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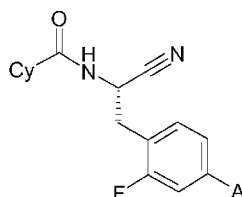
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## (54) Title: SPIROCYCLIC INHIBITORS OF CATHEPSIN C



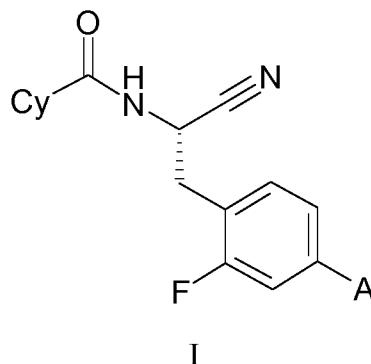
(I)

(57) Abstract: This invention relates to a compound of formula (I) wherein A and Cy have one of the meanings as indicated in the specification and their use as inhibitors of Cathepsin C, pharmaceutical compositions containing the same and methods of using the same as agents for treatment and/or prevention of diseases connected with dipeptidyl peptidase I activity, e.g. respiratory diseases.



**SPIROCYCLIC INHIBITORS OF CATHEPSIN C****FIELD OF INVENTION**

5 This invention relates to a compound of formula I



10 wherein A and Cy have one of the meanings as indicated in the specification and their use as inhibitors of Cathepsin C, pharmaceutical compositions containing the same and methods of using the same as agents for treatment and/or prevention of diseases connected with dipeptidyl peptidase I activity, e.g. respiratory diseases.

15 **BACKGROUND INFORMATION**

- WO2004110988 discloses peptidyl nitrile inhibitors as dipeptidyl-peptidase I (DPPI) inhibitors for the treatment of a series of diseases.
- WO2009074829 and WO2010142985 also disclose peptidyl nitrile inhibitors as  
20 dipeptidyl-peptidase I (DPPI) inhibitors for the treatment asthma, COPD or allergic rhinitis.
- WO2013041497 discloses substituted  
N-[1-cyano-2-(phenyl)ethyl]-2-azabicyclo[2.2.1]heptane-3-carboxamides as  
dipeptidyl-peptidase I (DPPI) inhibitors for the treatment of e.g. respiratory diseases.

## BRIEF SUMMARY OF THE INVENTION

Dipeptidyl-aminopeptidase I (DPPI or Cathepsin C; EC3.4.141), is a lysosomal cysteine protease capable of removing dipeptides from the amino terminus of protein substrates.

5 DPPI was first discovered by Gutman and Fruton in 1948 (J. Biol. Chem 174: 851-858, 1948). The cDNA of the human enzyme has been described in 1995 (Paris et al.; FEBS Lett 369: 326-330, 1995). The DPPI protein is processed into a mature proteolytically active enzyme consisting of a heavy chain, a light chain, and a propeptide that remains associated with the active enzyme (Wolters et al.; J. Biol. Chem. 273: 15514-15520, 1998).

10 Whereas the other cysteine Cathepsins (e.g. B, H, K, L and S) are monomers, DPPI is a 200-kD tetramer with 4 identical subunits, each composed of the 3 different polypeptide chains. DPPI is constitutively expressed in many tissues with highest levels in lung, kidney, liver and spleen (Kominami et al.; Biol. Chem. Hoppe Seyler 373: 367-373, 1992). Consistent with its role in the activation of serine proteases from hematopoietic cells, DPPI

15 is also relatively highly expressed in neutrophils, cytotoxic lymphocytes, natural killer cells, alveolar macrophages and mast cells. Recent data from DPPI deficient mice suggest that, besides being an important enzyme in lysosomal protein degradation, DPPI also functions as the key enzyme in the activation of granule serine proteases in cytotoxic T lymphocytes and natural killer cells (granzymes A and B; Pham et al.; Proc. Nat. Acad. Sci

20 96: 8627-8632, 1999), mast cells (chymase and tryptase; Wolter et al.; J Biol. Chem. 276: 18551-18556, 2001), and neutrophils (Cathepsin G, elastase and proteinase 3; Adkison et al.; J Clin. Invest. 109: 363.371, 2002). Once activated, these proteases are capable of degrading various extracellular matrix components, which can lead to tissue damage and chronic inflammation.

25

Thus, inhibitors of Cathepsin C could potentially be useful therapeutics for the treatment of neutrophil-dominated inflammatory diseases such as chronic obstructive pulmonary disease (COPD), pulmonary emphysema, asthma, multiple sclerosis, and cystic fibrosis (Guay et al.; Curr. Topics Med. Chem. 10: 708-716, 2010; Laine and Busch-Petersen;

30 Expert Opin. Ther. Patents 20: 497-506, 2010). Rheumatoid arthritis is also another chronic inflammatory disease where DPPI appears to play a role. Neutrophils are recruited to the site of joint inflammation and release Cathepsin G, elastase and proteinase 3,

proteases which are believed to be responsible for cartilage destruction associated with rheumatoid arthritis. Indeed, DPPI deficient mice were protected against acute arthritis induced by passive transfer of monoclonal antibodies against type II collagen (Adkison et al.; J Clin. Invest. 109: 363.371, 2002).

5

In light of the role DPPI plays in activating certain pro-inflammatory serine proteases, the problem of the present invention is to prepare compounds that inhibit its activity, which thereby inhibit downstream serine protease activity.

It has been surprisingly found that the spirocyclic compounds of the present invention possess

10

- potent Cathepsin C (DPPI) activity, preferably exhibiting an inhibition of DPPI  $IC_{50}$  [ $\mu$ M] < 0.0050, particularly preferred < 0.0030,

Moreover the compounds of the present invention exhibit the following capacities, which are favourable for their pharmacological efficacy:

15

- high cellular activity, e.g. inhibition of neutrophil elastase processing in U937 cell line, preferably exhibiting an  $IC_{50}$  [ $\mu$ M] < 0.5, particularly preferred < 0.003.
- high selectivity against other Cathepsins, e.g. Cathepsin K, and
- in general desirable pharmacokinetic properties, e.g. metabolic stability, preferably exhibiting an in vitro stability in human liver microsome incubations of  $t_{1/2}$  [min] > 110, particularly preferred  $\geq 120$ .

20

It has also been surprisingly found that compounds of the present invention show high inhibition of neutrophil elastase activity in the BALF (bronchoalveolar lavage fluid) cell lysate in a target engagement mouse model.

25

Moreover it has been surprisingly found that the spirocyclic compounds of the present invention form an additional salt-bridge to the Glu275 of the Cathepsin C which leads to the high enzymatic and cellular activity of this compound class. This additional interaction of the spiro-cyclic amine (e.g. spiro-azetidine in Example 11 and spiro-pyrrolidine in Example 16) has been verified by co-crystallization experiments of Cathepsin C protein

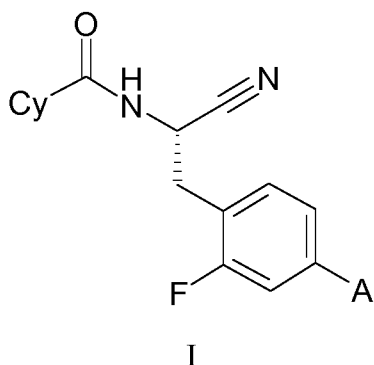
30

with Examples 11 and 16. In both cases the basic nitrogen atom forms a salt-bridge to Glu275.

## DETAILED DESCRIPTION OF THE INVENTION

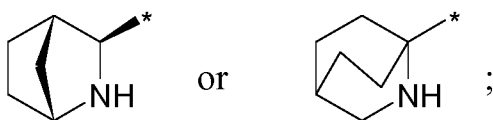
It has surprisingly been found that the problem mentioned above is solved by compounds of formula I of the present invention.

The present invention therefore relates to a compound of formula I or a pharmaceutically acceptable salt thereof,

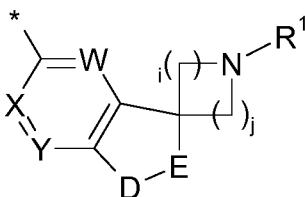


wherein

Cy is



A is



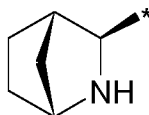
wherein

W is selected from the group consisting of CH and N;

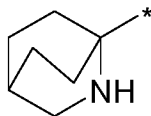
- X is selected from the group consisting of CH and N;  
 Y is selected from the group consisting of CH and N;  
 with the proviso that a maximum of one of W, X and Y can be N;  
 D-E is selected from the group consisting of  $N(R^2)-C(O)$ ,  $CH_2CH_2$ ,  $C(O)-O$  and  $CH_2-O$ ;  
 $R^2$  is selected from the group consisting of H and  $C_{1-3}$ -alkyl;  
 $R^1$  is selected from the group consisting of H,  $C_{1-3}$ -alkyl,  $CH_3OCH_2CH_2-$ ,  
 oxetanyl, tetrahydrofuranyl, 4-tetrahydropyranyl and 3-tetrahydropyranyl;  
 i is 1, 2 or 3;  
 j is 1, 2 or 3;  
 with the proviso that the sum of i+j is 2, 3 or 4.

#### PREFERRED EMBODIMENTS

- Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein  
 Cy is



- Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein  
 Cy is



- Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein  
 $R^1$  is selected from the group consisting of H,  $CH_3-$  and oxetanyl;

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

$R^2$  is selected from the group consisting of H and  $CH_3$ ;

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

$R^2$  is H.

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

$R^2$  is  $CH_3$ ;

10

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

D-E is  $CH_2-O$

15 Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

$R^1$  is selected from the group consisting of H,  $CH_3$  and oxetanyl;

$R^2$  is  $CH_3$ ;

W is selected from the group consisting of CH and N;

20 X is selected from the group consisting of CH and N;

Y is selected from the group consisting of CH;

with the proviso that a maximum of one of W, X and Y can be N;

D-E is selected from the group consisting of  $N(R^2)-C(O)$ ,  $CH_2CH_2$ ,  $C(O)-O$  and  $CH_2-O$ ;

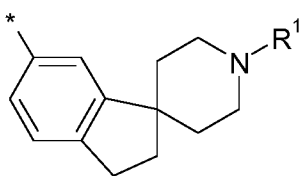
i is 1 or 2;

25 j is 1 or 2;

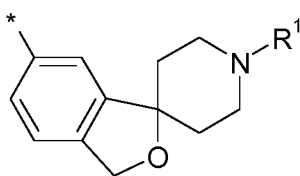
with the proviso that the sum of  $i+j$  is 2, 3 or 4.

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

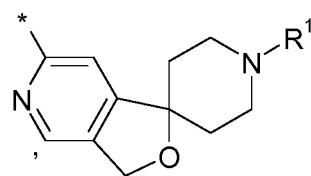
30 A is selected from the group consisting of formulas A1 to A14:



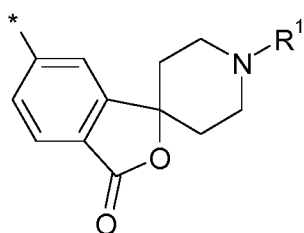
A1



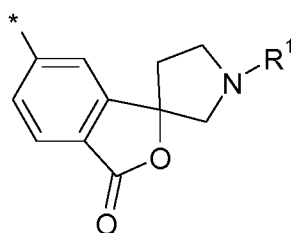
A2



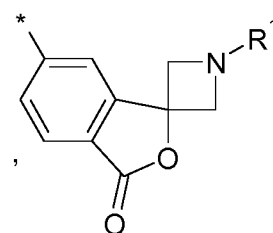
A3



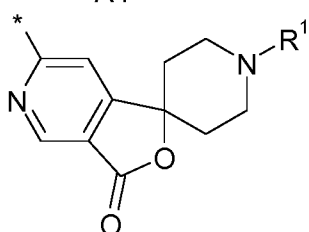
A4



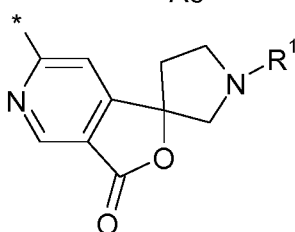
A5



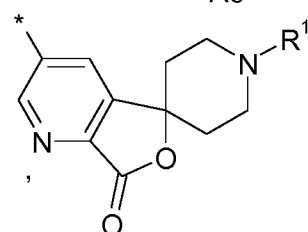
A6



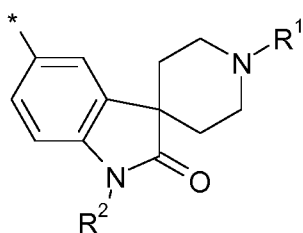
A7



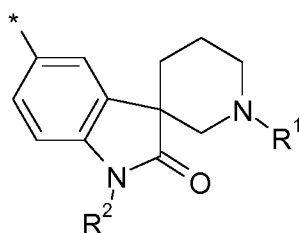
A8



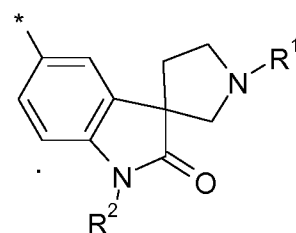
A9



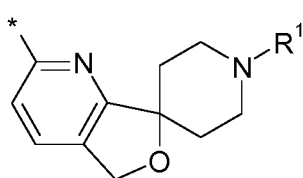
A10



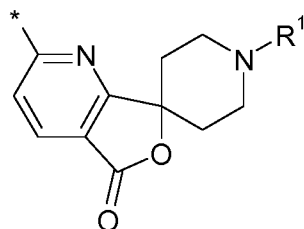
A11



A12



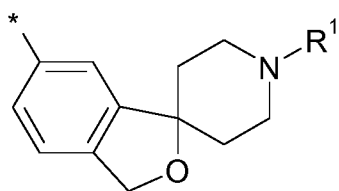
A13



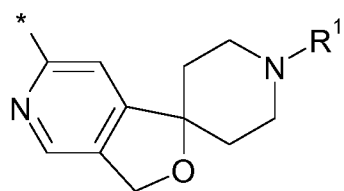
A14

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

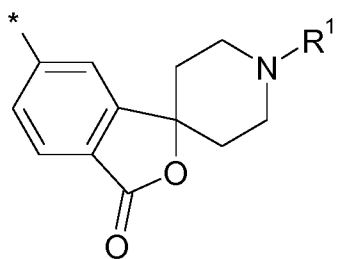
A is selected from the group consisting of A2, A3, A4, A5, A6, A7, A10, A13, and A14.



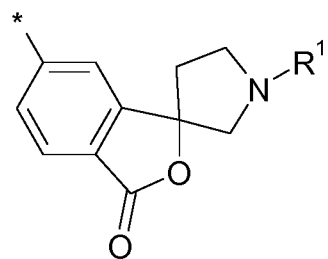
A2,



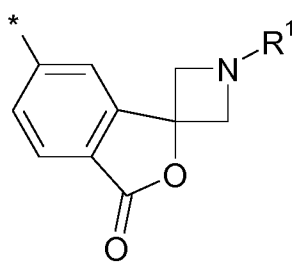
A3,



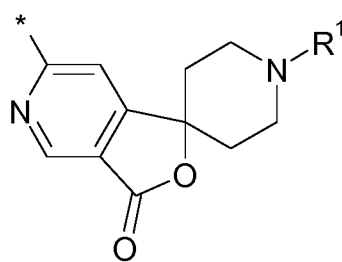
A4,



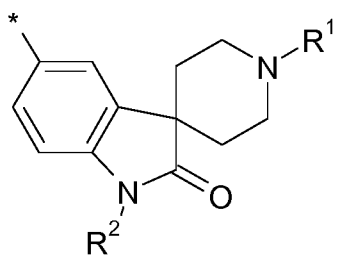
A5



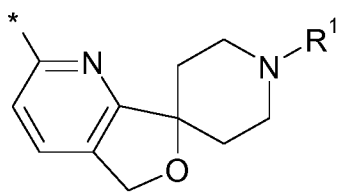
A6,



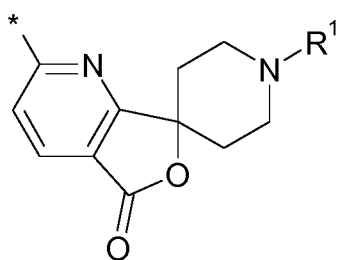
A7,



A10,



A13,

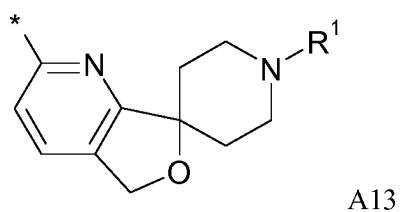
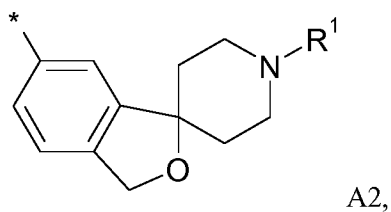


A14.

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

A is selected from the group consisting of A2 and A13

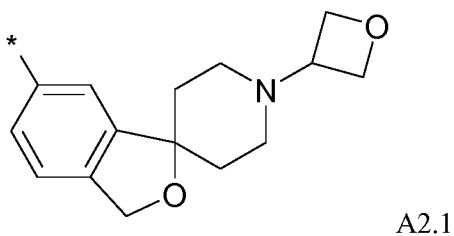
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Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

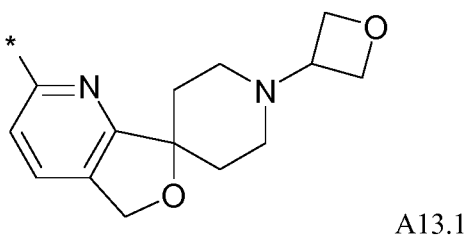
A is a group of formulas A2.1.



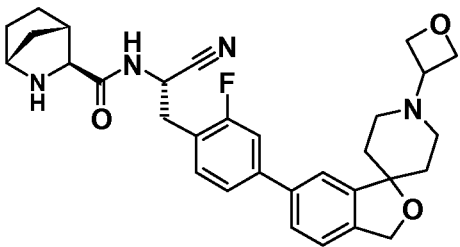
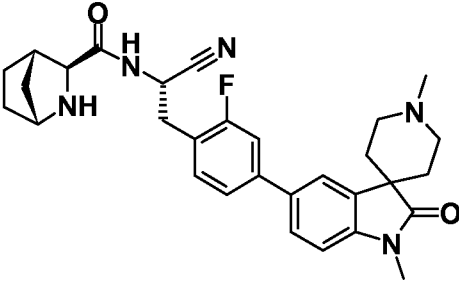
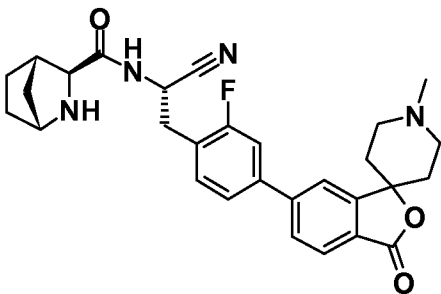
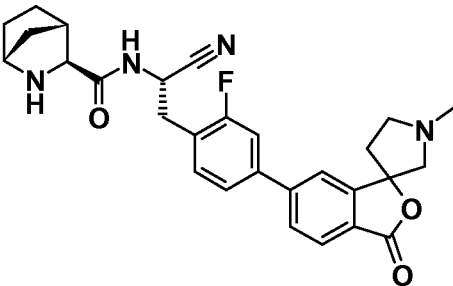
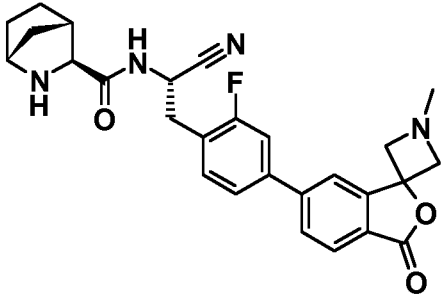
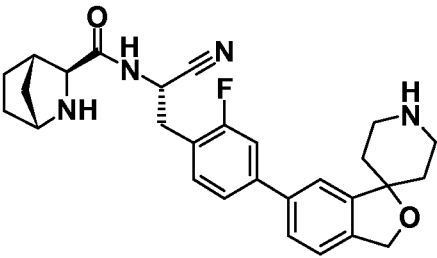
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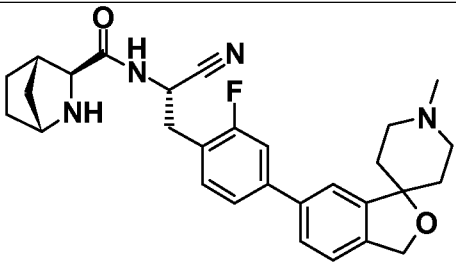
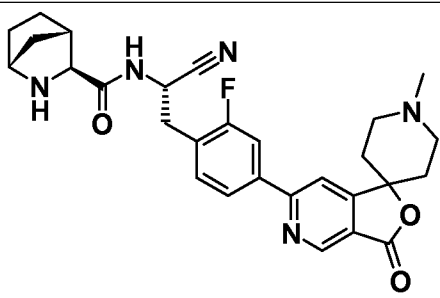
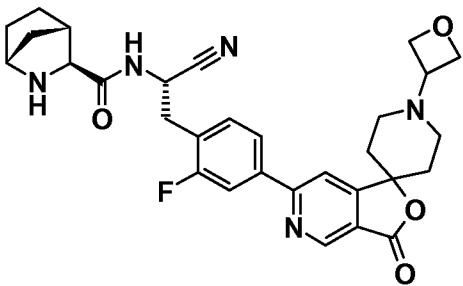
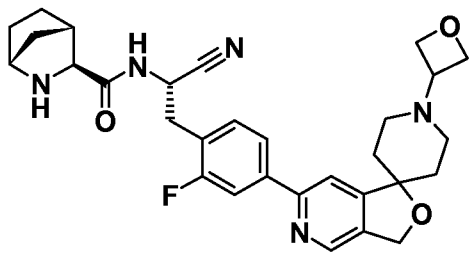
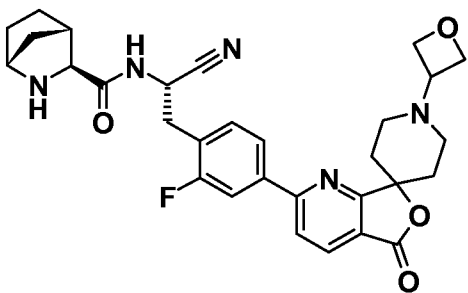
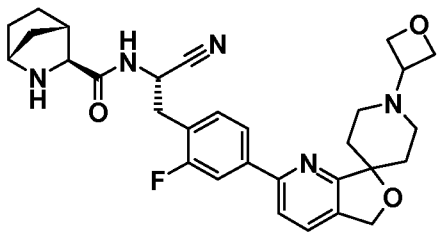
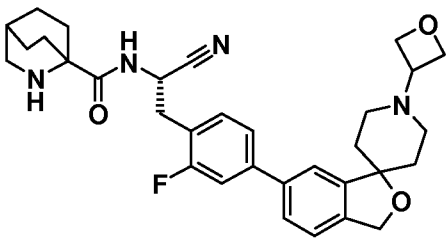
Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

A is a group of formula A13.1



Preferred are the above compounds of formula I, selected from the group consisting of examples 1, 5, 8, 10, 12, 13, 14, 19, 22, 23, 24, 25 and 27.

 Ex.1	 Ex.5
 Ex.8	 Ex.10
 Ex.12	 Ex.13

 <p>Ex. 14</p>	 <p>Ex.19</p>
 <p>Ex. 22</p>	 <p>Ex.23</p>
 <p>Ex.24</p>	 <p>Ex. 25</p>
 <p>Ex. 27</p>	

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

$R^1$  is selected from the group consisting of H and  $CH_3$ .

- 5 Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

$R^1$  is oxetanyl.

- 10 Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

$R^1$  is selected from the group consisting of H,  $CH_3$  and oxetanyl;

$R^2$  is selected from the group consisting of H and  $CH_3$ .

- 15 Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

$R^1$  is selected from the group consisting of H and  $CH_3$ ;

$R^2$  is selected from the group consisting of H and  $CH_3$ .

- 20 Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

D-E is selected from the group consisting of  $CH_2-O$ ,  $C(O)-O$  and  $N(R^2)-C(O)$ .

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

- 25 D-E is selected from the group consisting of  $CH_2-O$  and  $C(O)-O$ .

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

- 30  $R^1$  is selected from the group consisting of H,  $CH_3$  and oxetanyl;

$R^2$  is selected from the group consisting of H and  $CH_3$ .

D-E is selected from the group consisting of  $CH_2-O$ ,  $C(O)-O$  and  $N(R_2)-C(O)$ .

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup> is selected from the group consisting of H, CH<sub>3</sub>, oxetanyl;

D-E is selected from the group consisting of CH<sub>2</sub>-O and C(O)-O.

5

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup> is selected from the group consisting of oxetanyl;

D-E is selected from the group consisting of CH<sub>2</sub>-O and C(O)-O.

10

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

W is CH;

X is CH;

15 Y is CH.

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

W is CH;

20 X is N;

Y is CH.

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

25 W is N;

X is CH;

Y is CH.

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

30

W is CH;

X is CH;

Y is N.

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

- 5 R<sup>1</sup> is selected from the group consisting of H, CH<sub>3</sub>- and oxetanyl;  
R<sup>2</sup> is selected from the group consisting of H and CH<sub>3</sub>-;  
D-E is selected from the group consisting of CH<sub>2</sub>-O, C(O)-O and N(R<sub>2</sub>)-C(O);  
W is CH;  
X is CH;  
10 Y is CH.

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

- R<sup>1</sup> is selected from the group consisting of H, CH<sub>3</sub>- and oxetanyl;  
15 D-E is selected from the group consisting of CH<sub>2</sub>-O and C(O)-O;  
W is CH;  
X is CH;  
Y is CH.

- 20 Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

- R<sup>1</sup> is selected from the group consisting of H, CH<sub>3</sub>- and oxetanyl;  
R<sup>2</sup> is selected from the group consisting of H and CH<sub>3</sub>-;  
D-E is selected from the group consisting of CH<sub>2</sub>-O, C(O)-O and N(R<sub>2</sub>)-C(O);  
25 W is N;  
X is CH;  
Y is CH.

- Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

- 30 R<sup>1</sup> is selected from the group consisting of H, CH<sub>3</sub>- and oxetanyl;  
D-E is selected from the group consisting of CH<sub>2</sub>-O and C(O)-O;

W is N;  
X is CH;  
Y is CH.

5 Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup> is selected from the group consisting of H, CH<sub>3</sub>- and oxetanyl;  
R<sup>2</sup> is selected from the group consisting of H and CH<sub>3</sub>-;  
D-E is selected from the group consisting of CH<sub>2</sub>-O, C(O)-O and N(R<sub>2</sub>)-C(O);

10 W is CH;  
X is N;  
Y is CH.

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

15 R<sup>1</sup> is selected from the group consisting of H, CH<sub>3</sub>- and oxetanyl;  
D-E is selected from the group consisting of CH<sub>2</sub>-O and C(O)-O;  
W is CH;  
X is N;  
20 Y is CH.

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup> is selected from the group consisting of H, CH<sub>3</sub>- and oxetanyl;  
25 R<sup>2</sup> is selected from the group consisting of H and CH<sub>3</sub>-;  
D-E is selected from the group consisting of CH<sub>2</sub>-O, C(O)-O and N(R<sub>2</sub>)-C(O);  
W is CH;  
X is CH;  
Y is N.

30

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein

- R<sup>1</sup> is selected from the group consisting of H, CH<sub>3</sub>- and oxetanyl;  
D-E is selected from the group consisting of CH<sub>2</sub>-O and C(O)-O;  
W is CH;  
X is CH;  
5 Y is N.

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein A is selected from the group consisting of A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13 and A14.

10

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein A is selected from the group consisting of A1, A2, A3, A4, A6, A7, A9, A10, A13 and A14.

- 15 Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein A is selected from A4, A5, A6, A7 A8, A9 and A14.

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein A is selected from the group consisting of A10, A11 and  
20 A12.

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein A is selected from the group consisting of A2, A3, A9, A13 and A14.

25

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein A is selected from the group consisting of A2, A3 and A13.

- 30 Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein A is A2.

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein A is A13.

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein i is 2 and j is 1.

Preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein i is 1 and j is 1.

Particularly preferred are the above compounds of formula I, or a pharmaceutically acceptable salt thereof, wherein i is 2 and j is 2.

10

Preferred are the compounds of formula I, wherein the compounds are selected from the group consisting of examples 1, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26 and 27.

Any and each of the definitions of  $R^1$ ,  $R^2$ , Cy, A, D, E, W, X, Y, i and j may be combined with each other.

A further embodiment of the current invention is a compound of formula I or a pharmaceutically acceptable salt thereof for use as a medicament.

20

A further embodiment of the current invention is a compound of formula I or a pharmaceutically acceptable salt thereof for use as a medicament for the treatment of asthma and allergic diseases, gastrointestinal inflammatory diseases, glomerulonephritis, eosinophilic diseases, chronic obstructive pulmonary disease, infection by pathogenic microbes, rheumatoid arthritis, neutrophilic diseases, cystic fibrosis (CF), non-cystic fibrosis, idiopathic pulmonary fibrosis, bronchiectasis, ANCA-associated vasculitis, lung cancer, emphysema, chronic bronchitis, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), pulmonary hypertension, pulmonary arterial hypertension (PAH) and Alpha-1-antitrypsin deficiency (AATD), obesity and related inflammation, insulin resistance, diabetes, fatty liver and liver steatosis.

25

Preferred is a compound of formula I or a pharmaceutically acceptable salt thereof for use as a medicament for the treatment of asthma and allergic diseases, gastrointestinal

inflammatory diseases, eosinophilic diseases, chronic obstructive pulmonary disease, emphysema, infection by pathogenic microbes, rheumatoid arthritis and atherosclerosis. Particularly preferred is a compound of formula I or a pharmaceutically acceptable salt thereof for use as a medicament for the treatment of chronic obstructive pulmonary disease and emphysema.

A further embodiment of the current invention is a pharmaceutical composition, characterised in that it contains one or more compounds of formula I or a pharmaceutically active salt thereof.

A further embodiment of the current invention is a method of treatment or prevention of diseases in which DPPI activity inhibitors have a therapeutic benefit, which method comprises administration of a therapeutically or preventively effective amount of a compound of formula I to a patient in need thereof.

A further embodiment of the current invention is a pharmaceutical composition comprising additionally to a compound of formula I, a pharmaceutically active compound selected from the group consisting of betamimetics, anticholinergics, corticosteroids, PDE4 inhibitors, LTD4 antagonists, EGFR inhibitors, CRTH2 inhibitors, 5 LO inhibitors, Histamine receptor antagonists, CCR9 antagonists and SYK inhibitors, NE inhibitors, MMP9 inhibitors and MMP12 inhibitors, but also combinations of two or three active substances.

