutes. The supernatant is collected as (platelet-poor) plasma.

The prothrombin time (PT, synonyms: thromboplastin time, quick test) is determined in the presence
30 of varying concentrations of test substance or the corresponding solvent using a commercial test kit (Neoplastin® from Boehringer Mannheim or Hemoliance® RecombiPlastin from Instrumentation Laboratory). The test compounds are incubated with plasma at 37°C for 3 minutes. Coagulation is then started by addition of thromboplastin, and the timepoint, at which clotting of the sample occurs is determined. The concentration of test substance which effects a doubling of the prothrombin time
35 is determined.

The activated partial thromboplastin time (APTT) is determined in the presence of varying concentrations of test substance or the corresponding solvent using a commercial test kit (PTT reagent from Roche). The test compounds are incubated with the plasma and the PTT reagent (cephalin, kaolin) at 37°C for 3 minutes. Coagulation is then started by addition of 25 mM calcium chloride, and the time when coagulation occurs is determined. The concentration of test substance which leads to an extension by 50% or a doubling of the APTT is determined.

a.5) Determination of the plasma kallikrein activity

To determine the plasma kallikrein inhibition of the substances according to the invention, a biochemical test system is used which utilizes the reaction of a peptidic plasma kallikrein substrate to determine the enzymatic activity of human plasma kallikrein. Here, plasma kallikrein cleaves from the peptidic plasma kallikrein substrate the C-terminal aminomethylcoumarin (AMC), the fluorescence of which is measured. The determinations are carried out in microtitre plates.

Test substances are dissolved in dimethyl sulfoxide and serially diluted in dimethyl sulfoxide (3000 μM to 0.0078 μM ; resulting final concentrations in the test: 50 μM to 0.00013 μM). In each case 1 μl of the diluted substance solutions is placed into the wells of white microtitre plates from Greiner (384 wells). 20 μl of assay buffer (50 mM Tris/HCl pH 7.4; 100 mM sodium chloride solution; 5 mM of calcium chloride solution; 0.1% of bovine serum albumin) and 20 μl of plasma kallikrein from Kordia (0.6 nM in assay buffer) are then added successively. After 15 min of incubation, the enzyme reaction is started by addition of 20 μl of the substrate H-Pro-Phe-Arg-AMC dissolved in assay buffer (10 μM in assay buffer) from Bachem, the mixture is incubated at room temperature (22°C) for 30 min and fluorescence is then measured (excitation: 360 nm, emission: 460 nm). The measured emissions of the test batches with test substance are compared to those of control batches without test substance (only dimethyl sulfoxide instead of test substance in dimethyl sulfoxide), and IC_{50} values are calculated from the concentration/activity relationships. Activity data from this test are listed in Table B below (some as mean values from multiple independent individual determinations):

Table B

Example No.	IC_{50} [nM]		Example No.	IC_{50} [nM]
1	760		2	440
3	250		4	190
5	200		6	170
7	150		8	51
9	330		10	110
11	120		12	210

Example No.	IC ₅₀ [nM]		Example No.	IC ₅₀ [nM]
13	93		14	180
15	850		16	210
17	460		18	130
19	110		20	60
21	8700		22	1500
23	>10000		24	3900
25	2000		26	1300
27	540		28	170
29	190		30	91
31	47		32	40
33	660		34	280
35	300		36	380
37	510		38	780
39	>10000		40	950
41	520		42	340
43	340		44	170
45	890		46	220
47	430		48	120
49	330		50	130
51	160		52	59
53	370		54	110
55	250		56	130
57	250		58	89
59	630		60	230
61	160		62	150
63	35		64	850
65	180		66	190
67	130		68	550
69	430		70	310
71	390		72	110

Example No.	IC ₅₀ [nM]		Example No.	IC ₅₀ [nM]
73	520		74	190
75	120		76	95
77	210		78	140
79	130		80	65
81	330		82	310
83	190		84	180
85	150		86	250
87	160		88	460
89	380		90	130
91	190		92	71
93	200		94	110
95	44		96	220
97	110		98	110
99	480		100	190
101	430		102	130
103	190		104	170
105	720		106	490
107	200		108	660
109	350		110	1000
111	870		112	98

b) Determination of antithrombotic activity (*in vivo*)

b.1) Arterial thrombosis model (iron(II) chloride-induced thrombosis) in combination with ear bleeding time in rabbits

- 5 The antithrombotic activity of the FXIa inhibitors is tested in an arterial thrombosis model. Thrombus formation is triggered here by causing chemical injury to a region in the carotid artery in rabbits. Simultaneously, the ear bleeding time is determined.

