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(54) Title: SUBSTITUTED INDOLINE DERIVATIVES AS DENGUE VIRAL REPLICATION INHIBITORS

(57) Abstract: The present invention concerns substituted indoline derivatives, methods to prevent or treat dengue viral infections by using said compounds and also relates to said compounds for use as a medicine, more preferably for use as a medicine to treat or prevent dengue viral infections. The present invention furthermore relates to pharmaceutical compositions or combination preparations of the compounds, to the compositions or preparations for use as a medicine, more preferably for the prevention or treatment of dengue viral infections. The invention also relates to processes for preparation of the compounds.



## **SUBSTITUTED INDOLINE DERIVATIVES AS DENGUE VIRAL REPLICATION INHIBITORS**

The present invention relates to substituted indoline derivatives, methods to  
5 prevent or treat dengue viral infections by using said compounds and also relates  
to said compounds for use as a medicine, more preferably for use as a medicine  
to treat or prevent dengue viral infections. The present invention furthermore  
relates to pharmaceutical compositions or combination preparations of the  
10 compounds, to the compositions or preparations for use as a medicine, more  
preferably for the prevention or treatment of dengue viral infections. The invention  
also relates to processes for preparation of the compounds.

### **BACKGROUND OF THE INVENTION**

Flaviviruses, which are transmitted by mosquitoes or ticks, cause life-threatening  
15 infections in man, such as encephalitis and hemorrhagic fever. Four distinct, but  
closely related serotypes of the flavivirus dengue are known, so-called DENV-1, -2,  
-3, and -4. Dengue is endemic in most tropical and sub-tropical regions around the  
world, predominantly in urban and semi-urban areas. According to the World  
Health Organization (WHO), 2.5 billion people of which 1 billion children are at risk  
20 of DENV infection (WHO, 2002). An estimated 50 to 100 million cases of dengue  
fever [DF], half a million cases of severe dengue disease (i.e. dengue hemorrhagic  
fever [DHF] and dengue shock syndrome [DSS]), and more than 20,000 deaths  
occur worldwide each year. DHF has become a leading cause of hospitalization  
and death amongst children in endemic regions. Altogether, dengue represents  
25 the most common cause of arboviral disease. Because of recent large outbreaks  
in countries situated in Latin America, South-East Asia and the Western Pacific  
(including Brazil, Puerto Rico, Venezuela, Cambodia, Indonesia, Vietnam,  
Thailand), numbers of dengue cases have risen dramatically over the past years.  
Not only is the number of dengue cases increasing as the disease is spreading to  
30 new areas, but the outbreaks tend to be more severe.

Following infection with another serotype, pre-existing heterologous antibodies  
form complexes with the newly infecting dengue virus serotype but do not  
neutralize the pathogen. Instead, virus entry into cells is believed to be facilitated,  
35 resulting in uncontrolled virus replication and higher peak viral titers. In both  
primary and secondary infections, higher viral titers are associated with more  
severe dengue disease. Since maternal antibodies can easily pass on to infants by

breast feeding, this might be one of the reasons that children are more affected by severe dengue disease than adults.

In locations with two or more serotypes circulating simultaneously, also referred to as hyper endemic regions, the risk of serious dengue disease is significantly higher due to an increased risk of experiencing a secondary, more severe infection. Moreover, in a situation of hyper-endemicity, the probability of the emergence of more virulent strains is increased, which in turn augments the probability of dengue hemorrhagic fever (DHF) or dengue shock syndrome.

The mosquitoes that carry dengue, including *Aedes aegypti* and *Aedes albopictus* (tiger mosquito), are moving north on the globe. According to the United States (US) Centers for Disease Control and Prevention (CDC), both mosquitoes are currently omnipresent in southern Texas. The spread north of dengue-carrying mosquitoes is not confined to the US, but has also been observed in Europe.

Dengvaxia<sup>®</sup>, the dengue vaccine produced by Sanofi Pasteur was first approved in Mexico and has received in the meantime approval in more countries.

Nevertheless, the vaccine leaves considerable room for improvement due to limited efficacy, especially against DENV-1 and -2, low efficacy in flavivirus-naïve subjects and the lengthy dosing schedule.

Despite these shortcomings, the vaccine is a game changer in endemic settings as it will offer protection to a large part of the population, but likely not to very young infants, who bear the largest burden of dengue. In addition, the dosing schedule and very limited efficacy in flavivirus-naïve subjects make it unsuitable and likely not worthwhile/cost-effective for travelers from non-endemic areas to dengue-endemic areas. The above mentioned shortcomings of the dengue vaccines are the reason why there is a need for a pre-exposure prophylactic dengue antiviral.

Furthermore, today, specific antiviral drugs for the treatment or prevention of dengue fever virus infection are not available. Clearly, there is still a great unmet medical need for therapeutics for the prevention or treatment of viral infections in animals, more in particular in humans and especially for viral infections caused by flaviviruses, more in particular Dengue virus. Compounds with good anti-viral potency, no or low levels of side-effects, a broad spectrum activity against multiple Dengue virus serotypes, a low toxicity and/or good pharmacokinetic or -dynamic properties are highly needed.

WO-2010/021878 discloses 2-phenylpyrrolidine and indoline derivatives as cold menthol receptor antagonists for treatment of inflammatory and central diseases. WO-2013/045516 discloses indole and indoline derivatives for use in the treatment  
5 of dengue viral infections.

The present invention now provides compounds, substituted indoline derivatives, which show high potent activity against all four (4) serotypes of the Dengue virus.

## 10 **SUMMARY OF THE INVENTION**

The present invention is based on the unexpected finding that at least one of the above-mentioned problems can be solved by the current compounds of the invention.

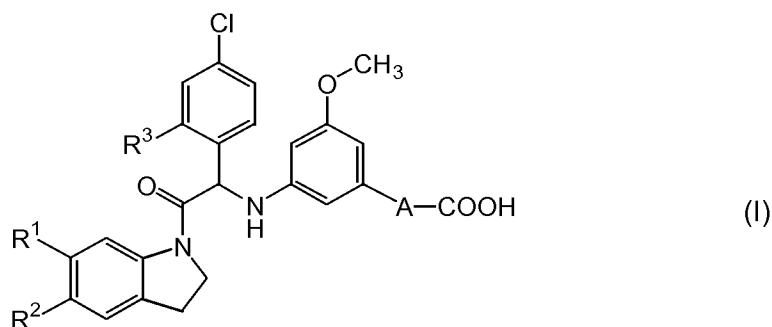
15 The present invention provides compounds which have been shown to possess potent antiviral activity against all four (4) serotypes currently known. The present invention furthermore demonstrates that these compounds efficiently inhibit proliferation of Dengue virus (DENV). Therefore, these compounds constitute a useful class of potent compounds that can be used in the treatment and/or  
20 prevention of viral infections in animals, mammals and humans, more specifically for the treatment and/or prevention of infections with Dengue viruses.

The present invention furthermore relates to the use of such compounds as medicines and to their use for the manufacture of medicaments for treating and/or  
25 preventing viral infections, in particular with viruses belonging to the family of the Dengue viruses in animals or mammals, more in particular in humans. The invention also relates to methods for the preparation of all such compounds and to pharmaceutical compositions comprising them in an effective amount.

30 The present invention also relates to a method of treatment or prevention of dengue viral infections in humans by the administration an effective amount of one or more such compounds, or a pharmaceutically acceptable salt thereof optionally in combination with one or more other medicines, like another antiviral agent, to a patient in need thereof.

35

One aspect of the invention is the provision of compounds of formula (I), including any stereochemically isomeric form thereof, :



5

wherein

R<sup>1</sup> is trifluoromethyl, trifluoromethoxy, or chloro;

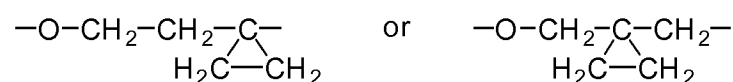
R<sup>2</sup> is hydrogen, fluoro, or methoxy;

R<sup>3</sup> is hydrogen, or methoxy;

10 A represents  $-(CH_2)_n-$  wherein n is 3 or 4;

$-O-(CH_2)_n-$  wherein n is 2 or 4;

$-O-(CH_2)_n-$  wherein n is 3 and one or two CH<sub>2</sub> are substituted with one or two CH<sub>3</sub>;



15

$-CH_2-O-(CH_2)_n-$  wherein n is 2; or

$-X-Y-$  wherein X is a  $-O-$ ,  $-OCH_2-$ , or  $-NH-$ ; and

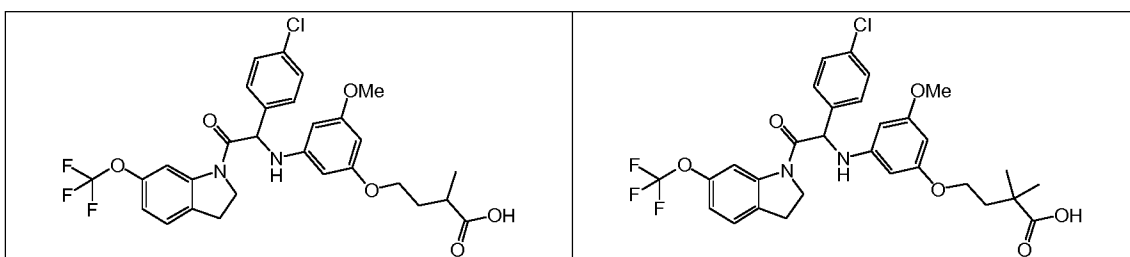
Y is C<sub>3-4</sub>cycloalkyl optionally substituted with fluoro, or

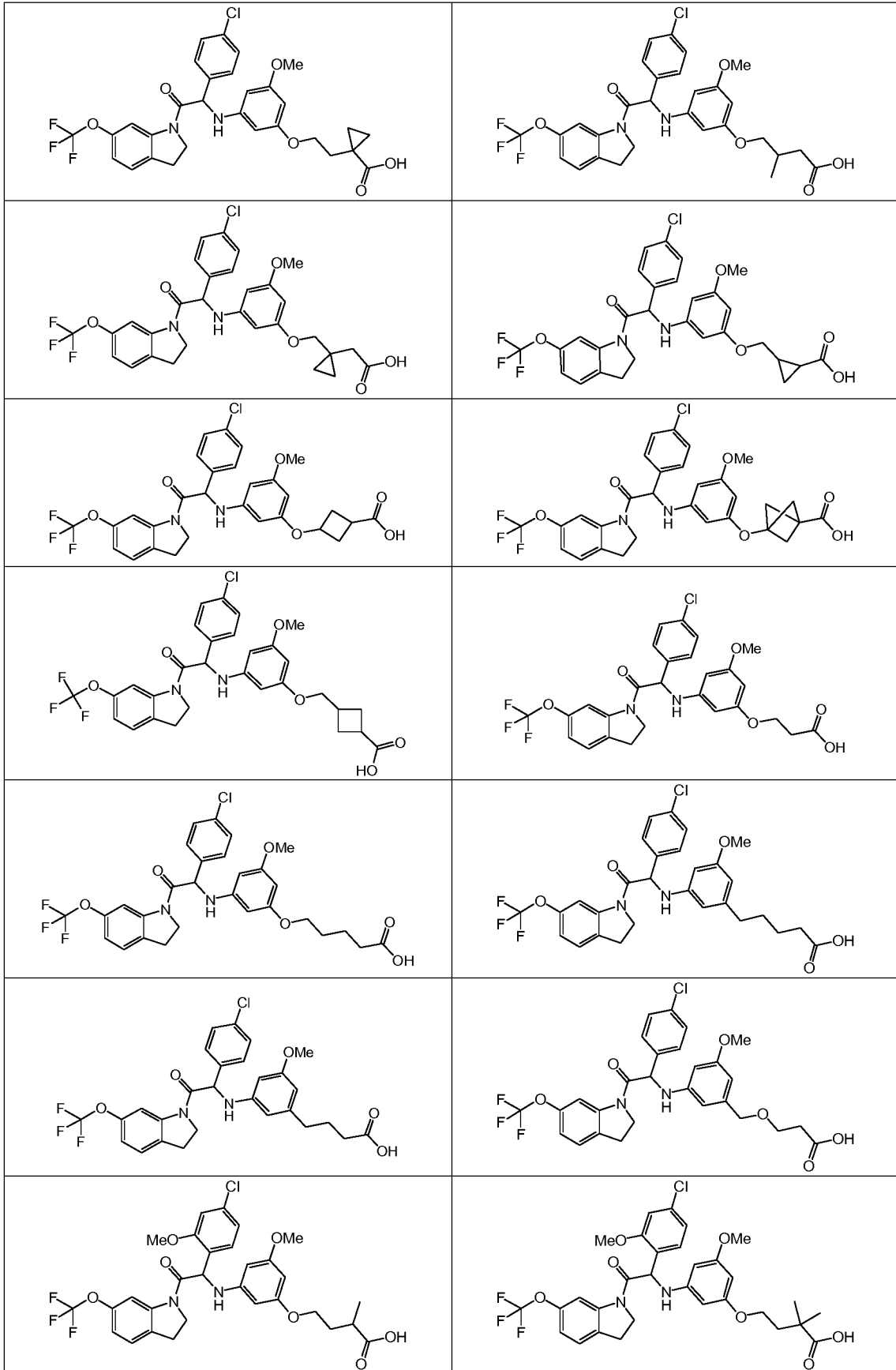
Y is bicyclo[1.1.1]pentanyl;

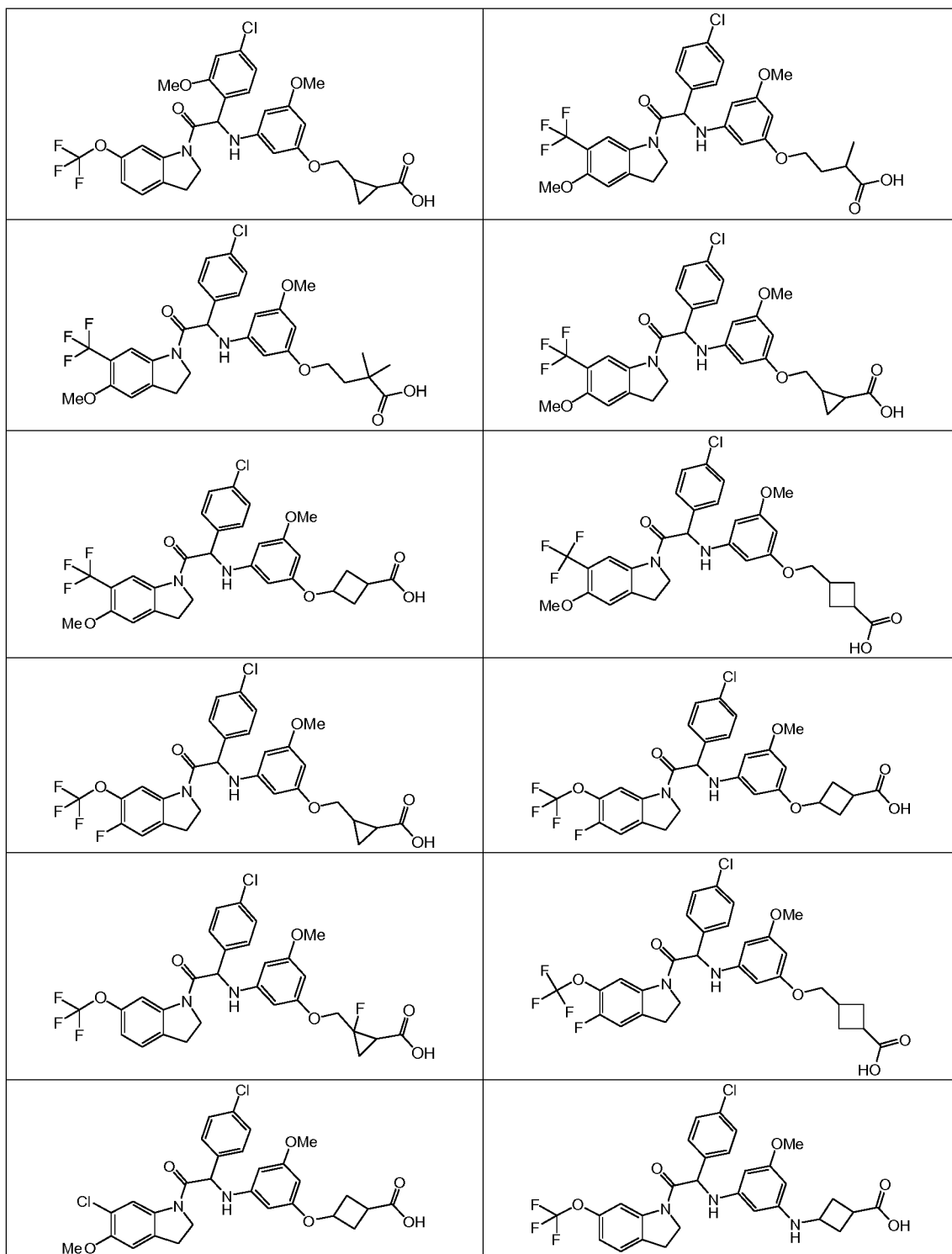
or a pharmaceutically acceptable salt, solvate or polymorph thereof.

20

Specifically above mentioned compounds are selected from the group comprising :







A first group of compounds are compounds of formula (I) wherein A represents  $-(CH_2)_n-$  wherein n is 3 or 4.

- 5 A second group of compounds are compounds of formula (I) wherein A represents  $-O-(CH_2)_n-$  wherein n is 2 or 4.

A third group of compounds are compounds of formula (I) wherein A represents  $-\text{O}-(\text{CH}_2)_n-$  wherein n is 3 and one or two  $\text{CH}_2$  are substituted with one or two  $\text{CH}_3$ ; or A represents  $-\text{O}-\text{CH}_2-\text{CH}_2-\text{C}-$  or  $-\text{O}-\text{CH}_2-\text{C}-\text{CH}_2-$  .  
 $\begin{array}{c} \text{H}_2\text{C}-\text{CH}_2 \\ \diagup \quad \diagdown \\ \text{C} \end{array}$

- 5 A fourth group of compounds are compounds of formula (I) wherein A represents  $-\text{CH}_2-\text{O}-(\text{CH}_2)_n-$  wherein n is 2.

A fifth group of compounds are compounds of formula (I) wherein A represents  $-\text{X}-\text{Y}-$  wherein X is a  $-\text{O}-$ ,  $-\text{OCH}_2-$ , or  $-\text{NH}-$ ; and Y is  $\text{C}_{3-4}$ cycloalkyl optionally substituted with fluoro.  
 10

A sixth group of compounds are compounds of formula (I) wherein A represents  $-\text{X}-\text{Y}-$  wherein X is a  $-\text{O}-$ ,  $-\text{OCH}_2-$ , or  $-\text{NH}-$ ; and Y is bicyclo[1.1.1]pentanyl.

- 15 A seventh group of compounds are compounds of formula (I) wherein  $\text{R}^1$  is trifluoromethoxy,  $\text{R}^2$  is hydrogen, and  $\text{R}^3$  is hydrogen.

An eighth group of compounds are compounds of formula (I) wherein  $\text{R}^1$  is trifluoromethoxy,  $\text{R}^2$  is hydrogen, and  $\text{R}^3$  is methoxy.  
 20

A ninth group of compounds are compounds of formula (I) wherein  $\text{R}^1$  is trifluoromethyl,  $\text{R}^2$  is methoxy, and  $\text{R}^3$  is hydrogen.

A tenth group of compounds are compounds of formula (I) wherein  $\text{R}^1$  is trifluoromethoxy,  $\text{R}^2$  is fluoro, and  $\text{R}^3$  is hydrogen.  
 25

An eleventh group of compounds are compounds of formula (I) wherein  $\text{R}^1$  is chloro,  $\text{R}^2$  is methoxy, and  $\text{R}^3$  is hydrogen.

- 30 Part of the current invention is also a pharmaceutical composition comprising a compound mentioned above or a stereoisomeric form, a pharmaceutically acceptable salt, solvate or polymorph thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

- 35 Pharmaceutically acceptable salts of said compounds include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts. Suitable base salts are formed from bases which form non-toxic salts.



The pharmaceutically acceptable acid salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms that the compounds of formula (I) are able to form. These pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butane-dioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-amino-salicylic, pamoic acid and the like acids.

The compounds of the invention may also exist in un-solvated and solvated forms. The term "solvate" is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol.

The term "polymorph" refers to the ability of the compound of the invention to exist in more than one form or crystal structure.

The compounds of the present invention may be administered as crystalline or amorphous products. They may be obtained for example as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs. Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient depends largely on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms

depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, for example, for oral or rectal administration. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions, and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. Also included are solid form preparations that can be converted, shortly before use, to liquid forms.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

Those of skill in the treatment of infectious diseases will be able to determine the effective amount from the test results presented hereinafter. In general it is contemplated that an effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, more preferably from 0.1 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of the invention used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective amount may be lowered or increased depending on the response of the treated

subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective amount ranges mentioned above are therefore only guidelines and are not intended to limit the scope or use of the invention to any extent.

5

The present disclosure is also intended to include any isotopes of atoms present in the compounds of the invention. For example, isotopes of hydrogen include tritium and deuterium and isotopes of carbon include C-13 and C-14.

10

As used herein, any chemical formula with bonds shown only as solid lines and not as solid wedged or hashed wedged bonds, or otherwise indicated as having a particular configuration (e.g. R, S) around one or more atoms, contemplates each possible stereoisomer, or mixture of two or more stereoisomers.

15

Hereinbefore and hereinafter, the terms "compound of formula (I)" and "intermediates of synthesis of formula (I)" are meant to include the stereoisomers thereof and the tautomeric forms thereof.

20

The terms "stereoisomers", "stereoisomeric forms" or "stereochemically isomeric forms" hereinbefore or hereinafter are used interchangeably.

The invention includes all stereoisomers of the compounds of the invention either as a pure stereoisomer or as a mixture of two or more stereoisomers.