## USED TERMS AND DEFINITIONS

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C<sub>1-6</sub>-alkyl means an alkyl group or radical having 1 to 6 carbon atoms.

- 5 In general in single groups like HO, H<sub>2</sub>N, S(O), S(O)<sub>2</sub>, NC (cyano), HOOC, F<sub>3</sub>C or the like, the skilled artisan can see the radical attachment point(s) to the molecule from the free valences of the group itself. For combined groups comprising two or more subgroups, the last named subgroup is the radical attachment point, for example, the substituent "aryl-C<sub>1-4</sub>-alkyl-" means an aryl group which is bound to a C<sub>1-4</sub>-alkyl-group, the latter of  
10 which is bound to the core or to the group to which the substituent is attached. Alternatively, "\*" indicates within a chemical entity, the point of attachment.

In case a compound of the present invention is depicted in form of a chemical name and as a formula in case of any discrepancy the formula shall prevail. An asterisk is may be used  
15 in sub-formulas to indicate the bond which is connected to the core molecule as defined.

Many of the followings terms may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

20 The term "substituted" as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded and that the substitution results in a stable compound.

25 The expressions "prevention", "prophylaxis", "prophylactic treatment" or "preventive treatment" used herein should be understood synonymous and in the sense that the risk to develop a condition mentioned hereinbefore is reduced, especially in a patient having elevated risk for said conditions or a corresponding anamnesis, e.g. elevated risk of  
30 developing metabolic disorder such as diabetes or obesity or another disorder mentioned herein. Thus the expression "prevention of a disease" as used herein means the management and care of an individual at risk of developing the disease prior to the clinical

onset of the disease. The purpose of prevention is to combat the development of the disease, condition or disorder and includes the administration of the active compounds to prevent or delay the onset of the symptoms or complications and to prevent or delay the development of related diseases, conditions or disorders. Success of said preventive treatment is reflected statistically by reduced incidence of said condition within a patient population at risk for this condition in comparison to an equivalent patient population without preventive treatment.

The expression "treatment" or "therapy" means therapeutic treatment of patients having already developed one or more of said conditions in manifest, acute or chronic form, including symptomatic treatment in order to relieve symptoms of the specific indication or causal treatment in order to reverse or partially reverse the condition or to delay the progression of the indication as far as this may be possible, depending on the condition and the severity thereof. Thus the expression "treatment of a disease" as used herein means the management and care of a patient having developed the disease, condition or disorder. The purpose of treatment is to combat the disease, condition or disorder. Treatment includes the administration of the active compounds to eliminate or control the disease, condition or disorder as well as to alleviate the symptoms or complications associated with the disease, condition or disorder.

20

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers etc...) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates of the free compounds or solvates of a salt of the compound.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without

excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include salts from ammonia, L-arginine, betaine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine (2, 2'-iminobis(ethanol)), diethylamine, 2-(diethylamino)-ethanol, 2-aminoethanol, ethylenediamine, N-ethyl-glucamine, hydrabamine, 1H-imidazole, lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine (2, 2', 2''-nitrilotris(ethanol)), tromethamine, zinc hydroxide, acetic acid, 2,2-dichloro-acetic acid, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 2, 5-dihydroxybenzoic acid, 4-acetamido-benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, decanoic acid, dodecylsulfuric acid, ethane-1, 2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, ethylenediaminetetraacetic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycine, glycolic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, DL-lactic acid, lactobionic acid, lauric acid, lysine, maleic acid, (-)-L-malic acid, malonic acid, DL-mandelic acid, methanesulfonic acid, galactaric acid, naphthalene-1, 5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, octanoic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid (embonic acid), phosphoric acid, propionic acid, (-)-L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like. (also see Pharmaceutical salts, Berge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (e.g. trifluoro acetate salts, ) also comprise a part of the invention.

The term halogen generally denotes fluorine, chlorine, bromine and iodine.

The term "C<sub>1-n</sub>-alkyl", wherein n is an integer selected from 2, 3, 4, 5 or 6, either alone or in combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C<sub>1-5</sub>-alkyl embraces the radicals H<sub>3</sub>C-, H<sub>3</sub>C-CH<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-CH(CH<sub>3</sub>)-, H<sub>3</sub>C-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-CH(CH<sub>3</sub>)-, H<sub>3</sub>C-CH(CH<sub>3</sub>)-CH<sub>2</sub>-, H<sub>3</sub>C-C(CH<sub>3</sub>)<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-CH<sub>2</sub>-CH(CH<sub>3</sub>)-, H<sub>3</sub>C-CH<sub>2</sub>-CH(CH<sub>3</sub>)-CH<sub>2</sub>-, H<sub>3</sub>C-CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>-, H<sub>3</sub>C-C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-CH(CH<sub>3</sub>)-CH(CH<sub>3</sub>)- and H<sub>3</sub>C-CH<sub>2</sub>-CH(CH<sub>2</sub>CH<sub>3</sub>)-.

The term "oxetanyl" denotes a 4-membered cyclic, saturated ring containing an oxygen atom in the 3-position with respect to the attachment point.

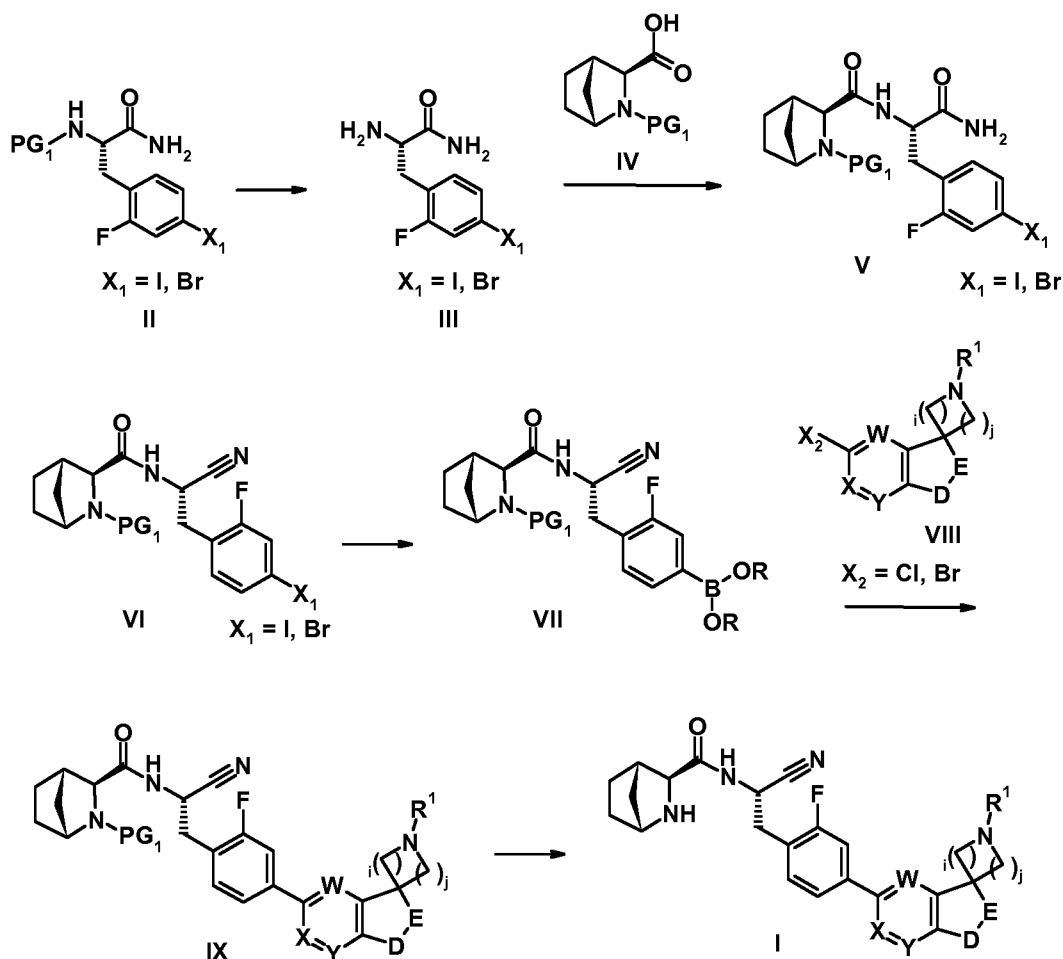
## PREPARATION

### GENERAL SYNTHETIC METHODS

The invention also provides processes for making a compound of Formula I.

Optimal reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific  
5 procedures are provided in the Synthetic Examples section. Typically, reaction progress may be monitored by thin layer chromatography (TLC) or LC-MS, if desired, and intermediates and products may be purified by chromatography on silica gel, HPLC and/or by recrystallization. The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for  
10 individual compounds without undue experimentation. Starting materials and intermediates used, in the methods below, are either commercially available or easily prepared from commercially available materials by those skilled in the art.

A compound of Formula **I** may be made by the method outlined in Scheme 1, 2, 3 or 4:



Scheme 1

As illustrated in Scheme 1 the protection and deprotection of functional groups is described in 'Protective Groups in Organic Synthesis', T. W. Greene and P. G. M. Wuts, Wiley-Interscience. For example, for the deprotection of *tert*-butoxycarbonyl group, an acid such as formic acid, trifluoroacetic acid, p-toluenesulfonic acid or HCl may be used in a suitable solvent such as water, DCM or dioxane to provide a compound of Formula III.

Reacting an acid of Formula IV, wherein PG<sub>1</sub> represents a protecting group (e.g. *tert*-butoxycarbonyl) using standard literature procedures for the formation of an amide, for example in the presence of a base such as N,N-diisopropylethylamine (DIPEA) and an activating agent such as HATU or TBTU, with an amine of Formula III in a suitable solvent, provides a compound of Formula V. Standard peptide coupling reactions known in

the art (see for example M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag) may be employed in these syntheses.

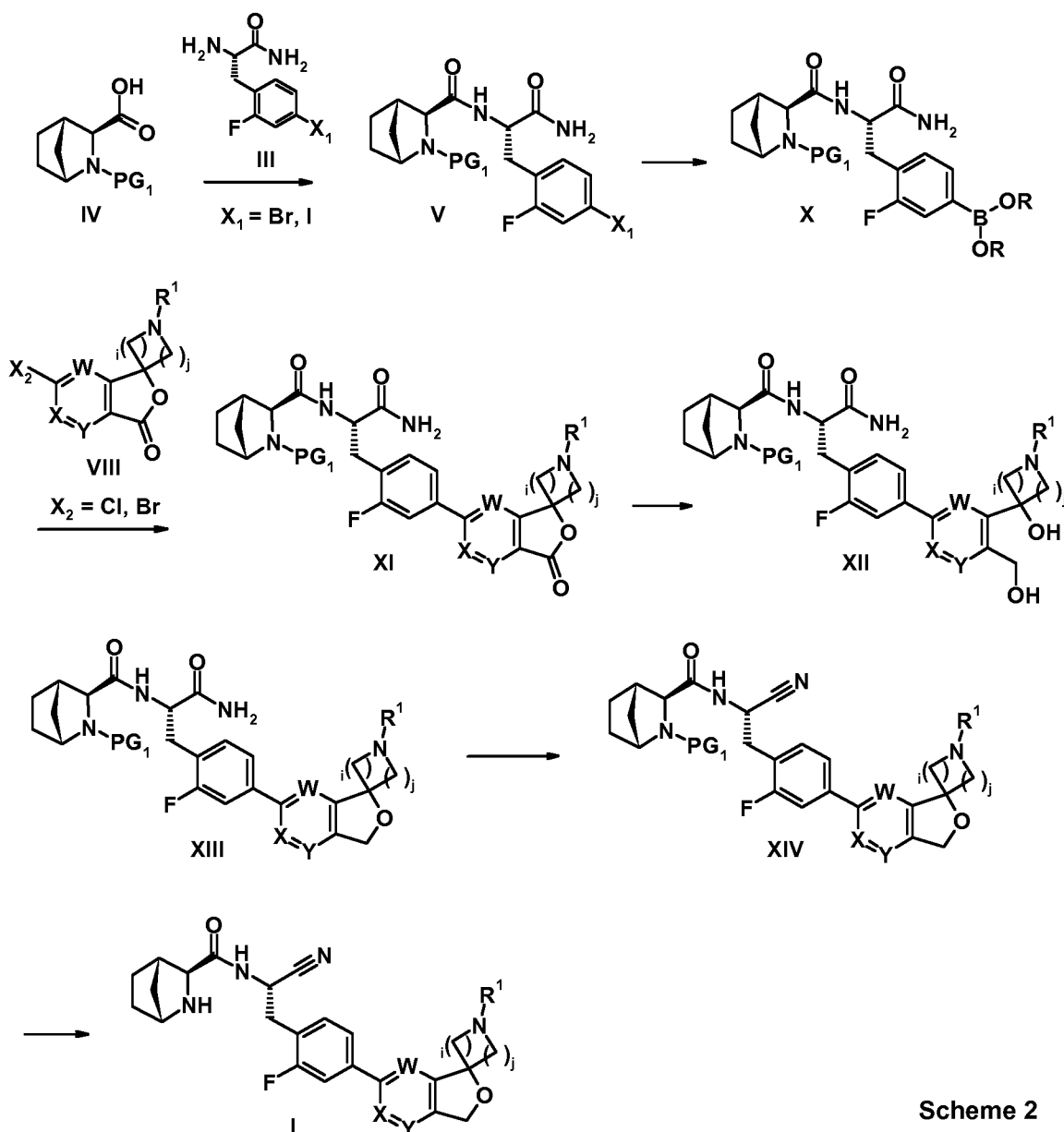
Dehydration of an amide such as in a compound of Formula V to the corresponding nitrile of Formula VI may be carried out by use of a dehydration agent such as

- 5 (methoxycarbonylsulfamoyl)triethyl ammonium hydroxide, in a suitable solvent such as dichloromethane (DCM).

- Compounds of Formula VI ( $X_1 = \text{I, Br}$ ) can be converted into the corresponding boronic acid derivatives VII, wherein R can be H or lower alkyl independently and the residues R
- 10 can form a ring. For example, VI can be reacted with bis(neopentyl glycolato)diboron in the presence of a suitable catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), and a suitable base such as potassium acetate or sodium, potassium or cesium carbonate or phosphate, in a suitable solvent such as dioxan, dimethylformamide (DMF), or dichloromethane (DCM) to yield
- 15 the boronic acid derivatives VII.

- These can be reacted in a (transition) metal catalyzed reaction of a compound of Formula VIII ( $X_2 = \text{Cl, Br}$ ). Coupling of these halogenides VIII provide a compound of Formula IX. For example, reaction of these halogenides with a boronic acid or the corresponding
- 20 boronic acid ester VII, in a suitable solvent such as dioxane, in the presence of a suitable catalyst such as 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride and a suitable base such as sodium, potassium or cesium carbonate, provides a compound of Formula IX.

- 25 The protection and deprotection of functional groups is described in 'Protective Groups in Organic Synthesis', T. W. Greene and P. G. M. Wuts, Wiley-Interscience. For example, for the deprotection of *tert*-butoxycarbonyl group, an acid such as *p*-toluenesulfonic acid monohydrate may be used in a suitable solvent such as acetonitrile to provide a compound of Formula I.



Scheme 2

As illustrated in Scheme 2 reacting an acid of Formula IV, wherein  $PG_1$  represents a protecting group (e.g. *tert*-butoxycarbonyl) using standard literature procedures for the formation of an amide, for example in the presence of a base such as N, N-diisopropylethylamine (DIPEA) and an activating agent such as HATU or TBTU, with an amine of Formula III in a suitable solvent, provides a compound of Formula V. Standard peptide coupling reactions known in the art (see for example M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag) may be employed in these syntheses.

Compounds of Formula V can be converted into the corresponding boronic acid derivatives X analogous to the reaction procedure described in Scheme 1.

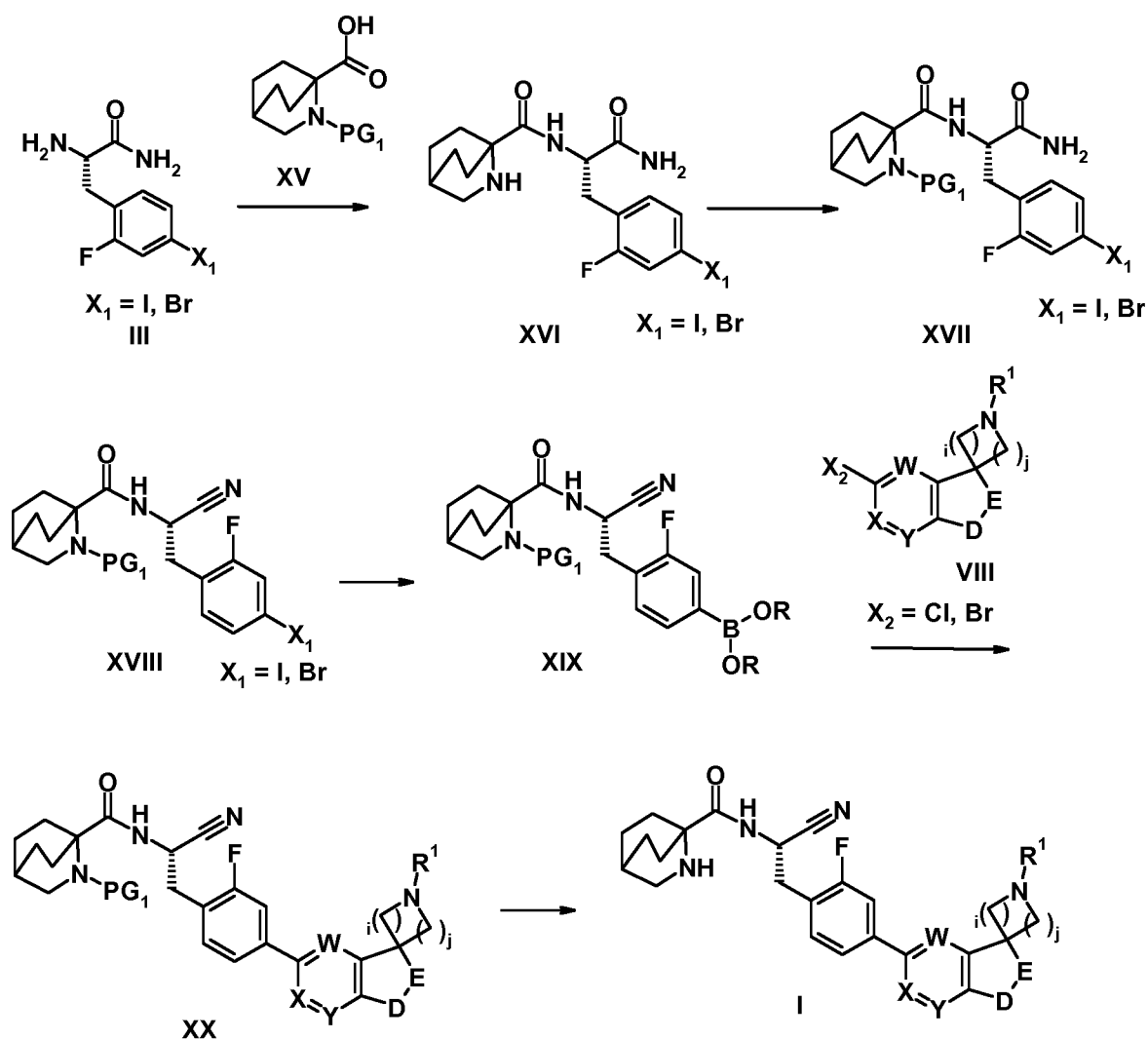
- These can be reacted in a (transition) metal catalyzed reaction of a compound of Formula VIII ( $X_2 = Cl, Br$ ) to yield a compound of the Formula XI analogous to the reaction procedure described in Scheme 1.

Compound of Formula XI can be converted into the compound of Formula XII using a reducing agent such as lithium or sodium borohydride in a suitable solvent such as tetrahydrofuran.

- Compound of Formula XII can be converted into the compound of Formula XIII using reagents such as p-toluenesulfonic anhydride or methansulfonyl chloride in the presence of base such as triethylamine or N,N-diisopropylethylamine (DIPEA) in a suitable solvent such as tetrahydrofuran.

- Dehydration of an amide such as in a compound of Formula XIII to the corresponding nitrile of Formula XIV may be carried out by use of a dehydration agent such as (methoxycarbonylsulfamoyl)triethyl ammonium hydroxide, in a suitable solvent such as dichloromethane (DCM).

- The protection and deprotection of functional groups is described in 'Protective Groups in Organic Synthesis', T. W. Greene and P. G. M. Wuts, Wiley-Interscience. For example, for the deprotection of *tert*-butoxycarbonyl group, an acid such as p-toluenesulfonic acid monohydrate may be used in a suitable solvent such as acetonitrile to provide a compound of Formula I.



Scheme 3

As illustrated in Scheme 3 reacting an acid of Formula XV, wherein  $\text{PG}_1$  represents a protecting group (e.g. *tert*-butoxycarbonyl) using standard literature procedures for the formation of an amide, for example in the presence of a base such as N-methylmorpholine and an activating agent such as 1-propanephosphonic acid cyclic anhydride (PPA) with an amine of Formula III in a suitable solvent, provides a compound of Formula XVI. Standard peptide coupling reactions known in the art (see for example M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag) may be employed in these syntheses.

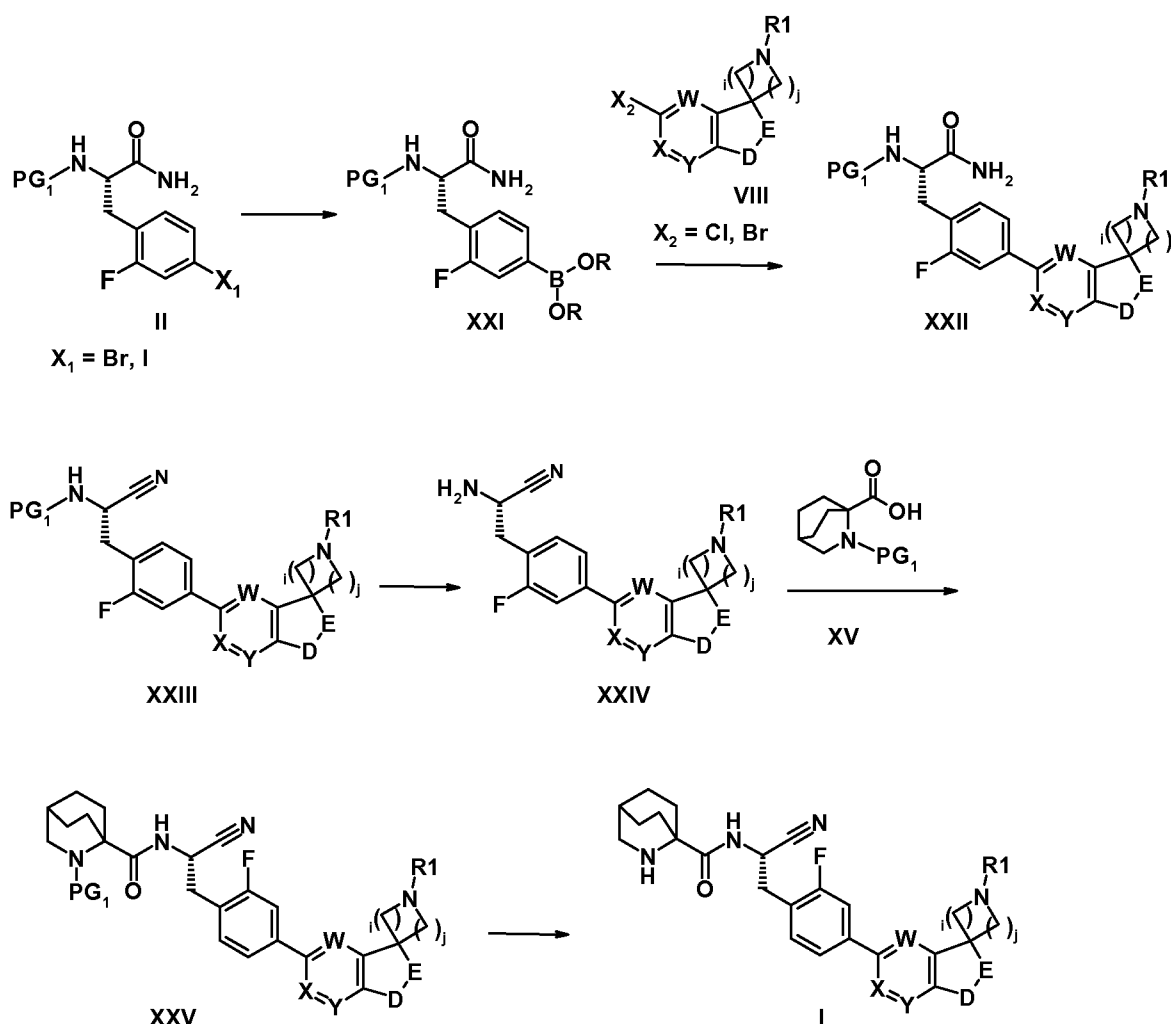
The protection and deprotection of functional groups is described in 'Protective Groups in Organic Synthesis', T. W. Greene and P. G. M. Wuts, Wiley-Interscience. For example, for the protection of an amine of Formula XVI, di-*tert*-butyl dicarbonate may be used in a suitable solvent such as dichloromethane to provide a compound of Formula XVII.

Dehydration of an amide such as in a compound of Formula XVII to the corresponding nitrile of Formula XVIII may be carried out by use of a dehydration agent such as (methoxycarbonylsulfamoyl)triethyl ammonium hydroxide, in a suitable solvent such as dichloromethane (DCM).

Compounds of Formula XVIII ( $X_1 = \text{I, Br}$ ) can be converted into the corresponding boronic acid derivatives XIX, wherein R can be H or lower alkyl independently and the residues R can form a ring. For example, XVIII can be reacted with bis(pinacolato)diboron in the presence of a suitable catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), and a suitable base such as potassium acetate or sodium, potassium or cesium carbonate or phosphate, in a suitable solvent such as dioxan, dimethylformamide (DMF), or dichloromethane (DCM) to yield the boronic acid derivatives XIX.

These can be reacted in a (transition) metal catalyzed reaction of a compound of Formula VIII ( $X_2 = \text{Cl, Br}$ ). Coupling of these halogenides VIII provide a compound of Formula XX. For example, reaction of these halogenides with a boronic acid or the corresponding boronic acid ester XIX, in a suitable solvent such as dioxane, in the presence of a suitable catalyst such as 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride and a suitable base such as sodium, potassium or cesium carbonate, provides a compound of Formula XX.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Synthesis', T. W. Greene and P. G. M. Wuts, Wiley-Interscience. For example, for the deprotection of *tert*-butoxycarbonyl group, an acid such as *p*-toluenesulfonic acid monohydrate may be used in a suitable solvent such as acetonitrile to provide a compound of Formula I.



### Scheme 4

As illustrated in Scheme 4 compound of Formula II can be converted into the corresponding boronic acid derivatives XXI, wherein R can be H or lower alkyl independently and the residues R can form a ring. For example, II can be reacted with bis(neopentyl glycolato)diboron in the presence of a suitable catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), and a suitable base such as potassium acetate or sodium, potassium or cesium carbonate or phosphate, in a suitable solvent such as dioxan, dimethylformamide (DMF), or dichloromethane (DCM) to yield the boronic acid derivatives XXI.

10 These can be reacted in a (transition) metal catalyzed reaction of a compound of Formula VIII analogous to the reaction procedure described in Scheme 1 to yield a compound of Formula XXII.

Dehydration of an amide such as a compound of Formula XXII to the corresponding nitrile of Formula XXIII may be carried out by use of a dehydration agent such as (methoxycarbonylsulfamoyl)triethyl ammonium hydroxide, in a suitable solvent such as dichloromethane (DCM).

5 The protection and deprotection of functional groups is described in 'Protective Groups in Organic Synthesis', T. W. Greene and P. G. M. Wuts, Wiley-Interscience. For example, for the deprotection of *tert*-butoxycarbonyl, an acid such as p-toluenesulfonic acid monohydrate may be used in a suitable solvent such as acetonitrile to provide a compound of Formula XXIV.

10 Reacting an acid of Formula XV, wherein PG1 represents a protecting group (e.g. *tert*-butoxycarbonyl) using standard literature procedures for the formation of an amide, for example in the presence of a base such as N-methylmorpholine and an activating agent such as 1-propanephosphonic acid cyclic anhydride (PPA), with an amine of Formula XXIV in a suitable solvent, provides a compound of Formula XXV. Standard peptide coupling reactions known in the art (see for example M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag) may be employed in these syntheses.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Synthesis', T. W. Greene and P. G. M. Wuts, Wiley-Interscience. For example, for the deprotection of *tert*-butoxycarbonyl, an acid such as p-toluenesulfonic acid  
20 monohydrate may be used in a suitable solvent such as acetonitrile to provide a compound of Formula I.

Further modifications of compounds of Formula I by methods known in the art and illustrated in the Examples below, may be used to prepare additional compounds of the  
25 invention.