Male rabbits (CrI:KBL (NZW)BR, Charles River) receiving a normal diet and having a body weight of 2.2 – 2.5 kg are anaesthetized by intramuscular administration of xylazine and ketamine (Rompun,

- 10 Bayer, 5 mg/kg and Ketavet, Pharmacia & Upjohn GmbH, 40 mg/kg body weight). Anaesthesia is

maintained by intravenous administration of the same preparations (continuous infusion) via the right auricular vein.

The right carotid artery is exposed and the vessel injury is caused by wrapping a piece of filter paper (10 mm x 10 mm) on a Parafilm® strip (25 mm x 12 mm) around the carotid artery without disturbing the blood flow. The filter paper contains 100 µL of a 13% strength solution of iron(II) chloride (Sigma) in water. After 5 min, the filter paper is removed and the vessel is rinsed twice with aqueous 0.9% strength sodium chloride solution. 30 min after the injury the injured region of the carotid artery is extracted surgically and any thrombotic material is removed and weighed.

The test substances are administered either intravenously to the anaesthetized animals via the femoral vein or orally to the awake animals via gavage, in each case 5 min and 2 h, respectively, before the injury.

Ear bleeding time is determined 2 min after injury to the carotid artery. To this end, the left ear is shaved and a defined 3-mm-long incision (blade Art. Number 10-150-10, Martin, Tuttlingen, Germany) is made parallel to the longitudinal axis of the ear. Care is taken not to damage any visible vessels. Any blood that extravasates is taken up in 15 second intervals using accurately weighed filter paper pieces, without touching the wound directly. Bleeding time is calculated as the time from making the incision to the point in time when no more blood can be detected on the filter paper. The volume of the extravasated blood is calculated after weighing of the filter paper pieces.

c) Determination of permeability (Caco assay)

The Caco cells (obtained from the Deutsche Sammlung für Mikroorganismen und Zellkulturen, DSMZ) are cultivated in 24-well Transwell plates for 15 or 16 days. The test is carried out using a Hamilton robot. The density of the cell monolayers is ensured by measuring the Lucifer yellow permeability. The test compounds are dissolved in DMSO and then diluted with assay buffer to a concentration of 2 µM (final DMSO concentration 1%). The permeability is examined in both directions by addition of the substance solutions to the apical or basolateral compartment. The covered plates are incubated at 37°C for 2 hours. The concentrations in the two compartments are determined by LC-MS/MS and the Papp values are calculated according to Artursson and Karlsson (PMID: 1673839).

d) Determination of pharmacokinetic parameters following intravenous administration

To examine the pharmacokinetic properties of a test substance, the respective test substances are administered to animals as a bolus injection, infusion or via oral administration. In the case of rats, the preferred formulation for intravenous administration of the test substances is plasma/dimethyl sulfoxide in a ratio of 99:1. The infusion solution of the test substance in the case of dogs and monkeys consists of polyethylene glycol/ethanol/water in a ratio of 50/10/40. Formulations for oral administration can be polyethylene glycol/ethanol/water or solutol/ethanol/water in a ratio of

50/10/40, or other formulations as appropriate (e.g. water, tylose, self-emulsifying drug dispersing systems, etc.). The administration volume for rats is 2-10 ml/kg, for dogs and monkeys 0.5-5 ml/kg.

Blood samples are removed from the test animals into sodium EDTA (or other anticoagulant)-containing tubes: in the case of bolus administration, blood samples are usually taken at 0.033, 0.083, 0.167, 0.25, 0.283, 0.333, 0.5, 0.75, 1, 2, 3, 5, 7, 24 hours after administration of the test substance. In the case of infusions, blood samples are usually taken at 0.083, 0.167, 0.25, 0.283, 0.333, 0.5, 0.75, 1, 2, 3, 5, 7, 24 hours after administration of the test substance. In the case of oral administration, blood samples are usually taken at 0.083, 0.25, 0.5, 0.75, 1, 2, 3, 5, 7, 24 hours after administration of the test substance. Other time points might be chosen as appropriate.