25

Enantiomers are stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a racemate or racemic mixture. Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers, *i.e.* they are not related as mirror images. Substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration; for example if a compound contains a disubstituted cycloalkyl group, the substituents may be in the cis or trans configuration.

30

The term "stereoisomers" also includes any rotamers, also called conformational isomers, the compounds of formula (I) may form.

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Therefore, the invention includes enantiomers, diastereomers, racemates, E isomers, Z isomers, cis isomers, trans isomers, rotamers, and any mixture thereof, whenever chemically possible.

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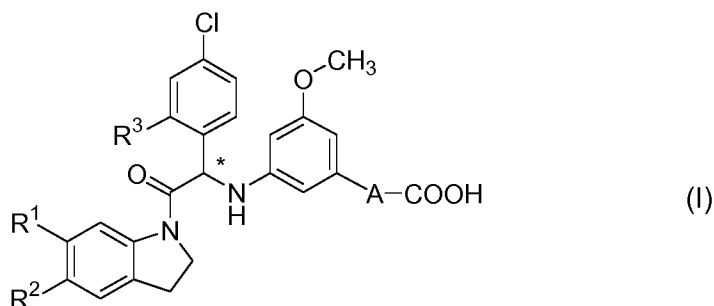
The meaning of all those terms, *i.e.* enantiomers, diastereomers, racemates, cis isomers, trans isomers and mixtures thereof are known to the skilled person.

The absolute configuration is specified according to the Cahn-Ingold-Prelog system. The configuration at an asymmetric atom is specified by either R or S. Resolved stereoisomers whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light. For instance, resolved enantiomers whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light.

When a specific stereoisomer is identified, this means that said stereoisomer is substantially free, *i.e.* associated with less than 50%, preferably less than 20%, more preferably less than 10%, even more preferably less than 5%, in particular less than 2% and most preferably less than 1%, of the other stereoisomers. Thus, when a compound of formula (I) is for instance specified as (R), this means that the compound is substantially free of the (S) isomer; when a compound of formula (I) is for instance specified as E, this means that the compound is substantially free of the Z isomer; when a compound of formula (I) is for instance specified as cis, this means that the compound is substantially free of the trans isomer.

Some of the compounds according to formula (I) may also exist in their tautomeric form. Such forms in so far as they may exist, although not explicitly indicated in the above formula (I) are intended to be included within the scope of the present invention.

The compounds of formula (I) of the present invention all have at least one asymmetric carbon atom as indicated in the figure below by the carbon atom labelled with \* :



30

Due to the presence of said chiral center, a "compound of formula (I)" can be the (R)-enantiomer, the (S)-enantiomer, the racemic form, or any possible combination of the two individual enantiomers in any ratio. When the absolute configuration of an asymmetric carbon atom was not known, a relative stereochemistry descriptor

was used : \*R or \*S (or R\* and S\*) to indicate the pure but unknown stereochemistry of the chiral center.

Since radical A allows for substituents introducing additional asymmetric carbon atoms, the compounds of formula (I) may have more than one asymmetric carbon atom. When the absolute stereochemistry of the more than one asymmetric carbon atoms was not determined, the relative stereochemistry was indicated using the relative stereochemistry descriptors \*R and \*S and where possible in combination with cis and trans when radical A contains a cyclic moiety.

In an aspect the present invention relates to a first group of compound of formula (I) wherein the compounds of formula (I) have the (-) specific rotation.

In a further aspect the present invention relates to a second ground of compounds of formula (I) wherein the compounds of formula (I) have the (+) specific rotation.

In an embodiment, the present invention relates to a compound of formula (I) having the (+) specific rotation wherein said compound is selected from the group consisting of compounds (1C), (1D), (2A), (4C), (4D), (5A), (6AB), (6BB), (7B), (8B), (9B), (10B), (11B), (12B), (13B), (14A), (15B), (17C), (17D), (18B), (19AB), (19BB), (20C), (20D), (21B), (22AB), (22BB), (23B), (24B), (25B), (27B), (28AB), (28BB), (29AB), (29BB), (30A), (31A), (32B), (33C), and (33D).

## **Examples**

### **LC/MS methods**

The High Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array (DAD) or a UV detector and a column as specified in the respective methods. If necessary, additional detectors were included (see table of methods below).

Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW). Data acquisition was performed with appropriate software.

Compounds are described by their experimental retention times ( $R_t$ ) and ions. If not specified differently in the table of data, the reported molecular ion

corresponds to the  $[M+H]^+$  (protonated molecule) and/or  $[M-H]^-$  (deprotonated molecule). In case the compound was not directly ionizable the type of adduct is specified (i.e.  $[M+NH_4]^+$ ,  $[M+HCOO]^-$ , etc...). For molecules with multiple isotopic patterns (Br, Cl), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

Hereinafter, "SQD" means Single Quadrupole Detector, "MSD" Mass Selective Detector, "RT" room temperature, "BEH" bridged ethylsiloxane/silica hybrid, "DAD" Diode Array Detector, "HSS" High Strength silica.

LC/MS Method codes (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes).

Method code	Instrument	Column	Mobile phase	Gradient	Flow ----- Col T	Run time (min)
LC-A	Waters: Acquity® UPLC® -DAD-SQD	Waters: BEH C18 (1.7 µm, 2.1x50mm)	A: 10mM CH <sub>3</sub> COONH <sub>4</sub> in 95% H <sub>2</sub> O + 5% CH <sub>3</sub> CN B: CH <sub>3</sub> CN	From 95% A to 5% A in 1.3 min, held for 0.7 min.	0.8 mL/min ----- 55°C	2
LC-B	Waters: Acquity® UPLC® -DAD-SQD	Waters: HSS T3 (1.8 µm, 2.1x100mm)	A: 10mM CH <sub>3</sub> COONH <sub>4</sub> in 95% H <sub>2</sub> O + 5% CH <sub>3</sub> CN B: CH <sub>3</sub> CN	From 100% A to 5% A in 2.10 min, to 0% A in 0.90 min, to 5% A in 0.5 min	0.7 mL/min ----- 55°C	3.5
LC-C	Waters: Acquity® UPLC® - DAD-Quattro Micro™	Waters: BEH C18 (1.7 µm, 2.1x100mm)	A: CH <sub>3</sub> COONH <sub>4</sub> 7mM 95%/ CH <sub>3</sub> CN 5%, B: CH <sub>3</sub> CN	84.2% A for 0.49 min, to 10.5% A in 2.18 min, held for 1.94 min, back to 84.2% A in 0.73 min, held for 0.73 min.	0.343 mL/min ----- 40°C	6.2
LC-D	Waters: Acquity® H-Class - DAD and SQD2™	Waters BEH® C18 (1.7 µm, 2.1x100mm)	A: CH <sub>3</sub> COONH <sub>4</sub> 7mM 95%/ CH <sub>3</sub> CN 5%, B: CH <sub>3</sub> CN	84.2% A/15.8% B to 10.5% A in 2.18 min, held for 1.96 min, back to 84.2% A/15.8% B in 0.73 min, held for 0.49 min.	0.343 mL/min ----- 40°C	6.1

**SFC/MS methods**

- The SFC measurement was performed using an Analytical Supercritical fluid chromatography (SFC) system composed by a binary pump for delivering carbon dioxide (CO<sub>2</sub>) and modifier, an autosampler, a column oven, a diode array detector equipped with a high-pressure flow cell standing up to 400 bars. If configured with a Mass Spectrometer (MS) the flow from the column was brought to the (MS). It is within the knowledge of the skilled person to set the tune parameters (e.g. scanning range, dwell time...) in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW).
- Data acquisition was performed with appropriate software.

Analytical SFC/MS Methods (Flow expressed in mL/min; column temperature (T) in °C; Run time in minutes, Backpressure (BPR) in bars.

Method code	column	mobile phase	gradient	Flow ----- Col T	Run time ----- BPR
SFC-A	Daicel Chiralpak® OD3 column (3.0 µm, 150 x 4.6 mm)	A:CO <sub>2</sub> B:EtOH (+0.2% iPrNH <sub>2</sub> )	25% B hold 6 min, to 50% in 1 min hold 2.5 min	2.5 ----- 40	9.5 ----- 110
SFC-B	Daicel Chiralpak® AD3 column (3.0 µm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH (+0.2% iPrNH <sub>2</sub> +3%H <sub>2</sub> O)	10%-50% B in 6 min, hold 3.5 min	2.5 ----- 40	9.5 ----- 110
SFC-C	Daicel Chiralpak® AD3 column (3.0 µm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: iPrOH (+0.2% iPrNH <sub>2</sub> )	10%-50% B in 6 min, hold 3.5 min	2.5 ----- 40	9.5 ----- 110
SFC-D	Daicel Chiralpak® OD3 column (3.0 µm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH (+0.2% iPrNH <sub>2</sub> )	10%-50% B in 6 min, hold 3.5 min	2.5 ----- 40	9.5 ----- 110
SFC-E	Daicel Chiralpak® AD3 column (3.0 µm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH (+0.2% iPrNH <sub>2</sub> )	10%-50% B in 6 min, hold 3.5 min	2.5 ----- 40	9.5 ----- 110
SFC-F	Daicel Chiralcel® OJ-H column (5 µm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: MeOH	30% B hold 7 min,	3 ----- 35	7 ----- 100

Method code	column	mobile phase	gradient	Flow ----- Col T	Run time ----- BPR
SFC-G	Daicel Chiralcel® OD-3 column (3 µm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: iPrOH	40% B hold 3 min,	3.5 ----- 35	3 ----- 103
SFC-H	Daicel Chiralcel® OD-3 column (3 µm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: MeOH	40% B hold 3 min,	3.5 ----- 35	3 ----- 103
SFC-I	Daicel Chiralcel® OD-3 column (3 µm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH	40% B hold 3 to 6 min,	3.5 ----- 35	3 to 6 ----- 103
SFC-J	Regis Whelk O1, S,S column (3 µm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: MeOH	40% B hold 3 min,	3.5 ----- 35	3 ----- 103
SFC-K	Daicel Chiralcel® OD-H column (5 µm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: iPrOH (+0.3% iPrNH <sub>2</sub> )	35% B hold 7 min,	3 ----- 35	7 ----- 100
SFC-L	Daicel Chiralcel® AD-3 column (3 µm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH	45% B hold 3 min,	3.5 ----- 35	3 ----- 103
SFC-M	Daicel Chiralcel® OD-H column (5 µm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: MeOH	40% B hold 7 min,	3 ----- 35	7 ----- 100
SFC-N	Daicel Chiralpak® AD-3 column (3 µm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH (+0.3% iPrNH <sub>2</sub> )	15% B hold 10 min,	3.5 ----- 35	10 ----- 103
SFC-O	Phenomenex Luxcellulose-2 column (3 µm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: MeOH	25% B hold 3 min,	3.5 ----- 35	3 ----- 103
SFC-P	Daicel Chiralcel® OD-3 column (3 µm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: MeOH	30% B hold 3 min,	3.5 ----- 35	3 ----- 103



Method code	column	mobile phase	gradient	Flow ----- Col T	Run time ----- BPR
SFC-Q	Daicel Chiralcel® AD-3 column (3 µm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: iPrOH (+0.3% iPrNH <sub>2</sub> )	60% B hold 3 min,	3.5 ----- 35	3 ----- 103
SFC-R	Daicel Chiralcel® OD-3 column (3 µm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH	50% B hold 3 to 6 min,	3.5 ----- 35	3 to 6 ----- 103
SFC-S	Daicel Chiralcel® OD-H column (5 µm, 150 x 4.6 mm)	A:CO <sub>2</sub> B: EtOH (+0.3% iPrNH <sub>2</sub> )	50% B hold 7 min,	3 ----- 35	7 ----- 100
SFC-T	Regis Whelk O1, S,S column (3 µm, 100 x 4.6 mm)	A:CO <sub>2</sub> B: MeOH	50% B hold 3 min,	3.5 ----- 35	3 ----- 103

### **Melting Points**

Values are either peak values or melt ranges, and are obtained with experimental uncertainties that are commonly associated with this analytical method.

5

### **DSC823e (indicated as DSC)**

For a number of compounds, melting points were determined with a DSC823e (Mettler-Toledo). Melting points were measured with a temperature gradient of 10°C/minute. Maximum temperature was 300°C.

10

### **Optical Rotations:**

Optical rotations were measured on a Perkin-Elmer 341 polarimeter with a sodium lamp and reported as follows:  $[\alpha]^{\circ}(\lambda, c \text{ g}/100\text{ml}, \text{solvent}, T^{\circ}\text{C})$ .

$[\alpha]_{\lambda}^T = (100\alpha) / (l \times c)$  : where  $l$  is the path length in dm and  $c$  is the concentration in g/100 ml for a sample at a temperature  $T$  (°C) and a wavelength  $\lambda$  (in nm). If the wavelength of light used is 589 nm (the sodium D line), then the symbol D might be used instead. The sign of the rotation (+ or -) should always be given. When using this equation the concentration and solvent are always provided in parentheses after the rotation. The rotation is reported using degrees and no units of concentration are given (it is assumed to be g/100 ml).

20

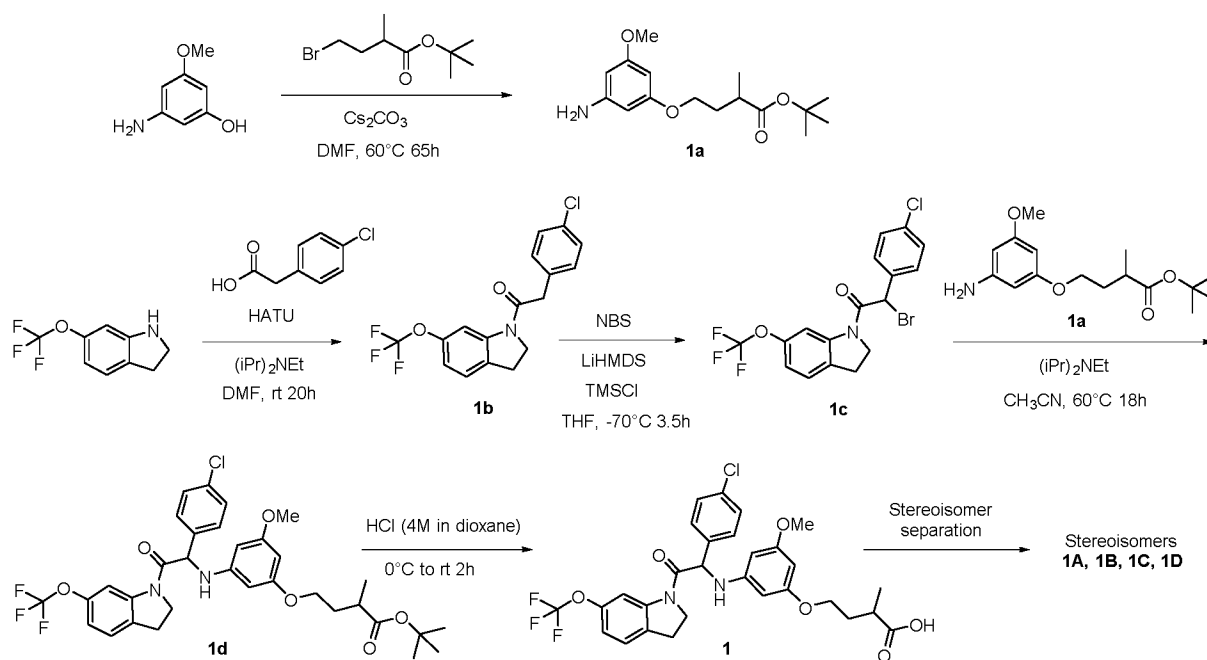
Stereochemistry note: In the below examples, the stereochemistry indications \*R and \*S refer to a pure but unknown stereochemistry of the chiral centers.

**Abbreviations used in experimental part**

(M+H) <sup>+</sup> MH <sup>+</sup>	protonated molecular ion	iPrNH <sub>2</sub>	isopropylamine
aq.	aqueous	iPrOH	2-propanol
Boc	<i>tert</i> -butyloxycarbonyl	K <sub>2</sub> CO <sub>3</sub>	potassium carbonate
Boc <sub>2</sub> O	di- <i>tert</i> -butyl dicarbonate	KNO <sub>3</sub>	potassium nitrate
br	broad	LiAlH <sub>4</sub>	lithium aluminium hydride
CH <sub>3</sub> CN	acetonitrile	m/z	mass-to-charge ratio
CHCl <sub>3</sub>	chloroform	Me	methyl
CH <sub>2</sub> Cl <sub>2</sub>	dichloromethane	MeOH	methanol
CH <sub>3</sub> OH	methanol	MgSO <sub>4</sub>	magnesium sulfate
CO <sub>2</sub>	carbon dioxide	min	minute(s)
CsCO <sub>3</sub>	cesium carbonate	MTBE	methyl- <i>tert</i> -butylether
d	doublet	N <sub>2</sub>	nitrogen
DCM	dichloromethane	Na <sub>2</sub> CO <sub>3</sub>	sodium carbonate
DIEA	diisopropylethylamine	Na <sub>2</sub> SO <sub>4</sub>	sodium sulfate
DIPE	diisopropyl ether	NaBH <sub>4</sub>	sodium borohydride
DMA	dimethylacetamide	NaCl	sodium chloride
DMAP	4-dimethylaminopyridine	NaHCO <sub>3</sub>	sodium bicarbonate
DME	1,2-dimethoxyethane	NaOH	sodium hydroxide
DMF	dimethylformamide	NH <sub>4</sub> Cl	ammonium chloride
DMSO	dimethyl sulfoxide	NH <sub>4</sub> HCO <sub>3</sub>	ammonium bicarbonate
EDCI	1-ethyl-3-(3-dimethylamino-propyl)carbodiimide	NMP	N-methylpyrrolidon
eq.	equivalent	q	quartet
Et <sub>2</sub> O	diethyl ether	rt or RT	room temperature
Et <sub>3</sub> N	triethylamine	SEMCI	2-(trimethylsilyl)ethoxymethyl chloride
EtOAc	ethyl acetate	s	singlet
EtOH	ethanol	t	triplet
H <sub>2</sub>	hydrogen	tBuOK	potassium <i>tert</i> -butanolaat
HNO <sub>3</sub>	nitric acid	TEA	triethylamine
H <sub>2</sub> O	water	TFA	trifluoroacetic acid
H <sub>2</sub> SO <sub>4</sub>	sulfuric acid	THF	tetrahydrofuran
HATU	O-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate - CAS [148893-10-1]	2-Me-THF	2-methyltetrahydrofuran

HCl	hydrochloric acid	TMSCl	trimethylsilyl chloride
HPLC	high performance liquid chromatography	TMSCF <sub>3</sub>	trifluoromethyltrimethylsilane

**Example 1** : synthesis of 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2-methylbutanoic acid (Compound **1**) and separation into Stereoisomers **1A**, **1B**, **1C** and **1D**



### Synthesis of intermediate 1a:

To a stirred solution of *tert*-butyl 4-bromo-2-methylbutanoate [CAS 1210410-44-8] (1.0 g, 4.22 mmol) in DMF (15 mL) was added 3-amino-5-methoxyphenol [CAS 162155-27-3] (587 mg, 4.22 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (2.75 g, 8.43 mmol). The reaction was stirred at 60°C for 65 h, and allowed to reach room temperature. The mixture was poured out into H<sub>2</sub>O (100 mL). The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 times). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (50 g) using a gradient of heptane/EtOAc from 100/0 to 50/50. The desired fractions were combined, evaporated under reduced pressure and co-evaporated with CH<sub>3</sub>CN, yielding *tert*-butyl 4-(3-amino-5-methoxyphenoxy)-2-methylbutanoate **1a** (440 mg).

### Synthesis of intermediate 1b:

A mixture of 6-(trifluoromethoxy)indoline [CAS 959235-95-1] (5 g, 24.6 mmol), 2-(4-chlorophenyl)acetic acid [CAS 1878-66-6] (4.2 g, 24.6 mmol), HATU (14.3 g,

36.9 mmol) and diisopropylethylamine (12.2 mL, 73.8 mmol) in DMF (60 mL) was stirred at room temperature for 20 h. The mixture was poured out slowly into stirring H<sub>2</sub>O (275 mL) and the resulting suspension was stirred for 50 minutes. The solids were filtered off and washed (4x) with H<sub>2</sub>O. The solid residue was taken up in toluene (125 mL), filtered over a paper filter, and the filtrate was evaporated under reduced pressure. The solid residue was stirred up in Et<sub>2</sub>O/heptane 2/1 (30 mL), filtered off, washed (3x) with Et<sub>2</sub>O/heptane 1/1, and dried under vacuum at 50°C to provide 2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1b** (7.33 g).

#### Synthesis of intermediate 1c:

At -70°C, under N<sub>2</sub> flow, LiHMDS 1M in THF (41.2 mL, 41.2 mmol) was added dropwise to a solution of 2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1b** (7.33 g, 20.6 mmol) in 2-Me-THF (300 mL). The mixture was stirred for 50 min at -70°C and trimethylsilyl chloride (4.21 mL, 33.0 mmol) was slowly added. Stirring was continued at -70°C for 35 min and a solution of *N*-bromosuccinimide (4.03 g, 22.7 mmol) in THF (40 mL) and 2-Me-THF (60 mL) was added dropwise. After stirring for 3.5 h at -70°C, the reaction was quenched with a saturated solution of NH<sub>4</sub>Cl (300 mL). The mixture was allowed to reach room temperature. Water (50 mL) and brine (50 mL) were added. The mixture was extracted with diisopropyl ether (150 mL). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered, the solvent was evaporated under reduced pressure and co-evaporated with CH<sub>3</sub>CN to give 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (7.87 g).