## SYNTHETIC EXAMPLES

30

The following are representative compounds of the invention which can be made by the general synthetic schemes, the examples, and known methods in the art. Starting materials

and intermediates were either commercially available and purchased from catalogues of ABCR, ACROS, ABLOCK PHARMATECH, ACTIVATE, ALDRICH, APOLLO SCIENTIFIC, ARK PHARM INC, ATLANTIC SCIENTIFIC TECHNOLOGY, BETAPHARM, BEFARM, CHEMBRIDGE CORPORATION, CNH-TECH, ENAMINE LTD, GOLDENBRIDGE PHARMA INC, GVK BIO, MERCACHEM, MOLBRIDGE, WUXI APPTEC, ZERENEX or were synthesized according to literature or as described below in "Synthesis of starting materials/ educts"

Liquid chromatography-mass spectroscopy (LCMS) retention time and observed  $m/z$  data for the compounds below are obtained by one of the following methods:

10

LC-MS Method **V001\_007**

Device-Description			Waters Alliance with DAD and MSD	
Column			Waters XBridge C18	
Column Dimension			4.6 x 30 mm	
Particle Size			3.5 $\mu$ m	
Gradient/Solvent	% Sol	% Sol [Methanol]	Flow [ml/min]	Temp [°C]
Time [min]	[H <sub>2</sub> O, 0.1%TFA]			
0.0	95	5	4	60
1.6	0	100	4	60
1.85	0	100	4	60
1.9	95	5	4	60

LC-MS Method **V003\_003**

Device-Description			Waters Alliance with DAD and MSD	
Column			Waters XBridge C18	
Column Dimension			4.6 x 30 mm	
Particle Size			3.5 $\mu$ m	
Gradient/Solvent	% Sol [H <sub>2</sub> O, 0.1% NH <sub>3</sub> ]	% Sol [Methanol]	Flow [ml/min]	Temp [°C]
Time [min]				
0.0	95	5	4	60
0.2	95	5	4	60

Device-Description		Waters Alliance with DAD and MSD		
Column		Waters XBridge C18		
Column Dimension		4.6 x 30 mm		
Particle Size		3.5 µm		
Gradient/Solvent	% Sol [H <sub>2</sub> O, 0.1% NH <sub>3</sub> ]	% Sol [Methanol]	Flow [ml/min]	Temp [°C]
Time [min]				
1.5	0	100	4	60
1.75	0	100	4	60

LC-MS Method **V011\_S01**

Device-Description		Waters Alliance with DAD and MSD		
Column		Waters XBridge C18		
Column Dimension		4.6 x 30 mm		
Particle Size		3.5 µm		
Solvent Gradient time	% Sol [H <sub>2</sub> O, 0.1% NH <sub>3</sub> ]	% Sol [Acetonitrile]	Flow [ml/min]	Temp [°C]
[min]				
0.0	97	3	5	60
0.2	97	3	5	60
1.6	0	100	5	60
1.7	0	100	5	60

LC-MS Method **V012\_S01**

Device-Description		Waters Alliance with DAD and MSD		
Column		Waters XBridge C18		
Column Dimension		4.6 x 30 mm		
Particle Size		3.5 µm		
Solvent Gradient time	% Sol [H <sub>2</sub> O, 0.1% TFA]	% Sol [Acetonitrile]	Flow [ml/min]	Temp [°C]
[min]				
0.0	97	3	5	60
0.2	97	3	5	60
1.6	0	100	5	60

Device-Description			Waters Alliance with DAD and MSD		
1.7	0	100	5	60	

LC-MS Method **X001\_004**

Device-Description			Waters Acquity with DAD and MSD		
Column			Waters XBridge C18		
Column Dimension			2.1 x 20 mm		
Particle Size			2.5 µm		
Gradient/Solvent	% Sol	% Sol [Methanol]	Flow [ml/min]	Temp [°C]	
Time [min]	[H <sub>2</sub> O,0.10%TFA]				
0.0	95	5	1.4	60	
0.05	95	5	1.4	60	
1.00	0	100	1.4	60	
1.1	0	100	1.4	60	

LC-MS Method **X011\_S03**

Device-Description			Waters Acquity with DAD and MSD		
Column			Waters Xbridge BEH C18		
Column Dimension			2.1 x 30 mm		
Particle Size			1.7 µm		
Solvent Gradient	% Sol	% Sol	Flow [ml/min]	Temp [°C]	
time	[H <sub>2</sub> O,0.1%NH <sub>3</sub> ]	[Acetonitrile]			
[min]					
0,00	95	5	1,3	60	
0,02	95	5	1,3	60	
1,00	0	100	1,3	60	
1,10	0	100	1,3	60	

5

LC-MS Method **X012\_S02**

Device-Description			Waters Acquity with DAD and MSD		
Column			Waters XBridge BEH C18		

Device-Description			Waters Acquity with DAD and MSD	
Column Dimension			2.1 x 30 mm	
Particle Size			1.7 µm	
Solvent Gradient time [min]	% Sol [H <sub>2</sub> O, 0.1% TFA]	% Sol [Acetonitrile]	Flow [ml/min]	Temp [°C]
0.0	99	1	1.3	60
0.02	99	1	1.3	60
1.00	0	100	1.3	60
1.10	0	100	1.3	60

LC-MS Method **Z011\_S03**

Device-Description			Agilent 1200 with DAD and MSD	
Column			Waters XBridge C18	
Column Dimension			3 x 30 mm	
Particle Size			2.5 µm	
Gradient/Solvent Time [min]	% Sol [H <sub>2</sub> O, 0.1% NH <sub>3</sub> ]	% Sol [Acetonitrile]	Flow [ml/min]	Temp [°C]
0.00	97	3	2.2	60
0.20	97	3	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

LC-MS Method **Z012\_S04**

Device-Description			Agilent 1200 with DAD and MSD	
Column			Waters XBridge C18	
Column Dimension			3 x 30 mm	
Particle Size			2.5 µm	
Gradient/Solvent Time [min]	% Sol [H <sub>2</sub> O, 0.1% NH <sub>3</sub> ]	% Sol [Acetonitrile]	Flow [ml/min]	Temp [°C]

0.00	97	3	2.2	60
0.20	97	3	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

LC-MS Method **Z018\_S04**

Device-Description			Agilent 1200 with DAD and MSD	
Column			Waters Sunfire C18	
Column Dimension			3 x 30 mm	
Particle Size			2.5 µm	
Solvent Gradient time [min]	% Sol [H <sub>2</sub> O,0.1%TFA]	% Sol [Acetonitrile]	Flow [ml/min]	Temp [°C]
0.00	97	3	2.2	60
0.20	97	3	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

LC-MS Method **Z020\_S01**

Device-Description			Agilent 1200 with DAD and MSD	
Column			Waters Sunfire C18	
Column Dimension			3 x 30 mm	
Particle Size			2.5 µm	
Solvent Gradient time [min]	% Sol [H <sub>2</sub> O,0.1%FA]	% Sol [Acetonitrile]	Flow [ml/min]	Temp [°C]
0.00	97	3	2.2	60
0.20	97	3	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

LC-MS Method **Z021\_S01**

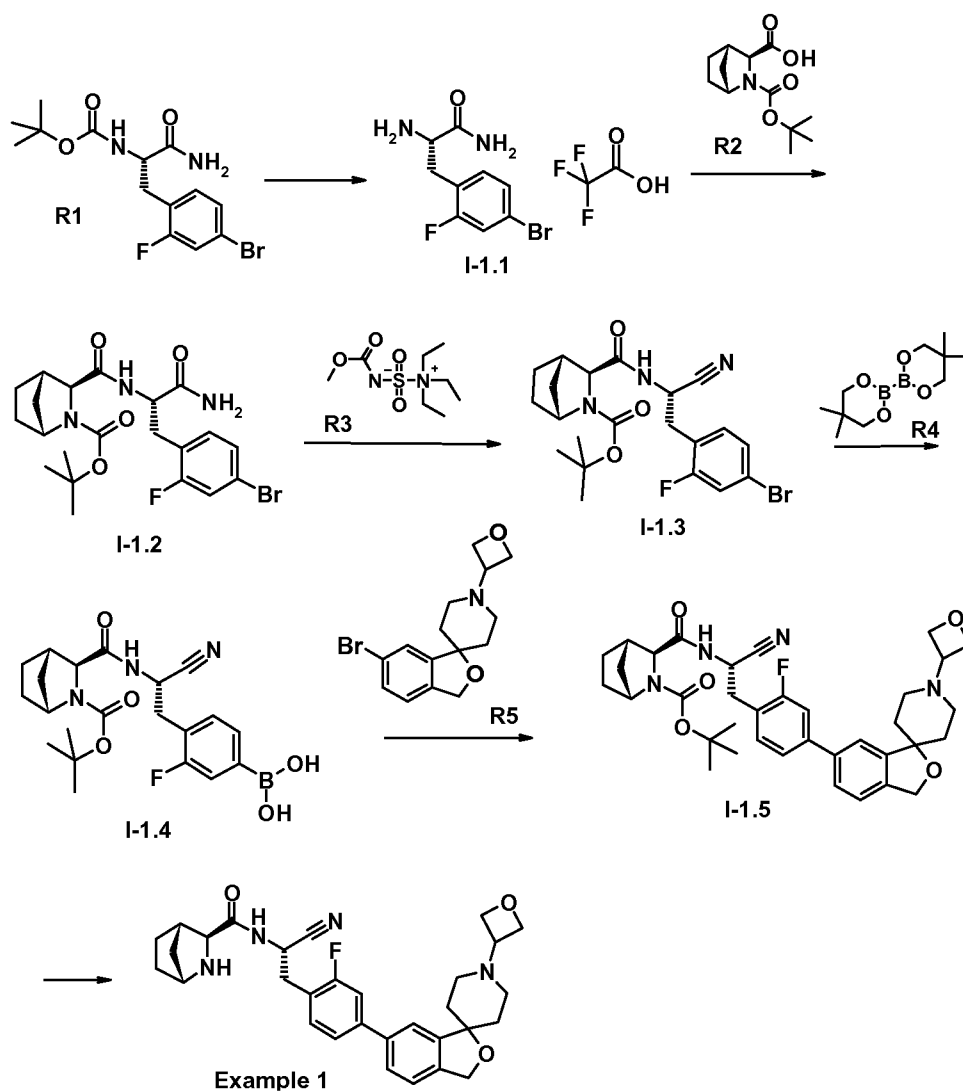
Device-Description			Agilent 1200 with DAD and MSD	
Column			XBridge C18	
Column Dimension			3 x 30 mm	
Particle Size			2.5 µm	
Solvent Gradient time [min]	% Sol [H <sub>2</sub> O,0.1%FA]	% Sol [Acetonitrile]	Flow [ml/min]	Temp [°C]
0.00	97	3	2.2	60
0.20	97	3	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

5

Synthesis Methods :**Method A**

10

**Synthesis of (1S,2S,4R)-N-[(1S)-1-cyano-2-[2-fluoro-4-[1'-(oxetan-3-yl)spiro[1H-isobenzofuran-3,4'-piperidine]-5-yl]phenyl]ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide (Example 1)**



### Step 1: Synthesis of Intermediate I-1.1

To R1 (20.00 g, 55.37 mmol) in dichloromethane (50 mL) is added trifluoroacetic acid (17.09 mL, 221.48 mmol) and the reaction mixture is stirred overnight at r.t.. The reaction mixture is concentrated, the residue is dissolved in dichloromethane (15 mL) and diisopropyl ether (140 mL). The precipitate is filtered off, washed with diisopropyl ether and dried to provide I-1.1 as TFA salt.

Yield 99%,  $m/z$  261  $[M+H]^+$ , rt 0.50 min, LC-MS Method Z018\_S04.

### Step 2: Synthesis of Intermediate I-1.2

To R2 (13.86 g, 55.72 mmol) in DMF (65 mL) is added DIPEA (9.02 mL, 50.67 mmol) and cooled down to 5°C. TBTU (17.89 g, 55.72 mmol) is added and the reaction mixture is stirred for 15 minutes. Afterwards I-1.1 (TFA salt) (19.0 g, 50.65 mmol), DMF (65 mL) and DIPEA (13.52 mL, 75.98 mmol) are added and the reaction mixture is stirred  
5 overnight at r.t.. The reaction mixture is diluted with ethyl acetate and extracted with water. The aqueous layer is extracted with ethyl acetate. The combined organic layers are washed with water, 1mol/L aqueous hydrochloric acid, water, aqueous sodium hydrogen carbonate solution (5%) and again with water. The organic layer is dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The crude residue is purified by flash chromatography (eluent:  
10 dichloromethane/ methanol 95:5).  
Yield 82%, *m/z* 484 [M+H]<sup>+</sup>, rt 0.91 min, LC-MS Method Z018\_S04.

### Step 3: Synthesis of Intermediate I-1.3

To I-1.2 (20.0 g, 41.29 mmol) in dichloromethane (200 mL) is added R3 (19.68 g, 82.58  
15 mmol) and the reaction mixture is stirred overnight at r.t.. The reaction mixture is concentrated in vacuo, the residue is dissolved in ethyl acetate and extracted with water, 1 mol/L aqueous acetic acid, and water. The organic layer is dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The residue is recrystallized from acetonitrile and filtered off.  
Yield 71%, *m/z* 466 [M+H]<sup>+</sup>, rt 0.98 min, LC-MS Method Z018\_S04.

### Step 4: Synthesis of Intermediate I-1.4

To I-1.3 (1.5 g, 3.22 mmol) in dioxane (20 mL) R4 (799.22 mg, 3.54 mmol), potassium acetate (0.947 g, 9.65 mmol) and [1,1'-  
bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane  
25 (1:1) (52.54 mg, 0.064 mmol) are added. The reaction mixture is purged with nitrogen and heated to 70 °C for 1.5 h. The reaction mixture is diluted with dichloromethane and water. The organic layer is separated and concentrated in vacuo. The residue is purified by reversed phase HPLC.  
Yield 94% *m/z* 332 [M+H-Boc]<sup>+</sup>, rt 0.96 min, LC-MS Method Z020\_S01.

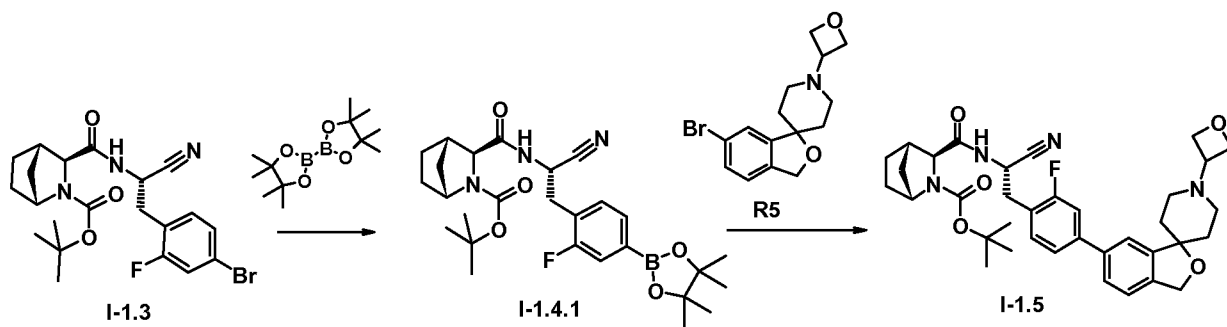
### Step 5: Synthesis of Intermediate I-1.5

To I-1.4 (400.0 mg, 0.93 mmol) in acetonitrile (18 mL) is added R5 (301.0 mg, 0.93 mmol) and mixture is purged with argon. Sodium carbonate aqueous solution 2 mol/L (928  $\mu$ L, 1.86 mmol) and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (60.5 mg, 0.09 mmol) are added, reaction mixture is purged again with argon and stirred at 80°C

5 in the microwave reactor for 45 minutes. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate several times. The organic layer is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude residue is purified by silica gel column chromatography (DCM : MeOH = 98:2 to 92:8) to afford I-1.5.

10 Yield 79%  $m/z$  631 [M+H]<sup>+</sup>, rt 1.09 min, LC-MS Method Z011\_S03.

#### Alternative synthesis of Intermediate I-1.5



#### 15 Synthesis of Intermediate I-1.4.1

To I-1.3 (20 g, 42.89 mmol) in dioxane (255 mL) bis(pinacolato)diboron (13.07 g, 51.46 mmol), potassium acetate (12.63 g, 128.66 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (1.75 g, 2.14 mmol) are added. The mixture is purged with nitrogen for 5 minutes,

20 heated to 70 °C and stirred overnight at this temperature. The reaction mixture is diluted with dichloromethane and water. The organic layer is separated and concentrated in vacuo. The residue is purified by silica gel column chromatography (petroleum ether : EtOAc = 92:8 to 34:66).

Yield 64%  $m/z$  332 [M+H – Boc – ((CH<sub>3</sub>)<sub>2</sub>CH)<sub>2</sub>]<sup>+</sup>, rt 0.73 min, LC-MS Method Z011\_S03.

25

#### Synthesis of Intermediate I-1.5

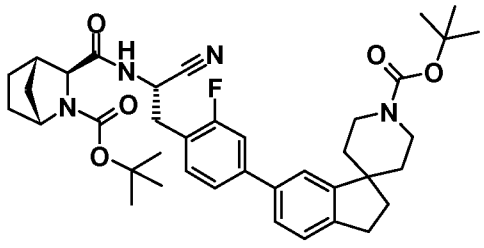
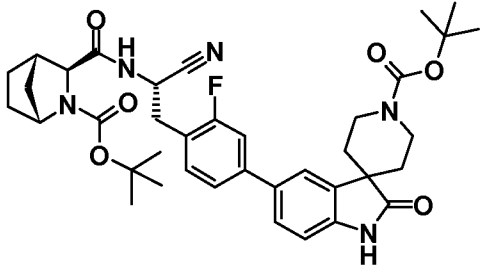
To I-1.4.1 (3.96 g, 7.71 mmol) in acetonitrile (60 mL) is added R5 (2.50 g, 7.71 mmol) and mixture is purged with argon. Sodium carbonate aqueous solution 2 mol/L (7.71 mL, 15.42 mmol) and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (502.6 mg, 0.77 mmol) are added, reaction mixture is purged again with argon and stirred at 80°C for 90 minutes. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate several times. The organic layer is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude residue is purified by silica gel column chromatography (DCM : MeOH = 99:1 to 94:6) to afford I-1.5.

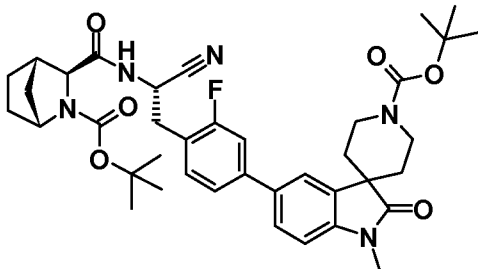
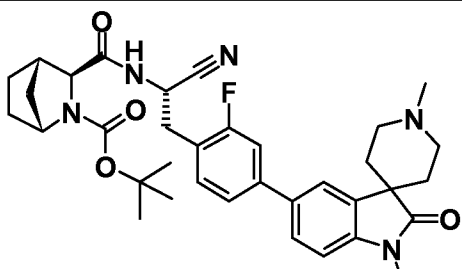
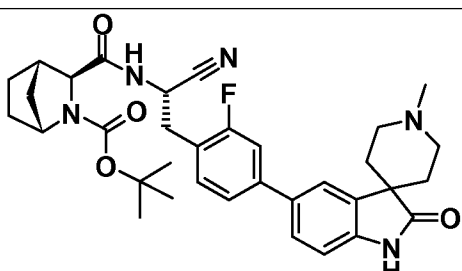
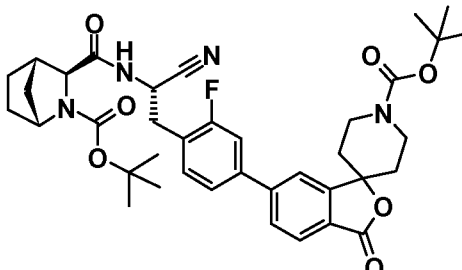
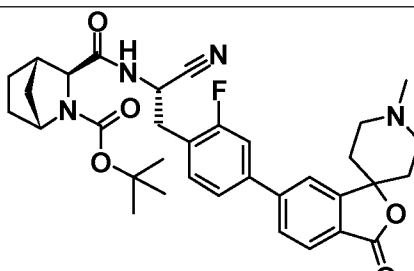
Yield 75% *m/z* 631 [M+H]<sup>+</sup>, rt 1.09 min, LC-MS Method Z011\_S03.

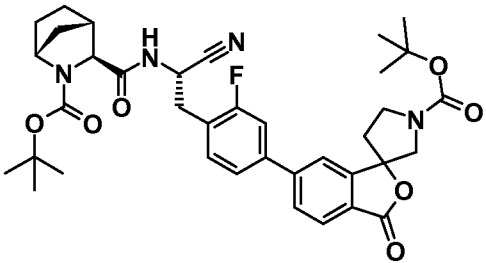
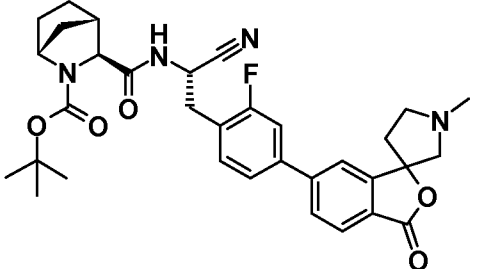
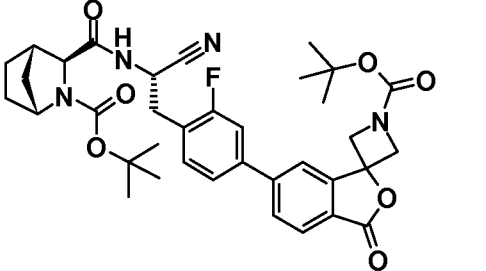
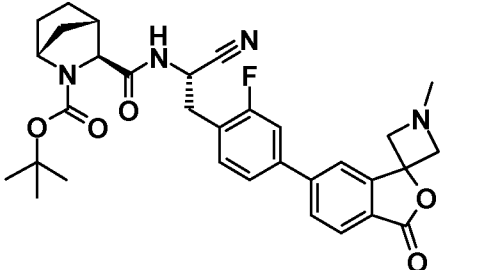
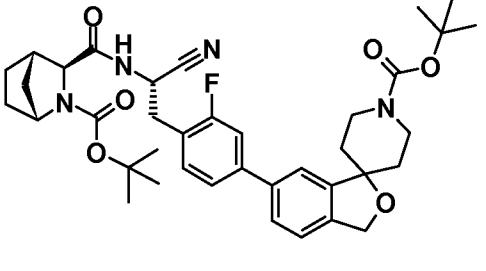
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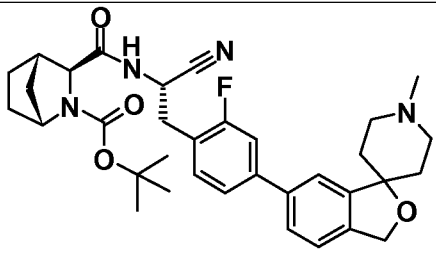
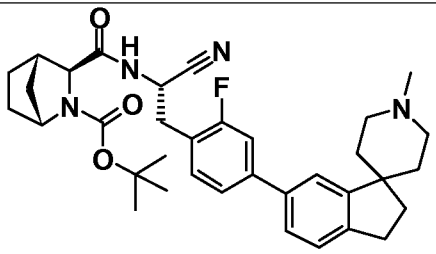
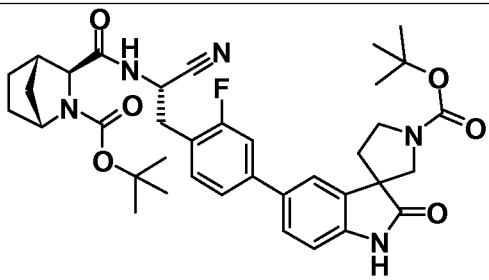
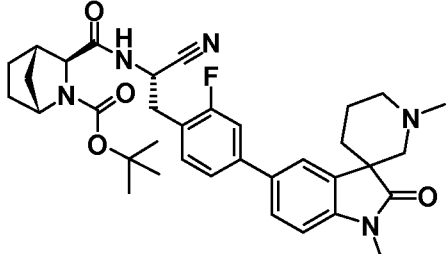
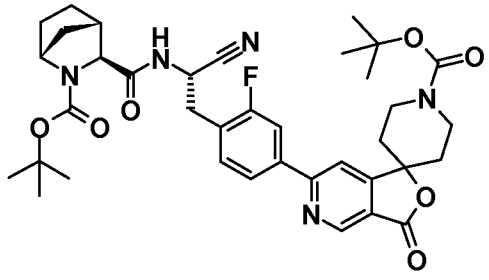
The following intermediates as shown in Table 1 are synthesized in a similar fashion from the intermediate I-1.4 and appropriate educts:

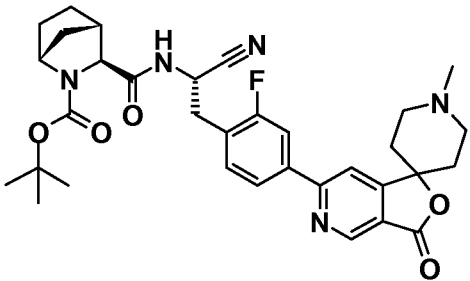
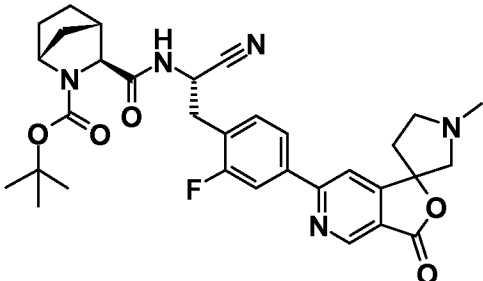
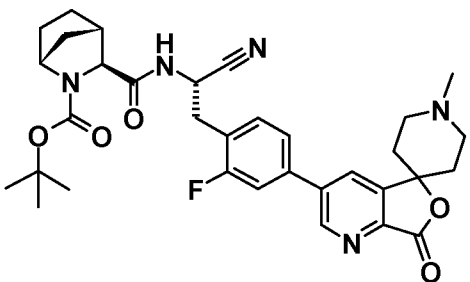
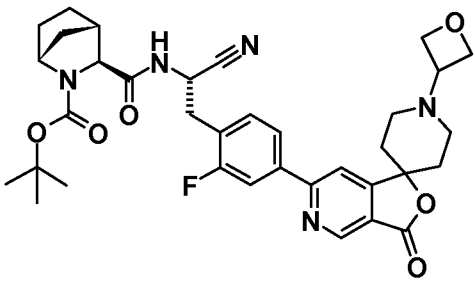
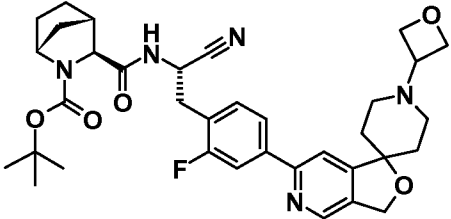
**Table 1**

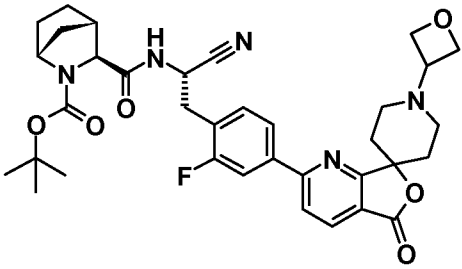
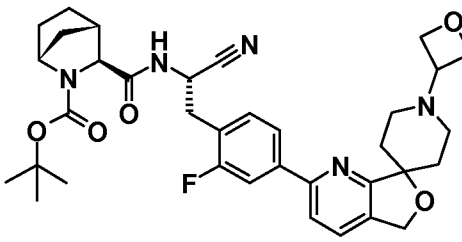
Inter-mediate	Educt	Structure of Intermediate	<i>m/z</i> [M+H] <sup>+</sup>	rt (min)	LC-MS method
I-1.5.1	R6		517 [M-Boc- t.but +H] <sup>+</sup>	1.29	Z012_S04
I-1.5.2	R8		532 [M-Boc- t.but +H] <sup>+</sup>	1.14	Z012_S04

I-1.5.3	R9		546 [M-Boc- t.but +H] <sup>+</sup>	1.19	Z012_S04
I-1.5.4	R10		616	0.95	Z012_S04
I-1.5.5	R10.1		602	0.91	Z012_S04
I-1.5.6	I-7.2		589 [M-Boc +H] <sup>+</sup>	1.19	Z012_S04
I-1.5.7	R10.2		603	0.94	Z012_S04

I-1.5.8	I-7.2.1		575 [M-Boc +H] <sup>+</sup>	1.15	Z011_S03
I-1.5.9	R10.3		589	0.95	Z012_S04
I-1.5.10	I-7.2.2		561 [M-Boc +H] <sup>+</sup>	1.17	Z012_S04
I-1.5.11	R10.4		575	1.04	Z011_S03
I-1.5.12	I-7.4		575 [M-Boc +H] <sup>+</sup>	1.24	Z011_S03

I- 1.5.13	R10.5		589	1.12	Z011_S03
I- 1.5.14	R7		587	1.19	Z011_S03
I- 1.5.15	R12		574 [M-Boc +H] <sup>+</sup>	1.10	Z011_S03
I- 1.5.16	R10.6		615	0.80	Z020_S01
I- 1.5.17	R14		590 [M-Boc +H] <sup>+</sup>	1.16	Z011_S03

I- 1.5.18	R10.7		604	1.04	Z011_S03
I- 1.5.19	I- 11.1.1		590	1.02	Z011_S03
I- 1.5.20	R15		604	1.03	Z011_S03
I- 1.5.21	R16		546 [M-Boc +H] <sup>+</sup>	1.00	Z011_S03
I- 1.5.22	R17		632	1.03	Z011_S03

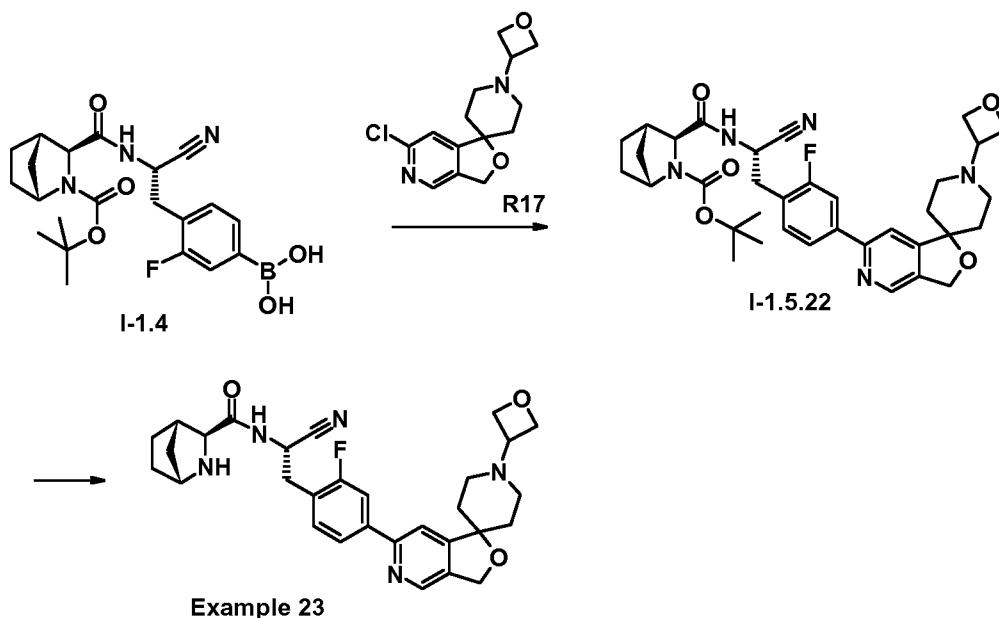
I- 1.5.23	R18		646	0.90	Z011_S03
I- 1.5.24	R19		632	1.04	Z011_S03

### 5 Step 6: Synthesis of Example 1

To I-1.5 (3.64 g, 5.78 mmol) in acetonitrile (60 mL) is added p-toluenesulfonic acid monohydrate (5.49 g, 28.88 mmol) and reaction mixture is stirred overnight at r.t.. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate several times. The organic layer is washed with brine, dried  
 10 over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The crude residue is purified by reversed phase HPLC.