- 10 After removal, the blood samples are centrifuged at 1280 g for 10 minutes. The supernatant (plasma) is taken off and either directly processed further or frozen for later sample preparation. For sample preparation, 50 µl of plasma are mixed with 250 µl of acetonitrile (the precipitating agent acetonitrile also contains the internal standard ISTD for later analytical determination) and then allowed to stand at room temperature for 5 minutes. The mixture is then centrifuged at 16 000 g for 3 minutes.
- 15 The supernatant is taken off, and 500 µl of a buffer suitable for the mobile phase are added. The samples are then examined by LC-MS/MS analysis (e.g. liquid chromatography using a Gemini 5 µM C18 110A 50 mm x 3 mm (or 150 mm x 3 mm) column from Phenomenex; by mass spectrometry using an API 5500 or API 6500; SCIEX, Canada) to determine the concentration of the test substance in the individual samples.
- 20 In addition to the the plasma concentrations, the concentration ratio whole blood to plasma for the test substance in question is determined. To this end, the test substance is incubated at a certain concentration in whole blood for 20 minutes. The samples are then processed as described above to determine the concentration of the test substance in the plasma. The concentration set divided by the concentration measured in the plasma gives the parameter C_b/C_p.
- 25 The pharmacokinetic parameters are calculated by non-compartmental analysis (NCA). The algorithms for calculating the parameters are defined in an internal process description and are based on rules published in general textbooks of pharmacokinetics.

The primary pharmacokinetic parameters clearance (CL) and distribution volume (V_{ss}) are calculated as follows:

Parameter	Formula
CL _{plasma} (plasma clearance)	CL _{plasma} = dose / AUC (AUC = area under the curve)
CL _{blood} (blood clearance)	CL _{blood} = CL _{plasma} / (C _b /C _p)
V _{ss}	V _{ss} = CL _{plasma} * MRT _{iv}

Parameter	Formula
MRT _{iv}	$MRT_{iv} = AUMC/AUC$
AUMC	$AUMC = AUMC(0-t_{last}) + t_{last} * C_{last,calculated}/\lambda_z + C_{last,calculated}/\lambda_z^2$
λ_z	Rate constant for the terminal phase; calculated from the logarithmic-linear regression of unweighted data from the terminal phase with data points above the detection limit
AUC	$AUC = AUC(0-t_{last}) + C_{last,calculated}/\lambda_z$
AUC _{norm}	AUC divided by dose (mg) per kg body weight

C) Working examples of pharmaceutical compositions

The substances according to the invention can be converted to pharmaceutical preparations as follows:

5 Tablet:

Composition:

100 mg of the compound of Example 1, 50 mg of lactose (monohydrate), 50 mg of maize starch, 10 mg of polyvinylpyrrolidone (PVP 25) (from BASF, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg. Diameter 8 mm, radius of curvature 12 mm.

10 Production:

The mixture of the compound of Example 1, lactose and starch is granulated with a 5% strength solution (m/m) of the PVP in water. After drying, the granules are mixed with the magnesium stearate for 5 min. This mixture is compressed in a conventional tableting press (see above for format of the tablet).

15 Oral suspension:

Composition:

1000 mg of the compound of Example 1, 1000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum) (from FMC, USA) and 99 g of water.

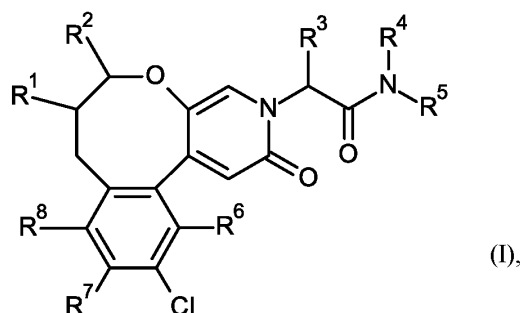
10 ml of oral suspension correspond to a single dose of 100 mg of the compound of the invention.

20 Production:

The Rhodigel is suspended in ethanol, and the compound of Example 1 is added to the suspension. The water is added while stirring. The mixture is stirred for about 6 h until swelling of the Rhodigel is complete.