#### Synthesis of intermediate 1d:

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (850 mg, 1.96 mmol), *tert*-butyl 4-(3-amino-5-methoxyphenoxy)-2-methylbutanoate **1a** (620 mg, 2.10 mmol) and diisopropylethylamine (506 µL, 2.93 mmol) in CH<sub>3</sub>CN (30 mL) was stirred at 60°C for 18 h. The mixture was allowed to reach room temperature, and was poured out into water (125 mL). The product was extracted (2x) with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered off, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (12 g) using a gradient of heptane/EtOAc/EtOH 100/0/0 to 40/45/15. The desired fractions were combined and evaporated under reduced pressure, and co-evaporated with dioxane to provide *tert*-butyl 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2-methylbutanoate **1d** (1.27 g).

**Synthesis of Compound 1 and separation into Stereoisomers 1A, 1B, 1C and 1D:**

A cooled (ice-bath) solution of *tert*-butyl 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2-methylbutanoate **1d** (1.27 g, 1.96 mmol) in 4M HCl in dioxane (9 mL) was stirred at 0°C for 20 min and at room temperature for 2 h. The precipitate was filtered off, washed (3x) with dioxane and the solid was air-dried to afford 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2-methylbutanoic acid as an HCl salt (Compound **1**, 900 mg).

The 4 stereoisomers of Compound **1** (900 mg) were separated via preparative chiral SFC (Stationary phase: Chiralpak<sup>®</sup> Diacel AD 20 x 250 mm, mobile phase: CO<sub>2</sub>, *i*PrOH + 0.4% *i*PrNH<sub>2</sub>). The product fractions were combined and evaporated under reduced pressure. The stereoisomers in the product fractions of the first two eluted peaks were not completely separated and required further separation via preparative chiral SFC (Stationary phase: Chiralpak<sup>®</sup> Diacel AD 20 x 250 mm, mobile phase: CO<sub>2</sub>, EtOH + 0.4% *i*PrNH<sub>2</sub>). The product fractions were combined and evaporated under reduced pressure.

The first eluted stereoisomer was purified by flash chromatography on silica gel (12 g) with heptane/EtOAc/EtOH/HOAc gradient 100/0/0/0 to 40/45/14.7/0.3. The desired fractions were combined and evaporated under reduced pressure, and co-evaporated with CH<sub>3</sub>CN. The product was lyophilized from a solvent mixture of CH<sub>3</sub>CN (2 mL) and H<sub>2</sub>O (1.2 mL) to provide Stereoisomer **1A** (63 mg).

The second eluted stereoisomer was purified by flash chromatography on silica gel (12 g) with heptane/EtOAc/EtOH/HOAc gradient 100/0/0/0 to 40/45/14.7/0.3. The desired fractions were combined and evaporated, and co-evaporated with CH<sub>3</sub>CN. The product was lyophilized from a solvent mixture of CH<sub>3</sub>CN (2 mL) and H<sub>2</sub>O (1.2 mL) to provide Stereoisomer **1B** (79 mg).

The third eluted stereoisomer was purified via preparative HPLC (Stationary phase: RP XBridge<sup>®</sup> Prep C18 OBD – 10 μm, 30 x 150 mm, mobile phase: 0.25% NH<sub>4</sub>HCO<sub>3</sub> solution in water, CH<sub>3</sub>CN). The desired fractions were combined and the organic volatiles were evaporated under reduced pressure. The residue was mixed with EtOAc (25 mL) and 1N HCl (0.5 mL). After stirring for 10 min, the layers were separated. The organic layer was isolated, washed with brine, dried over MgSO<sub>4</sub>, filtered, evaporated under reduced pressure, and co-evaporated with

CH<sub>3</sub>CN. The residue was lyophilized from a solvent mixture of CH<sub>3</sub>CN (1.5 mL) and H<sub>2</sub>O (0.75 mL) to provide Stereoisomer **1C** (62 mg).

5 The fourth eluted stereoisomer was purified by flash chromatography on silica gel (12 g) with heptane/EtOAc/EtOH/HOAc gradient 100/0/0/0 to 40/45/14.7/0.3. The desired fractions were combined and evaporated under reduced pressure, and co-evaporated with CH<sub>3</sub>CN. The product was lyophilized from a solvent mixture of CH<sub>3</sub>CN (2 mL) and H<sub>2</sub>O (1.2 mL) to provide Stereoisomer **1D** (105 mg)

10 **Compound 1:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.10 (dd, *J*=7.0, 1.3 Hz, 3 H) 1.69 (dq, *J*=13.6, 6.7 Hz, 1 H) 1.91 - 2.01 (m, 1 H) 2.43 - 2.48 (m, 1 H) 3.07 - 3.26 (m, 2 H) 3.61 (s, 3 H) 3.85 (br t, *J*=6.5 Hz, 2 H) 4.04 (td, *J*=10.3, 7.2 Hz, 1 H) 4.52 (td, *J*=10.2, 6.4 Hz, 1 H) 5.56 (d, *J*=8.8 Hz, 1 H) 5.75 (t, *J*=2.0 Hz, 1 H) 5.89 - 5.98 (m, 15 2 H) 6.43 (d, *J*=8.6 Hz, 1 H) 7.01 (dd, *J*=8.3, 1.4 Hz, 1 H) 7.33 (d, *J*=8.4 Hz, 1 H) 7.40 - 7.47 (m, 2 H) 7.51 - 7.58 (m, 2 H) 8.03 (s, 1 H) 12.16 (br s, 1 H)  
LC/MS (method LC-A): R<sub>t</sub> 1.14 min, MH<sup>+</sup> 593

**Stereoisomer 1A:**

20 <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.10 (d, *J*=7.0 Hz, 3 H) 1.69 (dq, *J*=13.5, 6.6 Hz, 1 H) 1.91 - 2.01 (m, 1 H) 2.46 - 2.48 (m, 1 H) 3.08 - 3.27 (m, 2 H) 3.61 (s, 3 H) 3.85 (t, *J*=6.6 Hz, 2 H) 4.04 (td, *J*=10.3, 6.9 Hz, 1 H) 4.45 - 4.57 (m, 1 H) 5.55 (d, *J*=8.8 Hz, 1 H) 5.75 (t, *J*=2.0 Hz, 1 H) 5.92 - 5.96 (m, 2 H) 6.43 (d, *J*=8.8 Hz, 1 H) 7.01 (dd, *J*=8.3, 1.7 Hz, 1 H) 7.33 (d, *J*=8.4 Hz, 1 H) 7.40 - 7.46 (m, 2 H) 7.55 (d, 25 *J*=8.6 Hz, 2 H) 8.03 (s, 1 H) 12.16 (br s, 1 H)  
LC/MS (method LC-A): R<sub>t</sub> 1.15 min, MH<sup>+</sup> 593  
[α]<sub>D</sub><sup>20</sup>: -37.6° (c 0.415, DMF)  
Chiral SFC (method SFC-A): R<sub>t</sub> 3.52 min, MH<sup>+</sup> 593 chiral purity 100%.

30 **Stereoisomer 1B:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.09 (d, *J*=7.0 Hz, 3 H) 1.69 (dq, *J*=13.6, 6.6 Hz, 1 H) 1.91 - 2.01 (m, 1 H) 2.44 - 2.48 (m, 1 H) 3.08 - 3.27 (m, 2 H) 3.61 (s, 3 H) 3.79 - 3.90 (m, 2 H) 4.04 (td, *J*=10.4, 7.2 Hz, 1 H) 4.52 (td, *J*=10.2, 6.6 Hz, 1 H) 5.55 (d, *J*=8.8 Hz, 1 H) 5.75 (t, *J*=2.0 Hz, 1 H) 5.92 - 5.97 (m, 2 H) 6.43 (d, *J*=8.8 Hz, 1 H) 7.01 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.33 (d, *J*=8.1 Hz, 1 H) 7.44 (d, *J*=7.8 Hz, 2 H) 7.55 (d, *J*=7.2 Hz, 2 H) 8.03 (s, 1 H) 12.16 (br s, 1 H) 35  
LC/MS (method LC-A): R<sub>t</sub> 1.15 min, MH<sup>+</sup> 593  
[α]<sub>D</sub><sup>20</sup>: -65.3° (c 0.455, DMF)  
Chiral SFC (method SFC-A): R<sub>t</sub> 4.15 min, MH<sup>+</sup> 593 chiral purity 97.1%.

**Stereoisomer 1C:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.11 (d, *J*=7.0 Hz, 3 H) 1.70 (dq, *J*=13.5, 6.5 Hz, 1 H) 1.90 - 2.03 (m, 1 H) 2.44 - 2.49 (m, 1 H) 3.07 - 3.25 (m, 2 H) 3.62 (s, 3 H) 3.86 (t, *J*=6.6 Hz, 2 H) 3.98 - 4.11 (m, 1 H) 4.46 - 4.57 (m, 1 H) 5.56 (d, *J*=8.6 Hz, 1 H) 5.76 (t, *J*=2.1 Hz, 1 H) 5.90 - 5.99 (m, 2 H) 6.44 (d, *J*=8.8 Hz, 1 H) 7.01 (dd, *J*=7.9, 1.8 Hz, 1 H) 7.34 (d, *J*=8.4 Hz, 1 H) 7.44 (d, *J*=8.4 Hz, 2 H) 7.55 (d, *J*=7.8 Hz, 2 H) 8.04 (s, 1 H) 12.18 (br s, 1 H)

LC/MS (method LC-A): R<sub>t</sub> 1.15 min, MH<sup>+</sup> 593

[α]<sub>D</sub><sup>20</sup>: +35.2° (c 0.455, DMF)

Chiral SFC (method SFC-A): R<sub>t</sub> 2.84 min, MH<sup>+</sup> 593 chiral purity 99.3%.

**Stereoisomer 1D:**

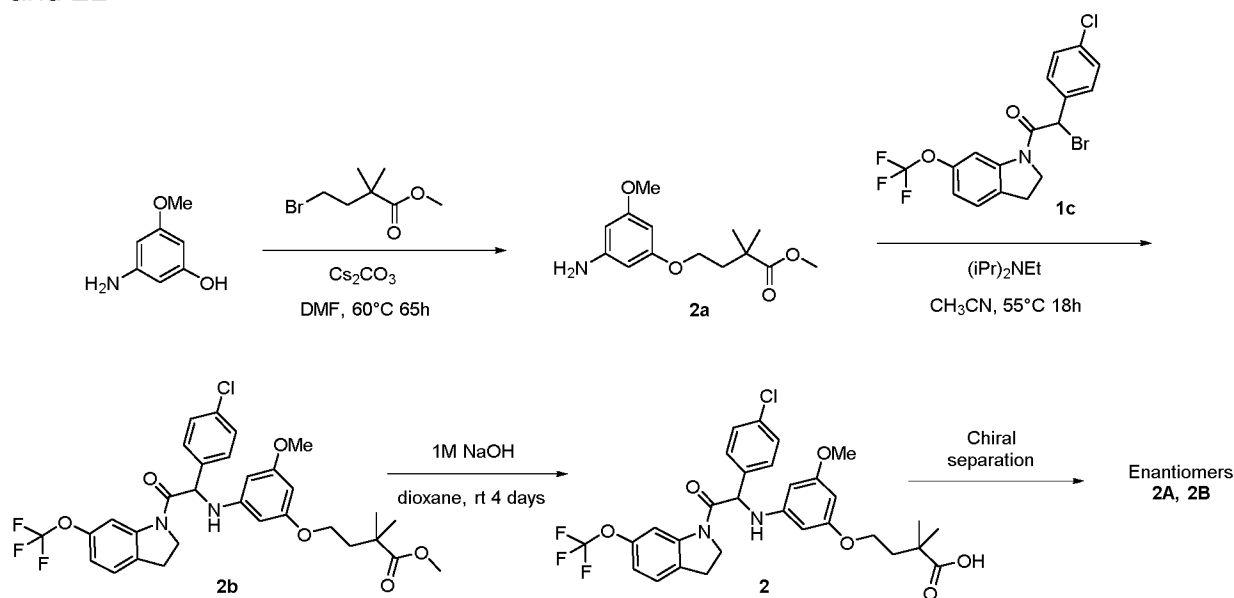
<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.10 (d, *J*=7.0 Hz, 3 H) 1.70 (dq, *J*=13.5, 6.6 Hz, 1 H) 1.92 - 2.02 (m, 1 H) 2.46 - 2.49 (m, 1 H) 3.09 - 3.29 (m, 2 H) 3.62 (s, 3 H) 3.80 - 3.92 (m, 2 H) 4.05 (td, *J*=10.5, 7.0 Hz, 1 H) 4.53 (td, *J*=10.4, 6.5 Hz, 1 H) 5.56 (d, *J*=8.8 Hz, 1 H) 5.76 (t, *J*=2.0 Hz, 1 H) 5.93 - 5.97 (m, 2 H) 6.44 (d, *J*=8.6 Hz, 1 H) 7.01 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.34 (d, *J*=8.1 Hz, 1 H) 7.40 - 7.47 (m, 2 H) 7.56 (d, *J*=8.4 Hz, 2 H) 8.04 (s, 1 H) 12.17 (br s, 1 H)

LC/MS (method LC-A): R<sub>t</sub> 1.15 min, MH<sup>+</sup> 593

[α]<sub>D</sub><sup>20</sup>: +64.3° (c 0.42, DMF)

Chiral SFC (method SFC-A): R<sub>t</sub> 2.65 min, MH<sup>+</sup> 593 chiral purity 98.1%.

**Example 2** : synthesis of 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2,2-dimethylbutanoic acid (Compound **2**) and chiral separation into Enantiomers **2A** and **2B**

**Synthesis of intermediate 2a:**

To a stirred solution of methyl 4-bromo-2,2-dimethylbutanoate [CAS 4833-99-2] (2.5 g, 12 mmol) in DMF (35 mL) was added 3-amino-5-methoxyphenol [CAS 162155-27-3] (1.66 g, 12 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (7.79 g, 23.9 mmol). The reaction was stirred at 60°C for 65 h, and allowed to reach room temperature. The mixture was poured out into H<sub>2</sub>O (150 mL). The product was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried over MgSO<sub>4</sub>, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (25 g) using a gradient of heptane/CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100/0/0 to 0/100/0 to 0/99/1. The desired fractions were combined, evaporated under reduced pressure and co-evaporated with toluene. The solids were dried under vacuum at 50°C to provide methyl 4-(3-amino-5-methoxyphenoxy)-2,2-dimethylbutanoate **2a** (440 mg).

#### Synthesis of intermediate 2b:

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (1.57 g, 3.61 mmol), methyl 4-(3-amino-5-methoxyphenoxy)-2,2-dimethylbutanoate **2a** (970 mg, 3.63 mmol) and diisopropylethylamine (961 µL, 5.58 mmol) in CH<sub>3</sub>CN (25 mL) was stirred at 55°C for 18 h. The mixture was allowed to reach room temperature, and poured out into water (125 mL). The product was extracted (2x) with Et<sub>2</sub>O. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (40 g) using a gradient of heptane/EtOAc/EtOH 100/0/0 to 40/45/15. The desired fractions were combined and evaporated under reduced pressure, and co-evaporated with dioxane to provide methyl 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2-methylbutanoate **2b** (2.24 g).

#### Synthesis of Compound 2 and separation into Enantiomers 2A and 2B:

1M NaOH in water (9 mL, 9 mmol) was added to a stirring solution of methyl 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2-methylbutanoate **2b** (2.24 g, 3.61 mmol) in dioxane (15 mL). The reaction mixture was stirred at room temperature for 4 days. 1N HCl (10 mL) was added slowly. After stirring for 20 min, the product was extracted with Et<sub>2</sub>O. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. The residue (2.9 g) was purified by flash chromatography on silica gel (80 g) with heptane/EtOAc/EtOH/HOAc gradient 100/0/0/0 to 40/45/14.7/0.3. The desired fractions were combined, evaporated under reduced pressure, and co-evaporated with diisopropyl ether. The residue (1.6 g) was



further purified via preparative HPLC (Stationary phase: RP XBridge<sup>®</sup> Prep C18 OBD – 10  $\mu$ m, 50 x 150 mm, mobile phase: 0.5% NH<sub>4</sub>Ac solution in water + 10% CH<sub>3</sub>CN, MeOH). The product fractions were combined, and the organic volatiles were evaporated under reduced pressure. The residue was partitioned between 2-  
5 Me-THF (300 mL) and brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated under reduced pressure. The residue was further purified by flash chromatography on silica gel (12 g) with heptane/EtOAc/EtOH/HOAc gradient 100/0/0/0 to 0/75/24.5/0.5 to 40/45/14.7/0.3. The product fractions were combined and evaporated under reduced pressure. The foamy solid was dried under  
10 vacuum at 45°C to provide 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2,2-dimethylbutanoic acid (Compound **2**, 0.97 g) as a racemic mixture.

The enantiomers of Compound **2** (800 mg) were separated via preparative chiral SFC (Stationary phase: Chiralpak<sup>®</sup> Diacel AD 20 x 250 mm, mobile phase: CO<sub>2</sub>,  
15 EtOH + 0.4% iPrNH<sub>2</sub>). The product fractions were combined and evaporated under reduced pressure. The first eluted product was mixed with EtOAc (15 mL), water (5 mL) and 1N HCl (1 mL). After stirring for 15 minutes, the layers were separated. The organic layer was dried over MgSO<sub>4</sub>, filtered, evaporated under reduced  
20 pressure, and co-evaporated with MeOH. The residue was triturated with water (4 mL) and MeOH (1.5 mL) while cooling on an ice-bath. The solids were filtered off, washed (4x) with H<sub>2</sub>O/MeOH 4/1, and dried under vacuum at 45°C to provide Enantiomer **2A** (292 mg). The second eluted product was mixed with EtOAc (15 mL), water (5 mL) and 1N HCl (1 mL). After stirring for 30 minutes, the layers were separated. The organic layer was dried over MgSO<sub>4</sub>, filtered, evaporated under  
25 reduced pressure, and co-evaporated with MeOH. The residue was triturated with water (4 mL) and MeOH (1.5 mL) while cooling on an ice-bath. The solids were filtered off, washed (4x) with H<sub>2</sub>O/MeOH 2/1, and dried under vacuum at 45°C to provide Enantiomer **2B** (342 mg).

30 **Compound 2:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.13 (d, *J*=2.6 Hz, 6 H) 1.87 (t, *J*=7.2 Hz, 2 H) 3.08 - 3.27 (m, 2 H) 3.61 (s, 3 H) 3.85 (t, *J*=7.2 Hz, 2 H) 4.04 (td, *J*=10.4, 7.2 Hz, 1 H) 4.52 (td, *J*=10.2, 6.2 Hz, 1 H) 5.54 (d, *J*=8.8 Hz, 1 H) 5.74 (t, *J*=2.0 Hz, 1 H) 5.90 - 5.96 (m, 2 H) 6.43 (d, *J*=8.6 Hz, 1 H) 7.01 (dd, *J*=8.3, 1.4 Hz, 1 H) 7.33  
35 (d, *J*=8.1 Hz, 1 H) 7.39 - 7.48 (m, 2 H) 7.50 - 7.60 (m, 2 H) 8.03 (s, 1 H) 12.19 (br s, 1 H)

LC/MS (method LC-A): R<sub>t</sub> 1.22 min, MH<sup>+</sup> 607

**Enantiomer 2A:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.13 (d, *J*=2.6 Hz, 6 H) 1.87 (t, *J*=7.3 Hz, 2 H) 3.08 - 3.27 (m, 2 H) 3.61 (s, 3 H) 3.85 (t, *J*=7.2 Hz, 2 H) 3.97 - 4.12 (m, 1 H) 4.52 (td, *J*=10.3, 6.5 Hz, 1 H) 5.54 (d, *J*=8.6 Hz, 1 H) 5.74 (t, *J*=2.1 Hz, 1 H) 5.90 - 5.96 (m, 2 H) 6.43 (d, *J*=8.6 Hz, 1 H) 7.01 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.33 (d, *J*=8.1 Hz, 1 H) 7.39 - 7.49 (m, 2 H) 7.55 (d, *J*=8.6 Hz, 2 H) 8.03 (s, 1 H) 12.20 (br s, 1 H)  
LC/MS (method LC-A): R<sub>t</sub> 1.23 min, MH<sup>+</sup> 607

[α]<sub>D</sub><sup>20</sup>: +49.6° (c 0.56, DMF)

Chiral SFC (method SFC-B): R<sub>t</sub> 6.47 min, MH<sup>+</sup> 607 chiral purity 100%.