Yield 84% *m/z* 531 [M+H]<sup>+</sup>, rt 1.00 min, LC-MS Method Z011\_S03.

### 15 Synthesis of (1S,2S,4R)-N-[(1S)-1-cyano-2-[2-fluoro-4-[1'-(oxetan-3-yl)spiro[3H-furo[3,4-c]pyridine-1,4'-piperidine]-6-yl]phenyl]ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide (Example 23)



### Step 1: Synthesis of Intermediate I-1.5.22

To I-1.4 (92.2 mg, 0.17 mmol) in acetonitrile (3 mL) is added R17 (48.0 mg, 0.17 mmol) and mixture is purged with argon. Caesium carbonate aqueous solution 2 mol/L (171  $\mu$ L, 0.34 mmol) and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (11.1 mg, 0.02 mmol) are added, reaction mixture is purged again with argon and stirred at 80°C in the microwave reactor for 45 minutes. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate several times. The organic layer is washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo. The crude residue is purified by reversed phase HPLC to afford I-1.5.22.

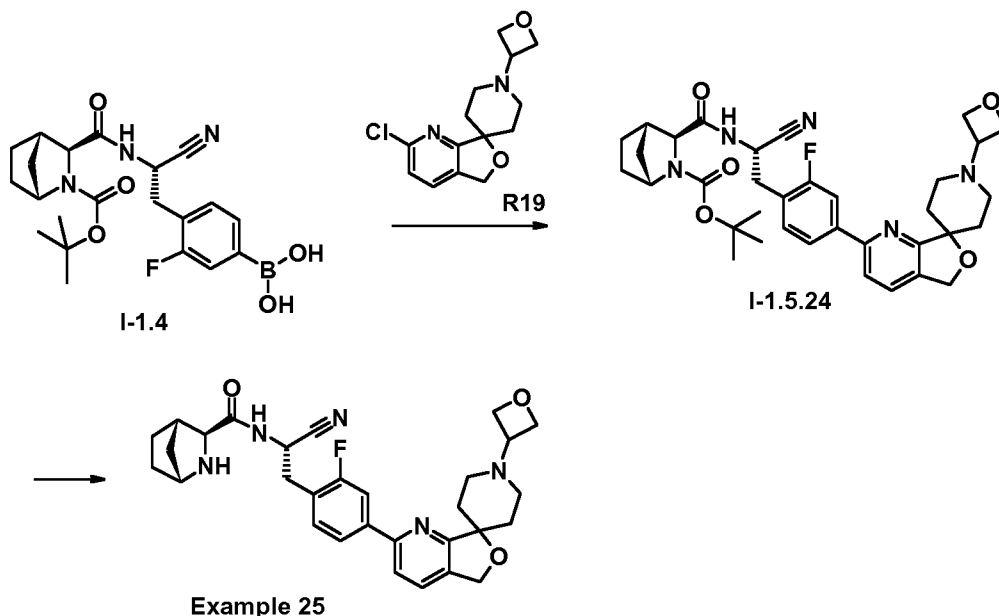
Yield 52%  $m/z$  632  $[\text{M}+\text{H}]^+$ , rt 1.04 min, LC-MS Method Z011\_S03.

### Step 2: Synthesis of Example 23

To I-1.5.22 (56.0 mg, 0.09 mmol) in acetonitrile (2 mL) is added p-toluenesulfonic acid monohydrate (84.3 mg, 0.44 mmol) and reaction mixture is stirred overnight at r.t.. The reaction mixture is basicified with TEA, filtered through membrane filter and purified by reversed phase HPLC.

Yield 83%  $m/z$  532  $[\text{M}+\text{H}]^+$ , rt 0.96 min, LC-MS Method Z011\_S03.

**Synthesis of (1S,2S,4R)-N-[(1S)-1-cyano-2-[2-fluoro-4-[1'-(oxetan-3-yl)spiro[5H-furo[3,4-b]pyridine-7,4'-piperidine]-2-yl]phenyl]ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide (Example 25)**



5

**Step 1: Synthesis of Intermediate I-1.5.24**

To I-1.4 (2.304 g, 5.34 mmol) in acetonitrile (50 mL) is added R19 (1.50 g, 5.34 mmol) and mixture is purged with argon. Sodium carbonate aqueous solution 2 mol/L (5.343 mL, 10.69 mmol) and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (348.2 mg, 0.53 mmol) are added, reaction mixture is purged again with argon and stirred at 70°C in the microwave reactor for 45 minutes. Additional amount of I-1.4 (150 mg, 0.35 mmol) is added and the reaction mixture is stirred at 70°C for 25 minutes. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate several times. The organic layer is washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The crude residue is purified by silica gel column chromatography (DCM : MeOH = 99:1 to 9:1) to afford I-1.5.24.

Yield 55% *m/z* 632 [M+H]<sup>+</sup>, rt 1.05 min, LC-MS Method Z011\_S03.

20

**Step 2: Synthesis of Example 25**

To I-1.5.24 (1.85 g, 2.93 mmol) in acetonitrile (50 mL) is added p-toluenesulfonic acid monohydrate (2.78 g, 14.64 mmol) and reaction mixture is stirred overnight at r.t.. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate several times. The organic layer is washed with brine, dried  
5 over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The crude residue is purified by reversed phase HPLC.

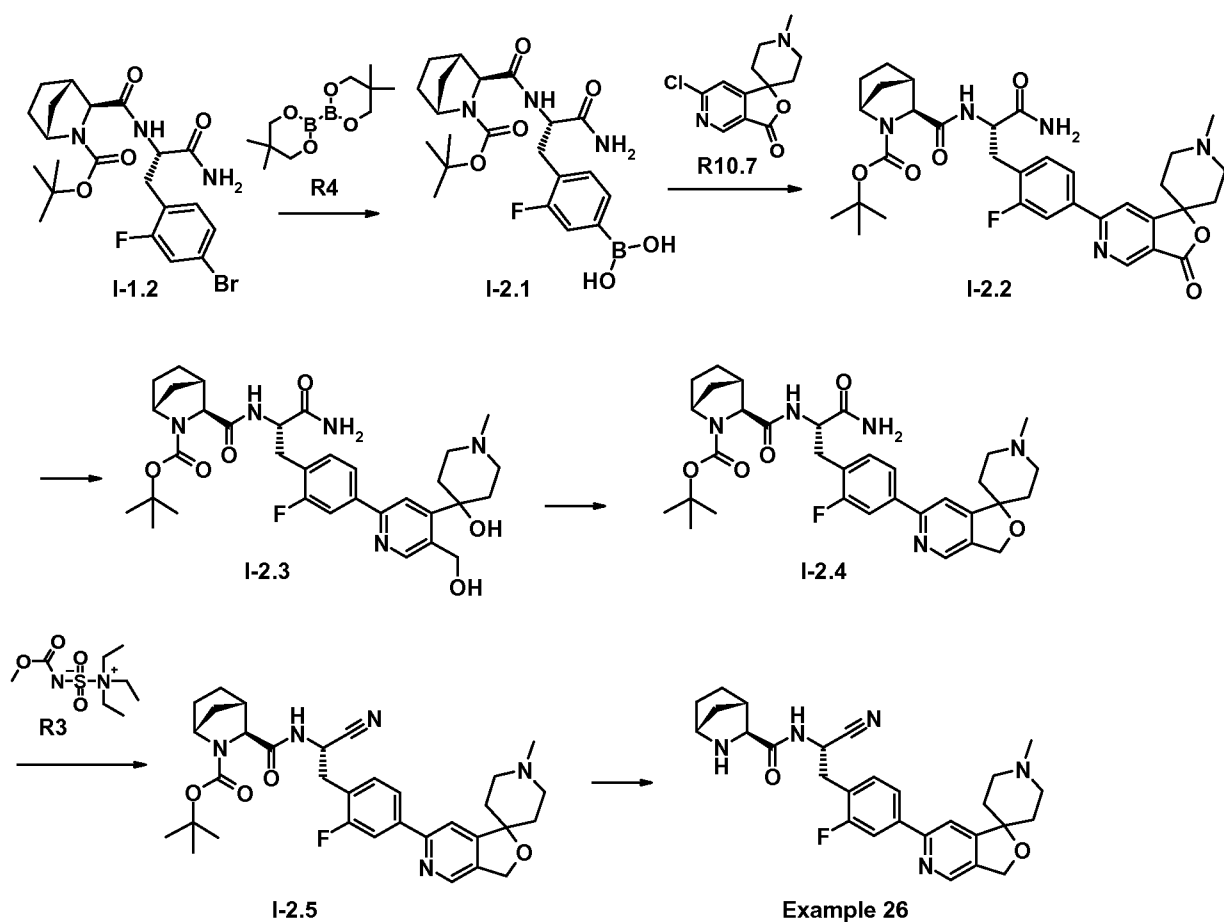
Yield 88% *m/z* 532 [M+H]<sup>+</sup>, rt 0.97 min, LC-MS Method Z011\_S03.

10

### Method B

**Synthesis of (1S,2S,4R)-N-[(1S)-1-cyano-2-[2-fluoro-4-(1'-methylspiro[3H-furo[3,4-c]pyridine-1,4'-piperidine]-6-yl)phenyl]ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide (Example 26)**

15



### 5 Step 1: Synthesis of Intermediate I-2.1

To I-1.2 (1.0 g, 2.07 mmol) in dioxane (10 mL) R4 (512.99 mg, 2.27 mmol), potassium acetate (607.92 mg, 9.65 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (33.72 mg, 0.041 mmol) are added. The reaction mixture is purged with nitrogen and heated to 70 °C overnight. Again R4 (100 mg, 0.44 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (10 mg, 0.01 mmol) are added and the reaction mixture is stirred at 70°C for 2 hours. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The residue is purified by reversed phase HPLC. Yield 50% *m/z* 450 [M+H]<sup>+</sup>.

**Step 2: Synthesis of Intermediate I-2.2**

To I-2.1 (204.46 mg, 0.46 mmol) in acetonitrile (4 mL) is added R10.7 (115 mg, 0.46 mmol) and mixture is purged with argon. Caesium carbonate solution 2mol/L (455.09  $\mu$ L, 0.91 mmol) and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (29.66 mg, 0.046 mmol) are added, reaction mixture is purged again with argon and stirred at 80°C in the microwave reactor for 45 minutes. The reaction mixture is diluted with water, and extracted with ethyl acetate. The organic layer is washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo. The residue is purified by reversed phase HPLC.

Yield 75%.

**Step 3: Synthesis of Intermediate I-2.3**

To I-2.2 (212 mg, 0.34 mmol) in THF (5 mL) is added lithium borohydride (2 mol/L, 0.26 mL, 0.51 mmol) and reaction mixture is stirred for 3 hours at r.t.. The reaction mixture is quenched with methanol, diluted with water and ethyl acetate. The organic layer is washed with sodium hydrogen carbonate solution and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo.

Yield 91%.

**Step 4: Synthesis of Intermediate I-2.4**

To I-2.3 (194 mg, 0.31 mmol) in THF (5 mL) are added TEA (0.22 mL, 1.55 mmol) and p-toluenesulfonic anhydride (121.43 mg, 0.37 mmol) at 0°C. The reaction mixture is allowed to come to r.t. and stirred overnight. The reaction mixture is quenched with water and concentrated in vacuo. The residue is diluted with sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. The residue is purified by reversed phase HPLC.

Yield 34%  $m/z$  608  $[\text{M}+\text{H}]^+$ .

**Step 5: Synthesis of Intermediate I-2.5**

To I-2.4 (65 mg, 0.11 mmol) in dichloromethane (2.5 mL) is added R3 (63.72 mg, 0.27 mmol) and reaction mixture is stirred overnight at r.t.. The reaction mixture is diluted with

ethyl acetate and extracted with water. The organic layer is washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo.

Yield >95%.

5    **Step 6: Synthesis of Example 26**

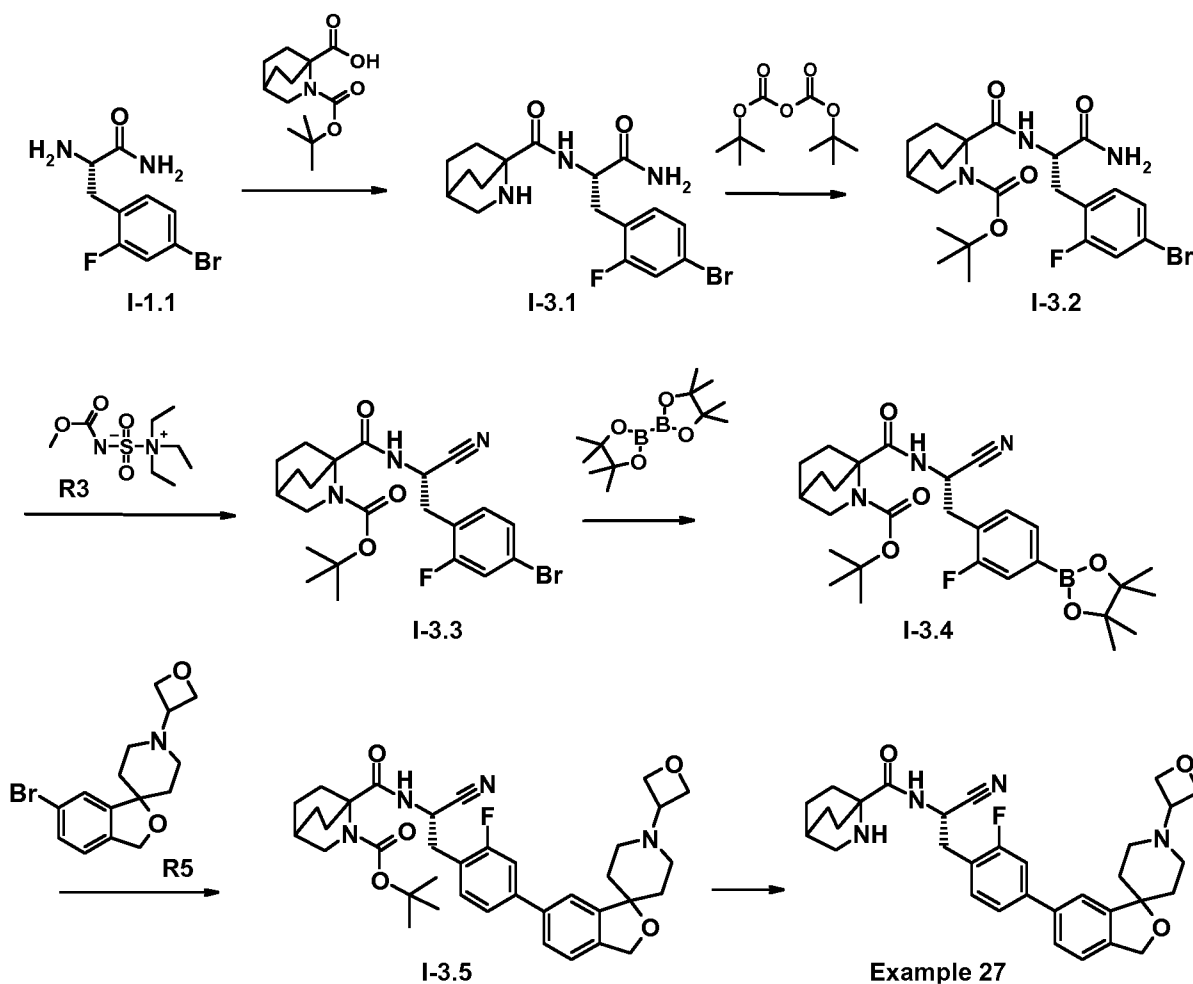
To I-2.5 (68 mg, 0.10 mmol) in acetonitrile (2 mL) is added p-toluenesulfonic acid monohydrate (98.70 mg, 0.52 mmol) and reaction mixture is stirred for 1h at r.t.. The reaction mixture is basified with TEA and purified by reversed phase HPLC.

Yield 28%  $m/z$  490  $[\text{M}+\text{H}]^+$ , rt 0.96 min, LC-MS Method Z011\_S03.

10

**Method C**

15    **Synthesis of N-[(1S)-1-cyano-2-[2-fluoro-4-[1'-(oxetan-3-yl)spiro[1H-isobenzofuran-3,4'-piperidine]-5-yl]phenyl]ethyl]-3-azabicyclo[2.2.2]octane-4-carboxamide (Example 27)**



### Step 1: Synthesis of intermediate I-3.1

- 5 To a cooled to 0°C solution of I-1.1 (5.80 g, 22.2 mmol), 3-tert-butoxycarbonyl-3-azabicyclo[2.2.2]octane-4-carboxylic acid, prepared according to Radchenko *et al. J. Org. Chem.* 2009, 5541-5544 (5.67 g, 22.2 mmol) and N-methyl-morpholine (12.2 mL, 111.0 mmol) in dry dichloromethane (67 mL) is added PPA (13.08 mL (50% in ethyl acetate), 22.2 mmol). The reaction mixture is allowed to reach r.t. and stirred overnight. The
- 10 reaction mixture is diluted with saturated sodium hydrogen carbonate solution and extracted with dichloromethane several times. The organic layer is washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to provide I-3.1, which was used in the next step without further purification.

Yield 73%, *m/z* 398/400 [M+H]<sup>+</sup>, rt 0.87 min, LC-MS Method Z011\_S03.

**Step 2: Synthesis of Intermediate I-3.2**

To a cooled to 0°C solution of I-3.1 (8.625 g, 21.66 mmol) in 300 mL of dry dichloromethane is added dropwise a solution of di-tert-butyl dicarbonate (6.26 g, 28.70 mmol) in 20 ml of dry dichloromethane. The reaction mixture is stirred for 2 h at 0°C, allowed to reach r.t., and stirred for 2 days. The reaction mixture is concentrated in vacuo to provide I-3.2 which was used in the next step without further purification.

Yield 98%,  $m/z$  398/400  $[M+H - Boc]^+$ , rt 1.04 min, LC-MS Method Z011\_S03.

**Step 3: Synthesis of Intermediate I-3.3**

To a suspension of I-3.2 (5.52 g, 11.07 mmol) in dry dichloromethane (70 mL) is added R3 (3.96 g, 16.60 mmol) in four portions and the reaction mixture is stirred overnight at r.t.. Additional amount of R3 (791.0 mg, 3.32 mmol) is added and the reaction mixture is stirred for 6 h at r.t.. Reaction mixture is diluted with dichloromethane, washed with 10% aqueous solution of tartaric acid, saturated sodium hydrogen carbonate solution, brine, dried over  $MgSO_4$ , filtered and concentrated in vacuo. Obtained residue is purified by silica gel column chromatography (petroleum ether : EtOAc = 94:6 to 69:31) to provide I-3.3.

Yield 77%  $m/z$  380/382  $[M+H - Boc]^+$ , rt 1.10 min, LC-MS Method Z011\_S03.

**Step 4: Synthesis of Intermediate I-3.4**

To I-3.3 (3.61 g, 7.52 mmol) in dioxane (45 mL) bis(pinacolato)diboron (3.24 g, 12.78 mmol), potassium acetate (2.21 g, 22.55 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (61.4 mg, 0.08 mmol) are added. The mixture is purged with nitrogen for 5 minutes and heated at 70 °C for 3 h. The reaction mixture is diluted with water and extracted with dichloromethane. The organic layer is washed with brine, dried over  $MgSO_4$ , filtered and concentrated in vacuo. The residue is purified by silica gel column chromatography (petroleum ether : EtOAc = 100:0 to 91:9) to provide I-3.4.

Yield 68%  $m/z$  346  $[M+H - Boc - ((CH_3)_2CH)_2]^+$ , rt 0.77 min, LC-MS Method Z011\_S03.

**Step 5: Synthesis of Intermediate I-3.5**

To I-3.4 (1.14 g, 2.16 mmol) in acetonitrile (30 mL) is added R5 (0.70 g, 2.16 mmol) and mixture is purged with argon. Sodium carbonate aqueous solution 2 mol/L (2.16 mL, 4.32 mmol) and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (141.0 mg, 0.22 mmol) are added, reaction mixture is purged again with argon for 5 minutes and stirred at 80°C for 70 minutes in the microwave reactor. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate several times. The organic layer is washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The crude residue is purified by silica gel column chromatography (DCM : MeOH = 99:1 to 9:1) to afford I-3.5.

Yield 81% *m/z* 645 [M+H]<sup>+</sup>, rt 1.11 min, LC-MS Method Z011\_S03.

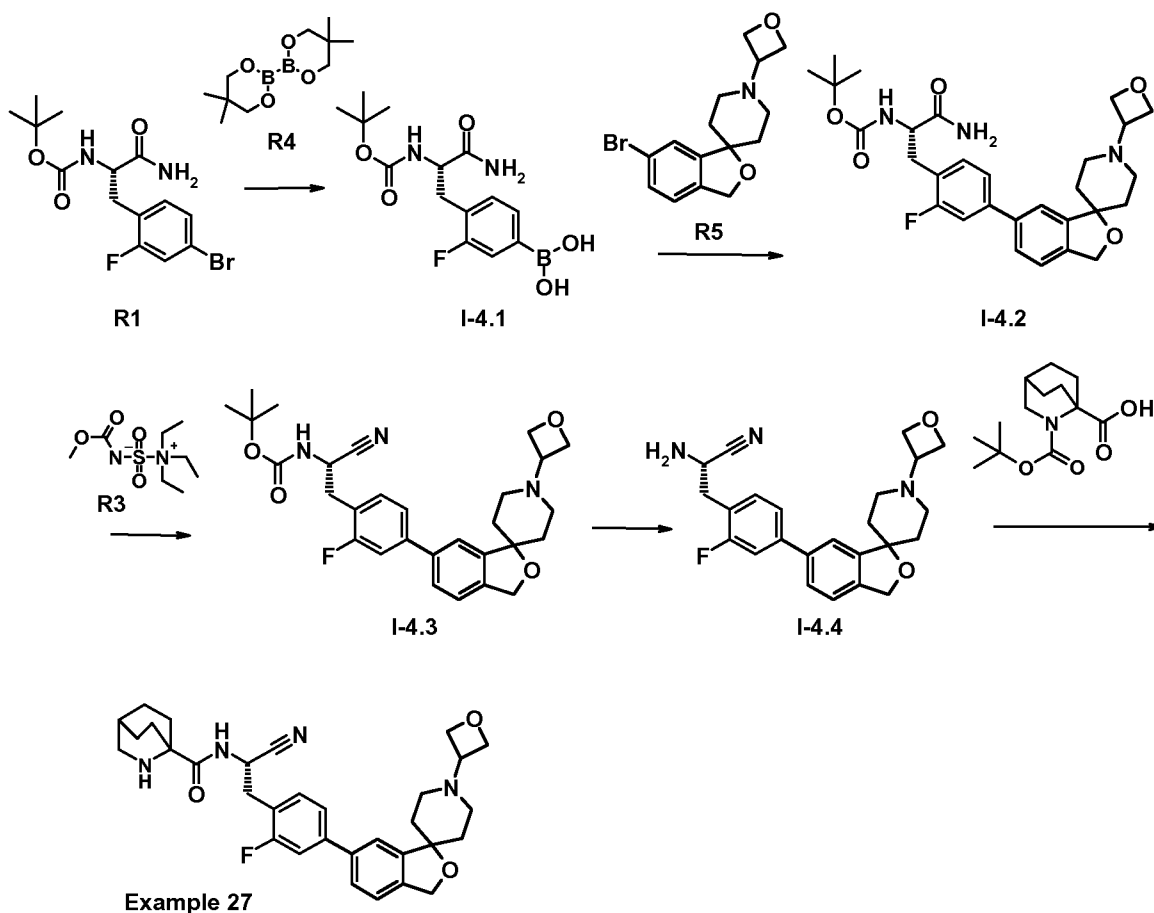
#### Step 6: Synthesis of Example 27

To I-3.5 (923.0 mg, 1.43 mmol) in acetonitrile (40 mL) is added p-toluenesulfonic acid monohydrate (681.0 mg, 3.58 mmol) and reaction mixture is stirred for 3 days at r.t.. The reaction mixture is neutralized with TEA and concentrated in vacuo. Water was added and the reaction mixture is extracted with ethyl acetate several times. The organic layer is washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The crude residue is purified by reversed phase HPLC.

Yield 61%, *m/z* 545 [M+H]<sup>+</sup>, rt 1.02 min, LC-MS Method Z011\_S03.

#### Method D

Alternative synthesis of N-[(1S)-1-cyano-2-[2-fluoro-4-[1'-(oxetan-3-yl)spiro[1H-isobenzofuran-3,4'-piperidine]-5-yl]phenyl]ethyl]-3-azabicyclo[2.2.2]octane-4-carboxamide ( Example 27)



### Step 1: Synthesis of Intermediate I-4.1

To R1 (340 mg, 0.94 mmol) in dioxane (7 mL) R4 (288 mg, 1.28 mmol), potassium acetate (277 mg, 2.82 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (15.3 mg, 0.02 mmol) are added. The mixture is purged with nitrogen and heated to 70 °C for 2h. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The residue is purified by reversed phase HPLC to provide I-4.1. Yield 90%, *m/z* 325 [M-H]<sup>-</sup>, rt 0.94 min, LC-MS Method Z020\_S01.

### Step 2: Synthesis of Intermediate I-4.2

To I-4.1 (228 mg, 0.70 mmol) in acetonitrile (10 mL) is added R5 (239 mg, 0.70 mmol) and mixture is purged with argon. Potassium carbonate aqueous solution 2mol/L (700 μL, 1.4 mmol) and 1,1-bis(di-tert-butylphosphino)ferrocene palladium dichloride (46 mg, 0.07

mmol) are added, reaction mixture is purged again with argon and stirred at 80°C for 45 minutes in the microwave reactor. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The residue is purified  
5 by reversed phase HPLC to provide I-4.2.  
Yield 80%, *m/z* 526 [M+H]<sup>+</sup>, rt 0.83 min, LC-MS Method Z011\_S03.

### Step 3: Synthesis of Intermediate I-4.3

To I-4.2 (294 mg, 0.56 mmol) in dichloromethane (10 mL) is added R3 (333 mg, 1.4  
10 mmol) and the reaction mixture is stirred for 40 minutes at r.t.. DCM is removed in vacuo, obtained residue is partitioned between ethyl acetate and 10% aqueous solution of tartaric acid, phases are separated and aqueous phase is extracted with ethyl acetate. The combined organic layer is washed with saturated sodium hydrogen carbonate solution, brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to provide I-4.3.  
15 Yield 95%, *m/z* 508 [M+H]<sup>+</sup>, rt 1.06 min, LC-MS Method Z011\_S03.

### Step 4: Synthesis of Intermediate I-4.4

To I-4.3 (320 mg, 0.63 mmol) in acetonitrile (8 mL) is added p-toluenesulfonic acid monohydrate (600 mg, 3.15 mmol) and reaction mixture is stirred overnight at r.t.. The  
20 reaction mixture is diluted with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate three times. The organic layer is washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo.  
Yield 80%, *m/z* 408 [M+H]<sup>+</sup>, rt 0.90 min, LC-MS Method Z011\_S03.

### Step 5: Synthesis of Example 27

To I-4.4 (30 mg, 0.07 mmol) in DMF (1 mL) are added 3-tert-butoxycarbonyl-3-azabicyclo[2.2.2]octane-4-carboxylic acid, prepared according to Radchenko *et al. J. Org. Chem.* 2009, 5541-5544 (19 mg, 0.07 mmol), N-methyl-morpholine (16 µL, 0.15 mmol) and PPA (43 µL, 50% in DMF) at r.t.. The reaction mixture is stirred for 2.5 hours at r.t.,  
30 diluted with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate several times. The organic layer is washed with brine, dried over MgSO<sub>4</sub>, filtered and

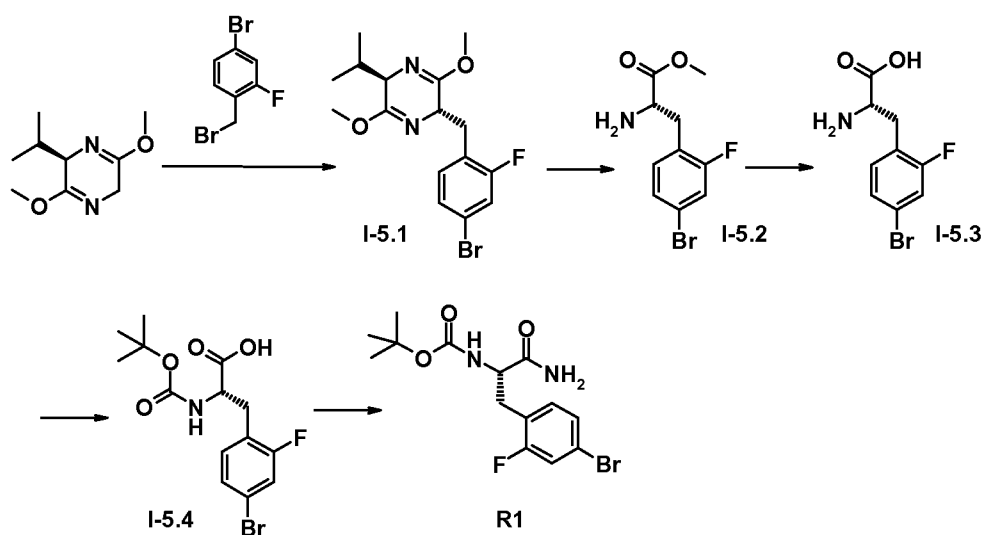
concentrated in vacuo. The residue is purified by reversed phase HPLC to provide Example 27 (During the work up and/or purification deprotection of Boc group occurs). Yield 32%,  $m/z$  545  $[M+H]^+$ , rt 1.02 min, LC-MS Method Z011\_S03.

5

## Synthesis of starting materials/ educts

### Synthesis of tert-butyl N-[(1S)-2-amino-1-[(4-bromo-2-fluoro-phenyl)methyl]-2-oxo-ethyl]carbamate (R1)

10



### Step 1: Synthesis of Intermediate I-5.1

(2R)-(-)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine (212 g, 1151 mmol) in dry tetrahydrofuran (600 mL) is cooled to  $-78^{\circ}\text{C}$ . Then n-butyllithium (2.5 M in hexanes, 552 mL, 1381 mmol) is added dropwise, keeping the temperature below  $-78^{\circ}\text{C}$ . After 30 min 4-bromo-2-fluorobenzyl bromide (324g, 1209 mmol) in dry tetrahydrofurane (120 mL) is added dropwise. The reaction mixture is stirred at  $-78^{\circ}\text{C}$  for 1 h. The mixture is quenched with saturated  $\text{NH}_4\text{Cl}$  solution and extracted three times with ethyl acetate. The organic layer is washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated in vacuo. The residue is purified by flash chromatography (heptane/ ethyl acetate = 80/20). Yield 60%.