Claims

1. Compound of the formula



in which

5 R^1 represents methyl, ethyl, difluoromethyl or trifluoromethyl,

R^2 represents hydrogen, methyl, difluoromethyl or trifluoromethyl,

or

R^1 and R^2 together with the carbon atoms to which they are attached form a cyclobutyl ring,

R^3 represents methyl, ethyl or n-propyl,

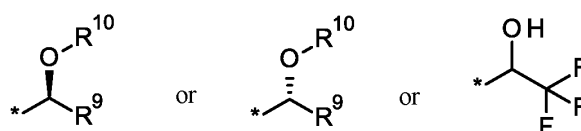
10 where methyl may be substituted with one substituent selected from the group consisting of cyclopropyl, cyclobutyl, oxetan-2-yl, oxetan-3-yl, tetrahydrofuran-2-yl, tetrahydro-2H-pyran-2-yl, tetrahydro-2H-pyran-4-yl and 1,4-dioxan-2-yl,

where oxetan-2-yl, tetrahydrofuran-2-yl, tetrahydro-2H-pyran-2-yl and 1,4-dioxan-2-yl may be substituted by 1 to 2 substituents independently of one another selected from the group consisting of fluorine and methyl,

15

or

where methyl may be substituted with one substituent of the formula



where

20

* is the attachment site to the methyl group,

R^9 represents methyl, ethyl, iso-propyl, cyclopropyl, difluoromethyl or trifluoromethyl,

R^{10} represents methyl or difluoromethyl,

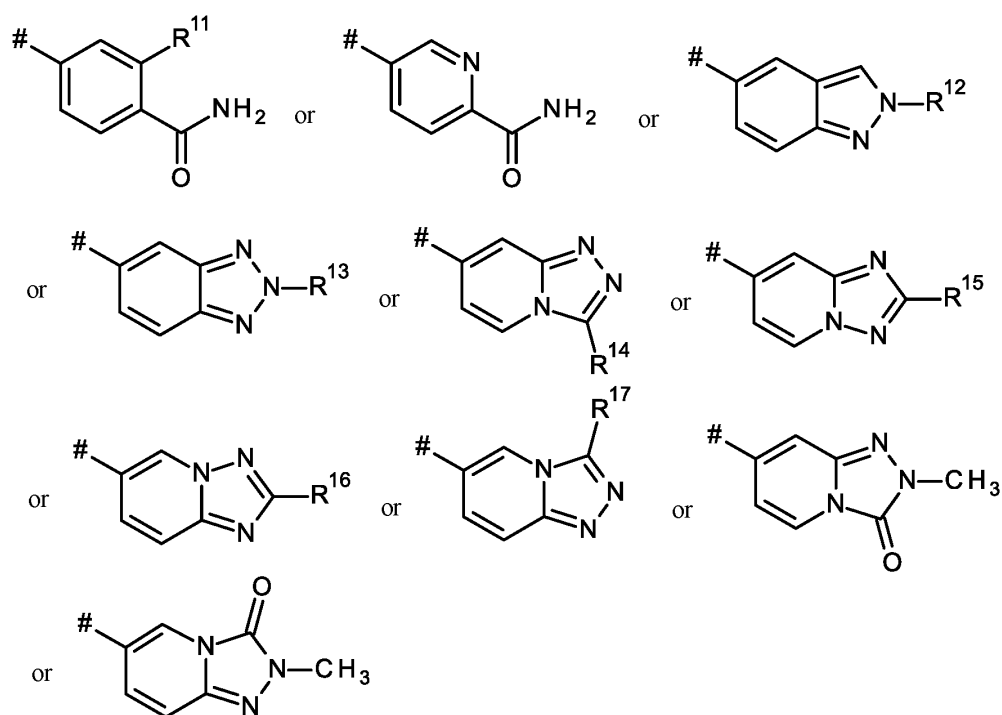
and

where ethyl may be substituted with one substituent selected from the group consisting of methoxy, ethoxy, iso-propoxy, tert-butoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, cyclopropyloxy and cyclobutyloxy,

where cyclopropyloxy and cyclobutyloxy may be substituted with one substituent selected from the group consisting of fluorine and methyl,

R^4 represents hydrogen,

R^5 represents a group of the formula



where

is the attachment site to the nitrogen atom,

R^{11} represents hydrogen or fluorine,

R^{12} represents methyl, difluoromethyl or trifluoromethyl,

R^{13} represents methyl, difluoromethyl or trifluoromethyl,

R^{14} represents hydrogen or methyl,

R¹⁵ represents hydrogen or methyl,

R¹⁶ represents hydrogen or methyl,

R¹⁷ represents hydrogen or methyl,

R⁶, R⁷ and R⁸ represent the following:

5 R⁶ represents hydrogen, fluorine or chlorine,

R⁷ represents hydrogen,

R⁸ represents hydrogen,

or

R⁶ represents hydrogen,

10 R⁷ represents fluorine or chlorine,

R⁸ represents hydrogen,

or

R⁶ represents hydrogen,

R⁷ represents hydrogen,

15 R⁸ represents fluorine,

or one of the salts thereof, solvates thereof or solvates of the salts thereof.