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**Enantiomer 2B:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.13 (d, *J*=2.6 Hz, 6 H) 1.87 (t, *J*=7.2 Hz, 2 H) 3.08 - 3.28 (m, 2 H) 3.61 (s, 3 H) 3.85 (t, *J*=7.2 Hz, 2 H) 4.04 (td, *J*=10.3, 7.3 Hz, 1 H) 4.52 (td, *J*=10.3, 6.5 Hz, 1 H) 5.54 (d, *J*=8.8 Hz, 1 H) 5.74 (t, *J*=2.0 Hz, 1 H) 5.90 - 5.96 (m, 2 H) 6.43 (d, *J*=8.6 Hz, 1 H) 7.01 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.33 (d, *J*=8.1 Hz, 1 H) 7.41 - 7.46 (m, 2 H) 7.55 (m, *J*=8.6 Hz, 2 H) 8.03 (s, 1 H) 12.20 (br s, 1 H)

LC/MS (method LC-A): R<sub>t</sub> 1.23 min, MH<sup>+</sup> 607

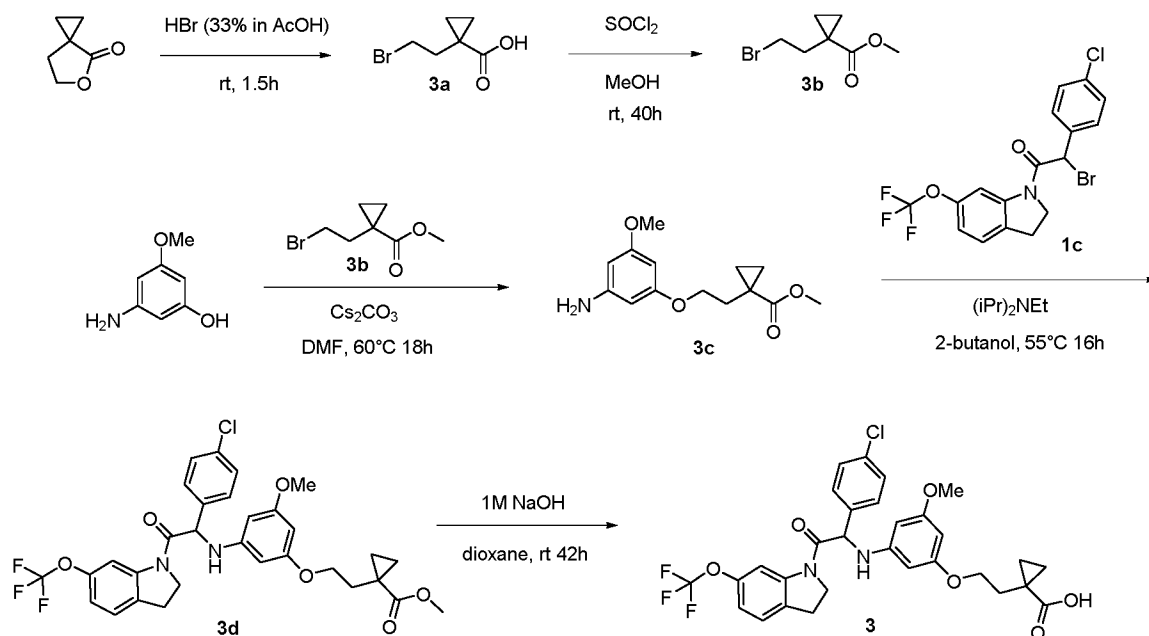
[α]<sub>D</sub><sup>20</sup>: -49.2° (c 0.445, DMF)

Chiral SFC (method SFC-B): R<sub>t</sub> 7.18 min, MH<sup>+</sup> 607 chiral purity 98.8%.

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**Example 3** : synthesis of 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2,2-dimethylbutanoic acid (Compound **3**)

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**Synthesis of intermediate 3a:**

5-Oxaspiro[2.4]heptan-4-one (930 mg, 8.29 mmol) was mixed with a solution of 33% HBr in AcOH (8 mL). The reaction mixture was stirred at room temperature for 1.5 h, and poured out into ice-water (50 mL). After stirring for 10 min, the product was filtered off, washed (5x) with water and dried under vacuum at 45°C to provide 1-(2-bromoethyl)cyclopropane-1-carboxylic acid **3a** (753 mg).

**Synthesis of intermediate 3b:**

A solution of 1-(2-bromoethyl)cyclopropane-1-carboxylic acid **3a** (540 mg, 2.8 mmol) in MeOH (11 mL) was stirred under N<sub>2</sub>-atm while cooling on an ice-bath. Thionyl chloride (304 µL, 4.2 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 40 h. The solvents were evaporated under reduced pressure, and co-evaporated with CH<sub>3</sub>CN to provide methyl 1-(2-bromoethyl)cyclopropane-1-carboxylate **3b** (380 mg).

**Synthesis of intermediate 3c:**

To a stirred solution of methyl 1-(2-bromoethyl)cyclopropane-1-carboxylate **3b** (380 mg, 1.84 mmol) in DMF (10 mL) was added 3-amino-5-methoxyphenol [CAS 162155-27-3] (250 mg, 1.80 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.17 g, 3.59 mmol). The reaction was stirred at 60°C for 18 h, and allowed to reach room temperature. The mixture was poured out into H<sub>2</sub>O (60 mL). The product was extracted (2x) with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was evaporated under reduced pressure and co-evaporated with toluene. The residue was purified by flash chromatography on silica gel (12 g) using a gradient of heptane/CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100/0/0 to 0/100/0 to 0/99/1. The product fractions were combined, evaporated under reduced pressure and co-evaporated with CH<sub>3</sub>CN to provide methyl 1-(2-(3-amino-5-methoxyphenoxy)ethyl)cyclopropane-1-carboxylate **3c** (220 mg).

**Synthesis of intermediate 3d:**

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (320 mg, 0.736 mmol), methyl 1-(2-(3-amino-5-methoxyphenoxy)ethyl)cyclopropane-1-carboxylate **3c** (220 mg, 0.829 mmol) and diisopropylethylamine (254 µL, 1.47 mmol) in 2-butanol (7.5 mL) was stirred at 55°C for 16 h. The mixture was allowed to reach room temperature, and poured out into water (25 mL). The product was extracted (2x) with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on

silica gel (12 g) using a gradient of heptane/EtOAc/EtOH 100/0/0 to 60/30/10. The product fractions were combined and evaporated under reduced pressure, and co-evaporated with dioxane to provide methyl 1-(2-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)ethyl)cyclopropane-1-carboxylate **3d** (456 mg).

### Synthesis of Compound 3:

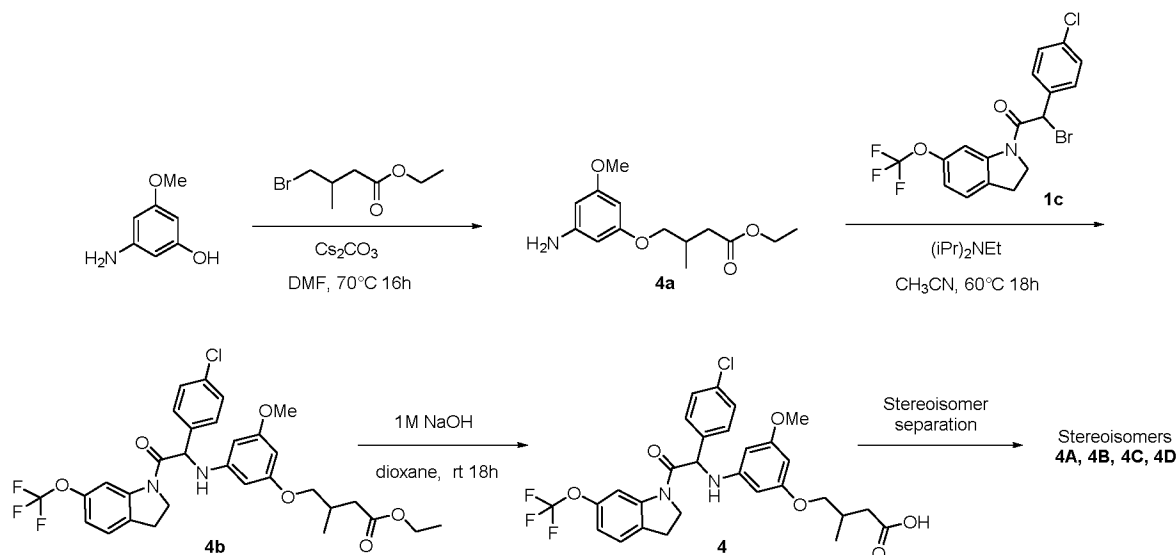
1M NaOH in water (1.84 mL, 1.84 mmol) was added to a stirring solution of methyl 1-(2-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)ethyl)cyclopropane-1-carboxylate **3d** (0.456 mg, 0.737 mmol) in dioxane (3 mL). The reaction mixture was stirred at room temperature under N<sub>2</sub>-atm for 42 h. Water (15 mL) and 1N HCl (2 mL) were added. After stirring for 10 min, the product was filtered off, washed (3x) with water and dried under vacuum at 45°C. The residue was purified via preparative HPLC (Stationary phase: RP XBridge<sup>®</sup> Prep C18 OBD – 10 μm, 30 x 150 mm, mobile phase: 0.25% NH<sub>4</sub>HCO<sub>3</sub> solution in water, CH<sub>3</sub>CN). The product fractions were combined and the organic solvents were evaporated. The remaining aqueous solution was extracted (2x) with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, evaporated under reduced pressure, and co-evaporated with MeOH. The resulting foam was stirred up in H<sub>2</sub>O/MeOH 3/1 (4 mL), filtered off, washed (3x) with H<sub>2</sub>O/MeOH 3/1, and dried under vacuum at 45°C to provide 1-(2-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)ethyl)cyclopropane-1-carboxylic acid (Compound **3**, 255 mg) as a racemic mixture.

### Compound 3:

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.73 - 0.84 (m, 2 H) 1.00 - 1.11 (m, 2 H) 1.81 - 1.91 (m, 2 H) 3.07 - 3.26 (m, 2 H) 3.62 (s, 3 H) 3.97 (t, *J*=7.3 Hz, 2 H) 4.05 (td, *J*=10.3, 7.3 Hz, 1 H) 4.52 (td, *J*=10.2, 6.6 Hz, 1 H) 5.55 (d, *J*=8.6 Hz, 1 H) 5.77 (t, *J*=2.1 Hz, 1 H) 5.90 - 5.98 (m, 2 H) 6.42 (d, *J*=8.6 Hz, 1 H) 7.00 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.33 (d, *J*=8.1 Hz, 1 H) 7.39 - 7.49 (m, 2 H) 7.55 (d, *J*=8.4 Hz, 2 H) 8.03 (s, 1 H) 12.19 (br s, 1 H)

LC/MS (method LC-B): R<sub>t</sub> 2.19 min, MH<sup>+</sup> 605

**Example 4** : synthesis of 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-3-methylbutanoic acid (Compound **4**) and separation into Stereoisomers **4A**, **4B**, **4C** and **4D**



#### 5 Synthesis of intermediate 4a:

To a stirred solution of ethyl 4-bromo-3-methylbutanoate [CAS 56703-10-7] (1.0 g, 4.78 mmol) in DMF (15 mL) was added 3-amino-5-methoxyphenol [CAS 162155-27-3] (666 mg, 4.78 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (3.12 g, 9.57 mmol). The reaction was stirred at 70°C for 16 h, and allowed to reach room temperature. The mixture was poured out into H<sub>2</sub>O (75 mL). The product was extracted (2x) with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (25 g) using a gradient of heptane/EtOAc from 100/0 to 50/50. The product fractions were combined, evaporated under reduced pressure and co-evaporated with CH<sub>3</sub>CN, yielding ethyl 4-(3-amino-5-methoxyphenoxy)-3-methylbutanoate **4a** (430 mg).

#### Synthesis of intermediate 4b:

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (430 mg, 1.15 mmol), ethyl 4-(3-amino-5-methoxyphenoxy)-3-methylbutanoate **4a** (430 mg, 1.61 mmol) and diisopropylethylamine (396 μL, 2.30 mmol) in CH<sub>3</sub>CN (15 mL) was stirred at 60°C for 18 h under N<sub>2</sub> atmosphere. The mixture was allowed to reach room temperature, and was poured out into water (75 mL). The product was extracted (2x) with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (12 g) using a gradient of heptane/EtOAc/EtOH 100/0/0 to 40/45/15. The product

fractions were combined and evaporated under reduced pressure, and co-evaporated with EtOH to provide ethyl 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-3-methylbutanoate **4b** (714 mg).

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**Synthesis of Compound 4 and separation into Stereoisomers 4A, 4B, 4C and 4D:**

1M NaOH in water (2.9 mL, 2.9 mmol) was added to a stirring solution of ethyl 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-3-methylbutanoate **4b** (714 mg, 1.15 mmol) in a solvent mixture of dioxane (5 mL) and EtOH (2 mL). The reaction mixture was stirred at room temperature for 18 h. 1N HCl (3 mL) was added slowly. After stirring for 2 min, the product was extracted (2x) with Et<sub>2</sub>O. The combined organic layers were separated, dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure.

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The residue was purified by flash chromatography on silica gel (40 g) using a gradient of heptane/EtOAc/EtOH/HOAc 100/0/0/0 to 40/45/14.7/0.3. The product fractions were combined and evaporated under reduced pressure. The residue was stirred up in Et<sub>2</sub>O (5 mL). The solids were filtered off, washed (3x) with Et<sub>2</sub>O, and dried under vacuum at 50°C to provide 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-3-methylbutanoic acid (Compound **4**, 290 mg) as a racemic mixture.

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The 4 stereoisomers of Compound **4** (274 mg) were separated via preparative chiral SFC (Stationary phase: Chiralpak<sup>®</sup> Diacel AD 20 x 250 mm, mobile phase: CO<sub>2</sub>, iPrOH + 0.4% iPrNH<sub>2</sub>). The product fractions were combined and evaporated under reduced pressure. The stereoisomers in the product fractions of the second and the third eluted peaks were not completely separated and required further separation via preparative chiral SFC (Stationary phase: Chiralpak<sup>®</sup> Diacel AD 20 x 250 mm, mobile phase: CO<sub>2</sub>, EtOH + 0.4% iPrNH<sub>2</sub>). The product fractions were combined and evaporated under reduced pressure. The 4 stereoisomers were solidified by lyophilization from a solvent mixture of CH<sub>3</sub>CN and water to provide Stereoisomers **4A** (72 mg), **4B** (35 mg), **4C** (35 mg) and **4D** (67 mg).

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**Compound 4:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.96 (d, *J*=6.6 Hz, 3 H) 2.05 - 2.15 (m, 1 H) 2.16 - 2.28 (m, 1 H) 2.39 (dd, *J*=15.4, 5.5 Hz, 1 H) 3.08 - 3.27 (m, 2 H) 3.62 (s, 3 H) 3.65 - 3.75 (m, 2 H) 4.05 (td, *J*=10.4, 7.2 Hz, 1 H) 4.43 - 4.59 (m, 1 H) 5.56 (d, *J*=8.8 Hz, 1 H) 5.76 (t, *J*=2.0 Hz, 1 H) 5.93 (t, *J*=1.8 Hz, 1 H) 5.97 (s, 1 H) 6.43 (d,

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$J=8.8$  Hz, 1 H) 7.01 (dd,  $J=8.1$ , 1.5 Hz, 1 H) 7.33 (d,  $J=8.1$  Hz, 1 H) 7.43 (d,  $J=7.8$  Hz, 2 H) 7.55 (d,  $J=8.4$  Hz, 2 H) 8.03 (br s, 1 H) 12.10 (br s, 1 H)

LC/MS (method LC-B):  $R_t$  2.07 min,  $MH^+$  593

5 **Stereoisomer 4A:**

$^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  ppm 0.96 (d,  $J=6.8$  Hz, 3 H) 2.05 - 2.13 (m, 1 H) 2.22 (dq,  $J=13.1$ , 6.6 Hz, 1 H) 2.33 - 2.40 (m, 1 H) 3.06 - 3.21 (m, 2 H) 3.62 (s, 3 H) 3.65 - 3.76 (m, 2 H) 4.05 (td,  $J=10.4$ , 7.2 Hz, 1 H) 4.52 (td,  $J=10.1$ , 6.4 Hz, 1 H) 5.56 (d,  $J=8.8$  Hz, 1 H) 5.76 (t,  $J=2.0$  Hz, 1 H) 5.93 (t,  $J=1.9$  Hz, 1 H) 5.97 (t,  $J=1.7$  Hz, 1 H) 6.43 (d,  $J=8.6$  Hz, 1 H) 7.00 (dd,  $J=8.1$ , 1.5 Hz, 1 H) 7.33 (d,  $J=8.1$  Hz, 1 H) 7.43 (m,  $J=8.6$  Hz, 2 H) 7.55 (m,  $J=8.6$  Hz, 2 H) 8.03 (br s, 1 H) 11.51 (br s, 1 H)

LC/MS (method LC-B):  $R_t$  2.04 min,  $MH^+$  593

$[\alpha]_D^{20}$ :  $-59.6^\circ$  (c 0.245, DMF)

15 Chiral SFC (method SFC-C):  $R_t$  5.84 min,  $MH^+$  593 chiral purity 100%.

**Stereoisomer 4B:**

$^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  ppm 0.96 (d,  $J=6.6$  Hz, 3 H) 2.07 - 2.14 (m, 1 H) 2.22 (dq,  $J=13.2$ , 6.5 Hz, 1 H) 2.38 (dd,  $J=15.2$ , 5.5 Hz, 1 H) 3.02 - 3.23 (m, 2 H) 20 3.62 (s, 3 H) 3.65 - 3.76 (m, 2 H) 4.04 (td,  $J=10.3$ , 7.3 Hz, 1 H) 4.52 (td,  $J=10.5$ , 6.2 Hz, 1 H) 5.56 (d,  $J=8.8$  Hz, 1 H) 5.76 (t,  $J=2.0$  Hz, 1 H) 5.93 (t,  $J=1.8$  Hz, 1 H) 5.97 (t,  $J=1.7$  Hz, 1 H) 6.43 (d,  $J=8.6$  Hz, 1 H) 7.00 (dd,  $J=8.0$ , 1.4 Hz, 1 H) 7.33 (d,  $J=8.1$  Hz, 1 H) 7.41 - 7.46 (m, 2 H) 7.55 (m,  $J=8.4$  Hz, 2 H) 8.03 (br s, 1 H) 12.00 (br s, 1 H)

25 LC/MS (method LC-B):  $R_t$  2.04 min,  $MH^+$  593

$[\alpha]_D^{20}$ :  $-47.5^\circ$  (c 0.255, DMF)

Chiral SFC (method SFC-C):  $R_t$  6.34 min,  $MH^+$  593 chiral purity 98.0%.

**Stereoisomer 4C:**

$^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  ppm 0.96 (d,  $J=6.6$  Hz, 3 H) 2.06 - 2.14 (m, 1 H) 2.22 (dq,  $J=13.3$ , 6.4 Hz, 1 H) 2.37 (dd,  $J=15.3$ , 5.6 Hz, 1 H) 3.08 - 3.22 (m, 2 H) 3.62 (s, 3 H) 3.66 - 3.74 (m, 2 H) 4.04 (td,  $J=10.5$ , 7.0 Hz, 1 H) 4.52 (td,  $J=10.2$ , 6.6 Hz, 1 H) 5.56 (d,  $J=8.8$  Hz, 1 H) 5.76 (t,  $J=2.1$  Hz, 1 H) 5.93 (t,  $J=1.7$  Hz, 1 H) 5.97 (t,  $J=1.8$  Hz, 1 H) 6.44 (d,  $J=8.8$  Hz, 1 H) 7.01 (dd,  $J=8.1$ , 1.5 Hz, 1 H) 7.33 35 (d,  $J=8.1$  Hz, 1 H) 7.44 (m,  $J=8.6$  Hz, 2 H) 7.55 (m,  $J=8.6$  Hz, 2 H) 8.03 (br s, 1 H) 10.85 - 12.62 (m, 1 H)

LC/MS (method LC-B):  $R_t$  2.04 min,  $MH^+$  593

$[\alpha]_D^{20}$ :  $+47.7^\circ$  (c 0.26, DMF)

Chiral SFC (method SFC-C):  $R_t$  6.31 min,  $MH^+$  593 chiral purity 100%.

#### Stereoisomer 4D:

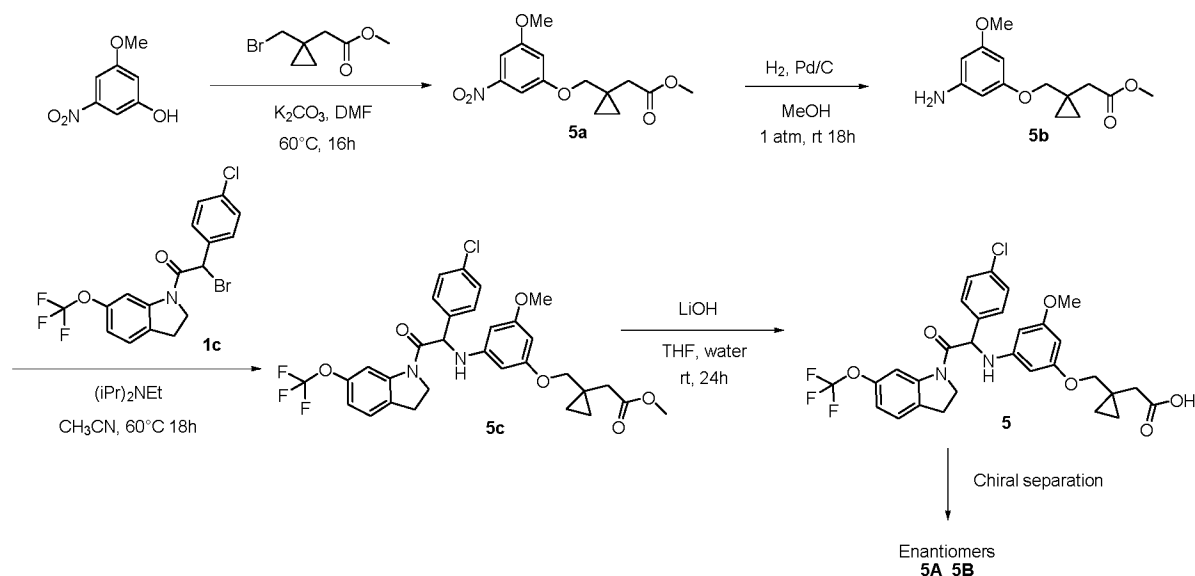
$^1H$  NMR (360 MHz,  $DMSO-d_6$ )  $\delta$  ppm 0.96 (d,  $J=7.0$  Hz, 3 H) 2.06 - 2.15 (m, 1 H)  
 5 2.17 - 2.28 (m, 1 H) 2.38 (dd,  $J=15.4, 5.5$  Hz, 1 H) 3.07 - 3.26 (m, 2 H) 3.62 (s, 3 H)  
 3.65 - 3.76 (m, 2 H) 4.05 (td,  $J=10.2, 7.3$  Hz, 1 H) 4.52 (td,  $J=10.3, 6.4$  Hz, 1 H)  
 5.57 (d,  $J=8.8$  Hz, 1 H) 5.76 (t,  $J=2.0$  Hz, 1 H) 5.93 (t,  $J=1.5$  Hz, 1 H) 5.97 (t,  $J=1.5$   
 10 H) 6.46 (d,  $J=8.4$  Hz, 1 H) 7.01 (dd,  $J=8.2, 1.6$  Hz, 1 H) 7.33 (d,  $J=8.4$  Hz, 1 H)  
 7.44 (m,  $J=8.4$  Hz, 2 H) 7.55 (m,  $J=8.4$  Hz, 2 H) 8.03 (br s, 1 H) 11.95 (br s, 1

LC/MS (method LC-B):  $R_t$  2.04 min,  $MH^+$  593

$[\alpha]_D^{20}$ : +60.7° (c 0.285, DMF)

Chiral SFC (method SFC-C):  $R_t$  7.58 min,  $MH^+$  593 chiral purity 100%.