20

### Step 2: Synthesis of Intermediate I-5.2

To I-5.1 (104 g, 265 mmol) in acetonitrile (600 mL) aq. 0.2 M HCl (2788 mL, 558 mmol) is added. The mixture is stirred at RT for 12 h. The mixture is extracted with diethyl ether and the pH of the aqueous layer is adjusted to ~8 with saturated NaHCO<sub>3</sub> solution. Then it is extracted three times with ethyl acetate. The organic layer is washed with brine, dried  
5 over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Yield 80%.

### Step 3: Synthesis of Intermediate I-5.3

I-5.2 (62.4 g, 211 mmol) is stirred in aqueous 3 M HCl (3 mol/L, 1000 mL) at 60°C for 16 h. The mixture is cooled down and the pH is adjusted to ~7 with aqueous 6 M NaOH. Then  
10 the reaction mixture is filtered, washed three times with water and dried in a vacuum oven at 40°C for 12 h. Yield 74%.

### Step 4: Synthesis of Intermediate I-5.4

To I-5.3 (151g, 546 mmol) in 1,4-dioxane (2.2 L) is added aqueous 2 M sodium carbonate  
15 (301 mL, 602 mmol) and di-tertbutyl dicarbonate (138 g, 632 mmol). The mixture is stirred for 4h. Then water is added and the pH is adjusted to ~4-5 with citric acid. The mixture is extracted three times with ethyl acetate. The organic layer is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue is stirred in heptane for 15 min and the product is filtered off. Yield 87%.

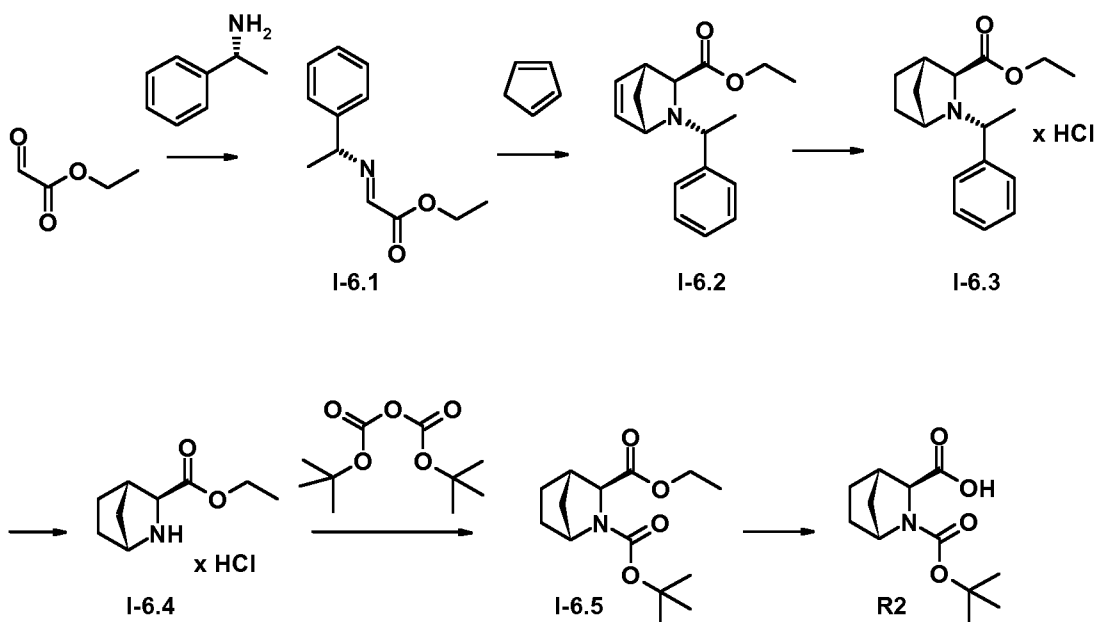
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### Step 5: Synthesis of R1

To I-5.4 (181 g, 476 mmol) in dry DMF (1200 mL) N-methylmorpholine (72 g, 713 mmol) and TBTU (153 g, 476 mmol) are added and the reaction mixture is stirred for 30 min. Then the reaction mixture is cooled to 0°C and aqueous 35% ammonium chloride solution  
25 (47 mL, 856 mmol) is added and the mixture is stirred at room temperature for 12 h. Water is added and the formed product is filtered off and washed three times with water. The product is dried in a vacuum oven at 40°C for 72 h. Yield 64%.

30 **Synthesis of (1S,2S,4R)-3-[(tert.-butoxy)carbonyl]-3-azabicyclo[2.2.1]heptane-2-carboxylate (R2)**

The compound is commercially available or can be synthesized in analogy to Tararov et al, Tetrahedron Asymmetry 13 (2002), 25-28.



5

### Step 1: Synthesis of Intermediate I-6.1

A solution of ethyl oxoacetate (44.9g, 0.44 mol), freshly distilled from a commercially available solution in toluene (at 50mbar, 55°C) in diethylether (300 ml) is cooled at -10°C, followed by dropwise addition of (R)-(+)-1-phenylethylamine (53 g, 440 mmol), keeping the temperature below 0°C. After complete addition,  $\text{MgSO}_4 \cdot \text{H}_2\text{O}$  (91g, 660 mmol) is added, and the resulting mixture stirred at room temperature overnight. The mixture is filtered, the mother liquor concentrated in vacuo and the residue distilled under reduced pressure to yield I-6.1 (47g,  $m/z$  206  $[\text{M}+\text{H}]^+$ , rt 1.29 min, LC-MS Method V003\_003). The product is used without further purification.

15

### Step 2: Synthesis of Intermediate I-6.2

A solution of I-6.1 (47g, 229 mmol) and 1,3-cyclopentadiene (30g, 458 mmol) (freshly distilled from dicyclopentadiene) in DMF (150 ml) and 120  $\mu\text{l}$  water is cooled to 0°C, before TFA (18 ml, 234 mmol) is added dropwise. The mixture is stirred overnight at room temperature, then added to a solution of 40g  $\text{NaHCO}_3$  in 1200 ml water and extracted with diethyl ether. The organic layer is separated, washed subsequently with aqueous  $\text{NaHCO}_3$

20

and water, dried over  $\text{MgSO}_4$ , and concentrated in vacuo. The residue is purified by silica gel column chromatography (cyclohexane/ethyl acetate = 9:1) to yield I-6.2 (Yield 52%  $m/z$  272  $[\text{M}+\text{H}]^+$ , rt 0.42 min, LC-MS Method X001\_004).

5    **Step 3: Synthesis of Intermediate I-6.3**

To a solution of I-6.2 (24.8 g, 91 mmol) in ethanol (250 ml), Raney-nickel is added (2.5 g) and reacted at 50 psi under a hydrogen atmosphere at room temperature. The catalyst is filtered off, the solution is concentrated in vacuo and the residue is purified by silica gel column chromatography (cyclohexane/ethyl acetate 9:1). After evaporation of the organic  
10 solvent, the obtained product is redissolved in diethyl ether and triturated with solution of HCl in dioxane, concentrated in vacuo, redissolved in 200 ml ethanol and concentrated in vacuo to yield I-6.3 (Yield 78%  $m/z$  274  $[\text{M}+\text{H}]^+$ , rt 0.42 min, LC-MS Method X001\_004).

15    **Step 4: Synthesis of Intermediate I-6.4**

To a solution of I-6.3 (22 g, 71 mmol) in ethanol (250 ml), 10% Pd/C is added (2.5 g) and reacted at 15 bar under a hydrogen atmosphere at room temperature. The catalyst is filtered off, the solution is concentrated in vacuo. The residue is washed with diisopropyl ether to yield I-6.4 (Yield 98%  $m/z$  170  $[\text{M}+\text{H}]^+$ , rt 0.48 min, LC-MS Method V001\_007).

20

**Step 5: Synthesis of Intermediate I-6.5**

To I-6.4 (14.3 g, 69.3 mmol) in a solution of triethylamin (24.6 ml, 175.3 mmol), THF (150 ml) and water (2 mL), di-tert-butyl dicarbonate (15.9 g, 73 mmol) is added and the resulting mixture is stirred for 40 hours at room temperature, then concentrated in vacuo.  
25 Ethyl acetate is added to the residue, subsequently extracted with water, 1N aqueous acetic acid and water, before the organic layer is dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo to yield I-6.5 (Yield 95%  $m/z$  270  $[\text{M}+\text{H}]^+$ , rt 1.33 min, LC-MS Method V003\_003).

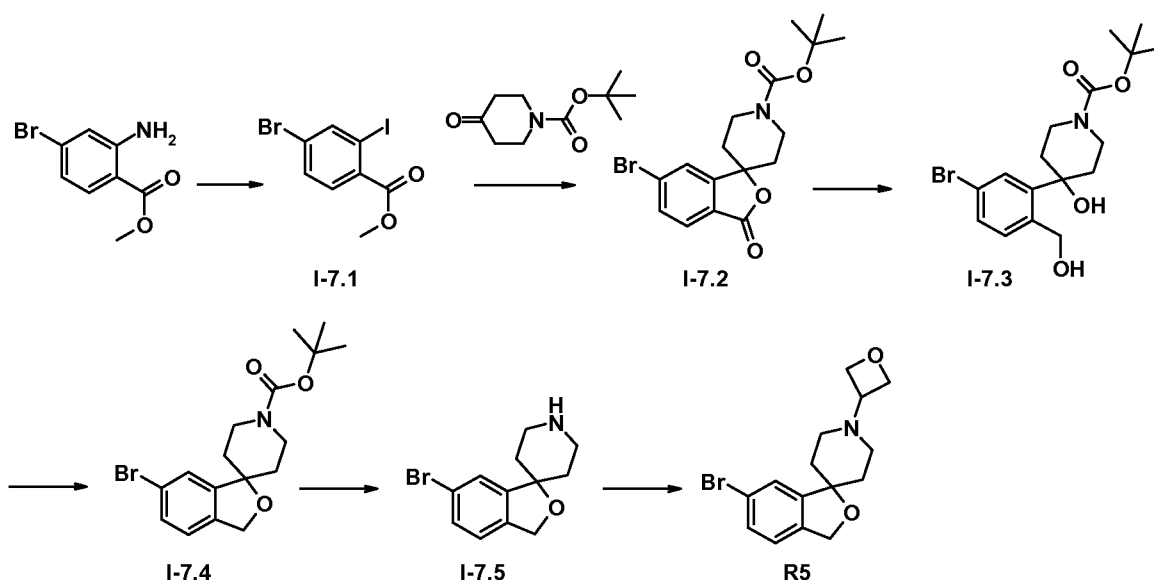
30    **Step 6: Synthesis of R2**

A mixture of I-6.5 (16.9 g; 63 mmol) in acetone (152 ml), water (50 ml) and lithium hydroxide (3g, 126 mmol) is stirred overnight at room temperature. Water (100 ml) is

added, the volume reduced in vacuo before cooling to 0°C followed by the addition of 1N aqueous HCl to acidify to a pH of 2-3, immediately followed by extraction with ethyl acetate. The organic layer is washed with water, dried (MgSO<sub>4</sub>) and concentrated. To the residue, dichloromethane (100 ml) and cyclohexane (100 ml) are added, the volume  
 5 reduced in vacuo by half and the mixture tempered at 15°C. The precipitate is filtered off, washed with cyclohexane to yield R2 (Yield 66%, *m/z* 242 [M+H]<sup>+</sup>).

### Synthesis of 5-bromo-1'-(oxetan-3-yl)spiro[1H-isobenzofuran-3,4'-piperidine] (R5)

10



#### Step 1: Synthesis of Intermediate I-7.1

Methyl 2-amino-4-bromobenzoate (10 g, 43.47 mmol) is suspended in sulphuric acid 20%  
 15 (200 mL) and obtained solution is cooled down to 0°C. Sodium nitrite (3.60 g, 52.16 mmol), dissolved in water (40 mL), is added dropwise between 0°C - 5°C and the reaction mixture is stirred for further 40 minutes at this temperature. Afterwards a cooled solution (ca. 0°C) of potassium iodide (14.43 g, 86.93 mmol) in water (40 mL) is added dropwise and the reaction mixture is stirred for 1 h at 5°C. The reaction mixture is poured onto ice-  
 20 water and extracted with ethyl acetate. The organic layer is washed with water, 10% aq. sodium thiosulfate solution, brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Yield 94%.

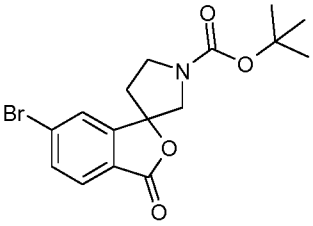
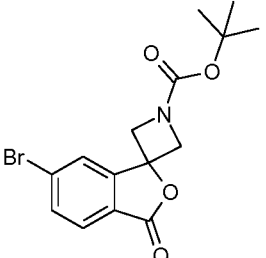
**Step 2: Synthesis of Intermediate I-7.2**

I-7.1 (9.42 g, 27.63 mmol) and tert-butyl 4-oxopiperidine-1-carboxylate (6.24 g, 30.40 mmol) in dry THF (200 mL) is cooled down to -70°C. Isopropylmagnesium chloride-lithium chloride complex (1.3 mol/L in THF, 23.38 mL, 30.40 mmol) is added dropwise and reaction mixture is stirred for further 20 minutes at this temperature, is allowed to come to r.t. and stirred for 45 minutes. The reaction mixture is quenched with water and extracted with ethyl acetate. The organic layer is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude residue is purified by flash column chromatography (petroleum ether : EtOAc = 95:5 to 40:60) to provide I-7.2.

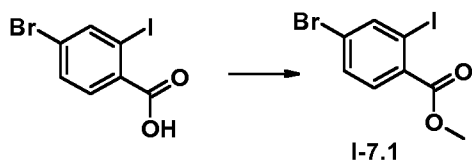
Yield 74%, *m/z* 326,328 [M+H – tert-Bu]<sup>+</sup>, rt 1.09 min, LC-MS Method Z011\_S03.

The following intermediates as shown in Table 2 are synthesized in a similar fashion from the appropriate intermediates:

**Table 2**

Intermediate	Structure	<i>m/z</i> [M+H] <sup>+</sup>	rt (min)	LC-MS method
I-7.2.1		312; 314 [M – tert-But+H] <sup>+</sup>	1.06	Z011_S03
I-7.2.2		298; 300 [M – tert-But+H] <sup>+</sup>	1.07	Z012_S04

**Alternative synthesis of Intermediate I-7.1**



To 4-bromo-2-iodobenzoic acid (9.0 g, 27.53 mmol) in methanol (50 mL) is added concentrated sulphuric acid (10 mL) and the reaction mixture is stirred for 90 minutes at 80°C. The reaction mixture is poured onto ice water, sodium hydrogen carbonate is added until a pH value of 7 is reached and the reaction mixture is extracted with ethyl acetate. The organic layer is washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. Yield 95%.

### Step 3: Synthesis of Intermediate I-7.3

To I-7.2 (8.11 g, 21.22 mmol) in THF (100 mL) is added lithium borohydride (2 mol/L in THF, 21.22 mL, 42.44 mmol) and the reaction mixture is stirred overnight at r.t.. HPLC-MS analysis indicated 20% conversion. Additional lithium borohydride (2 mol/L in THF, 27.0 mL, 54.0 mmol) is added dropwise and the reaction mixture is stirred for 6 days at r.t.. The reaction mixture is carefully quenched with water while cooling to ca. 0°C with an ice bath. Saturated sodium hydrogen carbonate solution is added to the reaction mixture, obtained precipitate is filtered off, and mother liquor is extracted with ethyl acetate several times. The organic layer is washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo.

Yield >95%, *m/z* 312/314 [M+H – tert-Butyl – H<sub>2</sub>O]<sup>+</sup>, rt 1.01 min, LC-MS Method Z011\_S03.

### Step 4: Synthesis of Intermediate I-7.4

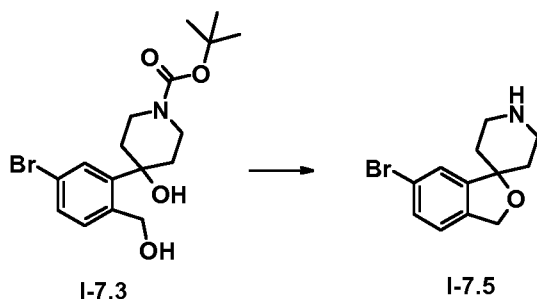
I-7.3 (605 mg, 1.57 mmol) is dissolved in dry THF (20 mL) and cooled down to 0°C, TEA (1.09 mL, 7.83 mmol) and p-toluenesulfonic anhydride (613.44 mg, 1.88 mmol) are added. The reaction mixture is allowed to come to r.t. and stirred overnight. The reaction mixture is diluted with water and saturated sodium hydrogen carbonate solution and extracted with ethyl acetate several times. The organic layer is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue is purified by reversed phase HPLC.

Yield 72%,  $m/z$  368; 370  $[M+H]^+$

### Step 5: Synthesis of Intermediate I-7.5

I-7.4 (240 mg, 1.57 mmol) is dissolved in dry DCM (2 mL) and TFA (500  $\mu$ L, 6.53 mmol) is added. The reaction mixture is allowed for 70 minutes at r.t.. The reaction mixture is concentrated in vacuo, the residue is redissolved in methanol, filtered through solid phase cartridge (StratoSpheres<sup>TM</sup> PL-HCO3 MP Resin) and methanol is removed in vacuo. Yield 97%,  $m/z$  268; 270  $[M+H]^+$ , rt 0.93 min, LC-MS Method Z011\_S03.

### Alternative synthesis of Intermediate I-7.5



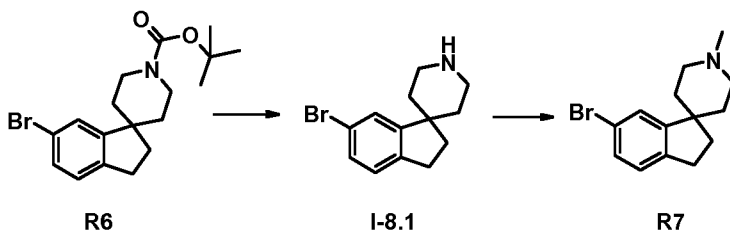
I-7.3 (8.39 g, 21.71 mmol) is dissolved in dry THF (25 mL), 5N aqueous HCl (25 mL) is added and the reaction mixture is stirred at 90°C for 30 h. Reaction mixture is cooled to r.t., basicified with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate several times. The organic layer is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo.

Yield 76%,  $m/z$  268; 270  $[M+H]^+$ , rt 0.93 min, LC-MS Method Z011\_S03.

### Step 6: Synthesis of R5

I-7.5 (5.0 g, 18.49 mmol) is dissolved in dry tetrahydrofuran (20 mL), 3-oxetanone (1.78 mL, 27.73 mmol) and acetic acid (1.06 mL, 18.49 mmol) are added and the reaction mixture is stirred for 25 minutes at r.t.. Sodium triacetoxyborohydride (6.82 g, 30.57 mmol) is added and the reaction mixture is stirred for further 30 minutes at r.t.. The reaction mixture is quenched with MeOH, diluted with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate several times. The organic layer is washed with brine, dried over MgSO<sub>4</sub> and concentrated in vacuo to provide R5.

Yield 89%,  $m/z$  324, 326  $[M+H]^+$ , rt 0.93 min, LC-MS Method Z011\_S03.

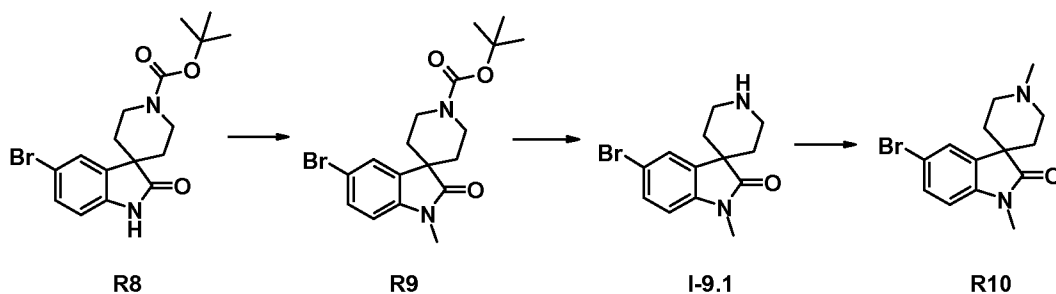
**Synthesis of 6-bromo-1'-methyl-spiro[indane-1,4'-piperidine] (R7)****Step 1: Synthesis of Intermediate I-8.1**

To R6, purchased from WUXI APPTEC (200 mg, 0.55 mmol) in dichloromethane (3 mL) is added trifluoroacetic acid (0.25 mL) and reaction mixture is stirred overnight at r.t.. The reaction mixture is concentrated in vacuo, the residue is redissolved in methanol, filtered  
10 through solid phase cartridge (StratoSpheres<sup>TM</sup> PL-HCO3 MP Resin) and methanol is removed in vacuo. Yield >95%.

**Step 2: Synthesis of R7**

To I-8.1 (152 mg, 0.57 mmol) in methanol (4 mL) are added formaldehyde (37% in water, 0.21 mL, 2.86 mmol) and acetic acid (0.05 mL, 0.86 mmol). The reaction mixture is stirred  
15 2 h at r.t.. Sodium triacetoxyborohydride (302.6 mg, 1.43 mmol) is added and the reaction mixture is stirred 80 minutes at r.t.. The reaction mixture is concentrated, triturated with water and saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed with saturated sodium hydrogen carbonate solution and brine.  
20 The precipitate is filtered off and the filtrate is dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to yield R7.  
Yield 89%.

**Synthesis of 5-bromo-1,1'-dimethyl-spiro[indoline-3,4'-piperidine]-2-one (R10)**



### Step 1: Synthesis of R9

To R8, purchased from ACTIVATE (200 mg, 0.53 mmol) in DMF (4 mL) is added sodium hydride (60% dispersion in mineral oil, 31.5 mg, 0.79 mmol) under cooling to 0°C and reaction mixture is stirred for further 30 minutes at r.t.. Methyl iodide (36  $\mu$ L, 0.58 mmol) is added and the reaction mixture is stirred for 40 minutes at r.t.. The reaction mixture is diluted with water and extracted with ethyl acetate. The organic layer is washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to provide R9. Yield 98%.

### Step 2: Synthesis of Intermediate I-9.1

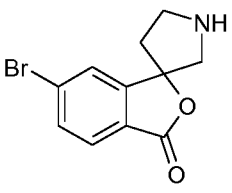
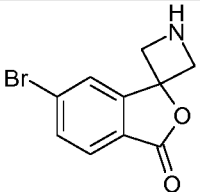
To R9 (191 mg, 0.48 mmol) in dichloromethane (5 mL) is added trifluoroacetic acid (0.5 mL) and reaction mixture is stirred for 20 minutes at r.t.. The reaction mixture is concentrated in vacuo, the residue is redissolved in methanol, filtered through solid phase cartridge (StratoSpheres<sup>TM</sup> PL-HCO3 MP Resin) and methanol is removed in vacuo.

Yield > 95%

The following intermediates as shown in Table 3 are synthesized in a similar fashion from the appropriate intermediates:

**Table 3**

Intermediate	Structure	m/z [M+H] <sup>+</sup>	rt (min)	LC-MS method
I-9.1.1		282; 284	0.69	Z012_S04

I-9.1.2		268; 270	0.57	Z021_S01
I-9.1.3		254; 256	0.62	Z012_S04

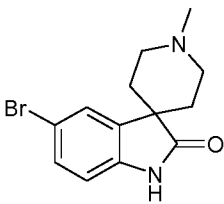
### Step 3: Synthesis of R10

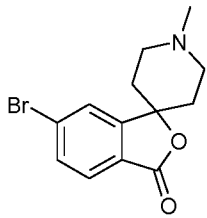
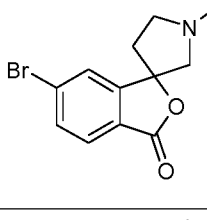
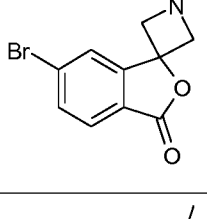
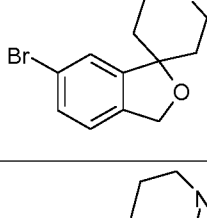
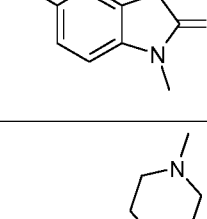
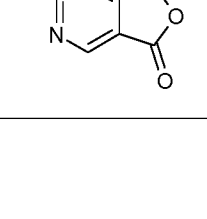
To I-9.1 (152 mg, 0.52 mmol) in methanol (5 mL) are added formaldehyde (37% in water,  
 5 0.19 mL, 2.58 mmol) and acetic acid (0.044 mL, 0.77 mmol). The reaction mixture is  
 stirred for 2 hours at r.t.. Sodium triacetoxyborohydride (273.0 mg, 1.29 mmol) is added  
 and the reaction mixture is stirred for 40 minutes at r.t.. The reaction mixture is  
 concentrated, diluted with water and saturated sodium hydrogen carbonate solution and  
 extracted with ethyl acetate. The organic layer is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>,  
 10 filtered and concentrated in vacuo.  
 Yield >95%, 309; 311 [M+H]<sup>+</sup>, rt 0.75 min, LC-MS Method Z012\_S04.

The following intermediates as shown in Table 4 are synthesized in a similar fashion from  
 the appropriate intermediates:

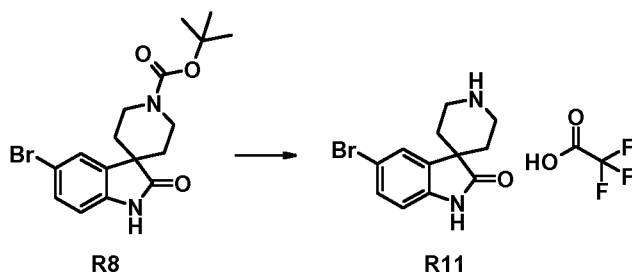
15

**Table 4**

Intermediate	Structure	m/z [M+H] <sup>+</sup>	rt (min)	LC-MS method
R10.1		295; 297	0.69	Z012_S04

R10.2		296; 298	0.70	Z012_S04
R10.3		282; 284	0.68	Z012_S04
R10.4		268; 270	0.62	Z012_S04
R10.5		282; 284	0.77	Z012_S04
R10.6		309; 311	0.59	Z020_S01
R10.7		253	0.24	Z021_S01

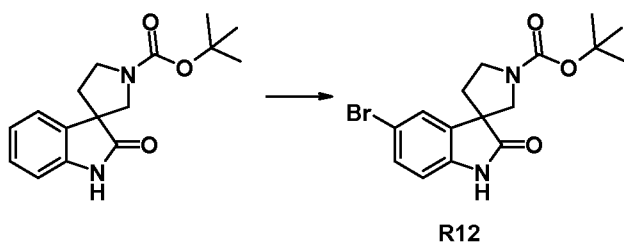
**Synthesis of TFA salt of 5-bromospiro[indoline-3,4'-piperidine]-2-one (R11)**



To R8, purchased from ACTIVATE (150 mg, 0.39 mmol) in dichloromethane (3 mL) is added trifluoroacetic acid (0.5 mL) and reaction mixture is stirred for 45 minutes at r.t..

5 The reaction mixture is concentrated. Yield 100%.

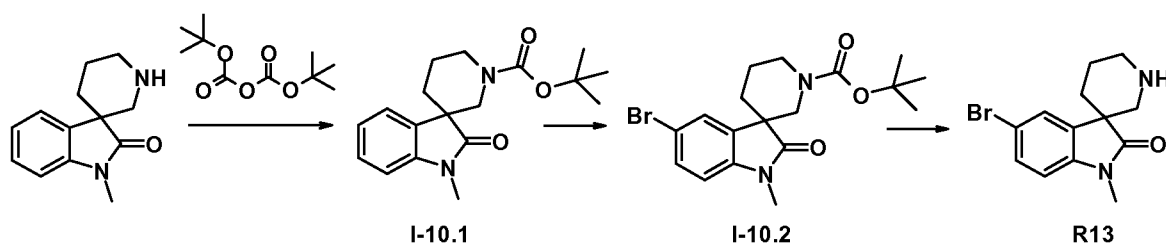
### Synthesis of tert-butyl 5-bromo-2-oxo-spiro[indoline-3,3'-pyrrolidine]-1'-carboxylate (R12)



10

To tert-butyl 2-oxospiro[indoline-3,3'-pyrrolidine]-1'-carboxylate, purchased from Zerenex (50.0 mg, 0.17 mmol) in acetonitrile (1.5 mL) is added N-bromosuccinimide (30.5 mg, 0.17 mmol) and the reaction mixture is stirred for 5 h at r.t.. The reaction mixture is diluted  
 15 with water and saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed with brine, dried and concentrated in vacuo. Yield 80%,  $m/z$  367; 369  $[M+H]^+$

### 20 Synthesis of 5-bromo-1-methyl-spiro[indoline-3,3'-piperidine]-2-one (R13)



### Step 1: Synthesis of Intermediate I-10.1

To 1-methylspiro[indole-3,3'-piperidine]-2(1H)-one, purchased from ChemBridge Corporation (1.0 g, 4.62 mmol) in dichloromethane (20 mL) are added TEA (0.64 mL, 4.62 mmol) and di-tert-butyl dicarbonate (958.6 mg, 4.39 mmol). The reaction mixture is stirred for 10 minutes at r.t., diluted with water and saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The phases are separated and aqueous layer is extracted with DCM. The combined organic layers are dried over MgSO<sub>4</sub> and concentrated in vacuo.

Yield >95%, *m/z* 261 [M+H – tert-Butyl]<sup>+</sup>, rt 1.06 min, LC-MS Method Z020\_S01.

### Step 2: Synthesis of Intermediate I-10.2

To I-10.1 (1.54 g, 4.87 mmol) in acetonitrile (35 mL) is added N-bromosuccinimide (856.7 mg, 5 mmol) and the reaction mixture is stirred overnight at r.t.. The reaction mixture is diluted with water and saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed with saturated sodium hydrogen carbonate solution and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo.