2. Compound according to Claim 1, characterized in that

R¹ represents methyl, ethyl or trifluoromethyl,

R² represents hydrogen or methyl,

20 or

R¹ and R² together with the carbon atoms to which they are attached form a cyclobutyl ring,

R³ represents methyl, ethyl or n-propyl,

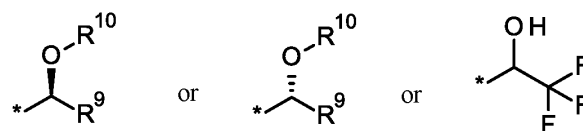
where methyl may be substituted with one substituent selected from the group consisting of cyclobutyl, tetrahydrofuran-2-yl, tetrahydro-2H-pyran-2-yl and 1,4-dioxan-2-yl,

25

where tetrahydrofuran-2-yl may be substituted by 1 to 2 substituents methyl,

or

where methyl may be substituted with one substituent of the group of the formula



where

* is the attachment site to the methyl group,

R⁹ represents methyl, cyclopropyl, difluoromethyl or trifluoromethyl,

5 R¹⁰ represents methyl or difluoromethyl,

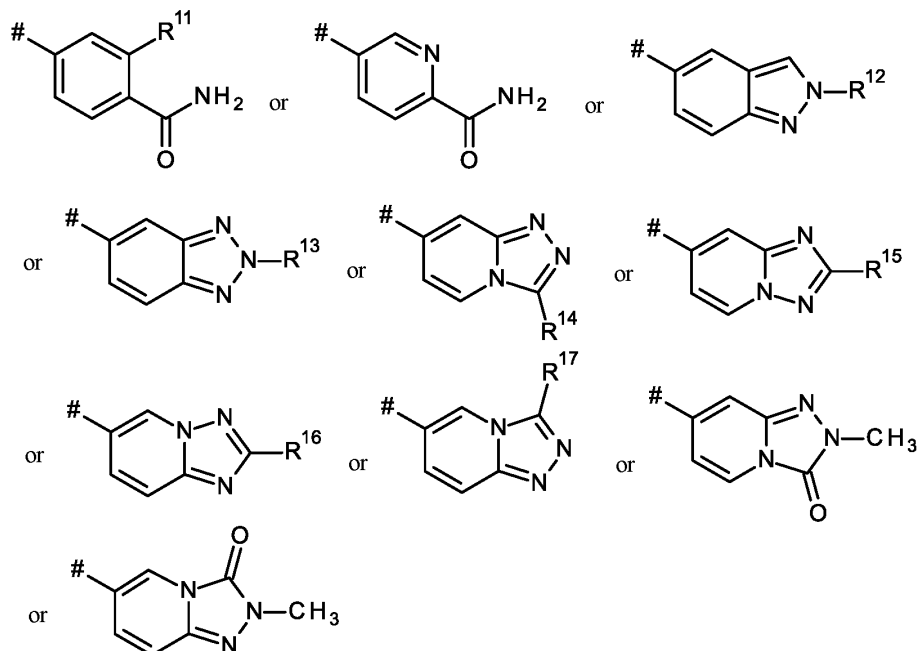
and

where ethyl may be substituted with one substituent selected from the group consisting of methoxy, iso-propoxy, tert-butoxy, difluoromethoxy, trifluoromethoxy, 2,2-difluoroethoxy, cyclopropyloxy and cyclobutyloxy,

10 where cyclopropyloxy and cyclobutyloxy may be substituted with one substituent selected from the group consisting of fluorine and methyl,

R⁴ represents hydrogen,

R⁵ represents a group of the formula



15 where

is the attachment site to the nitrogen atom,

- 5
- R¹¹ represents hydrogen or fluorine,
 R¹² represents difluoromethyl or trifluoromethyl,
 R¹³ represents methyl,
 R¹⁴ represents hydrogen or methyl,
 R¹⁵ represents hydrogen or methyl,
 R¹⁶ represents hydrogen,
 R¹⁷ represents hydrogen,

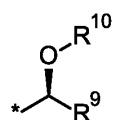
R⁶, R⁷ and R⁸ represent the following:

- 10
- R⁶ represents hydrogen, fluorine or chlorine,
 R⁷ represents hydrogen,
 R⁸ represents hydrogen,

or one of the salts thereof, solvates thereof or solvates of the salts thereof.