15 **Example 5** : synthesis of 2-(1-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclopropyl)acetic acid (Compound **5**) and chiral separation into Enantiomers **5A** and **5B**



#### 20 Synthesis of intermediate 5a:

Methyl 2-(1-(bromomethyl)cyclopropyl)acetate [855473-50-6] (306 mg, 1.478 mmol) was added dropwise to a solution of 3-methoxy-5-nitrophenol [7145-49-5] (250 mg, 1.478 mmol) and  $K_2CO_3$  (306 mg, 2.217 mmol) in DMF (2.5 mL). The mixture was stirred at  $60^\circ C$  for 16 h. The reaction was cooled to  $0^\circ C$ , and diluted with water and ice. The mixture was extracted with EtOAc. The organic layer was washed with water, dried over  $MgSO_4$ , filtered and the solvent was concentrated under reduced pressure to give methyl 2-(1-((3-methoxy-5-

25



nitrophenoxy)methyl)cyclopropyl)acetate **5a**. The yield was considered as quantitative. The compound was used as such in the next step.

#### Synthesis of intermediate **5b**:

5 A solution of methyl 2-(1-((3-methoxy-5-nitrophenoxy)methyl)cyclopropyl)acetate **5a** (520 mg, 1.761 mmol) in MeOH (8 mL), containing a catalytic amount of 10% Pd/C (300 mg, 0.282 mmol) was hydrogenated under atmospheric pressure of H<sub>2</sub> at room temperature for 18 h. The catalyst was removed by filtration over a short pad of Celite<sup>®</sup> and the filter cake was rinsed several times with EtOAc. The  
10 combined filtrates were evaporated to give methyl 2-(1-((3-amino-5-methoxyphenoxy)methyl)cyclopropyl)acetate **5b** (390 mg), which was used without further purification in the next step.

#### Synthesis of intermediate **5c**:

15 A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (250 mg, 0.575 mmol), methyl 2-(1-((3-amino-5-methoxyphenoxy)methyl)cyclopropyl)acetate **5b** (184 mg, 0.575 mmol) and diisopropylethylamine (200  $\mu$ L, 1.15 mmol) in CH<sub>3</sub>CN (7.5 mL) was stirred at 60°C for 18 h. The solvent was concentrated under reduced pressure. Ice/water was  
20 added and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30  $\mu$ m, 24 g, heptane/EtOAc 75/25). The product fractions were combined and evaporated under reduced pressure. The residue was crystalized from CH<sub>3</sub>CN/diisopropyl  
25 ether and dried to give methyl 2-(1-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclopropyl)acetate **5c** (206 mg).

#### Synthesis of Compound **5** and separation into Enantiomers **5A** and **5B**:

30 LiOH monohydrate (63 mg, 1.502 mmol) in water (1.63 mL) was added dropwise to a solution of methyl 2-(1-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclopropyl)acetate **5c** (186 mg, 0.3 mmol) in THF (3.7 mL). The reaction mixture was stirred at room temperature for 24 h. 3N HCl was added to acidify the reaction mixture, and the  
35 aqueous solution was extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was crystalized from CH<sub>3</sub>CN/diisopropyl ether and dried to give 2-(1-((3-((1-(4-

chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclopropyl)acetic acid (Compound **5**, 115 mg).

the separation of the enantiomers of Compound **5** (71 mg) was performed via preparative chiral SFC (Stationary phase: Chiralpak<sup>®</sup> Diacel AD 20 x 250 mm, mobile phase: CO<sub>2</sub>, EtOH + 0.4% iPrNH<sub>2</sub>). For both enantiomers, the product fractions were combined and evaporated under reduced pressure. The residues were partitioned between water and Et<sub>2</sub>O. The mixtures were acidified to pH 1-2 by the addition of 1N HCl and the layers were separated. The aqueous layer was extracted again with Et<sub>2</sub>O. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. The residues were dried under vacuum at 50°C to provide Enantiomer **5A** (22 mg) and Enantiomer **5B** (23 mg) as off-white powders.

#### Compound **5**:

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.49 – 0.55 (m, 4 H) 2.33 (s, 2 H) 2.99 - 3.25 (m, 2 H) 3.62 (s, 3 H) 3.73 (s, 2 H) 4.05 (td, *J*=10.40, 7.25 Hz, 1 H) 4.52 (td, *J*=10.25, 6.31 Hz, 1 H) 5.57 (d, *J*=9.14 Hz, 1 H) 5.74 (s, 1 H) 5.92 (s, 1 H) 5.95 (s, 1 H) 6.45 (d, *J*=9.14 Hz, 1 H) 7.02 (br d, *J*=9.14 Hz, 1 H) 7.34 (d, *J*=8.20 Hz, 1 H) 7.44 (d, *J*=8.20 Hz, 2 H) 7.55 (d, *J*=8.51 Hz, 3 H) 8.03 (s, 1 H) 12.01 (br s, 1 H)  
LC/MS (method LC-C): R<sub>t</sub> 3.18 min, MH<sup>+</sup> 605  
MP = 111°C

#### Enantiomer **5A**:

<sup>1</sup>H NMR (360 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.46 - 0.58 (m, 4 H) 2.33 (s, 2 H) 3.04 - 3.27 (m, 2 H) 3.61 (s, 3 H) 3.72 (s, 2 H) 4.05 (td, *J*=10.2, 7.3 Hz, 1 H) 4.52 (td, *J*=10.2, 6.6 Hz, 1 H) 5.57 (d, *J*=9.1 Hz, 1 H) 5.74 (t, *J*=2.0 Hz, 1 H) 5.92 (t, *J*=1.6 Hz, 1 H) 5.94 - 5.97 (m, 1 H) 6.45 (d, *J*=8.8 Hz, 1 H) 7.01 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.33 (d, *J*=8.4 Hz, 1 H) 7.44 (d, *J*=8.4 Hz, 2 H) 7.51 - 7.59 (m, 2 H) 8.03 (s, 1 H) 12.12 (br s, 1 H)  
LC/MS (method LC-A): R<sub>t</sub> 1.15 min, MH<sup>+</sup> 605  
[α]<sub>D</sub><sup>20</sup>: +37.0° (c 0.135, DMF)  
Chiral SFC (method SFC-E): R<sub>t</sub> 5.84 min, MH<sup>+</sup> 605 chiral purity 100%.

#### Enantiomer **5B**:

<sup>1</sup>H NMR (360 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.46 - 0.57 (m, 4 H) 2.33 (s, 2 H) 3.05 - 3.26 (m, 2 H) 3.61 (s, 3 H) 3.72 (s, 2 H) 4.05 (td, *J*=10.4, 7.3 Hz, 1 H) 4.52 (td, *J*=10.3, 6.4 Hz, 1 H) 5.57 (d, *J*=8.8 Hz, 1 H) 5.74 (t, *J*=2.0 Hz, 1 H) 5.92 (t, *J*=1.8 Hz, 1 H) 5.94 - 5.97 (m, 1 H) 6.45 (d, *J*=8.8 Hz, 1 H) 7.01 (dd, *J*=8.2, 1.6 Hz, 1 H) 7.33 (d,

$J=8.1$  Hz, 1 H) 7.44 (d,  $J=8.4$  Hz, 2 H) 7.50 - 7.61 (m, 2 H) 8.03 (s, 1 H) 12.11 (br s, 1 H)

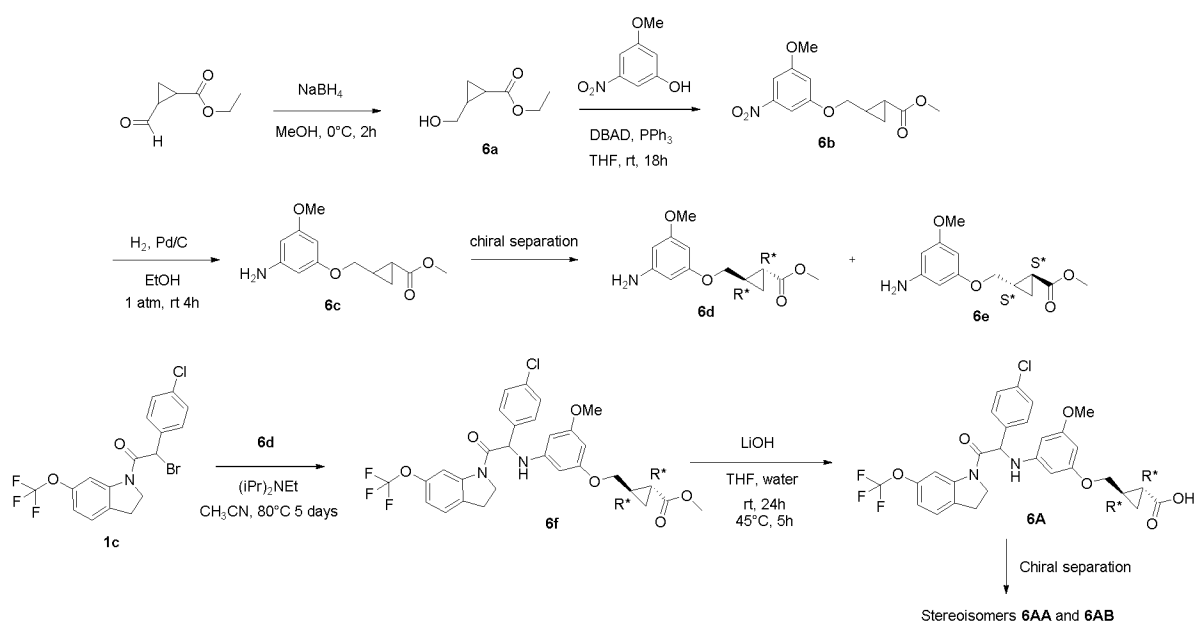
LC/MS (method LC-A):  $R_t$  1.15 min,  $MH^+$  605

$[\alpha]_D^{20}$ :  $-48.8^\circ$  (c 0.16, DMF)

5 Chiral SFC (method SFC-E):  $R_t$  6.53 min,  $MH^+$  605 chiral purity 100%.

**Example 6A** : synthesis of (1*R*\*,2*R*\*)-2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylic acid (Compound **6A**) and separation into Stereoisomers

10 **6AA** and **6AB**



### Synthesis of intermediate **6a**:

To a solution of ethyl 2-formylcyclopropanecarboxylate [20417-61-2] (9 mL, 67.996 mmol) in MeOH (200 mL) was added portionwise  $\text{NaBH}_4$  (5.15 g, 133.993 mmol) at  $0^\circ\text{C}$  and the mixture was stirred at  $0^\circ\text{C}$  for 2 h.  $\text{CH}_2\text{Cl}_2$  and water were added. The layers were separated; the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organic layers were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to give ethyl 2-(hydroxymethyl)cyclopropanecarboxylate **6a** (9.15 g). The compound was used as such in the next step.

### Synthesis of intermediate **6b**:

Di-*tert*-butyl azodicarboxylate (4.8 g, 20.809 mmol) was added portionwise to a solution of 3-methoxy-5-nitrophenol [7145-49-5] (3.2 g, 18.917 mmol), ethyl 2-(hydroxymethyl)cyclopropanecarboxylate **6a** (3 g, 20.809 mmol), and  $\text{PPh}_3$  (5.46 g, 20.809 mmol) in THF (150 mL). The reaction was stirred at room temperature under  $\text{N}_2$  for 18 h. The solution was concentrated under reduced pressure. The

crude residue was purified by preparative LC (irregular SiOH 20-45  $\mu\text{m}$ , 220 g, heptane/EtOAc from 85/15 to 75/25). The pure fractions were combined and concentrated under reduced pressure to give methyl 2-((3-methoxy-5-nitrophenoxy)methyl)cyclopropanecarboxylate **6b** (1.4 g).

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**Synthesis of intermediate 6c and chiral separation into enantiomers 6d and 6e:**

A solution of methyl 2-((3-methoxy-5-nitrophenoxy)methyl)cyclopropanecarboxylate **6b** (1.3 g, 4.402 mmol) in EtOH (65 mL) containing a catalytic amount of 10% Pd/C (750 mg, 0.704 mmol) was hydrogenated under atmospheric pressure of H<sub>2</sub> at room temperature for 4 h. The catalyst was removed by filtration over a short pad of Celite<sup>®</sup> and the filter cake was rinsed several times with EtOAc. The combined filtrates were evaporated. The crude residue was purified by preparative LC (Irregular SiOH 20-45  $\mu\text{m}$ , 40 g, heptane/EtOAc 80/20). The pure fractions were combined and the solvent was evaporated to dryness to give methyl 2-((3-amino-5-methoxyphenoxy)methyl)cyclopropanecarboxylate **6c** (780 mg). The enantiomers were separated via chiral SFC (Stationary phase: Chiralpak<sup>®</sup> AD-H 5  $\mu\text{m}$  250 x 30 mm, mobile phase: 80% CO<sub>2</sub>, 20% EtOH) to give the first eluted enantiomer **6d** (*trans* R\*,R\*, 344 mg,  $[\alpha]_{\text{D}}^{20}$ : -78.6° (c 0.257, DMF)) and the second eluted enantiomer **6e** (*trans* S\*,S\*, 371 mg,  $[\alpha]_{\text{D}}^{20}$ : +74.5° (c 0.251, DMF)).

**Synthesis of intermediate 6f:**

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (376 mg, 0.864 mmol), (1R\*,2R\*)-methyl 2-((3-amino-5-methoxyphenoxy)methyl)cyclopropanecarboxylate methoxyphenoxy)methyl)cyclopropyl)acetate **6d** (344 mg, 1.297 mmol) and diisopropylethylamine (298  $\mu\text{L}$ , 1.729 mmol) in CH<sub>3</sub>CN (12 mL) was stirred at 80°C for 5 days. The solvent was concentrated under reduced pressure. Ice/water was added and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (25-30  $\mu\text{m}$ , 40 g, heptane/EtOAc 80/20). The product fractions were combined and evaporated under reduced pressure to give (1R\*,2R\*)-methyl 2-(((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylate **6f** (500 mg).

35

**Synthesis of Compound 6A and chiral separation into Stereoisomers 6AA and 6AB:**

LiOH monohydrate (169 mg, 4.039 mmol) in water (10 mL) was added dropwise to a solution of (1*R*\*,2*R*\*)-methyl 2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclopropanecarboxylate **6f** (500 mg, 0.808 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 18 h and at 45°C for 5 h. 3N HCl was added to acidify the solution, and the mixture was extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20-45 μm, 40 g, heptane/EtOAc 80/20). The product fractions were combined and evaporated under reduced pressure to give (1*R*\*,2*R*\*)-2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclopropanecarboxylic acid (Compound **6A**, 780 mg).

The two stereoisomers were separated via chiral SFC (Stationary phase: Chiralcel<sup>®</sup> OD-H 5 μm 250 x 30 mm, mobile phase: 55% CO<sub>2</sub>, 45% iPrOH) to give, after solidification from heptane/diisopropyl ether, the first eluted Stereoisomer **6AA** (123 mg) and the second eluted Stereoisomer **6AB** (125 mg).

**Stereoisomer 6AA:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.75 - 0.96 (m, 1 H) 1.00 - 1.07 (m, 1 H) 1.44 - 1.57 (m, 1 H) 1.57 - 1.70 (m, 1 H) 3.09 - 3.27 (m, 2 H) 3.62 (s, 3 H) 3.69 (br dd, *J*=10.25, 7.72 Hz, 1 H) 3.80 - 3.95 (m, 1 H) 4.00 - 4.09 (m, 1 H) 4.39 - 4.65 (m, 1 H) 5.57 (br d, *J*=8.51 Hz, 1 H) 5.76 (s, 1 H) 5.95 (s, 1 H) 5.97 (s, 1 H) 6.46 (br d, *J*=8.83 Hz, 1 H) 7.02 (br d, *J*=8.20 Hz, 1 H) 7.34 (d, *J*=8.20 Hz, 1 H) 7.44 (d, *J*=8.51 Hz, 2 H) 7.55 (br d, *J*=8.20 Hz, 2 H) 8.04 (br s, 1 H) 12.02 (br s, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.95 min, MH<sup>+</sup> 591

[α]<sub>D</sub><sup>20</sup>: -78.0° (c 0.282, DMF)

Chiral SFC (method SFC-G): R<sub>t</sub> 1.08 min, MH<sup>+</sup> 591 chiral purity 99.82%.

**Stereoisomer 6AB:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.79 - 0.90 (m, 1 H) 1.00 - 1.08 (m, 1 H) 1.43 - 1.57 (m, 1 H) 1.57 - 1.72 (m, 1 H) 2.95 - 3.27 (m, 2 H) 3.62 (s, 3 H) 3.63 - 3.78 (m, 1 H) 3.78 - 3.98 (m, 1 H) 4.00 - 4.09 (m, 1 H) 4.29 - 4.65 (m, 1 H) 5.57 (br d, *J*=8.83 Hz, 1 H) 5.76 (br s, 1 H) 5.95 (s, 1 H) 5.96 (s, 1 H) 6.46 (br d, *J*=8.51 Hz, 1 H) 7.01 (br d, *J*=7.57 Hz, 1 H) 7.34 (br d, *J*=7.88 Hz, 1 H) 7.44 (br d, *J*=7.88 Hz, 2 H) 7.55 (br d, *J*=7.88 Hz, 2 H) 8.04 (br s, 1 H) 11.88 (br s, 1 H)

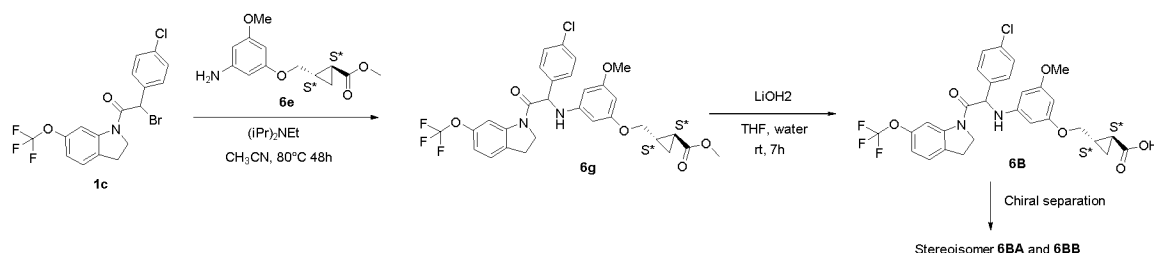
LC/MS (method LC-C): R<sub>t</sub> 2.95 min, MH<sup>+</sup> 591

[α]<sub>D</sub><sup>20</sup>: +12.9° (c 0.272, DMF)

Chiral SFC (method SFC-G): R<sub>t</sub> 1.87 min, MH<sup>+</sup> 591 chiral purity 99.55%.

**Example 6B** : synthesis of ((1*S*\*,2*S*\*)-2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylic acid (Compound **6B**) and separation into Stereoisomers **6BA** and **6BB**

5



### Synthesis of intermediate **6g**:

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (405 mg, 0.932 mmol), (1*S*\*,2*S*\*)-methyl 2-((3-amino-5-methoxyphenoxy)methyl)cyclopropanecarboxylate (6*e*) (371 mg, 1.398 mmol) and diisopropylethylamine (321  $\mu$ L, 1.864 mmol) in  $\text{CH}_3\text{CN}$  (12 mL) was stirred at 80°C for 48 h. The solvent was concentrated under reduced pressure. Ice/water was added and the mixture was extracted with EtOAc. The organic layer was washed with water, dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (25-30  $\mu\text{m}$ , 40 g, heptane/EtOAc 80/20). The product fractions were combined and evaporated under reduced pressure to give (1*S*\*,2*S*\*)-methyl 2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylate **6g** (580 mg).

### Synthesis of Compound **6B** and chiral separation into Stereoisomers **6BA** and **6BB**:

LiOH monohydrate (203 mg, 4.846 mmol) in water (10 mL) was added dropwise to a solution of (1*S*\*,2*S*\*)-methyl 2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclopropanecarboxylate **6g** (600 mg, 0.969 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 7 h. 3N HCl was added to acidify the solution, and the mixture was extracted with EtOAc. The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20-45  $\mu\text{m}$ , 40 g, heptane/EtOAc 80/20). The product fractions were combined and evaporated under reduced pressure to give (1*S*\*,2*S*\*)-2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-

methoxyphenoxy)methyl)cyclopropanecarboxylic acid (Compound **6B**, 348 mg).

The two stereoisomers were separated via chiral SFC (Stationary phase:

Chiralcel<sup>®</sup> OD-H 5  $\mu$ m 250 x 30 mm, mobile phase: 55% CO<sub>2</sub>, 45% iPrOH) to give, after solidification from heptane/diisopropyl ether, the first eluted Stereoisomer

5 **6BA** (109 mg) and the second eluted Stereoisomer **6BB** (102 mg).