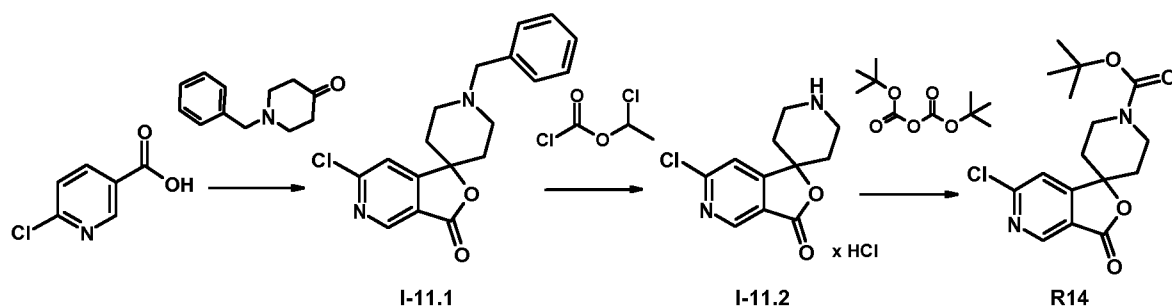
Yield 93%, *m/z* 340 [M+H – tert-Butyl]<sup>+</sup>, rt 1.13 min, LC-MS Method Z020\_S01.

### Step 3: Synthesis of R13

To I-10.2 (200 mg, 0.51 mmol) in dichloromethane (10 mL) is added trifluoroacetic acid (5 mL) and the reaction mixture is stirred for 15 minutes at r.t.. The reaction mixture is concentrated in vacuo and lyophilized. The residue is dissolved in dichloromethane and extracted with 1mol/L aqueous sodium hydroxide and brine. The organic layer is dried and concentrated in vacuo.

Yield 88%, *m/z* 295; 297 [M+H]<sup>+</sup>, rt 0.59 min, LC-MS Method Z020\_S01.

**Synthesis of tert-butyl 6-chloro-3-oxo-spiro[furo[3,4-c]pyridine-1,4'-piperidine]-1'-carboxylate (R14)**



**Step 1: Synthesis of Intermediate I-11.1**

5 The synthesis of the intermediate I-11.1 is described in EP2072519 A1, p. 36.

At -78°C, a hexane solution (94 mL, 150.81 mmol) of 1.6 M n-butyllithium is added dropwise to a THF solution (110 mL) of 2,2,6,6-tetramethylpiperidine (16.14 g, 113.10 mmol) and obtained solution is stirred for 1 hour. Afterwards a THF solution (50 mL) of 6-chloronicotinic acid (6.0 g, 37.70 mmol) is added dropwise over 1 hour and the reaction

10 mixture is stirred for 2 hours. A THF solution (50 mL) of 1-benzyl-4-piperidone (21.6 g, 113.10 mmol) is added dropwise at -78°C. After stirred for 2 hours, water (70 mL) is added, and the reaction mixture is warmed to room temperature.

The aqueous layer is separated, and the organic layer is extracted with aqueous 1 N sodium hydroxide solution (2x75 mL). The obtained aqueous layer is extracted with diethyl ether

15 (100 mL), and the aqueous layer is acidified (pH~1) by adding concentrated hydrochloric acid.

After stirring for 1 hour, the precipitate is filtered off, washed with water, and dissolved in ethyl acetate.

The organic layer is washed with aqueous saturated sodium hydrogen carbonate solution,

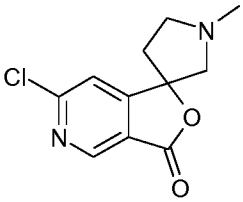
20 dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue is washed with diethyl ether.

Yield 66%, *m/z* 329 [M+H]<sup>+</sup>, rt 0.72 min, LC-MS Method Z012\_S04.

The following intermediate as shown in Table 5 is synthesized in a similar fashion from the appropriate intermediate:

25

**Table 5**

Intermediate	Structure	m/z [M+H] <sup>+</sup>	rt (min)	LC-MS method
I-11.1.1		239	0.75	Z011_S03

### Step 2: Synthesis of Intermediate I-11.2

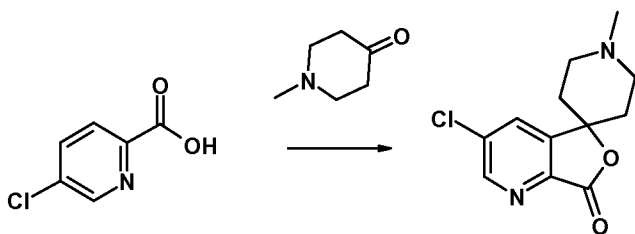
I-11.1 (2.0 g, 6.08 mmol) in dichloroethane (15 mL) is cooled down to 0°C. A solution of  
 5 1-chloroethyl chloroformate (1.98 mL, 18.25 mmol) in dichloroethane (5 mL) is added  
 slowly and the reaction mixture is stirred for further 15 minutes at 0°C. Afterwards the  
 reaction mixture is heated to reflux and stirred overnight. The reaction mixture is  
 concentrated in vacuo. The residue is dissolved in methanol and heated to reflux for 30  
 minutes, during this time precipitate is formed. The reaction mixture is diluted with  
 10 dichloromethane and the precipitate is filtered off to provide I-11.2 (hydrochloride).  
 Yield 61%.

### Step 3: Synthesis of R14

To I-11.2 (500 mg, 1.82 mmol) in dichloromethane (10 mL) are added TEA (0.51 mL,  
 15 3.64 mmol) and di-tert-butyl dicarbonate (396.6 mg, 1.82 mmol). The reaction mixture is  
 stirred for 20 minutes at r.t., diluted with water and saturated sodium hydrogen carbonate  
 solution and extracted with dichloromethane. The organic layer is dried and concentrated  
 in vacuo. Yield 91%.

20

### Synthesis of 3-chloro-1'-methyl-spiro[furo[3,4-b]pyridine-5,4'-piperidine]-7-one (R15)



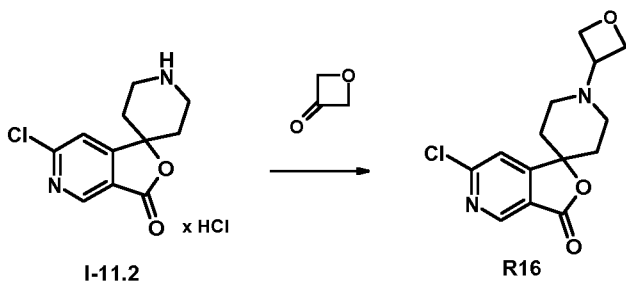
R15

At -78°C, a hexane solution (2.38 mL, 3.81 mmol) of 1.6 M n-butyllithium is added dropwise to a THF solution (5 mL) of 2,2,6,6-tetramethylpiperidine (0.76 mL, 4.43 mmol) and obtained solution is stirred for 1 hour at this temperature. Afterwards a THF solution (1 mL) of 5-chloro-2-pyridinecarboxylic acid (0.2 g, 1.27 mmol) is added dropwise over 5 minutes and reaction mixture is stirred for 45 minutes. A THF solution (1 mL) of 1-methyl-4-piperidone (0.44 mL, 3.81 mmol) is added dropwise at -78°C. After 1 hour, water (10 mL) is added, and reaction mixture is warmed to room temperature.

Ethyl acetate (15 mL) and aqueous saturated NaHCO<sub>3</sub> solution (15 mL) are added to the reaction mixture and the aqueous layer is separated. The organic layer is extracted with aqueous saturated NaHCO<sub>3</sub> solution (2x10 mL). The combined aqueous phase is acidified (pH~1) by adding concentrated hydrochloric acid.

After stirring for 1 hour reaction mixture is basified by adding aqueous saturated NaHCO<sub>3</sub> solution and extracted with ethyl acetate (4x25 mL). The organic layer is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to provide R15. Yield 21%, *m/z* 253, 255 [M+H]<sup>+</sup>, rt 0.41 min, LC-MS Method Z012\_S04.

### Synthesis of 6-chloro-1'-(oxetan-3-yl)spiro[furo[3,4-c]pyridine-1,4'-piperidine]-3-one (R16)



a) Generation of free base:

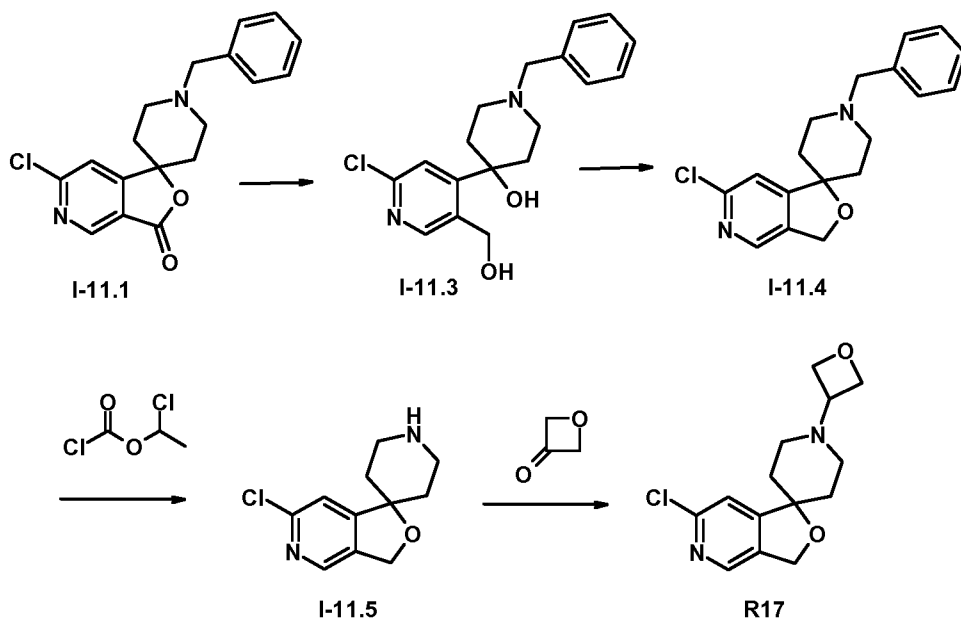
I-11.2 (200 mg, 0.73 mmol) was partly dissolved in dried methanol, polymer-bound tetraalkyl- ammonium carbonate (Aldrich, 540293) is added and this mixture is stirred for 2 hours at r.t. Polymer-bound tetraalkyl- ammonium carbonate is filtered off and methanol is removed in vacuo to deliver free base of I-11.2.

5

b) Free base of I-11.2 is dissolved in the dry dichloromethane (3 mL) / dry tetrahydrofuran (1 mL) mixture, 3-oxetanone (0.23 mL, 3.64 mmol) and acetic acid (0.06 mL, 1.1 mmol) are added. The reaction mixture is stirred for 75 minutes at r.t., then sodium triacetoxyborohydride is added and the reaction mixture stirred for 15 minutes at r.t. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Yield 80%, *m/z* 295 [M+H]<sup>+</sup>, rt 0.75 min, LC-MS Method Z011\_S03.

10

15 **Synthesis of 6-chloro-1'-(oxetan-3-yl)spiro[3H-furo[3,4-c]pyridine-1,4'-piperidine] (R17)**



**Step 1: Synthesis of Intermediate I-11.3**

To I-11.1 (1.00 g, 3.04 mmol) in methanol (15 mL) is added sodium borohydride (345 mg, 9.12 mmol) in small portions and the reaction mixture is stirred for 20 h at r.t.. Additional sodium borohydride (750 mg, 19.82 mmol) is added in 3 portions (each 250 mg) over 5 h

20

to the reaction mixture. The reaction mixture is quenched with water and diluted with ethyl acetate. The organic layer is separated and aqueous layer is extracted with ethyl acetate. Combined organic layer is washed with saturated sodium hydrogen carbonate solution, brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The residue is purified by reversed  
5 phase HPLC to provide I-11.3. Yield 40%, *m/z* 333 [M+H]<sup>+</sup>, rt 0.91 min, LC-MS Method Z011\_S03.

#### Step 2: Synthesis of Intermediate I-11.4

To I-11.3 (378 mg, 1.14 mmol) in dry THF (5 mL) are added TEA (0.95 mL, 6.81 mmol)  
10 and methanesulfonyl chloride (0.26 mL, 3.5 mmol) at 0°C. The reaction mixture is allowed to come to r.t. and stirred for 1 h. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to provide crude product which is used in the next step without further purification.  
15 Yield 95%, *m/z* 315 [M+H]<sup>+</sup>, rt 1.06 min, LC-MS Method Z011\_S03.

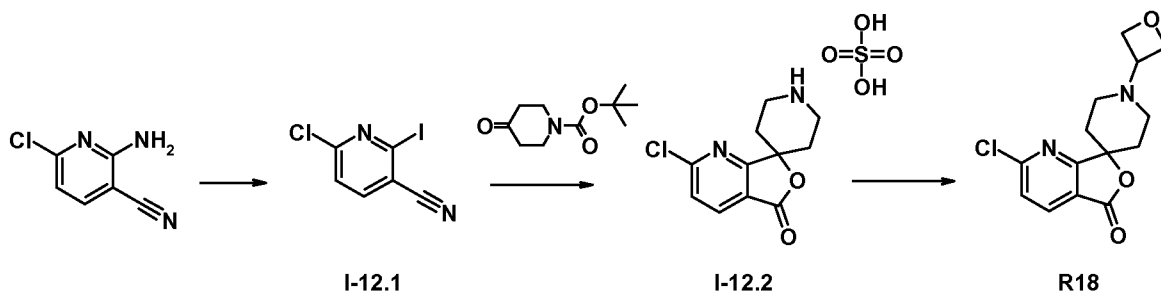
#### Step 3: Synthesis of Intermediate I-11.5

To a solution of I-11.4 (246 mg, 0.78 mmol) in dichloroethane (4 mL) is added 1-chloroethyl chloroformate (0.42 mL, 3.91 mmol) and the reaction mixture is heated to  
20 reflux and stirred for 3 hours. Dichloroethane was removed in vacuo, obtained residue is redissolved in methanol (3 mL) and obtained solution is refluxed for 30 min. Reaction mixture is cooled to r.t. and purified by reversed phase HPLC to provide I-11.5. Yield 72%, *m/z* 225 [M+H]<sup>+</sup>, rt 0.71 min, LC-MS Method Z011\_S03.

#### 25 Step 4: Synthesis of R17

I-11.5 (114 mg, 0.51 mmol) is dissolved in dry tetrahydrofuran (2 mL), 3-oxetanone (0.05 mL, 0.76 mmol) and acetic acid (0.044 mL, 0.76 mmol) are added and the reaction mixture is stirred for 1 hour at r.t.. Sodium triacetoxyborohydride (269 mg, 1.27 mmol) is added and the reaction mixture is stirred for further 15 min at r.t.. The reaction mixture is diluted  
30 with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed with brine, dried over MgSO<sub>4</sub> and concentrated in vacuo to provide R17. Yield 62%, *m/z* 281 [M+H]<sup>+</sup>, rt 0.76 min, LC-MS Method Z011\_S03.

**Synthesis of 2-chloro-1'-(oxetan-3-yl)spiro[furo[3,4-b]pyridine-7,4'-piperidine]-5-one (R18)**



**Step 1: Synthesis of Intermediate I-12.1**

2-Amino-6-chloronicotinonitrile, purchased from ABLOCK PHARMATECH (2.0 g, 13.02 mmol) is dissolved in dry tetrahydrofuran (40 mL), copper (I) iodide (3.72 g, 19.54 mmol), diiodomethane (8.39 mL, 104.2 mmol) and tert-butyl nitrite (6.20 mL, 52.1 mmol) are added. Reaction mixture is refluxed for 1.5 h, cooled to RT and all volatiles are removed in vacuo. Obtained residue is dissolved in ethyl acetate (100 mL) and washed with 10% aqueous sodium thiosulfate solution (25 mL), saturated sodium hydrogen carbonate solution (25 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo. The crude residue is purified by flash column chromatography to provide I-12.1 (eluent: petroleum ether / ethyl acetate).

Yield 74%,  $m/z$  265  $[\text{M}+\text{H}]^+$ , rt 0.90 min, LC-MS Method Z012\_S04.

**Step 2: Synthesis of Intermediate I-12.2**

I-12.1 (1.0 g, 3.78 mmol) and tert-butyl 4-oxopiperidine-1-carboxylate (753 mg, 3.78 mmol) are dissolved in dry THF (10 mL) and the reaction mixture is cooled down to  $-65^\circ\text{C}$ . Isopropylmagnesium chloride-lithium chloride complex (1.3 mol/L in THF, 3.78 mL, 4.92 mmol) is added dropwise and the reaction mixture is stirred for further 10 min at this temperature. Afterwards the reaction mixture is allowed to reach r.t., stirred for 20 minutes and methanol (0.8 mL, 19.7 mmol) is added. The reaction mixture is cooled to  $0^\circ\text{C}$  and 50% aqueous sulphuric acid solution (2.0 mL) is added dropwise. The reaction mixture is warmed to r.t. and stirred overnight. White precipitate formed is filtered off, washed

with THF and dried in vacuum to provide crude I-12.2 (sulfate salt) as a white solid. Crude product was used in the next step without further purification.

Yield 94%,  $m/z$  239  $[M+H]^+$ , rt 0.69 min, LC-MS Method Z011\_S03.

5 **Step 3: Synthesis of R18**

a) Generation of free base:

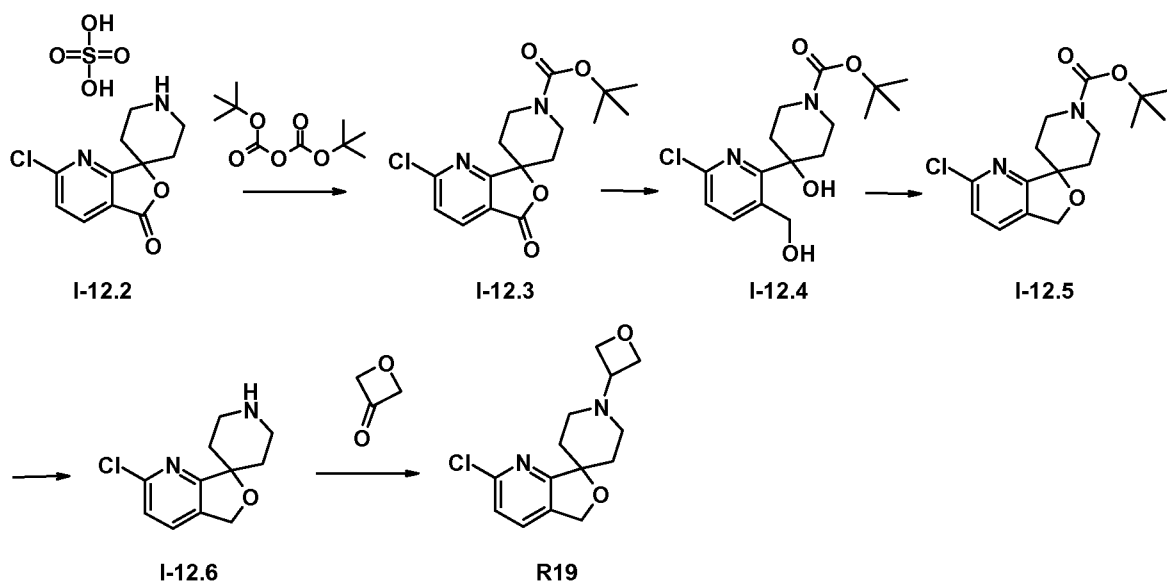
I-12.2 (150 mg, 0.45 mmol) was dissolved in methanol (2 mL) / water (2 mL) mixture, polymer-bound tetraalkylammonium carbonate (Aldrich, 540293) is added and this mixture is stirred for 1 hour at r.t.. Polymer-bound tetraalkylammonium carbonate is  
10 filtered off, methanol and water are removed in vacuo to deliver free base of I-12.2.

b) Obtained residue is redissolved in THF (2 mL) / water (0.1 mL) mixture, 3-oxetanone (0.04 mL, 0.67 mmol) and acetic acid (0.038 mL, 0.67 mmol) are added and the reaction mixture is stirred for 1 hour at r.t.. Sodium triacetoxyborohydride is added and the reaction  
15 mixture is stirred overnight at r.t.. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer is washed with brine, dried over  $MgSO_4$  and concentrated in vacuo. The crude residue is purified by flash column chromatography to provide R18 (eluent: DCM / MeOH).

Yield 18%,  $m/z$  295  $[M+H]^+$ , rt 0.74 min, LC-MS Method Z011\_S03.

20

**Synthesis of 2-chloro-1'-(oxetan-3-yl)spiro[5H-furo[3,4-b]pyridine-7,4'-piperidine] (R19)**



### Step 1: Synthesis of Intermediate I-12.3

To I-12.2 (3.25 g, 9.65 mmol) in dichloromethane (50 mL) is added TEA (4.04 mL, 28.95 mmol), the reaction mixture is stirred for 20 minutes at r.t., and di-tert-butyl dicarbonate (2.11 g, 9.65 mmol) is added. The reaction mixture is stirred for 90 minutes at r.t., diluted with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate several times. The organic layer is washed with brine, dried over  $\text{MgSO}_4$ , concentrated in vacuo and obtained residue is purified by flash column chromatography (petroleum ether : EtOAc = 95:5 to 60:40) to provide I-12.3.

Yield 49%,  $m/z$  239  $[\text{M}-\text{Boc}+\text{H}]^+$ , rt 1.03 min, LC-MS Method Z011\_S03.

### Step 2: Synthesis of Intermediate I-12.4

To I-12.3 (10.0 g, 29.52 mmol) in ethanol (500 mL) is added sodium borohydride (2.23 g, 59.03 mmol) and calcium chloride (6.55 g, 59.03 mmol) in two portions and the reaction mixture is stirred overnight at r.t.. HPLC-MS indicated 85% conversion to the desired product. Additional amount of sodium borohydride (350 mg, 9.25 mmol) is added and the reaction mixture is stirred for 6 h at r.t.. The reaction mixture is quenched with saturated sodium hydrogen carbonate solution, ethanol is removed in vacuo and obtained residue is triturated with ethyl acetate. Precipitate formed is filtered off and mother liquor is extracted with ethyl acetate several times. Combined organic layer is washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo. Obtained residue is triturated with acetonitrile,

precipitate formed is filtered off, mother liquor is concentrated in vacuo and this procedure is repeated two more times. Precipitates are combined and dried in vacuo to provide I-12.4. Yield 54%,  $m/z$  243  $[M+H-Boc]^+$ , rt 0.97 min, LC-MS Method Z011\_S03.

5     **Step 3: Synthesis of Intermediate I-12.5**

To I-12.4 (6.77 g, 17.77 mmol) in dry THF (75 mL) are added TEA (14.84 mL, 106.64 mmol) and methanesulfonyl chloride (5.50 mL, 71.09 mmol) at 0°C. The reaction mixture is allowed to reach r.t. and stirred for 1 h. The reaction mixture is diluted with saturated sodium hydrogen carbonate solution and extracted with dichloromethane several times.

10    The organic layer is washed with brine, dried over  $MgSO_4$ , concentrated in vacuo and obtained residue is purified by flash column chromatography (petroleum ether : EtOAc = 95:5 to 72:28) to provide I-12.5.

Yield 65%,  $m/z$  225  $[M+H-Boc]^+$ , rt 1.07 min, LC-MS Method Z011\_S03.

15    **Step 4: Synthesis of Intermediate I-12.6**

To I-12.5 (4.13 g, 12.07 mmol) in dichloromethane (15 mL) is added trifluoroacetic acid (5 mL) and reaction mixture is stirred for 3 h at r.t.. The reaction mixture is concentrated in vacuo, obtained residue is redissolved in methanol (50 mL), polymer-bound tetraalkyl-ammonium carbonate (Aldrich, 540293) is added and this mixture is stirred for 30 minutes

20    at r.t. Polymer-bound tetraalkyl- ammonium carbonate is filtered off and methanol is removed in vacuo to deliver I-12.6.

Yield 99%,  $m/z$  225  $[M+H]^+$ , rt 0.74 min, LC-MS Method Z011\_S03.

**Step 5: Synthesis of R19**

25    I-12.6 (3.62 g, 12.08 mmol) was dissolved in dry tetrahydrofuran (40 mL), 3-oxetanone (1.16 mL, 18.13 mmol) and acetic acid (691  $\mu$ L, 12.08 mmol) are added and the reaction mixture is stirred for 20 minutes at r.t.. Sodium triacetoxyborohydride (6.74 g, 30.21 mmol) is added and the reaction mixture is stirred for 25 min at r.t.. The reaction mixture is quenched with methanol, diluted with saturated sodium hydrogen carbonate solution and

30    extracted with ethyl acetate several times. The organic layer is washed with brine, dried over  $MgSO_4$  and concentrated in vacuo. Obtained residue is triturated with acetonitrile / methanol mixture (9:1), precipitate formed is filtered off, mother liquor is concentrated in

vacuo and this procedure is repeated two more times. Precipitates are combined and dried in vacuo to provide 2.47 g of R19. Mother liquor is concentrated in vacuo, obtained residue is redissolved in acetonitrile and purified by reversed phase HPLC to provide additional amount (0.32 g) of R19.

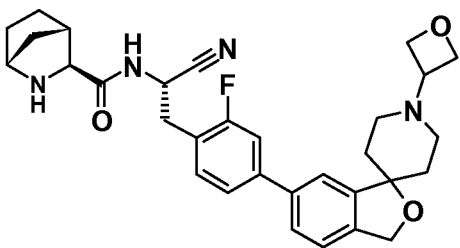
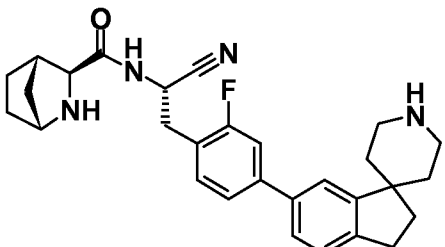
5 Yield 78%,  $m/z$  281  $[M+H]^+$ , rt 0.78 min, LC-MS Method Z011\_S03.

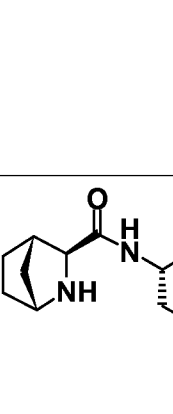
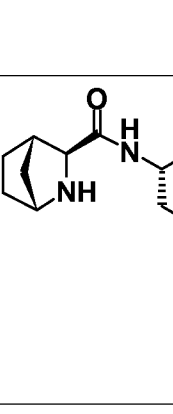

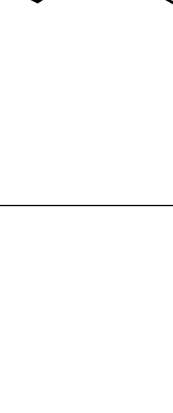

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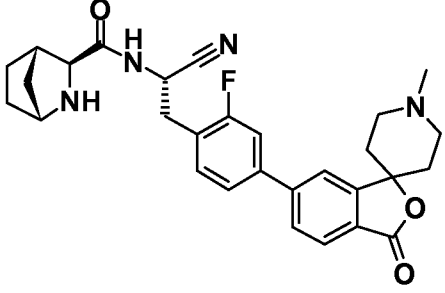
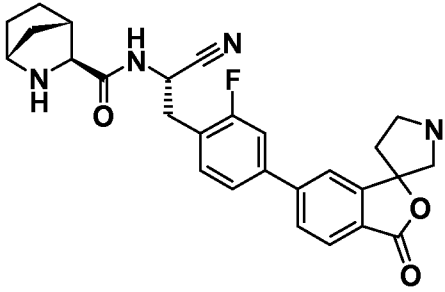
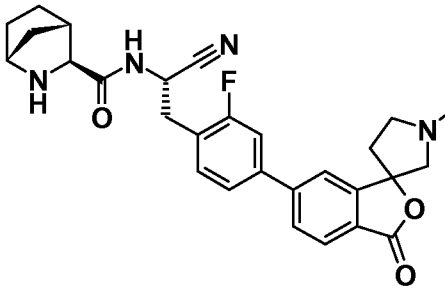
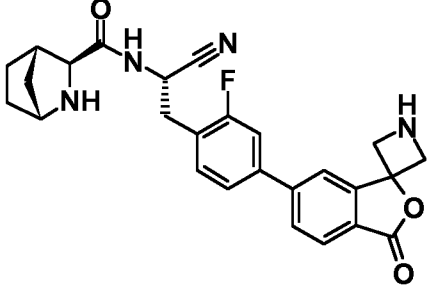
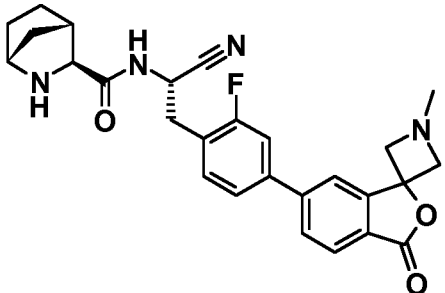
## EXAMPLES

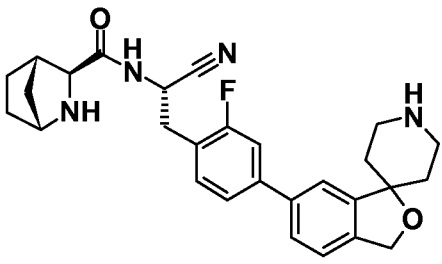
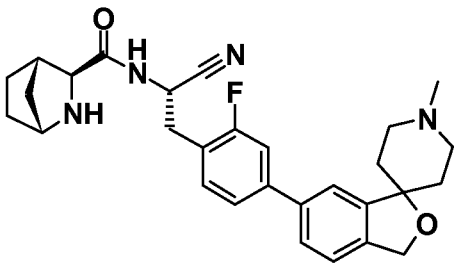
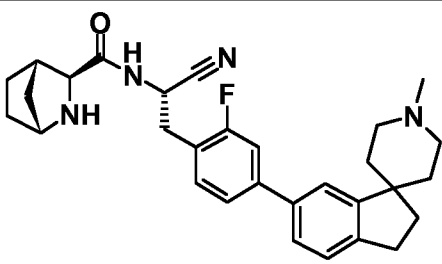
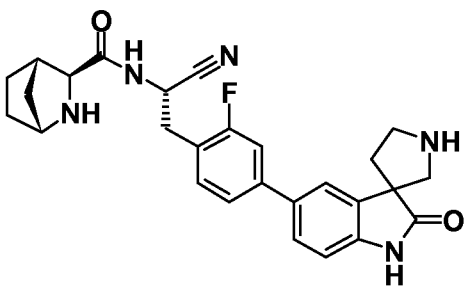
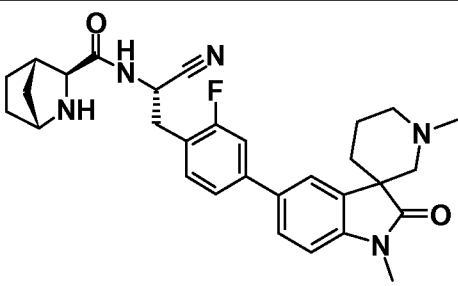
(rt = retention time). Deprotection Methods: TSA (toluene sulfonic acid cf. Example 1). Stereochemistry at the carbon atom adjacent to the nitrile group is assigned: stereo bond  
 15 means S-isomer.