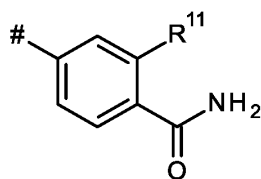
3. Compound according to Claim 1 or 2, characterized in that
- 15
- R¹ represents methyl or trifluoromethyl,
 R² represents hydrogen,
 R³ represents methyl,

where methyl is substituted with one substituent of the group of the formula



where

- 20
- * is the attachment site to the methyl group,
 R⁹ represents methyl,
 R¹⁰ represents methyl or difluoromethyl,
 R⁴ represents hydrogen,
 R⁵ represents a group of the formula



where

is the attachment site to the nitrogen atom,

R¹¹ represents hydrogen,

5 R⁶, R⁷ and R⁸ represent the following:

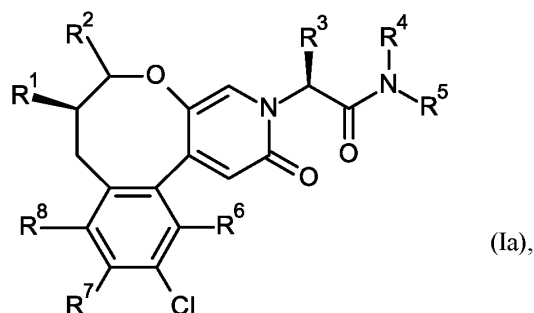
R⁶ represents hydrogen or fluorine,

R⁷ represents hydrogen,

R⁸ represents hydrogen,

or one of the salts thereof, solvates thereof or solvates of the salts thereof.

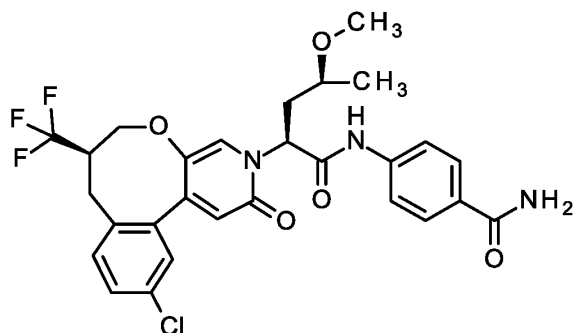
10 4. Compound according to any of Claims 1 to 3, characterized in that it has the formula (Ia)



in which R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are as defined in Claims 1 to 3.

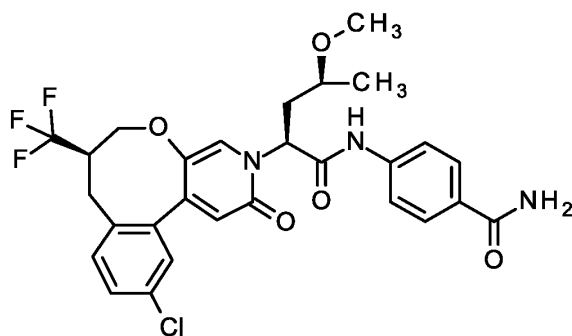
5. 4-({(2*S*,4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benz-oxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-pentanoyl}amino)benzamide (single stereoisomer)

15 according to Claim 1 of the formula below

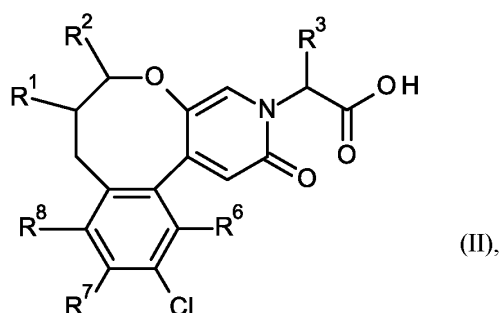


or one of the salts thereof, solvates thereof or solvates of the salts thereof.