**Stereoisomer 6BA:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 0.73 - 0.98 (m, 1 H) 0.98 - 1.08 (m, 1 H) 1.49

- 1.58 (m, 1 H) 1.58 - 1.71 (m, 1 H) 3.00 - 3.27 (m, 2 H) 3.61 (s, 3 H) 3.68 (dd,

10 *J*=10.40, 7.57 Hz, 1 H) 3.84 (dd, *J*=10.56, 6.15 Hz, 1 H) 4.00 - 4.08 (m, 1 H) 4.50 -

4.57 (m, 1 H) 5.57 (d, *J*=8.83 Hz, 1 H) 5.75 (s, 1 H) 5.95 (s, 1 H) 5.96 (s, 1H) 6.46

(br d, *J*=8.83 Hz, 1 H) 7.01 (br d, *J*=7.25 Hz, 1 H) 7.33 (d, *J*=7.88 Hz, 1 H) 7.44 (d,

*J*=8.51 Hz, 2 H) 7.55 (d, *J*=8.51 Hz, 2 H) 8.03 (s, 1 H) 12.26 (br s, 1H)

LC/MS (method LC-D): R<sub>t</sub> 2.82 min, MH<sup>+</sup> 591

15  $[\alpha]_D^{20}$ : -12.5° (c 0.28, DMF)

Chiral SFC (method SFC-G): R<sub>t</sub> 1.10 min, no MH<sup>+</sup>, chiral purity 100%.

**Stereoisomer 6BB:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 0.78 - 0.95 (m, 1 H) 1.00 -1.08 (m, 1H) 1.48

20 - 1.59 (m, 1 H) 1.59 - 1.68 (m, 1 H) 2.91 - 3.25 (m, 2 H) 3.61 (s, 3 H) 3.68 (br dd,

*J*=10.40, 7.57 Hz, 1 H) 3.84 (dd, *J*=10.56, 6.15 Hz, 1 H) 4.00- 4.09 (m, 1 H) 4.30 -

4.58 (m, 1 H) 5.57 (d, *J*=8.83 Hz, 1 H) 5.75 (s, 1 H) 5.95 (s, 1 H), 5.96 (s, 1H) 6.45

(br d, *J*=8.83 Hz, 1 H) 7.01 (br d, *J*=7.88 Hz, 1 H) 7.33 (d, *J*=8.20 Hz, 1 H) 7.44 (d,

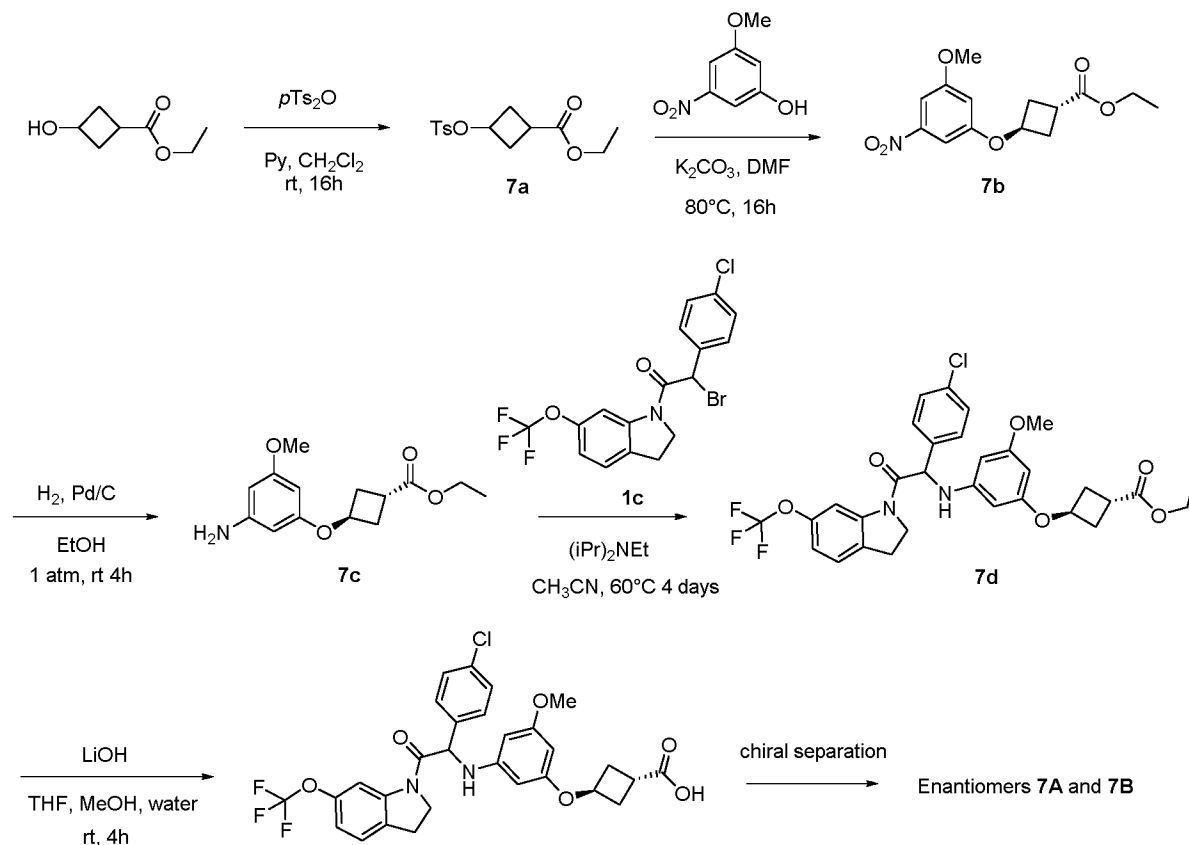
*J*=8.20 Hz, 2 H) 7.55 (d, *J*=8.20 Hz, 2 H) 8.03 (s, 1 H) 12.11 (br s, 1 H)

25 LC/MS (method LC-D): R<sub>t</sub> 2.81 min, MH<sup>+</sup> 591

$[\alpha]_D^{20}$ : +81.4° (c 0.28, DMF)

Chiral SFC (method SFC-G): R<sub>t</sub> 1.87 min, no MH<sup>+</sup>, chiral purity 99.02%.

**Example 7** : synthesis of (1*r*,3*r*)-3-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)cyclobutene-carboxylic acid (Compound **7**) and separation into Enantiomers **7A** and **7B**



5

### Synthesis of intermediate **7a**:

Under a N<sub>2</sub> flow, to a solution of ethyl 3-hydroxycyclobutanecarboxylate [17205-02-6] (1 g, 6.936 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) were added pyridine (0.838 mL) and tosyl anhydride (2.49 g, 7.63 mmol). The mixture was stirred overnight at room temperature. The mixture was concentrated under vacuum, suspended in diethyl ether (200 mL) and washed with 0.5 M hydrochloric acid (2×60 mL), a saturated solution of sodium hydrogen carbonate (2×60 mL), water (60 mL) and brine (50 mL). The solution was dried over sodium sulfate, filtered and concentrated under reduced pressure to yield ethyl 3-(tosyloxy)cyclobutanecarboxylate **7a** (2.0 g).

### Synthesis of intermediate **7b**:

Ethyl 3-(tosyloxy)cyclobutanecarboxylate **7a** (1.94 g, 6.504 mmol) was added dropwise to a mixture of 3-methoxy-5-nitrophenol [7145-49-5] (1.0 g, 5.912 mmol) and K<sub>2</sub>CO<sub>3</sub> (981 mg, 7.095 mmol) in DMF (10 mL). The mixture was stirred at 80°C for 16 h. The mixture was diluted with water and extracted with EtOAc. The

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organic layer was washed with water, dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under reduced pressure. Purification was performed by flash chromatography on silica gel (15-40 μm, 80 g, heptane/EtOAc 95/5 to 85/15). The pure fractions were combined and evaporated to dryness to give (1*r*,3*r*)-ethyl 3-(3-methoxy-5-nitrophenoxy)cyclobutanecarboxylate **7b** (1.1 g).

#### Synthesis of intermediate **7c**:

A solution of (1*r*,3*r*)-ethyl 3-(3-methoxy-5-nitrophenoxy)cyclobutanecarboxylate **7b** (1.1 g, 3.725 mmol) in EtOH (20 mL) containing a catalytic amount of 10% Pd/C (396 mg, 0.373 mmol) was hydrogenated under atmospheric pressure of H<sub>2</sub> at room temperature for 4 h. The catalyst was removed by filtration over a short pad of Celite<sup>®</sup> and the filter cake was rinsed several times with MeOH. The combined filtrates were evaporated under reduced pressure to give (1*r*,3*r*)-ethyl 3-(3-amino-5-methoxyphenoxy)cyclobutanecarboxylate **7c** (920 mg). The compound was used as such in the next step.

#### Synthesis of intermediate **7d**:

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (1.072 g, 2.467 mmol), (1*r*,3*r*)-ethyl 3-(3-amino-5-methoxyphenoxy)cyclobutanecarboxylate **7c** (720 mg, 2.714 mmol) and diisopropylethylamine (850 μL, 4.934 mmol) in CH<sub>3</sub>CN (32 mL) was stirred at 60°C for 4 days. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with 1N HCl and brine, dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under vacuum to give (1*r*,3*r*)-ethyl 3-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)cyclobutanecarboxylate **7d** (1.6 g), which was used as such in the next step.

#### Synthesis of Compound **7** and chiral separation into Enantiomers **7A** and **7B**:

At 0°C, LiOH monohydrate (325 mg, 7.75 mmol) was added portionwise to a solution of (1*r*,3*r*)-ethyl 3-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)cyclobutanecarboxylate **7d** (1.6 g, 2.585 mmol) in THF/water/MeOH (1/1/1) (30 mL). The reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with water and 3N HCl was added to acidify the solution. The mixture was extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica

gel (15-40  $\mu\text{m}$ , 80 g,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  100/0 to 98/2). The product fractions were combined and evaporated under reduced pressure to give (1*r*,3*r*)-3-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)cyclobutene-carboxylic acid (Compound **7**, 1.16 g). The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel<sup>®</sup> OD-H 5  $\mu\text{m}$  250 x 30 mm, mobile phase: 55%  $\text{CO}_2$ , 45% MeOH) to give, after solidification from heptane/diisopropyl ether, the first eluted Enantiomer **7A** (358 mg) and the second eluted Enantiomer **7B** (388 mg).

10 **Compound 7:**

$^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 2.19 - 2.30 (m, 2 H) 2.57 (qd,  $J=6.8, 3.6$  Hz, 2 H) 2.95 - 3.05 (m, 1 H) 3.08 - 3.27 (m, 2 H) 3.61 (s, 3 H) 4.03 (td,  $J=10.4, 7.3$  Hz, 1 H) 4.53 (td,  $J=10.4, 6.3$  Hz, 1 H) 4.68 (quin,  $J=6.7$  Hz, 1 H) 5.54 (d,  $J=8.5$  Hz, 1 H) 5.62 (s, 1 H) 5.85 (s, 1 H) 5.92 (s, 1 H) 6.53 (d,  $J=8.5$  Hz, 1 H) 7.01 (br d,  $J=7.9$  Hz, 1 H) 7.33 (d,  $J=8.2$  Hz, 1 H) 7.45 (d,  $J=8.2$  Hz, 2 H) 7.55 (d,  $J=8.5$  Hz, 2 H) 8.04 (s, 1 H) 12.34 (br s, 1 H)

15 LC/MS (method LC-C):  $R_t$  2.95 min,  $\text{MH}^+$  591

**Enantiomer 7A:**

20  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 2.20 - 2.28 (m, 2 H) 2.53 - 2.60 (m, 2 H) 2.95 - 3.04 (m, 1 H) 3.07 - 3.26 (m, 2 H) 3.60 (s, 3 H) 4.03 (td,  $J=10.4, 7.3$  Hz, 1 H) 4.52 (td,  $J=10.2, 6.3$  Hz, 1 H) 4.67 (t,  $J=6.8$  Hz, 1 H) 5.53 (d,  $J=8.5$  Hz, 1 H) 5.61 (t,  $J=2.0$  Hz, 1 H) 5.84 (s, 1 H) 5.91 (s, 1 H) 6.52 (d,  $J=8.5$  Hz, 1 H) 7.01 (dd,  $J=8.2, 1.6$  Hz, 1 H) 7.33 (d,  $J=8.2$  Hz, 1 H) 7.44 (d,  $J=8.5$  Hz, 2 H) 7.55 (d,  $J=8.5$  Hz, 2 H) 8.03 (s, 1 H) 12.24 - 12.40 (m, 1 H)

25 LC/MS (method LC-C):  $R_t$  2.96 min,  $\text{MH}^+$  591

$[\alpha]_D^{20}$ :  $-41.6^\circ$  (c 0.298, DMF)

Chiral SFC (method SFC-H):  $R_t$  1.25 min,  $\text{MH}^+$  591, chiral purity 100%.

30 **Enantiomer 7B:**

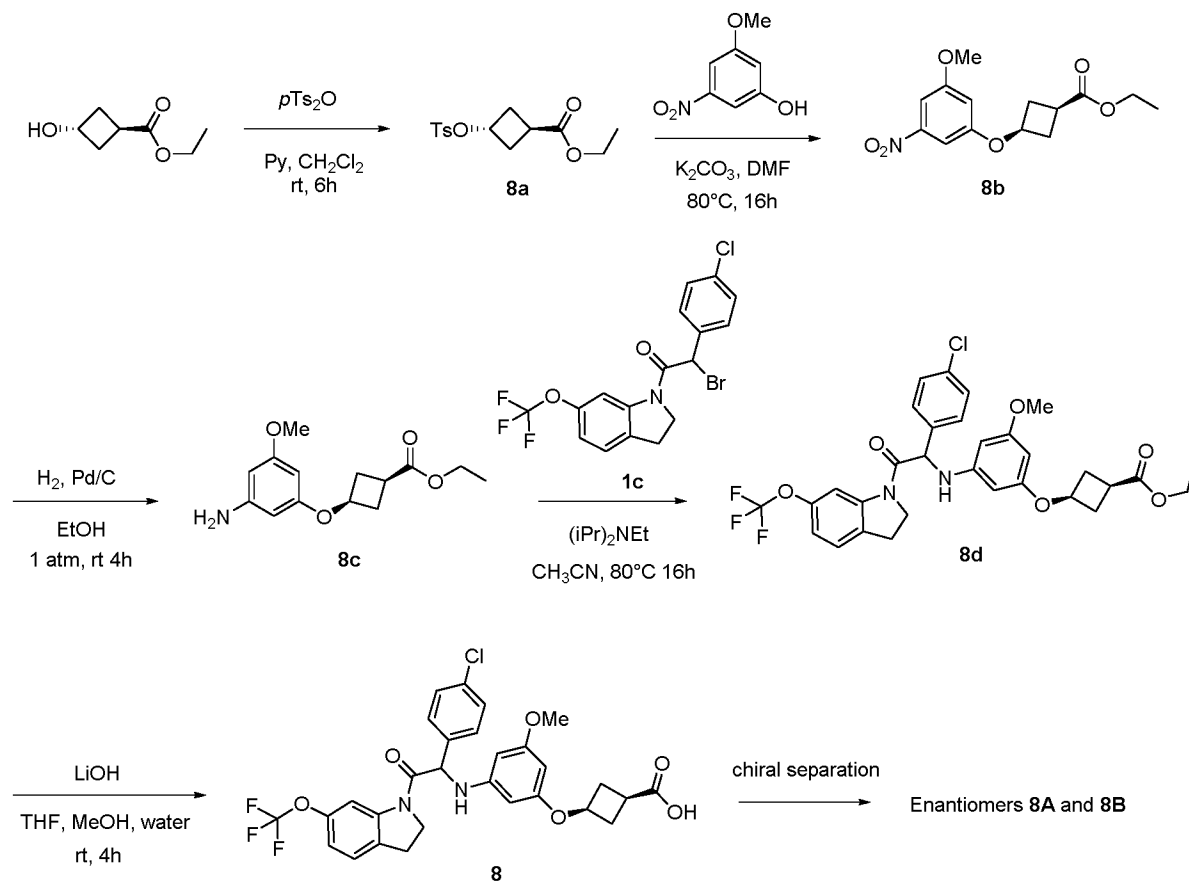
$^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 2.19 - 2.28 (m, 2 H) 2.57 (qd,  $J=6.8, 3.9$  Hz, 2 H) 2.95 - 3.04 (m, 1 H) 3.08 - 3.25 (m, 2 H) 3.60 (s, 3 H) 4.03 (td,  $J=10.5, 7.1$  Hz, 1 H) 4.53 (td,  $J=10.4, 6.3$  Hz, 1 H) 4.67 (quin,  $J=6.7$  Hz, 1 H) 5.53 (d,  $J=8.5$  Hz, 1 H) 5.61 (t,  $J=2.0$  Hz, 1 H) 5.84 (s, 1 H) 5.91 (s, 1 H) 6.52 (d,  $J=8.5$  Hz, 1 H) 7.01 (dd,  $J=8.0, 1.4$  Hz, 1 H) 7.33 (d,  $J=8.2$  Hz, 1 H) 7.44 (d,  $J=8.5$  Hz, 2 H) 7.55 (d,  $J=8.5$  Hz, 2 H) 8.03 (s, 1 H) 12.32 (br s, 1 H)

35 LC/MS (method LC-C):  $R_t$  2.95 min,  $\text{MH}^+$  591

$[\alpha]_D^{20}$ :  $+43.7^\circ$  (c 0.332, DMF)

Chiral SFC (method SFC-H):  $R_t$  2.05 min,  $\text{MH}^+$  591, chiral purity 100%.

**Example 8** : synthesis of (1*s*,3*s*)-3-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)cyclobutene-carboxylic acid (Compound **8**) and separation into Enantiomers **8A** and **8B**



5

### Synthesis of intermediate **8a**:

Under a  $\text{N}_2$  flow, to a solution of (1*r*,3*r*)-ethyl 3-hydroxycyclobutanecarboxylate [160351-88-2] (1.86 g, 12.901 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) were added pyridine (1.56 mL) and tosyl anhydride (4.63 g, 14.192 mmol). The mixture was stirred for 6 h at room temperature. The mixture was concentrated under vacuum, suspended in diethyl ether (200 mL) and washed with 0.5 M hydrochloric acid ( $2 \times 60$  mL), a saturated solution of sodium hydrogen carbonate ( $2 \times 60$  mL), water (60 mL) and brine (50 mL), and then dried over sodium sulfate, filtered and concentrated under reduced pressure to yield (1*r*,3*r*)-ethyl 3-(tosyloxy)cyclobutanecarboxylate **8a** (3.97 g). The compound was used as such in the next step.

### Synthesis of intermediate **8b**:

(1*r*,3*r*)-ethyl 3-(tosyloxy)cyclobutanecarboxylate **8a** (3.85 g, 12.904 mmol) was added dropwise to a mixture of 3-methoxy-5-nitrophenol [7145-49-5] (1.98 g, 11.73 mmol) and  $\text{K}_2\text{CO}_3$  (1.95 g, 14.07 mmol) in DMF (20 mL). The mixture was

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stirred at 80°C for 16 h. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water, dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under reduced pressure. Purification was performed by flash chromatography on silica gel (15-40 μm, 120 g, heptane/EtOAc 95/5 to 85/15) The pure fractions were combined and evaporated to dryness to give (1*s*,3*s*)-ethyl 3-(3-methoxy-5-nitrophenoxy)cyclobutanecarboxylate **8b** (2.04 g).

#### Synthesis of intermediate **8c**:

A solution of (1*s*,3*s*)-ethyl 3-(3-methoxy-5-nitrophenoxy)cyclobutanecarboxylate **8b** (2.04 g, 6.908 mmol) in EtOH (50 mL) containing a catalytic amount of 10% Pd/C (735 mg, 0.691 mmol) was hydrogenated under atmospheric pressure of H<sub>2</sub> at room temperature for 4 h. The catalyst was removed by filtration over a short pad of Celite<sup>®</sup> and the filter cake was rinsed several times with EtOH. The combined filtrates were evaporated under reduced pressure to give (1*s*,3*s*)-ethyl 3-(3-amino-5-methoxyphenoxy)cyclobutanecarboxylate **8c** (1.8 g). The compound was used as such in the next step.

#### Synthesis of intermediate **8d**:

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (1.5 g, 3.462 mmol), (1*s*,3*s*)-ethyl 3-(3-amino-5-methoxyphenoxy)cyclobutanecarboxylate **8c** (870 mg, 3.462 mmol) and diisopropylethylamine (1.19 mL, 6.924 mmol) in CH<sub>3</sub>CN (30 mL) was stirred at 80°C for 16 h. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with 1N HCl and brine, dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under vacuum. The compound was crystallized from CH<sub>3</sub>CN/Et<sub>2</sub>O to give intermediate **8** (fraction 1, 820 mg). The filtrate was concentrated under reduced pressure to give another batch of crude intermediate **8** (fraction 2, 1 g).

The reaction was duplicated starting from 692 mg (1.592 mmol) of **1c** (using the same reaction conditions as described above). The reaction product was crystallized from Et<sub>2</sub>O to give intermediate **8** (fraction 3, 400 mg). The filtrate was concentrated under reduced pressure to give another batch of intermediate **8** (fraction 4, 600 mg). Fractions 2 and 4 were combined and purified by flash chromatography on silica gel (15-40 μm, 80 g, heptane/EtOAc 90/10 to 70/30) The pure fractions were combined and evaporated to dryness to give fraction 5 (250 mg). Fractions 1, 3 and 5 were combined and dried to give (1*s*,3*s*)-ethyl 3-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)cyclobutanecarboxylate **8d** (1.53 g).

**Synthesis of Compound 8 and chiral separation into Enantiomers 8A and 8B:**

At 0°C, LiOH monohydrate (318 mg, 7.58 mmol) was added portionwise to a solution of (1*s*,3*s*)-ethyl 3-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)cyclobutanecarboxylate **8d** (1.53 g, 2.529 mmol) in THF/water/MeOH (1/1/1) (30 mL). The reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with water and 3N HCl was added to acidify the solution. The mixture was extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (15-40 μm, 40 g, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100/0 to 98.5/1.5). The pure fractions were combined and evaporated under reduced pressure to give (1*s*,3*s*)-3-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)cyclobutanecarboxylic acid (Compound **8**, 1.26 g). The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5 μm 250 x 20 mm, mobile phase: 55% CO<sub>2</sub>, 45% EtOH) to give, after solidification from ether/diisopropyl ether, the first eluted Enantiomer **8A** (442 mg) and the second eluted Enantiomer **8B** (433 mg).