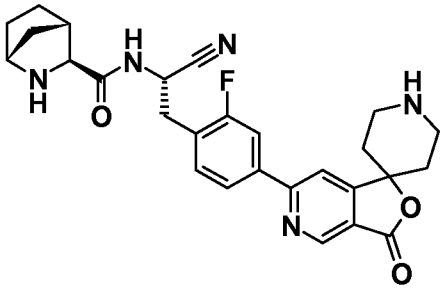
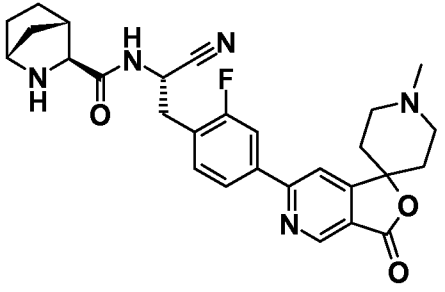
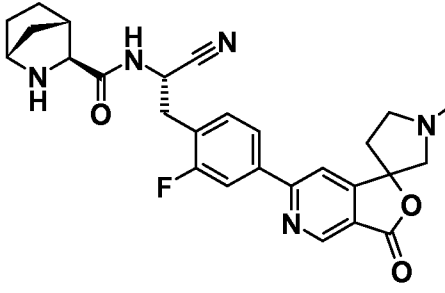
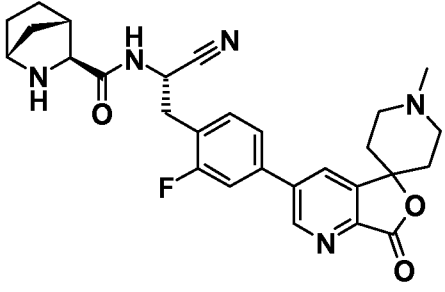
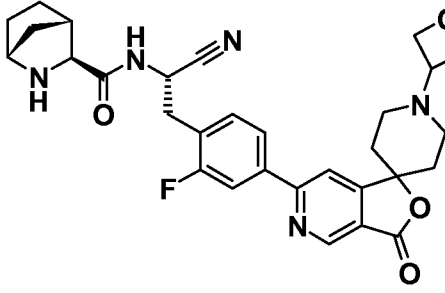
**Table 6**

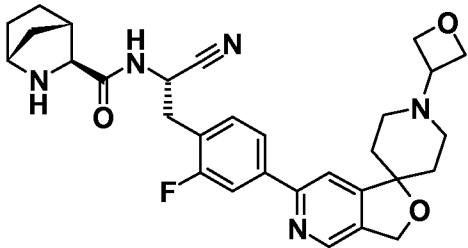
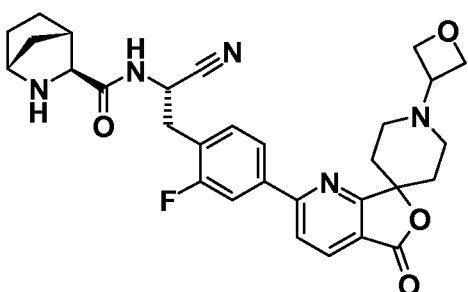
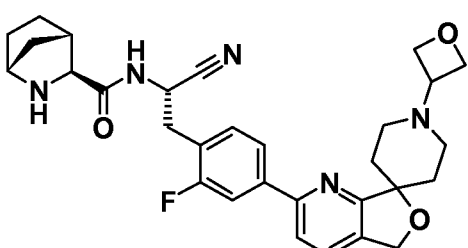
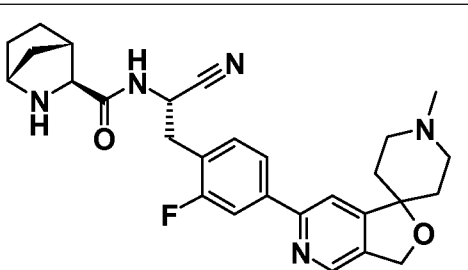
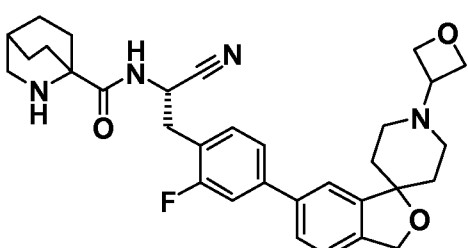
#	Structure	Educt	Synth. / Deprot. Method	Yield [%]
1		I-1.5	A/TSA	84
2		I-1.5.1	A/TSA	>95

3		I-1.5.2	A/TSA	35
4		I-1.5.3	A/TSA	48
5		I-1.5.4	A/TSA	48
6		I-1.5.5	A/TSA	7
7		I-1.5.6	A/TSA	43

8		I-1.5.7	A/TSA	41
9		I-1.5.8	A/TSA	90
10		I-1.5.9	A/TSA	16
11		I-1.5.10	A/TSA	20
12		I-1.5.11	A/TSA	54

13		I-1.5.12	A/TSA	9
14		I-1.5.13	A/TSA	43
15		I-1.5.14	A/TSA	49
16		I-1.5.15	A/TSA	58
17		I-1.5.16	A/TSA	46

18		I-1.5.17	A/TSA	35
19		I-1.5.18	A/TSA	73
20		I-1.5.19	A/TSA	47
21		I-1.5.20	A/TSA	36
22		I-1.5.21	A/TSA	35

23		I-1.5.22	A/TSA	83
24		I-1.5.23	A/TSA	>95
25		I-1.5.24	A/TSA	88
26		I-2.5	B/TSA	28
27		I-3.5	C/TSA	61

## ANALYTICAL DATA OF EXAMPLES

**Table 7**

Ex.	m/z [M+H] <sup>+</sup>	rt [min]	LC-MS- Method
1	531	1.00	Z011_S03
2	473	1.19	Z011_S03
3	488	0.89	Z012_S04
4	502	0.73	Z012_S04
5	516	0.74	Z012_S04
6	502	0.70	Z012_S04
7	489	0.72	Z012_S04
8	503	0.72	Z012_S04
9	475	0.91	Z011_S03
10	489	0.96	Z011_S03
11	461	0.91	Z011_S03
12	475	0.97	Z011_S03
13	475	0.76	Z012_S04
14	489	1.05	Z011_S03

Ex.	m/z [M+H] <sup>+</sup>	rt [min]	LC-MS- Method
15	487	1.17	Z011_S03
16	474	0.89	Z011_S03
17	516	0.60	Z020_S01
18	490	0.90	Z011_S03
19	504	0.95	Z011_S03
20	490	0.92	Z011_S03
21	504	0.92	Z011_S03
22	546	0.94	Z011_S03
23	532	0.96	Z011_S03
24	546	0.93	Z011_S03
25	532	0.97	Z011_S03
26	490	0.96	Z011_S03
27	545	1.02	Z011_S03

5

**Table 8**

List of abbreviations

ACN	acetonitrile
aq.	aqueous
BOC, boc	tert-butyloxycarbonyl
d	day
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEA	diethylamine
DIPEA	N,N-diisopropylethylamine
DIPE	diisopropyl ether
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
EA, EtOAc	ethyl acetate
FA	formic acid
h	hour
HATU	o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate
LiOH	lithium hydroxide
MeOH	methanol
MeTHF	methyl tetrahydrofuran
min	minute
NaH	sodium hydride
PE	petroleum ether
PPA	1-propanephosphonic acid cyclic anhydride
RT, r.t.	room temperature, e.g. 15 - 25 °C
rt	retention time
TBME	tert-butyl methyl ether
TBTU	o-(1H-benzo-1,2,3-triazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TSA	p-toluenesulfonic acid monohydrate

## PHARMACOLOGICAL DATA

5

Other features and advantages of the present invention will become apparent from the following more detailed examples which illustrate, by way of example, the principles of the invention.

### 10 INHIBITION OF HUMAN DPPI (CATHEPSIN C)

Materials: Microtiterplates (Optiplate-384 F) were purchased from PerkinElmer (Prod.No. 10 6007270). The substrate Gly-Arg-AMC was from Biotrend (Prod.-No.808756 Custom peptide).

15 Bovine serum albumin (BSA; Prod.No. A3059) and Dithiothreitol (DTT; Prod.No D0632) were from Sigma. TagZyme buffer was from Riedel-de-Haen (Prod.-No. 04269), NaCl was from Merck (Prod.-No. 1.06404.1000) and morpholinoethane sulfonic acid (MES), was from Serva (Prod.-No. 29834). The DPP1 inhibitor Gly-Phe-DMK was purchased from MP Biomedicals (Prod.-No.03DK00625). The recombinant human DPPI was  
20 purchased from Prozymex. All other materials were of highest grade commercially available.

The following buffers were used: MES buffer: 25 mM MES, 50 mM NaCl, 5 mM DTT, adjusted to pH 6.0, containing 0.1% BSA; TAGZyme Buffer: 20 mM NaH<sub>2</sub>PO<sub>4</sub>, 150 mM  
25 NaCl adjusted to pH 20 6.0 with HCl

**Assay conditions:** The recombinant human DPPI was diluted in TAGZyme buffer to 1 U/ml (38.1µg/ml, respectively), and then activated by mixing in a 1:2 ratio with a Cysteamine aqueous solution ( 2mM) and incubating for 5 min at room temperature.

30

Five  $\mu\text{L}$  test compound (final concentration 0.1 nM to 100  $\mu\text{M}$ ) in aqua bidest 5  
(containing 4% DMSO, final DMSO concentration 1%) were mixed with 10  $\mu\text{L}$  of DPPI in  
MES buffer (final concentration 0.0125 ng/ $\mu\text{L}$ ) and incubated for 10 min. Then, 5  $\mu\text{L}$  of  
substrate in MES buffer (final concentration 50  $\mu\text{M}$ ) were added. The microtiter plates  
5 were then incubated at room temperature for 30 min. Then, the reaction was stopped by  
adding 10  $\mu\text{L}$  of Gly-Phe-DMK in 10 MES-buffer (final concentration 1  $\mu\text{M}$ ). The  
fluorescence in the wells was determined using a Molecular Devices SpectraMax M5  
Fluorescence Reader (Ex 360 nm, Em 460 nm) or an Envision Fluorescence Reader (Ex  
355 nm, Em 460 nm).

Each assay microtiter plate contained wells with vehicle controls (1% DMSO in bidest +  
0.075% BSA) as reference for non-inhibited enzyme activity (100% Ctl; high values)  
and wells with inhibitor (Gly-Phe-DMK, in bidest + 1% DMSO + 0.075% BSA, final  
concentration 1  $\mu\text{M}$ ) as controls for background fluorescence (0% Ctl; low values).

15 The analysis of the data was performed by calculating the percentage of fluorescence in the  
presence of test compound in comparison to the fluorescence of the vehicle control after  
20 subtracting the background fluorescence using the following formula:

$$(\text{RFU}(\text{sample}) - \text{RFU}(\text{background})) * 100 / (\text{RFU}(\text{control}) - \text{RFU}(\text{background}))$$

20 Data from these calculations were used to generate IC<sub>50</sub> values for inhibition of DPPI,  
respectively.

**Table 9**

Example	Inhibition of DPPI IC <sub>50</sub> [ $\mu\text{M}$ ]
1	0.0011
2	0.0006
3	0.0003
4	0.0004
5	0.0006

6	0.0002
7	0.0005
8	0.0007
9	0.0005
10	0.0006
11	0.0007
12	0.0005
13	0.0006
14	0.0010
15	0.0005
16	0.0005
17	0.0016
18	0.0016
19	0.0010
20	0.0016
21	0.0014
22	0.0048
23	0.0050
24	0.0027
25	0.0018
26	0.0020
27	0.0029

**DETERMINATION OF NEUTROPHIL ELASTASE ACTIVITY IN U937****5 CYTOSOLIC LYSATE PREPARATION AFTER INCUBATION WITH TEST COMPOUND**

Materials:

Optiplate 384F were purchased from PerkinElmer (Prod. No. #6007270). 24well Nunclon cell culture plates (No. 142475) and 96well plates (No. 267245) were from Nunc.

Dimethylsulfoxid (DMSO) was from Sigma (Prod.No. D8418). Nonidet-P40 (NP40) was from USBiological (Prod.No. N3500)

- 5 Substrate, specific for Neutrophil elastase, was from Bachem (MeOSuc-Ala-Ala-Pro-Val-AMC; Prod.No. I-1270).

Human neutrophil elastase was from Calbiochem (Prod.No. 324681)

#### Buffers:

- 10 Tris-buffer (100mM Tris; 1M NaCl; pH 7.5)

Tris-buffer + HSA 0.1%; Human Serum Albumin from Calbiochem (Cat#. 126658)

Serine-protease buffer (20mM Tris; 100mM NaCl; pH 7.5) + 0.1%HSA

Serine protease lysis buffer: 20mM Tris-HCl; 100mM NaCl pH 7.5; + 0.2% Nonidet-P40;

PBS: phosphate buffered saline, without Ca and Mg, from Gibco

15

#### Cell culture:

U937 from ECACC (Cat.No. 85011440) cultured in suspension at 37°C and 5% CO<sub>2</sub>.

Cell density: 0.2-1 Mio. Cells/ml.

Medium: RPMI1640 GlutaMAX (No. 61870) with 10% FCS from Gibco

20

#### Cell seeding and treatment:

Compounds in 100% DMSO were diluted in Medium (-FCS) with 10% DMSO and further diluted according to the experiment planned.

- 25 20 µl of the compound solution was transferred in the respective wells of the 24 well plate and diluted with 2ml cell suspension/well containing  $1 \times 10^5$  cells/ml (final concentration of DMSO = 0.1%). Compound dilution factor = 100

Compounds (up to 7 concentrations) were tested in triplicates with 3 wells for the DMSO 0.1% control, incubated for 48 hours without medium change at 37°C, 5% CO<sub>2</sub> and 95% relative humidity.

30

#### Cell harvesting and cell lysate:

Transfer the cell suspension in 2 ml 96 well assay block. Separate cells from medium by centrifugation (500 X g; 10 min; RT); discard the supernatant. Resuspend in 1ml PBS; centrifugation (500 X g; 10 min; RT); wash cells twice with PBS. Add 80 µl Serine protease lysis buffer (ice cold) to the cell pellet; resuspend the pellet and store on ice for 10 minutes. Remove debris by centrifugation at 1000 X g for 10 min at 4°C. Transfer 80-100 µl lysate supernatant in 96 well plate and store immediately at -80°C.

#### Neutrophil elastase activity assay:

Frozen lysates were thaw at 37°C for 10 minutes and stored on ice. Protein content was determined with Bradford protein assay. Lysates were diluted to 0.2-0.5 mg/ml protein in serine protease buffer + HSA.

Standard: NE (100 µg/ml stock solution in Tris-buffer; stored at -80°C) was diluted in Tris-buffer + HSA to 750 ng/ml, and further serially diluted 1:2 for the standard curve. Buffer, blank, standard and lysate samples were transferred into 384 well plate

#### Pipetting plan

Blank:	5µl Tris-buffer	+ 10µl Serine protease buffer	+ 5µl Substrate
Standard:	5µl Tris-buffer	+ 10µl NE (diff.conc.)	+ 5µl Substrate
Lysate:	5µl Tris-buffer	+ 10µl Lysat	+ 5µl Substrate

The increase in fluorescence (Ex360nm/Em 460nm) is determined after 30 minutes with a Molecular Device Spectramax M5 Fluorescence Reader. The result is interpolated to ng/mg lysate protein using excel formula functions. Percent inhibition in the compound-treated lysate samples is calculated relative to the DMSO-treated control-sample (100- (compound-sample\*100)/control-sample)

A test compound will give values between 0% and 100% inhibition of neutrophil elastase. IC50 is calculated using Graphpad Prism; nonlinear fitting (log(inhibitor) vs. response -- Variable slope). The IC50 value is interpolated as the concentration of test compound which leads to a neutrophil elastase activity reduction of 50% (relative to the DMSO-treated control).

Table 10

Example	Reduction of NE- activity in U937 cells IC50 [ $\mu$ M]
1	0.0010
2	0.0068
3	0.5030
4	0.0910
5	0.0023
6	0.0222
7	0.0349
8	0.0008
9	0.0215
10	0.0014
11	0.0107
12	0.0012
13	0.0167
14	0.0011
15	0.0002
16	0.0738
17	0.0006
18	0.2202
19	0.0050
20	0.0232

Example	Reduction of NE- activity in U937 cells IC50 [ $\mu$ M]
21	0.0637
22	0.0157
23	0.0075
24	0.0060
25	0.0016
26	0.0046
27	0.0007

## INHIBITION OF HUMAN CATHEPSIN K

### 5 Materials:

Microtiterplates (Optiplate-384 F were purchased from PerkinElmer (Prod.No. 6007270). The substrate Z-Gly-Pro-Arg-AMC was from Biomol (Prod.-No. P-142). L-Cysteine (Prod.No. 168149) was from Sigma. Sodium acetate was from Merck (Prod.-No. 6268.0250), EDTA was from Fluka (Prod.-No. 03680). The inhibitor E-64 was purchased  
10 from Sigma (Prod.-No. E3132). The recombinant human Cathepsin K proenzyme was purchased from Biomol (Prod.No. SE-367). All other materials were of highest grade commercially available.

The following buffers were used: Activation buffer: 32.5 mM sodium acetate, adjusted to  
15 pH 3.5 with HCl; Assay buffer: 150 mM sodium acetate, 4 mM EDTA, 20 mM L-Cysteine, adjusted to pH 5.5 with HCl,

### Assay conditions:

To activate the proenzyme, 5 µl procathepsin K were mixed with 1ul activation buffer, and incubated at room temperature for 30 min.

5 5 µL test compound (final concentration 0.1 nM to 100 µM) in aqua bidest (containing 4% DMSO, final DMSO concentration 1%) were mixed with 10 µL of Cathepsin K in assay buffer (final concentration 2 ng/µL) and incubated for 10 min. Then 5 µL of substrate in assay buffer (final concentration 12.5 µM) were added. The plates were then incubated at room temperature for 60min. Then, the reaction was stopped by adding 10 µL of E64 in assay buffer (final concentration 1 µM). The fluorescence in the wells was determined  
10 using a Molecular Devices SpectraMax M5 Fluorescence Reader (Ex 360 nm, Em 460 nm).

Each assay microtiter plate contains wells with vehicle controls (1% DMSO in bidest) as reference for non-inhibited enzyme activity (100% Ctl; high values) and wells with  
15 inhibitor (E64 in bidest + 1% DMSO, final concentration 1 µM) as controls for background fluorescence (0% Ctl; low values). The analysis of the data was performed by calculating the percentage of fluorescence in the presence of test compound in comparison to the fluorescence of the vehicle control after subtracting the background fluorescence:

20 
$$(\text{RFU}(\text{sample}) - \text{RFU}(\text{background})) * 100 / (\text{RFU}(\text{control}) - \text{RFU}(\text{background}))$$

Data from these calculations were used to generate IC<sub>50</sub> values for inhibition of Cathepsin K, respectively.

25

## **DETERMINATION OF METABOLIC STABILITY WITH HUMAN LIVER MICROSOMES**

The metabolic degradation of the test compound is assayed at 37 °C with pooled human  
30 liver microsomes. The final incubation volume of 100 µl per time point contains TRIS buffer pH 7.6 (0.1 M), magnesium chloride (5 mM), microsomal protein (1 mg/ml) and the test compound at a final concentration of 1 µM. Following a short preincubation period at

37 °C, the reactions are initiated by addition of beta-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH, 1 mM) and terminated by transferring an aliquot into acetonitrile after different time points. Additionally, the NADPH-independent degradation is monitored in incubations without NADPH, terminated at the last time point. The [%]  
 5 remaining test compound after NADPH independent incubation is reflected by the parameter c(control) (metabolic stability). The quenched incubations are pelleted by centrifugation (10'000 g, 5 min). An aliquot of the supernatant is assayed by LC-MS/MS for the amount of parent compound.

The half-life (t<sub>1/2</sub> INVITRO) is determined by the slope of the semilogarithmic plot of the  
 10 concentration-time profile. The intrinsic clearance (CL\_INTRINSIC) is calculated by considering the amount of protein in the incubation:

$$\text{CL\_INTRINSIC } [\mu\text{l/min/mg protein}] = (\ln 2 / (\text{half-life [min]} * \text{protein content [mg/ml]})) * 1'000.$$

The half-life (t<sub>1/2</sub> INVITRO) values of selected compounds in the metabolic stability  
 15 assay described above are listed in the following table.

**Table 11**

Example	In vitro stability in human liver microsome incubations t <sub>1/2</sub> [min]
1	>130
2	>130
3	>130
4	>130
5	>130
6	110
7	>130
8	74

Example	In vitro stability in human liver microsome incubations t <sub>1/2</sub> [min]
9	>130
10	>130
11	>130
12	46
13	>130
14	>130
15	>130
16	>130
17	60
18	>130
19	>130
20	>130
21	>130
22	>130
23	>130
24	>130
25	>130
26	55
27	120

## TARGET ENGAGEMENT MOUSE MODEL

### Compound treatment:

- 5 To monitor the effect of the test compounds on neutrophil elastase activity in peripheral neutrophils, female Crl:NMRI mice were treated as follows:

Group 1 (6 animals): 0.5 mg/kg test compound in 0.5% Natrosol (pH 2-3)

Group 2 (6 animals): 0.5% Natrosol (pH 2-3)

Group 3 (2 animals): 0.5% Natrosol (pH 2-3)

- 10 Test compounds or Natrosol solution were applied on Monday to Friday at 7:00 am and 4:00 pm each day of the first week of the study and on Monday and Tuesday (7:00 am and 4:00 pm) the second week. Test compounds or Natrosol were applied orally.

### LPS challenge and Bronchioalveolar lavage preparation:

- 15 On Wednesday the second week, animals were treated with test compound or Natrosol solution as described above (7:00 am) followed by a LPS (lipopolysaccharide) inhalation challenge:

Group 1 and 2: 20 minutes inhalation of LPS (E.coli Serotype 055:B5; 1mg/ml in PBS) using a MiniHeart Hi-Flo continuous nebulizer (Westmed)

- 20 Group 3: No LPS challenge

4 hours after the LPS challenge a bronchioalveolar lavage using 2x1ml Hank's salt solution per animal was prepared from all animals and the cell numbers in the lavage fluid determined using a Sysmex XT-1800i. The cells in the lavage fluid were separated by centrifugation and lysed in lysis buffer (100 mM TRIS pH 7.5, 1 M NaCl, 0.2% NP40).

25

### Neutrophile elastase (NE) measurement:

- NE activity in the BALF (bronchioalveolar lavage fluid) cell lysate was measured using the fluorescent NE substrate MeOSuc-Ala-Ala-Pro-Val-AMC (Bachem): 10 µl cell lysate were mixed with 5 µl assay buffer (20 mM Tris pH 7.5, 100 mM NaCl, 0.1% human serum albumin) and 5 µl substrate (1 mM in assay buffer) in a 384 well plate (Optiplat 384f, PerkinElmer). The reaction mixture was incubated for 60 min at room temperature and the fluorescence measured (360 nm excitation, 460 nm emission). The obtained fluorescence
- 30

values were normalized to the BALF neutrophil numbers for each animal. To calculate the inhibition of NE activity by test compounds, the mean fluorescence value of group 3 was subtracted from the fluorescence values for group 1 and 2 and the % inhibition of NE activity in group 1 compared to the mean fluorescence value in group 2 calculated.

5

Neutrophil elastase activity in BALF lysate after the pretreatment with Cathepsin C inhibitors (7d bid (twice a day) administration) are listed in the following table:

**Table 12**

<b>Example</b>	<b>Inhibition of neutrophil elastase activity in BALF lysate after the pretreatment with Cathepsin C inhibitor (dosage: 0.5 mg/kg bid for 7 days)</b>
1	96
25	94

10

## CRYSTAL STRUCTURES OF CATHEPSIN C LIGAND COMPLEXES

### 15 METHODS

#### Protein:

Recombinant human Cathepsin C (Cat C) was produced according to standard molecular biological protocols (**Literature: 1 - 3**).

#### 20 Crystallization and Soaking:

Prior to crystallization protein buffer was exchanged to 20 mM Bis-Tris pH 7.0, 150 mM NaCl, 2 mM EDTA, 2 mM DTT with a NAP10 column (GE Healthcare). The protein sample was concentrated to 9-10 mg/mL. Crystals were grown at 20°C in hanging drops using 1.0 µL of protein and 1.0 µL of well solution (0.1 M Bis-Tris-Propane pH 6.0-6.5, 5 18-20% (w/v) PEG 3350, 200 mM NaF, 1 mM DDT). Crystals appeared overnight and grew to full size within 2-3 days. Ligand co-structures were obtained by soaking apo-crystals in well solution supplemented with 1 mM of the respective ligand (via dilution from 100 mM stock solution in DMSO) overnight. Crystals were then frozen in liquid nitrogen prior to data collection using 20% glycerol and well solution as cryo protectant.

10

#### Data Collection, Structure Solution and Refinement:

All diffraction data were collected at 100 K on a rotating anode generator (Rigaku) using CuK $\alpha$  radiation and processed with XDS (**Literature: 4**). Ligand co-structures were solved by the difference fourier method and refined with program autoBuster (Global 15 Phasing Ltd.) iterated with manual rebuilding using the program coot (**Literature: 5**). The final data processing and refinement statistics are listed in **Table 13**. The program PyMOL (DeLano Scientific LLC) was used for figure preparation.

## **RESULTS**

### Structure of Cathepsin C ligand complexes:

The structure of human Cathepsin C (Cat C) is described in the literature (**Literature 2**) as  
5 a tetramer containing four identical subunits. Each subunit is comprised of three chains:  
light and heavy chains form the catalytic domain, while the so-called exclusion domain  
blocks the active site cleft beyond the S2 pocket and is responsible for the exopeptidase  
activity of Cat C. The structures of Cat C in complex with Examples 11 and 16 (**Table 14,**  
**Figure 1**) were determined to elucidate the binding mode of this class of compounds.

10 Examples 11 and 16 bind via a covalent interaction of the nitrile group with Cys234.  
Example 11 is a single enantiomer with the carbon atom adjacent to the nitrile group in (S)  
configuration while Example 16 (spirocyclic carbon atom has *RS* stereochemistry) is a  
mixture of diastereomers. The bicyclic amino acid reaches into the enzyme S1 pocket  
where it is anchored via hydrogen bonds to backbone atoms of Gly277 and Asn380 as well  
15 as to the side chain of Asp1. The bis-aryl system is oriented into the S2 pocket where it is  
involved in van der Waals interactions to residues Asp1 and Pro3 of the exclusion domain.  
Surprisingly, we observed an additional interaction of the spiro-cyclic amine: spiro-  
azetidine in Example 11 and spiro-pyrrolidine in Example 16. In both cases the basic  
nitrogen atom forms a salt-bridge to Glu275 consistent with the high enzyme activity of  
20 this compound class.

### **References:**

- (1) Søren W. Dahl, Torben Halkier, Conni Lauritzen, Iztok Dolenc, John Pedersen, Vito  
Turk and Boris Turk. (2001) Human Recombinant Pro-dipeptidyl Peptidase I

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- (2) Dusan Turk, Vojko Janjic, Igor Stern, Marjetka Podobnik, Dorian Lamba, Søren Weis Dahl, Connie Lauritzen, John Pedersen, Vito Turk and Boris Turk (2001) Structure of  
5 human dipeptidyl peptidase I (cathepsin C): exclusion domain added to an  
endopeptidase framework creates the machine for activation of granular serine  
proteases. *The EMBO Journal* **20**, 6570-6582 .
- (3) Furber, M. et al. (2014) Cathepsin C Inhibitors: Property Optimization and  
Identification of a Clinical Candidate. *J. Med. Chem.*, **57**, 2357–2367.
- 10 (4) Kabsch, W. (2010) XDS. *Acta Crystallogr. D. Biol. Crystallogr.* **66**, 125-132.
- (5) Emsley, P. & Cowtan, K. (2004) Coot: model-building tools for molecular graphics.  
*Acta Crystallogr. D. Biol. Crystallogr.* **60**, 2126-2132.

**Table 13. Data Collection and Refinement Statistics****Data collection <sup>1</sup>**

Data set	Example 11	Example 16
Detector	Saturn944	Mar345
Space Group	I222	I222
Unit cell dimensions		
a, b, c (Å)	86.0, 89.3, 114.6	86.5, 88.7, 114.5
Resolution (Å)	1.7	1.5
Completeness (%)	81.0 (9.1)	93.3 (43.5)
R <sub>sym</sub> (%)	4.2 (31.6)	3.5 (28.0)
< I/σ(I) >	32.1 (2.9)	32.5 (4.7)

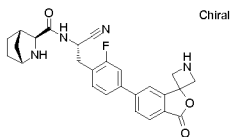
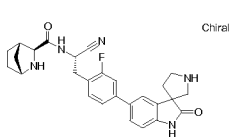
**Refinement <sup>2</sup>**

R-factor / R-free (%)	17.8/19.2	21.3/21.7
Rmsd bond length (Å)	0.008	0.008
Rmsd bond angles (°)	0.90	0.93

<sup>1</sup> Values in parentheses are for the highest resolution shell;  $R_{\text{sym}} = \sum_{hkl} \sum_i |I_i - \langle I \rangle| / \sum_{hkl} \sum_i I_i$

<sup>2</sup> R-factor =  $\sum_{hkl} | |F_{\text{obs}}| - k |F_{\text{calc}}| | / \sum_{hkl} |F_{\text{obs}}|$ ; R-free was calculated using 5% of data excluded from refinement; Rmsd, root mean square deviation.

**Table 14. Compounds examined in X-ray crystallography**

Compound	Example 11	Example 16
Structure		
Stereo isomer	single diastereomer	mixture of diastereomers
CatC IC <sub>50</sub> (nM)	0.7	0.5

## PHARMACEUTICAL COMPOSITIONS

Suitable preparations for administering the compounds of formula I will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, 5 suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives and powders etc., preferably tablets.

Suitable tablets may be obtained, for example, by mixing one or more compounds according to formula I with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants. The tablets may also 10 consist of several layers.