6. 4-({(2*S*,4*S*)-2-[(7*R*)-11-Chloro-2-oxo-7-(trifluoromethyl)-2,6,7,8-tetrahydro-3*H*-[3]benz-oxocino[2,1-*c*]pyridin-3-yl]-4-methoxy-pentanoyl}amino)benzamide (single stereoisomer)
- 5 according to Claim 5 of the formula below



7. Process for preparing a compound of the formula (I) or one of the salts thereof, solvates thereof or solvates of the salts thereof according to Claim 1, characterized in that
- [A] a compound of the formula

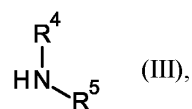


10

in which

R^1 , R^2 , R^3 , R^6 , R^7 and R^8 are as defined in claim 1,

is reacted with a compound of the formula



in which

R^4 and R^5 are as defined in claim 1,

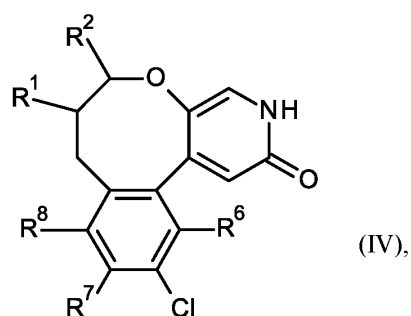
in the presence of a dehydrating agent to give a compound of the formula (I)

5 or

[B] a compound of the formula (II) is converted in a one-pot reaction to the acid chloride of the compound of the formula (II) and then the acid chloride is reacted with a compound of the formula (III) to give a compound of the formula (I)

or

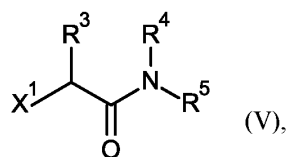
10 [C] a compound of the formula



in which

R^1 , R^2 , R^6 , R^7 and R^8 are as defined in claim 1,

is reacted with a compound of the formula



15

in which

X^1 represents bromine, iodine or trifluoromethane-sulfonyloxy,

in the presence of a base to give a compound of the formula (I).

8. Compound according to any of Claims 1 to 6 for the treatment and/or prophylaxis of diseases.

9. Use of a compound according to any of Claims 1 to 6 for producing a medicament for the treatment and/or prophylaxis of diseases.
10. Use of a compound according to any of Claims 1 to 6 for producing a medicament for the treatment and/or prophylaxis of thrombotic or thromboembolic disorders.
- 5 11. Use of a compound according to any of Claims 1 to 6 for producing a medicament for the treatment and/or prophylaxis of disorders in the coronary arteries of the heart, such as acute coronary syndrome (ACS), myocardial infarction with ST segment elevation (STEMI) and without ST segment elevation (non-STEMI), stable angina pectoris, unstable angina pectoris, stent thrombosis, reocclusions and restenoses after coronary interventions such as angioplasty, stent implantation or aortocoronary bypass, disorders in the cerebrovascular
10 arteries, such as transitory ischaemic attacks (TIA), ischemic strokes including cardioembolic strokes, such as strokes due to atrial fibrillation, non-cardioembolic strokes, such as lacunar stroke, strokes due to large or small artery diseases, or strokes due to undetermined cause, cryptogenic strokes, embolic strokes, embolic strokes of undetermined
15 source, or events of thrombotic and/or thromboembolic origin leading to stroke or TIA, and disorders of peripheral arteries, leading to peripheral artery disease, including peripheral artery occlusion, acute limb ischemia, amputation, reocclusions and restenoses after interventions such as angioplasty, stent implantation or surgery and bypass.
- 20 12. Medicament comprising a compound according to any of Claims 1 to 6 in combination with an inert, nontoxic, pharmaceutically suitable excipient.
13. Medicament according to Claim 12 for the treatment and/or prophylaxis of thrombotic or thromboembolic disorders.
- 25 14. Compound according to any of Claims 1 to 6 for use in a method for the treatment and/or prophylaxis of thrombotic or thromboembolic disorders using a therapeutically effective amount of a compound according to the invention.
- 30 15. Method for the treatment and/or prophylaxis of thrombotic or thromboembolic disorders in humans and animals by administration of a therapeutically effective amount of at least one compound according to any of Claims 1 to 6, of a medicament according to Claim 12 or of a medicament obtained according to Claim 9 or 10.