**Compound 8:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.03 - 2.13 (m, 2 H) 2.57 - 2.66 (m, 2 H) 2.66 - 2.76 (m, 1 H) 3.08 - 3.26 (m, 2 H) 3.61 (s, 3 H) 4.04 (td, *J*=10.2, 7.3 Hz, 1 H) 4.44 - 4.58 (m, 2 H) 5.54 (d, *J*=8.5 Hz, 1 H) 5.66 (s, 1 H) 5.87 (s, 1 H) 5.94 (s, 1 H) 6.49 (d, *J*=8.5 Hz, 1 H) 7.02 (br d, *J*=8.2 Hz, 1 H) 7.34 (d, *J*=8.2 Hz, 1 H) 7.45 (d, *J*=8.2 Hz, 2 H) 7.55 (d, *J*=8.2 Hz, 2 H) 8.04 (s, 1 H) 12.27 (br s, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.90 min, MH<sup>+</sup> 591

**Enantiomer 8A:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.01 - 2.14 (m, 2 H) 2.55 - 2.72 (m, 3 H) 3.08 - 3.24 (m, 2 H) 3.61 (s, 3 H) 4.04 (td, *J*=10.4, 7.3 Hz, 1 H) 4.41 - 4.57 (m, 2 H) 5.54 (d, *J*=8.8 Hz, 1 H) 5.66 (s, 1 H) 5.86 (s, 1 H) 5.93 (s, 1 H) 6.48 (br d, *J*=8.8 Hz, 1 H) 7.01 (br d, *J*=8.2 Hz, 1 H) 7.33 (d, *J*=8.2 Hz, 1 H) 7.44 (d, *J*=8.5 Hz, 2 H) 7.55 (d, *J*=8.2 Hz, 2 H) 8.03 (s, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.90 min, MH<sup>+</sup> 591

[α]<sub>D</sub><sup>20</sup>: -47.1° (c 0.274, DMF)

Chiral SFC (method SFC-I): R<sub>t</sub> 1.18 min, MH<sup>+</sup> 591, chiral purity 100%.

**Enantiomer 8B:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.02 - 2.13 (m, 2 H) 2.55 - 2.70 (m, 3 H) 3.06 - 3.25 (m, 2 H) 3.61 (s, 3 H) 4.04 (td, *J*=10.2, 7.3 Hz, 1 H) 4.39 - 4.57 (m, 2 H) 5.54 (d, *J*=8.8 Hz, 1 H) 5.66 (s, 1 H) 5.86 (s, 1 H) 5.93 (s, 1 H) 6.48 (br d, *J*=8.8 Hz, 1 H) 7.01 (br d, *J*=7.9 Hz, 1 H) 7.33 (d, *J*=8.2 Hz, 1 H) 7.44 (d, *J*=8.2 Hz, 2 H) 7.55 (d, *J*=8.5 Hz, 2 H) 8.03 (s, 1 H)

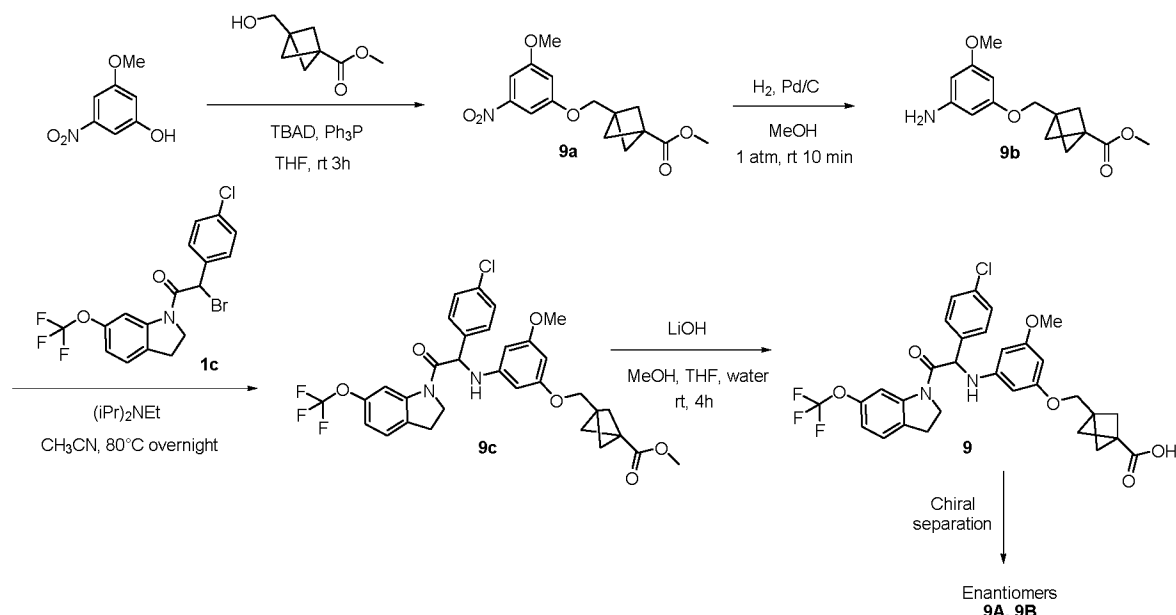
LC/MS (method LC-C): *R*<sub>t</sub> 2.91 min, MH<sup>+</sup> 591

[α]<sub>D</sub><sup>20</sup>: +40.0° (c 0.25, DMF)

Chiral SFC (method SFC-I): *R*<sub>t</sub> 2.16 min, MH<sup>+</sup> 591, chiral purity 100%.

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**Example 9** : synthesis of 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)-indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid (Compound **9**) and chiral separation into Enantiomers **9A** and **9B**



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**Synthesis of intermediate 9a:**

3-Methoxy-5-nitrophenol [7145-49-5] (1.1 g, 6.4 mmol), di-*tert*-butyl azodicarboxylate (TBAD, 1.65 g, 7.04 mmol) and triphenylphosphine (2.35 g, 8.96 mmol) were dissolved in dry THF (25 mL) at room temperature under N<sub>2</sub> atmosphere. A solution of methyl 3-(hydroxymethyl)bicyclo[1.1.1]pentane-1-carboxylate [180464-87-3] (1.0 g, 6.4 mmol) in dry THF (5 mL) was added dropwise (exothermic). The reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the residual yellow oil was purified by column chromatography on silica gel (100 g) using a gradient of EtOAc:EtOH(3:1)/heptane 0/100 to 50/50. The product fractions were combined and evaporated under reduced pressure. The residue was triturated with a small

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amount of Et<sub>2</sub>O. The solid was filtered off and washed with a small amount of Et<sub>2</sub>O and dried under vacuum at 50°C to give methyl 3-((3-methoxy-5-nitrophenoxy)methyl)bicyclo[1.1.1]pentane-1-carboxylate **9a** (1.06 g).

5 **Synthesis of intermediate 9b:**

A solution of methyl 3-((3-methoxy-5-nitrophenoxy)methyl)bicyclo[1.1.1]pentane-1-carboxylate **9a** (1.06 g, 3.44 mmol) in MeOH (150 mL) containing a catalytic amount of 10% Pd/C (366 mg, 0.34 mmol) was hydrogenated under atmospheric pressure of H<sub>2</sub> at room temperature for 10 min. The catalyst was removed by  
10 filtration over a short pad of Celite<sup>®</sup> under N<sub>2</sub>-atmosphere and the filter cake was rinsed several times with MeOH. The combined filtrates were evaporated to give methyl 3-((3-amino-5-methoxyphenoxy)methyl)bicyclo[1.1.1]pentane-1-carboxylate **9b** (961 mg) as a black oil which was used without further purification in the next step.

15

**Synthesis of intermediate 9c:**

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (1.16 g, 2.67 mmol), methyl 3-((3-amino-5-methoxyphenoxy)methyl)bicyclo[1.1.1]pentane-1-carboxylate **9b** (961 mg, 3.47  
20 mmol) and diisopropylethylamine (689 µL, 4.0 mmol) in CH<sub>3</sub>CN (50 mL) was stirred at 80°C overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>. The organic solution was washed with 1N HCl and water, dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (100  
25 g) using a gradient of EtOAc:EtOH(3:1)/heptane 0/100 to 50/50. The product fractions were combined and evaporated under reduced pressure. The residue was suspended in a small amount of heptane/EtOAc 10/1 and the solid was filtered off and washed with a small amount of heptane. The solids were dried under vacuum at 50°C to give methyl 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-  
30 methoxyphenoxy)methyl)bicyclo[1.1.1]pentane-1-carboxylate **9c** (1.21 g) as a white powder.

**Synthesis of Compound 9 and separation into Enantiomers 9A and 9B:**

35 LiOH (92 mg, 3.84 mmol) was added to a solution of methyl 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)bicyclo[1.1.1]pentane-1-carboxylate **9c** (1.21 g, 1.92 mmol) in a solvent mixture of MeOH (20 mL), THF (40 mL) and water (20 mL). The

reaction mixture was stirred at room temperature for 4 h. 1N HCl (1 mL) was added and the organic volatiles were evaporated under reduced pressure. The residual aqueous mixture was diluted with water, acidified with 1N HCl to pH 2, and extracted twice with Et<sub>2</sub>O. The combined organic layers were dried over  
5 MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. The residue was dried under vacuum at 50°C to give 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid (Compound **9**, 1.06 g) as a pale yellow solid.

The enantiomers of Compound **9** (994 mg) were separated by preparative chiral  
10 SFC (Stationary phase: Chiralcel<sup>®</sup> Diacel OD 20 x 250 mm, mobile phase: CO<sub>2</sub>, EtOH + 0.4% iPrNH<sub>2</sub>). The product fractions were combined and evaporated under reduced pressure. The first eluted product was partitioned between EtOAc and water. 1N HCl was added and the layers were separated. The aqueous layer was extracted again with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>,  
15 filtered, evaporated under reduced pressure and dried under vacuum at 50°C to give Enantiomer **9A** (353 mg). The second eluted product was partitioned between EtOAc and water. 1N HCl was added and the layers were separated. The aqueous layer was extracted again with EtOAc. The combined organic layers were dried  
20 over MgSO<sub>4</sub>, filtered, evaporated under reduced pressure and dried under vacuum at 50°C to give Enantiomer **9B** (193 mg).

#### Compound **9**:

<sup>1</sup>H NMR (360 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.92 (s, 6 H) 3.06 - 3.27 (m, 2 H) 3.62 (s, 3  
H) 3.87 (s, 2 H) 4.06 (td, *J*=10.3, 7.1 Hz, 1 H) 4.52 (td, *J*=10.2, 6.6 Hz, 1 H) 5.58  
25 (d, *J*=8.8 Hz, 1 H) 5.75 (t, *J*=2.0 Hz, 1 H) 5.92 - 5.97 (m, 2 H) 6.46 (d, *J*=9.1 Hz, 1  
H) 7.01 (dd, *J*=8.2, 1.6 Hz, 1 H) 7.34 (d, *J*=8.1 Hz, 1 H) 7.41 - 7.47 (m, 2 H) 7.51 -  
7.58 (m, 2 H) 8.03 (br s, 1 H) 12.37 (br s, 1 H)  
LC/MS (method LC-A): R<sub>t</sub> 1.09 min, MH<sup>+</sup> 617

#### Enantiomer **9A**:

<sup>1</sup>H NMR (360 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.92 (s, 6 H) 3.07 - 3.25 (m, 2 H) 3.61 (s, 3  
H) 3.87 (s, 2 H) 3.98 - 4.11 (m, 1 H) 4.51 (td, *J*=10.2, 6.4 Hz, 1 H) 5.57 (d, *J*=8.8  
Hz, 1 H) 5.75 (t, *J*=2.0 Hz, 1 H) 5.92 - 5.96 (m, 2 H) 6.46 (d, *J*=9.1 Hz, 1 H) 7.01  
35 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.33 (d, *J*=8.1 Hz, 1 H) 7.44 (d, *J*=8.4 Hz, 2 H) 7.50 - 7.59  
(m, 2 H) 8.03 (br s, 1 H) 12.37 (br s, 1 H)  
LC/MS (method LC-B): R<sub>t</sub> 1.91 min, MH<sup>+</sup> 617  
[α]<sub>D</sub><sup>20</sup>: -43.6° (c 0.5, DMF)  
Chiral SFC (method SFC-D): R<sub>t</sub> 5.26 min, MH<sup>+</sup> 617 chiral purity 98.6%.



**Enantiomer 9B:**

<sup>1</sup>H NMR (360 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.93 (s, 6 H) 3.08 - 3.25 (m, 2 H) 3.62 (s, 3 H) 3.88 (s, 2 H) 4.00 - 4.11 (m, 1 H) 4.52 (td, *J*=10.2, 6.6 Hz, 1 H) 5.58 (d, *J*=8.8 Hz, 1 H) 5.76 (t, *J*=1.8 Hz, 1 H) 5.92 - 5.98 (m, 2 H) 6.47 (d, *J*=8.8 Hz, 1 H) 7.01 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.33 (d, *J*=8.4 Hz, 1 H) 7.44 (d, *J*=8.4 Hz, 2 H) 7.51 - 7.60 (m, 2 H) 8.04 (br s, 1 H) 12.38 (br s, 1 H)

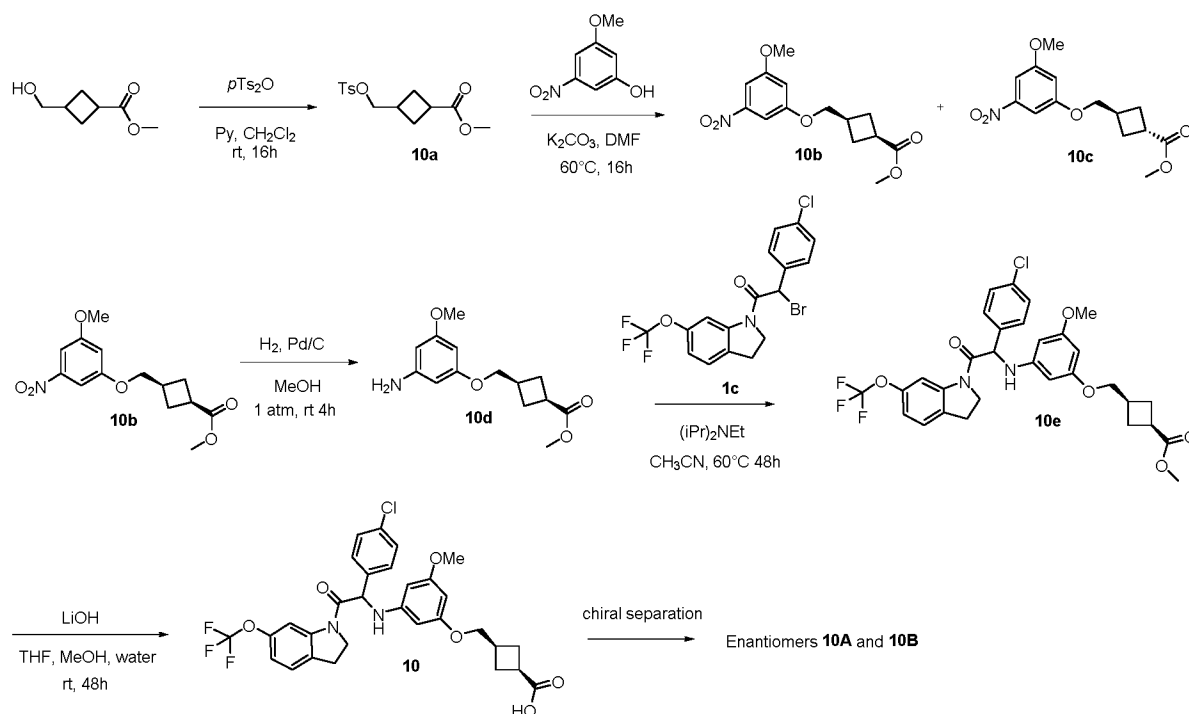
LC/MS (method LC-B): R<sub>t</sub> 1.91 min, MH<sup>+</sup> 617

[α]<sub>D</sub><sup>20</sup>: +42.2° (c 0.41, DMF)

Chiral SFC (method SFC-D): R<sub>t</sub> 6.47 min, MH<sup>+</sup> 617 chiral purity 99.5%.

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**Example 10** : synthesis of (1*s*,3*s*)-3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclobutenecarboxylic acid (Compound **10**) and chiral separation into Enantiomers **10A** and **10B**

**Synthesis of intermediate 10a:**

Under a N<sub>2</sub> flow, to a solution of methyl 3-(hydroxymethyl)cyclobutanecarboxylate [89941-55-9] (1.4 g, 9.71 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) were added pyridine (1.17 mL) and tosyl anhydride (3.49 g, 10.682 mmol). The mixture was stirred for 16 h at room temperature. The mixture was concentrated under vacuum, suspended in diethyl ether (200 mL) and washed with 0.5 M hydrochloric acid (2×50 mL), a saturated solution of sodium hydrogen carbonate (2×50 mL), and brine (50 mL). The mixture was dried over sodium sulfate, filtered and concentrated under

reduced pressure to yield methyl 3-((tosyloxy)methyl)cyclobutanecarboxylate **10a** (2.15 g). The compound was used as such in the next step.

#### Synthesis of intermediates **10b** and **10c**:

- 5 3-((tosyloxy)methyl)cyclobutanecarboxylate **10a** (2.15 g, 7.206 mmol) was added dropwise to a mixture of 3-methoxy-5-nitrophenol [7145-49-5] (1.22 g, 7.206 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.5 g, 10.809 mmol) in DMF (14 mL). The mixture was stirred at 60°C for 16 h. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water, dried over MgSO<sub>4</sub>, filtered and the
- 10 solvent was evaporated under reduced pressure. Purification was performed by flash chromatography on silica gel (15-40 μm, 80 g, heptane/EtOAc 85/15 to 80/20). The pure fractions were combined and evaporated to dryness. The stereoisomers were separated via chiral SFC (Stationary phase: Chiralpack® AD-H 5 μm 250 x 30 mm, mobile phase: 55% CO<sub>2</sub>, 45% MeOH) to give (1*s*,3*s*)-methyl
- 15 3-((3-methoxy-5-nitrophenoxy)methyl)cyclobutanecarboxylate **10b** (541 mg) and (1*r*,3*r*)-methyl 3-((3-methoxy-5-nitrophenoxy)methyl)cyclobutanecarboxylate **10c** (428 mg).

#### Synthesis of intermediate **10d**:

- 20 A solution of (1*s*,3*s*)-methyl 3-((3-methoxy-5-nitrophenoxy)methyl)cyclobutene-carboxylate **10b** (530 mg, 1.795 mmol) in MeOH (10 mL) containing a catalytic amount of 10% Pd/C (191 mg, 0.179 mmol) was hydrogenated under atmospheric pressure of H<sub>2</sub> at room temperature for 4 h. The catalyst was removed by filtration over a short pad of Celite® and the filter cake was rinsed several times with
- 25 MeOH. The combined filtrates were evaporated under reduced pressure to give (1*s*,3*s*)-methyl 3-((3-amino-5-methoxyphenoxy)methyl)cyclobutanecarboxylate **10d** (480 mg). The compound was used as such in the next step.

#### Synthesis of intermediate **10e**:

- 30 A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (580 mg, 1.334 mmol), (1*s*,3*s*)-methyl 3-((3-amino-5-methoxyphenoxy)methyl)cyclobutanecarboxylate **10d** (460 mg, 1.734 mmol) and diisopropylethylamine (460 μL, 2.667 mmol) in CH<sub>3</sub>CN (10 mL) was stirred at 60°C for 48 h. The mixture was concentrated under reduced pressure and taken-up with
- 35 EtOAc. The organic layer was washed with 1N HCl and water, dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under vacuum to give, after crystallization from Et<sub>2</sub>O/diisopropyl ether (1*s*,3*s*)-methyl 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-

(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclobutene-carboxylate **10e** (625 mg).

**Synthesis of Compound 10 and chiral separation into Enantiomers 10A and 10B:**

At 0°C, LiOH monohydrate (127 mg, 3.029 mmol) was added portionwise to a solution of (1*s*,3*s*)-methyl 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclobutanecarboxylate **10e** (625 mg, 1.01 mmol) in THF/water/MeOH (1/1/1) (15 mL). The reaction mixture was stirred at room temperature for 48 h. The mixture was cooled to 0°C and was diluted with water. 3N HCl was added to acidify the solution and the mixture was extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was crystallized from Et<sub>2</sub>O/diisopropyl ether to give (1*s*,3*s*)-3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclobutene-carboxylic acid (Compound **10**, 440 mg). The two enantiomers were separated via chiral SFC (Stationary phase: Whelk<sup>®</sup> O1 (S,S) 5 μm 250 x 21.1 mm, mobile phase: 58% CO<sub>2</sub>, 42% MeOH) to give, after solidification from heptane /diisopropyl ether/ether, the first eluted Enantiomer **10A** (116 mg) and the second eluted Enantiomer **10B** (119 mg).