## COMBINATIONS

The compounds of general formula I may be used on their own or combined with other 15 active substances of formula I according to the invention. The compounds of general formula I may optionally also be combined with other pharmacologically active substances. These include,  $\beta$ 2-adrenoceptor-agonists (short and long-acting), anti-cholinergics (short and long-acting), anti-inflammatory steroids (oral and topical corticosteroids), cromoglycate, methylxanthine, dissociated-glucocorticoidmimetics, PDE3 20 inhibitors, PDE4- inhibitors, PDE7- inhibitors, LTD4 antagonists, EGFR- inhibitors, Dopamine agonists, PAF antagonists, Lipoxin A4 derivatives, FPRL1 modulators, LTB4-receptor (BLT1, BLT2) antagonists, Histamine H1 receptor antagonists, Histamine H4 receptor antagonists, dual Histamine H1/H3-receptor antagonists, PI3-kinase inhibitors, inhibitors of non-receptor tyrosine kinases as for example LYN, LCK, SYK, ZAP-70, 25 FYN, BTK or ITK, inhibitors of MAP kinases as for example p38, ERK1, ERK2, JNK1, JNK2, JNK3 or SAP, inhibitors of the NF- $\kappa$ B signalling pathway as for example IKK2 kinase inhibitors, iNOS inhibitors, MRP4 inhibitors, leukotriene biosynthesis inhibitors as for example 5-Lipoxygenase (5-LO) inhibitors, cPLA2 inhibitors, Leukotriene A4 Hydrolase inhibitors or FLAP inhibitors, Non-steroidal anti-inflammatory agents 30 (NSAIDs), CRTH2 antagonists, DP1-receptor modulators, Thromboxane receptor antagonists, CCR3 antagonists, CCR<sup>4</sup> antagonists, CCR1 antagonists, CCR5 antagonists, CCR6 antagonists, CCR7 antagonists, CCR8 antagonists, CCR9 antagonists, CCR30

antagonists, , CXCR<sup>3</sup> antagonists, CXCR<sup>4</sup> antagonists, CXCR<sup>2</sup> antagonists, CXCR<sup>1</sup> antagonists, CXCR5 antagonists, CXCR6 antagonists, CX3CR<sup>3</sup> antagonists, Neurokinin (NK1, NK2) antagonists, Sphingosine 1-Phosphate receptor modulators, Sphingosine 1 phosphate lyase inhibitors, Adenosine receptor modulators as for example A2a-agonists, modulators of purinergic receptors as for example P2X7 inhibitors, Histone Deacetylase (HDAC) activators, Bradykinin (BK1, BK2) antagonists, TACE inhibitors, PPAR gamma modulators, Rho-kinase inhibitors, interleukin 1-beta converting enzyme (ICE) inhibitors, Toll-Like receptor (TLR) modulators, HMG-CoA reductase inhibitors, VLA-4 antagonists, ICAM-1 inhibitors, SHIP agonists, GABA<sub>A</sub> receptor antagonist, ENaC-inhibitors, Prostate-inhibitors, Matriptase-inhibitors, Melanocortin receptor (MC1R, MC2R, MC3R, MC4R, MC5R) modulators, CGRP antagonists, Endothelin antagonists, TNF $\alpha$  antagonists, anti-TNF antibodies, anti-GM-CSF antibodies, anti-CD46 antibodies, anti-IL-1 antibodies, anti-IL-2 antibodies, anti-IL-4 antibodies, anti-IL-5 antibodies, anti-IL-13 antibodies, anti-IL-4/IL-13 antibodies, anti-TSLP antibodies, anti-OX40 antibodies, mucoregulators, immunotherapeutic agents, compounds against swelling of the airways, compounds against cough, VEGF inhibitors, NE-inhibitors, MMP9 inhibitors, MMP12 inhibitors, but also combinations of two or three active substances.

Preferred are betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, CRTH2 inhibitors, 5-LO-inhibitors, Histamine receptor antagonists and SYK-inhibitors, NE-inhibitors, MMP9 inhibitors, MMP12 inhibitors, but also combinations of two or three active substances, i.e.:

- Betamimetics with corticosteroids, PDE4-inhibitors, CRTH2-inhibitors or LTD4-antagonists,
- Anticholinergics with betamimetics, corticosteroids, PDE4-inhibitors, CRTH2-inhibitors or LTD4-antagonists,
- Corticosteroids with PDE4-inhibitors, CRTH2-inhibitors or LTD4-antagonists
- PDE4-inhibitors with CRTH2-inhibitors or LTD4-antagonists
- CRTH2-inhibitors with LTD4-antagonists.

## INDICATIONS

The compounds of the invention and their pharmaceutically acceptable salts have activity as pharmaceuticals, in particular as inhibitors of dipeptidyl peptidase I activity, and thus  
5 may be used in the treatment of:

1. respiratory tract: obstructive diseases of the airways including: asthma, including  
bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin  
and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all  
10 severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary  
disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema;  
alpha1-antitrypsin deficiency, bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and  
related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic  
fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic  
15 therapy and chronic infection, including tuberculosis and aspergillosis and other fungal  
infections; complications of lung transplantation; vasculitic and thrombotic disorders of the  
lung vasculature, polyangiitis (Wegener Granulomatosis) and pulmonary hypertension;  
antitussive activity including treatment of chronic cough associated with inflammatory and  
secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis  
20 including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic  
rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection  
including the common cold, and infection due to respiratory syncytial virus, influenza,  
coronavirus (including SARS) and adenovirus;
- 25 2. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and  
delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic  
dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma  
gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid,  
epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous  
30 eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian  
syndrome, erythema multiforme; cellulitis, both infective and non-infective;

panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

3. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis;  
5 iritis; anterior and posterior uveitis; choroiditis; autoimmune, degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;

4. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic  
10 syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);

5. allograft rejection: acute and chronic following, for example, transplantation of kidney,  
15 heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

6. other auto-immune and allergic disorders including rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis,  
20 Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome;

7. oncology: treatment of common cancers including prostate, breast, lung, ovarian,  
25 pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

30 8. infectious diseases: virus diseases such as genital warts, common warts, plantar warts, hepatitis B, hepatitis C, herpes simplex virus, molluscum contagiosum, variola, human immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus (CMV),

varicella zoster virus (VZV), rhinovirus, adenovirus, coronavirus, influenza, para-influenza; bacterial diseases such as tuberculosis and mycobacterium avium, leprosy; other infectious diseases, such as fungal diseases, chlamydia, Candida, aspergillus, cryptococcal meningitis, Pneumocystis carinii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection and leishmaniasis.

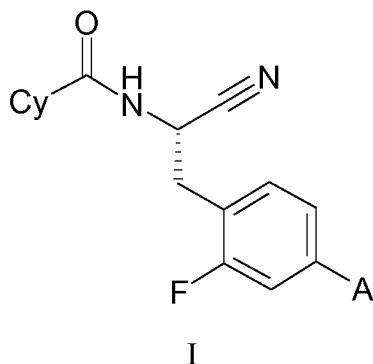
9. pain: Recent literature data from Cathepsin C-deficient mice point to a modulatory role of Cathepsin C in pain sensation. Accordingly, inhibitors of Cathepsin C may also be useful in the clinical setting of various form of chronic pain, e.g. inflammatory or neuropathic pain.

For treatment of the above-described diseases and conditions, a therapeutically effective dose will generally be in the range from about 0.01 mg to about 100 mg/kg of body weight per dosage of a compound of the invention; preferably, from about 0.1 mg to about 20 mg/kg of body weight per dosage. For Example, for administration to a 70 kg person, the dosage range would be from about 0.7 mg to about 7000 mg per dosage of a compound of the invention, preferably from about 7.0 mg to about 1400 mg per dosage. Some degree of routine dose optimization may be required to determine an optimal dosing level and pattern. The active ingredient may be administered from 1 to 6 times a day.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the active ingredient will be administered at dosages and in a manner which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

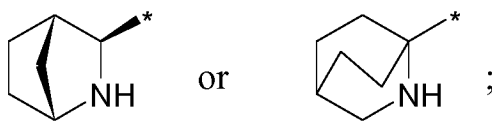
## WHAT IS CLAIMED

1. A compound of formula I or a pharmaceutically acceptable salt thereof,

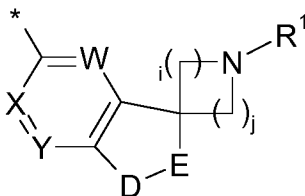


wherein

Cy is



A is



wherein

W is selected from the group consisting of CH and N;

X is selected from the group consisting of CH and N;

Y is selected from the group consisting of CH and N;

with the proviso that a maximum of one of W, X and Y can be N;

D-E is selected from the group consisting of N(R<sup>2</sup>)-C(O), CH<sub>2</sub>CH<sub>2</sub>, C(O)-O and CH<sub>2</sub>-O;

R<sup>2</sup> is selected from the group consisting of H and C<sub>1-3</sub>-alkyl;

R<sup>1</sup> is selected from the group consisting of H, C<sub>1-3</sub>-alkyl, CH<sub>3</sub>OCH<sub>2</sub>CH<sub>2</sub>-, oxetanyl, tetrahydrofuranyl, 4-tetrahydropyranyl and 3-tetrahydropyranyl;

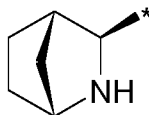
i is 1, 2 or 3;

j is 1, 2 or 3;

with the proviso that the sum of i+j is 2, 3 or 4.

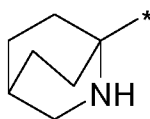
- 5 2. A compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

Cy is



- 10 3. A compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

Cy is



- 15 4. A compound of formula I according to claim 1, 2 or 3, or a pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup> is selected from the group consisting of H, CH<sub>3</sub>- and oxetanyl;

5. A compound of formula I according to any one of claims 1 to 4, or a  
20 pharmaceutically acceptable salt thereof, wherein

R<sup>2</sup> is selected from the group consisting of H and CH<sub>3</sub>;

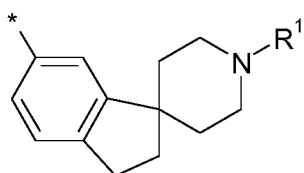
6. A compound of formula I according to any one of claims 1 to 5, or a  
pharmaceutically acceptable salt thereof, wherein

25 D-E is CH<sub>2</sub>-O;

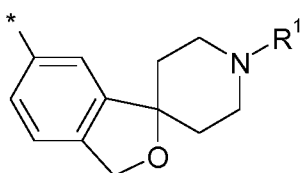
7. A compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

- R<sup>1</sup> is selected from the group consisting of H, CH<sub>3</sub> and oxetanyl;  
R<sup>2</sup> is CH<sub>3</sub>;  
W is selected from the group consisting of CH and N;  
X is selected from the group consisting of CH and N;  
5 Y is selected from the group consisting of CH;  
with the proviso that a maximum of one of W, X and Y can be N;  
D-E is selected from the group consisting of N(R<sup>2</sup>)-C(O), CH<sub>2</sub>CH<sub>2</sub>, C(O)-O and CH<sub>2</sub>-O;  
i is 1 or 2;  
j is 1 or 2;  
10 with the proviso that the sum of i+j is 2, 3 or 4.

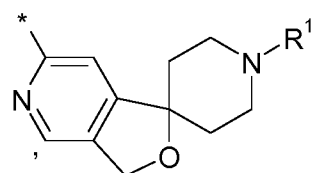
8. A compound of formula I, according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein  
15 A is selected from the group consisting of formulas A1 to A14:



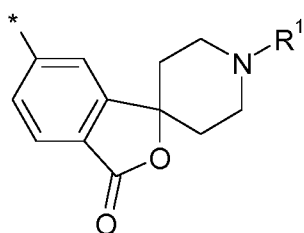
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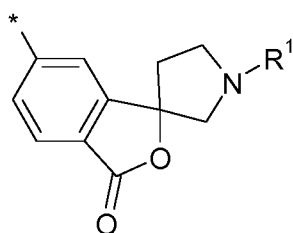
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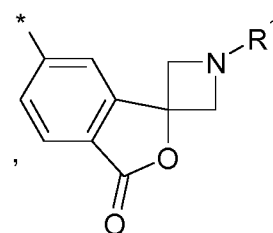
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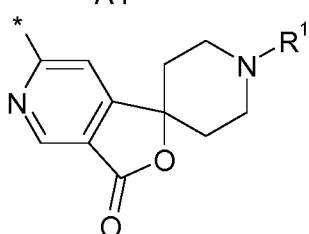
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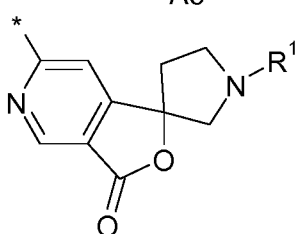
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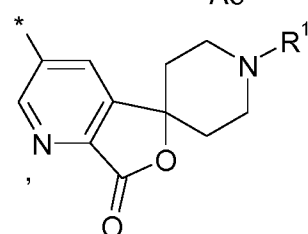
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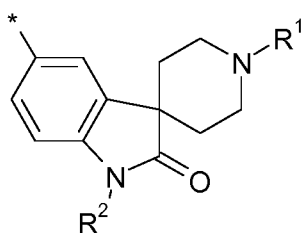
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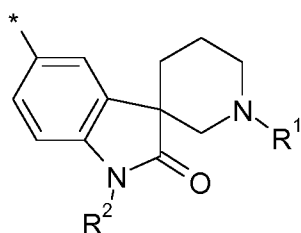
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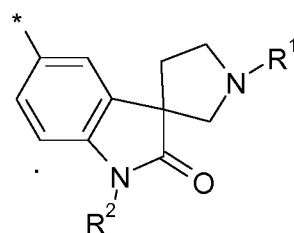
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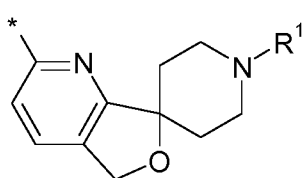
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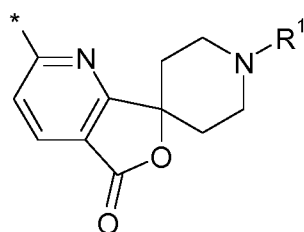
A11



A12



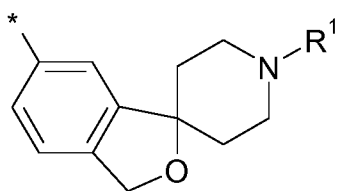
A13



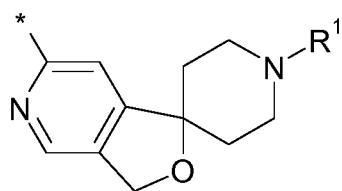
A14

9. A compound of formula I, according to claim 8, or a pharmaceutically acceptable  
 5 salt thereof, wherein

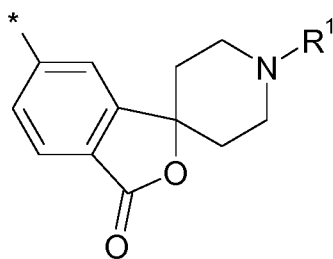
A is selected from the group consisting of A2, A3, A4, A5, A6, A7, A10, A13, and A14.



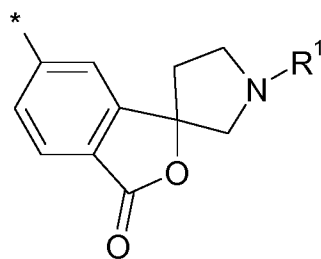
A2,



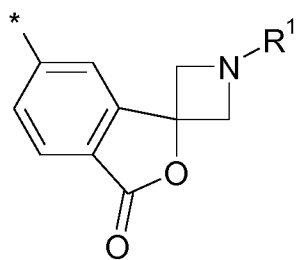
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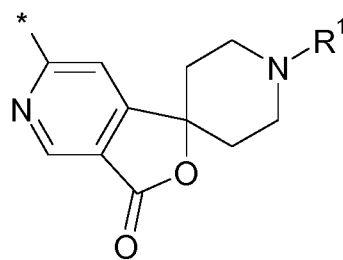
A4,



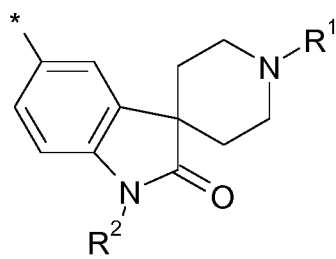
A5



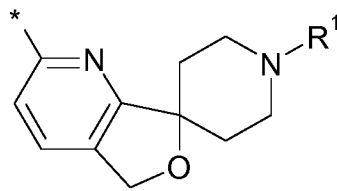
A6,



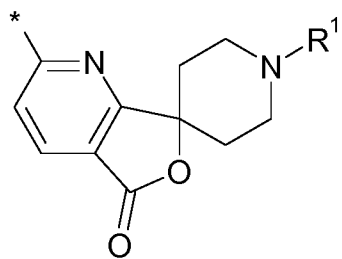
A7,



A10,



A13,

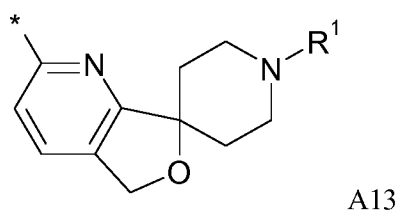
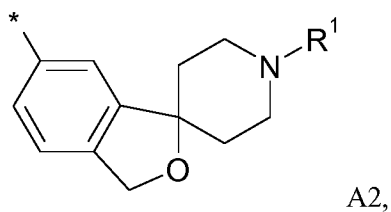


A14.

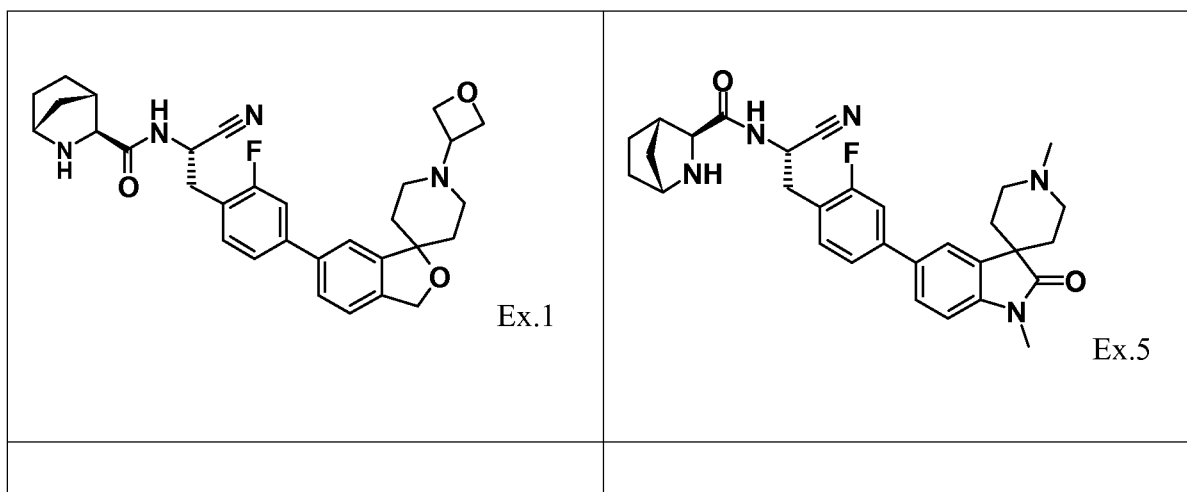
10. A compound of formula I, according to claim 8 or 9, or a pharmaceutically acceptable salt thereof, wherein

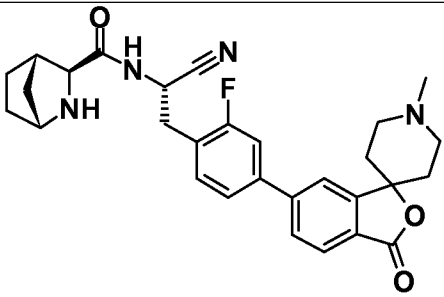
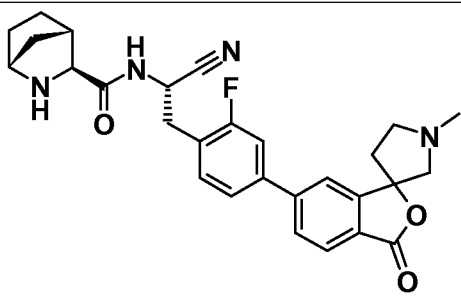
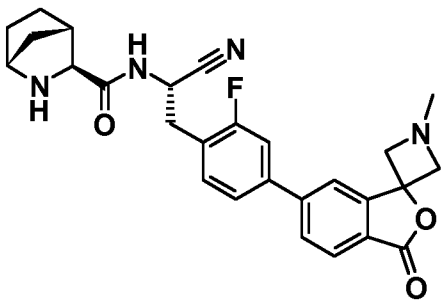
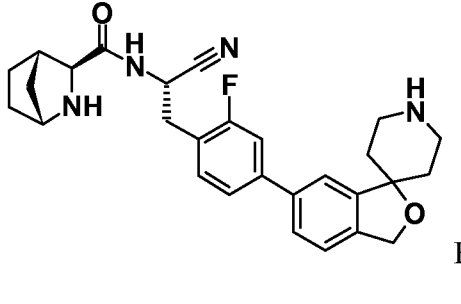
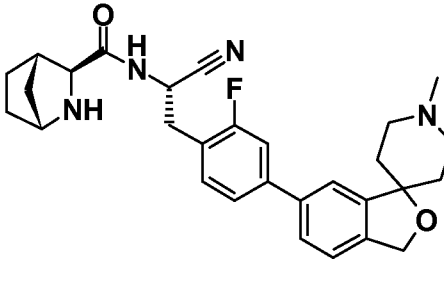
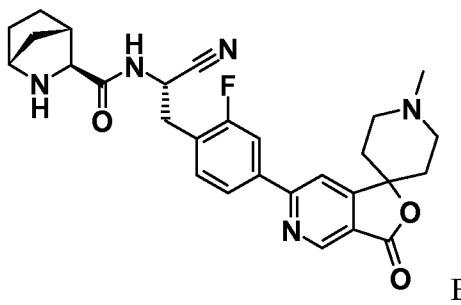
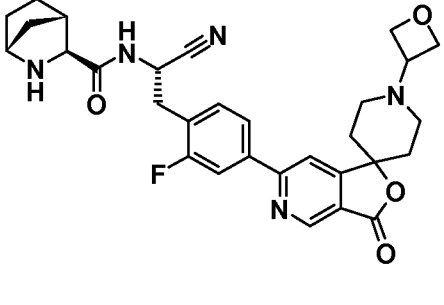
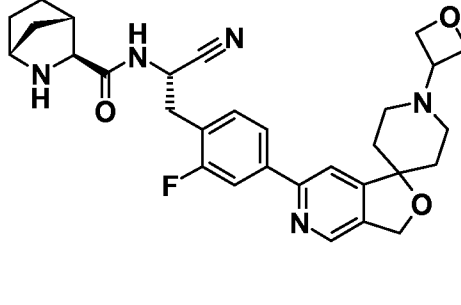
A is selected from the group consisting of A2 and A13

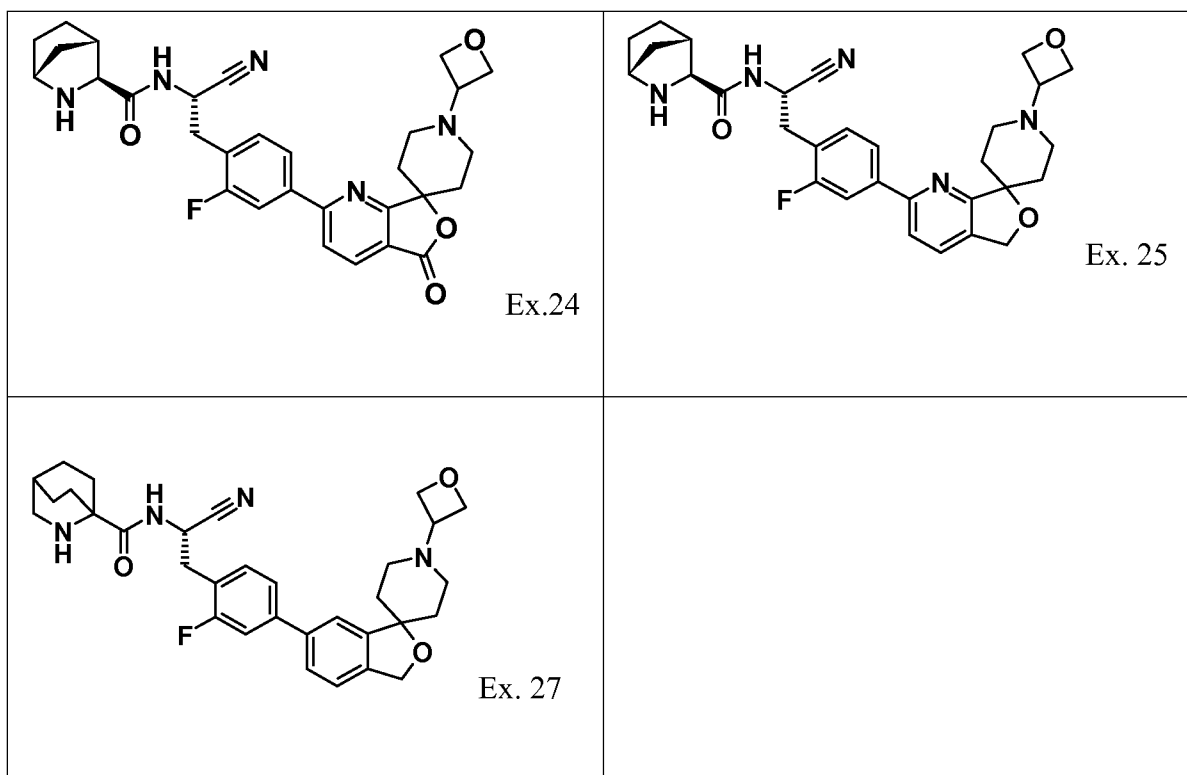
5



10 11. A compound of formula I, according to claim 1 selected from the group consisting of examples 1, 5, 8, 10, 12, 13, 14, 19, 22, 23, 24, 25 and 27.



 <p>Ex. 8</p>	 <p>Ex. 10</p>
 <p>Ex. 12</p>	 <p>Ex. 13</p>
 <p>Ex. 14</p>	 <p>Ex. 19</p>
 <p>Ex. 22</p>	 <p>Ex. 23</p>



12. A compound of formula I according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof for use as a medicament.

5

13. A compound of formula I according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof for use as a medicament for the treatment of asthma and allergic diseases, gastrointestinal inflammatory diseases, glomerulonephritis, eosinophilic diseases, chronic obstructive pulmonary disease, infection by pathogenic  
 10 microbes, rheumatoid arthritis, neutrophilic diseases, cystic fibrosis (CF), non-cystic fibrosis, idiopathic pulmonary fibrosis, bronchiectasis, ANCA-associated vasculitis, lung cancer, emphysema, chronic bronchitis, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), pulmonary hypertension, pulmonary arterial hypertension (PAH) and Alpha-1-antitrypsin deficiency (AATD), obesity and related inflammation, insulin  
 15 resistance, diabetes, fatty liver and liver steatosis.

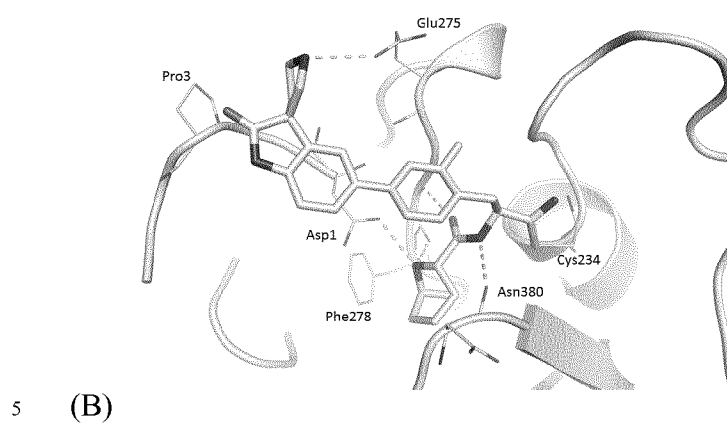
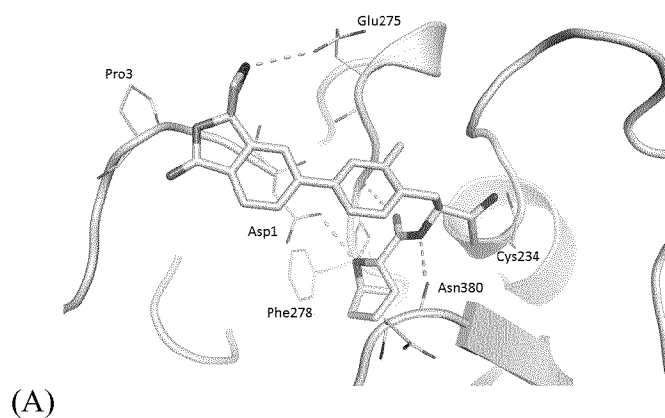
14. Pharmaceutical composition, characterised in that it contains one or more compounds of formula I according to any one of claims 1 to 11 or a pharmaceutically active salt thereof.

5 15. Method of treatment or prevention of diseases in which DPPI activity inhibitors have a therapeutic benefit, which method comprises administration of a therapeutically or preventively effective amount of a compounds of formula I according to one of claims 1 to 11 to a patient in need thereof.

10 16. A pharmaceutical composition comprising additionally to a compound of formula I, according to any one of claims 1 to 11, a pharmaceutically active compound selected from the group consisting of betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, CRTH2 inhibitors, 5-LO-inhibitors, Histamine  
15 inhibitors, MMP12 inhibitors, but also combinations of two or three active substances.

## ANNEX

## Figures



**Figure 1.** Structures of Cathepsin C ligand complexes. (A) Example 11; (B) Example 16. The protein is shown in ribbon representation, with selected residues shown as sticks. Ligands are shown as stick representation, hydrogen bonds as dotted lines.

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2015/070449

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C07D471/10 C07D491/10 A61K31/439 A61P11/00  
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BEILSTEIN Data, BIOSIS, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/041497 A1 (BOEHRINGER INGELHEIM INT [DE]) 28 March 2013 (2013-03-28) cited in the application claims; examples 134, 136, 138, 139 -----	1-16



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

8 October 2015

Date of mailing of the international search report

22/10/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040,  
Fax: (+31-70) 340-3016

Authorized officer

Stroeter, Thomas

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/070449

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013041497	A1	28-03-2013	
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		AU 2012311656 A1	13-02-2014
		CA 2848929 A1	28-03-2013
		CL 2014000299 A1	26-09-2014
		CN 103814028 A	21-05-2014
		EA 201400358 A1	30-09-2014
		EP 2758398 A1	30-07-2014
		JP 2014526492 A	06-10-2014
		KR 20140078626 A	25-06-2014
		US 2013172327 A1	04-07-2013
		WO 2013041497 A1	28-03-2013
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