**Compound 10:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.87 - 1.99 (m, 2 H) 2.18 - 2.30 (m, 2 H) 2.53 - 2.61 (m, 1 H) 2.97 (quin, *J*=8.9 Hz, 1 H) 3.08 - 3.27 (m, 2 H) 3.62 (s, 3 H) 3.78 (br d, *J*=6.3 Hz, 2 H) 4.05 (td, *J*=10.4, 7.2 Hz, 1 H) 4.52 (td, *J*=10.3, 6.5 Hz, 1 H) 5.57 (d, *J*=8.8 Hz, 1 H) 5.72 - 5.78 (m, 1 H) 5.94 (s, 2 H) 6.45 (br d, *J*=8.8 Hz, 1 H) 6.95 - 7.06 (m, 1 H) 7.34 (d, *J*=8.2 Hz, 1 H) 7.44 (d, *J*=8.2 Hz, 2 H) 7.55 (d, *J*=8.5 Hz, 2 H) 8.04 (s, 1 H) 12.08 (br s, 1 H)

LC/MS (method LC-D): R<sub>t</sub> 2.94 min, MH<sup>+</sup> 605

MP = 128°C

**Enantiomer 10A:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.84 - 1.97 (m, 2 H) 2.15 - 2.30 (m, 2 H) 2.53 - 2.61 (m, 1 H) 2.94 (quin, *J*=8.9 Hz, 1 H) 3.07 - 3.25 (m, 2 H) 3.61 (s, 3 H) 3.77 (br d, *J*=6.3 Hz, 2 H) 4.05 (td, *J*=10.4, 6.9 Hz, 1 H) 4.52 (td, *J*=10.3, 6.1 Hz, 1 H) 5.57 (d, *J*=8.8 Hz, 1 H) 5.74 (t, *J*=1.9 Hz, 1 H) 5.93 (s, 2 H) 6.44 (d, *J*=8.8 Hz, 1 H) 7.01 (dd, *J*=8.0, 1.4 Hz, 1 H) 7.33 (d, *J*=8.2 Hz, 1 H) 7.44 (d, *J*=8.5 Hz, 2 H) 7.55 (d, *J*=8.2 Hz, 2 H) 8.03 (s, 1 H)

LC/MS (method LC-C):  $R_t$  3.08 min,  $MH^+$  605

$[\alpha]_D^{20}$ : -44.0 (c 0.314, DMF)

Chiral SFC (method SFC-J):  $R_t$  1.63 min,  $MH^+$  605, chiral purity 100%.

### 5 Enantiomer 10B:

$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.85 - 1.97 (m, 2 H) 2.17 - 2.28 (m, 2 H) 2.53 - 2.58 (m, 1 H) 2.94 (quint,  $J=8.8$  Hz, 1 H) 3.07 - 3.24 (m, 2 H) 3.61 (s, 3 H) 3.72 - 3.82 (m, 2 H) 4.05 (td,  $J=10.4, 7.3$  Hz, 1 H) 4.52 (td,  $J=10.4, 6.9$  Hz, 1 H) 5.57 (d,  $J=8.8$  Hz, 1 H) 5.72 - 5.77 (m, 1 H) 5.93 (s, 2 H) 6.44 (d,  $J=8.8$  Hz, 1 H) 7.01 (dd,  $J=8.0, 1.4$  Hz, 1 H) 7.33 (d,  $J=7.9$  Hz, 1 H) 7.44 (d,  $J=8.5$  Hz, 2 H) 7.55 (d,  $J=8.5$  Hz, 2 H) 8.03 (s, 1 H)

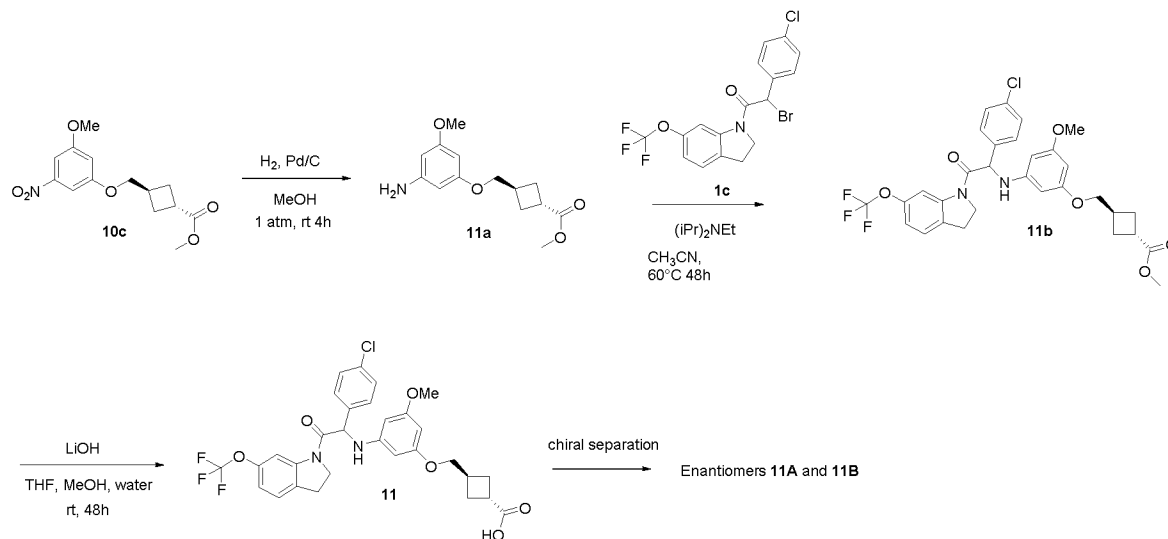
LC/MS (method LC-C):  $R_t$  3.08 min,  $MH^+$  605

$[\alpha]_D^{20}$ : +45.5° (c 0.308, DMF)

Chiral SFC (method SFC-J):  $R_t$  2.14 min,  $MH^+$  605, chiral purity 99.57%.

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**Example 11** : synthesis of (1*r*,3*r*)-3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclobutene-carboxylic acid (Compound **11**) and chiral separation into Enantiomers **11A** and **11B**



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### Synthesis of intermediate 11a:

A solution of (1*r*,3*r*)-methyl 3-((3-methoxy-5-nitrophenoxy)methyl)cyclobutene-carboxylate **10c** (410 mg, 1.388 mmol) in MeOH (10 mL) containing a catalytic amount of 10% Pd/C (148 mg, 0.139 mmol) was hydrogenated under atmospheric pressure of  $H_2$  at room temperature for 4 h. The catalyst was removed by filtration over a short pad of Celite® and the filter cake was rinsed several times with MeOH. The combined filtrates were evaporated under reduced pressure to give (1*r*,3*r*)-

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methyl 3-((3-amino-5-methoxyphenoxy)methyl)cyclobutanecarboxylate **11a** (370 mg). The compound was used as such in the next step.

#### Synthesis of intermediate **11b**:

5 A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (460 mg, 1.058 mmol), (1*r*,3*r*)-methyl 3-((3-amino-5-methoxyphenoxy)methyl)cyclobutanecarboxylate **11a** (365 mg, 1.376 mmol) and diisopropylethylamine (365  $\mu$ L, 2.117 mmol) in CH<sub>3</sub>CN (8 mL) was stirred at 60°C for 48 h. The mixture was concentrated under reduced pressure and taken-up with  
10 EtOAc. The organic layer was washed with 1N HCl and water, dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under vacuum to give, after crystallization from Et<sub>2</sub>O/diisopropyl ether (1*r*,3*r*)-methyl 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclobutanecarboxylate **11b** (515 mg).

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#### Synthesis of Compound **11** and chiral separation into Enantiomers **11A** and **11B**:

At 0°C, LiOH monohydrate (105 mg, 2.496 mmol) was added portionwise to a solution of ((1*r*,3*r*)-methyl 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclobutanecarboxylate **11b**  
20 (515 mg, 0.832 mmol) in THF/water/MeOH (1/1/1) (15 mL). The reaction mixture was stirred at room temperature for 48 h. The mixture was cooled to 0°C and was diluted with water. 3N HCl was added to acidify the solution and the mixture was extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>,  
25 filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15-40  $\mu$ m, 24 g, CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 100/0 to 98/2). The pure fractions were combined and evaporated to dryness to give (1*r*,3*r*)-3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclobutanecarboxylic acid (Compound **11**, 460 mg). The  
30 two enantiomers were separated via chiral SFC (Stationary phase: Whelk<sup>®</sup> O1 (S,S) 5  $\mu$ m 250 x 21.1 mm, mobile phase: 58% CO<sub>2</sub>, 42% MeOH) to give, after crystallization from ether/diisopropyl ether, the first eluted Enantiomer **11A** (121 mg) and the second eluted Enantiomer **11B** (120 mg).

#### 35 Compound **11**:

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.92 - 2.04 (m, 2 H) 2.21 - 2.31 (m, 2 H) 2.57 - 2.62 (m, 1 H) 3.04 - 3.26 (m, 3 H) 3.63 (s, 3 H) 3.88 (br d, *J*=6.9 Hz, 2 H) 4.00 - 4.11 (m, 1 H) 4.47 - 4.58 (m, 1 H) 5.57 (d, *J*=8.8 Hz, 1 H) 5.78 (s, 1 H) 5.96 (br d,

$J=9.7$  Hz, 2 H) 6.45 (br d,  $J=8.8$  Hz, 1 H) 7.02 (br d,  $J=8.2$  Hz, 1 H) 7.34 (d,  $J=8.2$  Hz, 1 H) 7.45 (d,  $J=8.2$  Hz, 2 H) 7.55 (d,  $J=8.5$  Hz, 2 H) 8.04 (s, 1 H) 12.12 (br s, 1 H)

LC/MS (method LC-D):  $R_t$  2.95 min,  $MH^+$  605

5

**Enantiomer 11A:**

$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.94 - 2.03 (m, 2 H) 2.21 - 2.31 (m, 2 H) 2.55 - 2.62 (m, 1 H) 3.04 - 3.25 (m, 3 H) 3.62 (s, 3 H) 3.87 (d,  $J=7.3$  Hz, 2 H) 4.04 (td,  $J=10.4$ , 6.9 Hz, 1 H) 4.52 (td,  $J=10.2$ , 6.3 Hz, 1 H) 5.57 (d,  $J=8.8$  Hz, 1 H) 5.78 (t,  $J=1.9$  Hz, 1 H) 5.94 (s, 1 H) 5.96 (s, 1 H) 6.45 (d,  $J=8.5$  Hz, 1 H) 7.01 (dd,  $J=8.2$ , 1.6 Hz, 1 H) 7.33 (d,  $J=8.2$  Hz, 1 H) 7.44 (d,  $J=8.5$  Hz, 2 H) 7.55 (d,  $J=8.5$  Hz, 2 H) 8.03 (s, 1 H) 12.12 (br s, 1 H)

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LC/MS (method LC-C):  $R_t$  3.08 min,  $MH^+$  605

$[\alpha]_D^{20}$ :  $-43.3^\circ$  (c 0.319, DMF)

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Chiral SFC (method SFC-J):  $R_t$  1.73 min,  $MH^+$  605, chiral purity 100%.

**Enantiomer 11B:**

$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.92 - 2.02 (m, 2 H) 2.21 - 2.32 (m, 2 H) 2.55 - 2.62 (m, 1 H) 3.04 - 3.25 (m, 3 H) 3.62 (s, 3 H) 3.87 (d,  $J=6.9$  Hz, 2 H) 4.05 (td,  $J=10.3$ , 7.1 Hz, 1 H) 4.52 (td,  $J=10.3$ , 6.5 Hz, 1 H) 5.57 (d,  $J=8.8$  Hz, 1 H) 5.78 (t,  $J=1.9$  Hz, 1 H) 5.94 (s, 1 H) 5.96 (s, 1 H) 6.45 (br d,  $J=8.8$  Hz, 1 H) 7.01 (br d,  $J=8.2$  Hz, 1 H) 7.33 (d,  $J=8.2$  Hz, 1 H) 7.44 (d,  $J=8.5$  Hz, 2 H) 7.55 (d,  $J=8.5$  Hz, 2 H) 8.03 (s, 1 H) 12.16 (br s, 1 H)

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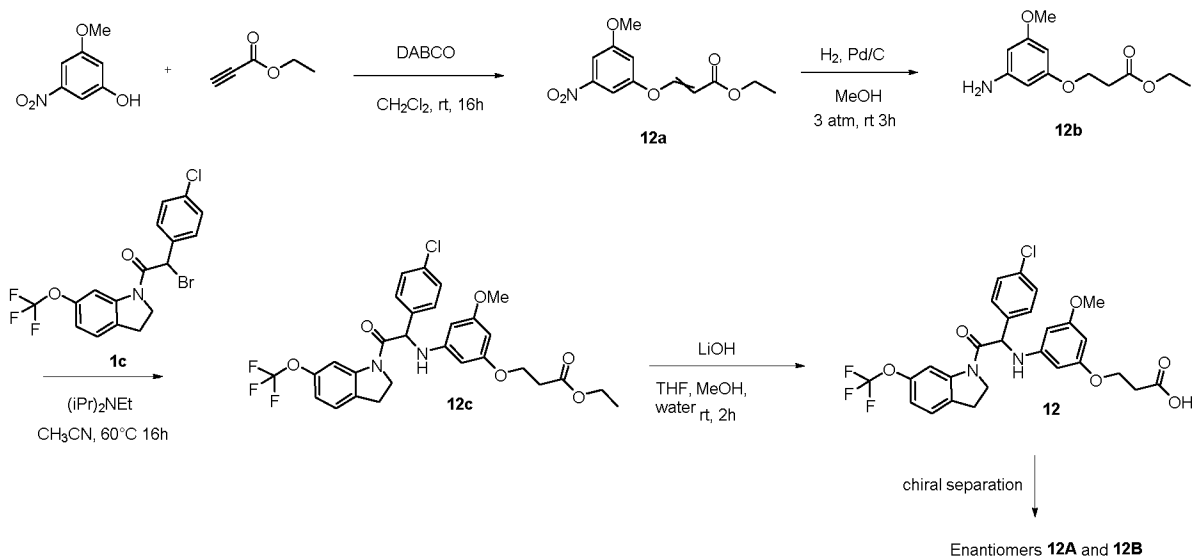
LC/MS (method LC-C):  $R_t$  3.08 min,  $MH^+$  605

$[\alpha]_D^{20}$ :  $+45.5^\circ$  (c 0.323, DMF)

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Chiral SFC (method SFC-J):  $R_t$  2.36 min,  $MH^+$  605, chiral purity 99.61%.

**Example 12** : synthesis of 3-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)propanoic acid (Compound **12**) and chiral separation into Enantiomers **12A** and **12B**



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### Synthesis of intermediate **12a**:

1,4-diazabicyclo[2.2.2]octane (66 mg, 0.591 mmol) was added to a solution of 3-methoxy-5-nitrophenol [7145-49-5] (2.0 g, 11.825 mmol), ethylacetylenecarboxylate (1.2 mL, 11.825 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL). The mixture was stirred at room temperature for 16 h. The mixture was poured out into water and the layers were decanted. The organic layer was washed with water, brine, dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated under reduced pressure to give ethyl 3-(3-methoxy-5-nitrophenoxy)acrylate **12a** (3.22 g, E/Z mixture).

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### Synthesis of intermediate **12b**:

A mixture of ethyl 3-(3-methoxy-5-nitrophenoxy)acrylate **12a** (3.2 g, 11.97 mmol) and Pd/C (10%) (2.5 g, 2.395 mmol) in  $\text{CH}_3\text{OH}$  (100 mL) was hydrogenated under a pressure of 3 bar for 3 h. The catalyst was removed by filtration through a pad of Celite<sup>®</sup>. The filter cake was rinsed with  $\text{CH}_3\text{OH}$  and the combined filtrates were concentrated under reduced pressure. Purification was performed by flash chromatography on silica gel (15-40  $\mu\text{m}$ , 80 g, heptane/EtOAc 75/25). The pure fractions were combined and evaporated to dryness to give ethyl 3-(3-amino-5-methoxyphenoxy)propanoate **12b** (1.8 g).

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**Synthesis of intermediate 12c:**

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (1.0 g, 2.301 mmol), ethyl 3-(3-amino-5-methoxyphenoxy)propanoate **12b** (716 mg, 2.991 mmol) and diisopropylethylamine (793  $\mu$ L, 4.602 mmol) in CH<sub>3</sub>CN (29 mL) was stirred at 60°C for 16 h. The mixture was concentrated under reduced pressure and taken-up with EtOAc. The organic layer was washed with 1N HCl and water, dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under vacuum. Purification was performed by flash chromatography on silica gel (15-40  $\mu$ m, 80 g, heptane/EtOAc 75/25). The pure fractions were combined and evaporated to dryness to give 3-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)propanoic acid **12c** (660 mg).

**Synthesis of Compound 12 and chiral separation into Enantiomers 12A and 12B:**

At 0°C, LiOH monohydrate (79 mg, 1.889 mmol) was added portionwise to a solution of 3-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)propanoic acid **12c** (560 mg, 0.944 mmol) in THF/water/MeOH (1/1/1) (15 mL). The reaction mixture was stirred at room temperature for 2 h. The mixture was cooled to 0°C and was diluted with water. 3N HCl was added to acidify the solution. The mixture was extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified via reverse phase (Stationary phase: YMC-DispoPack AT ODS-25: 120 g, mobile phase: Gradient from 75% NH<sub>4</sub>HCO<sub>3</sub> 0.2%, 25% CH<sub>3</sub>CN to 35% NH<sub>4</sub>HCO<sub>3</sub> 0.2%, 65% CH<sub>3</sub>CN). The pure fractions were combined and evaporated to dryness to give 3-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)propanoic acid (Compound **12**, 126 mg). The two enantiomers were separated on a 70 mg batch via chiral SFC (Stationary phase: Chiralcel® OD-H 5  $\mu$ m 250 x 20 mm, mobile phase: 65% CO<sub>2</sub>, 35% iPrOH (+0.3% iPrNH<sub>2</sub>) to give, after freeze-drying in a mixture of CH<sub>3</sub>CN (2 mL)/water (8 mL), the first eluted Enantiomer **12A** (30 mg) and the second eluted Enantiomer **12B** (35 mg).

**Compound 12:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 2.56 (t, *J*=6.1 Hz, 2 H) 3.04 - 3.26 (m, 2 H) 3.61 (s, 3 H) 3.95 - 4.11 (m, 3 H) 4.43 - 4.61 (m, 1 H) 5.56 (d, *J*=8.6 Hz, 1 H) 5.74 (s, 1 H) 5.94 (br d, *J*=7.1 Hz, 2 H) 6.46 (d, *J*=9.1 Hz, 1 H) 7.00 (br d, *J*=8.1 Hz, 1 H) 7.33 (d, *J*=8.1 Hz, 1 H) 7.43 (d, *J*=8.1 Hz, 2 H) 7.55 (d, *J*=8.6 Hz, 2 H) 8.03 (s, 1 H)



LC/MS (method LC-C):  $R_t$  2.84 min,  $MH^+$  565

### Enantiomer 12A:

$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 2.62 (br t,  $J=6.0$  Hz, 2 H) 3.09 - 3.24 (m, 2 H) 3.62 (s, 3 H) 4.00 - 4.10 (m, 3 H) 4.47 - 4.57 (m, 1 H) 5.58 (d,  $J=8.8$  Hz, 1 H) 5.75 (s, 1 H) 5.95 (br d,  $J=6.6$  Hz, 2 H) 6.49 (br d,  $J=8.8$  Hz, 1 H) 7.02 (br d,  $J=8.2$  Hz, 1 H) 7.34 (d,  $J=8.2$  Hz, 1 H) 7.44 (d,  $J=8.5$  Hz, 2 H) 7.55 (d,  $J=8.5$  Hz, 2 H) 8.04 (s, 1 H) 12.04 - 12.63 (m, 1 H)

LC/MS (method LC-C):  $R_t$  2.83 min,  $MH^+$  565

$[\alpha]_D^{20}$ :  $-47.3^\circ$  (c 0.275, DMF)

Chiral SFC (method SFC-K):  $R_t$  2.50 min,  $MH^+$  565, chiral purity 100%.

### Enantiomer 12B:

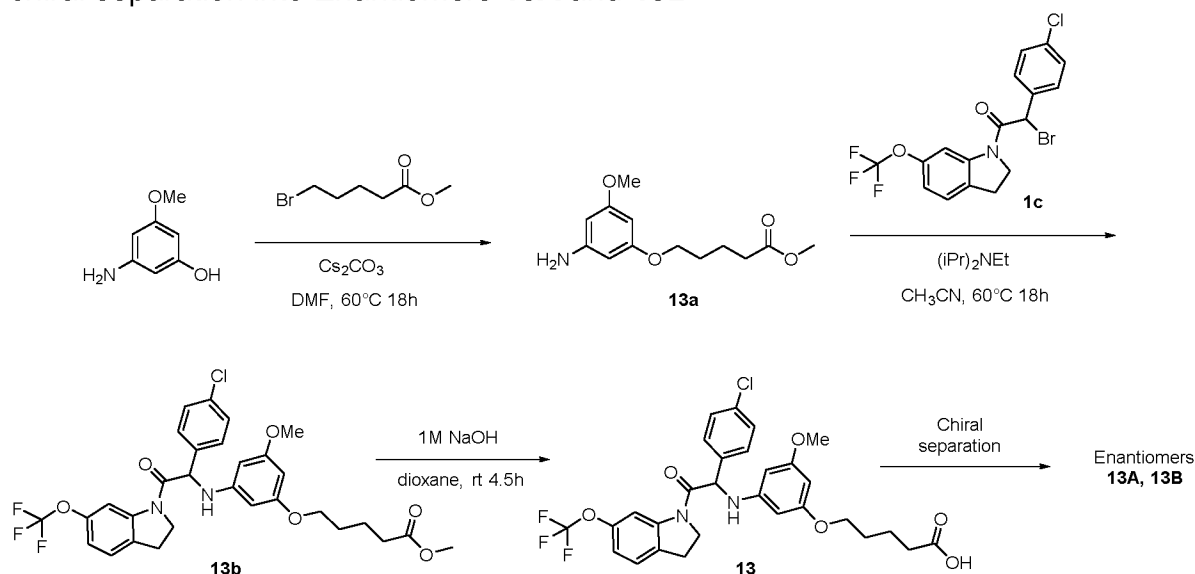
$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 2.58 - 2.67 (m, 2 H) 3.08 - 3.25 (m, 2 H) 3.62 (s, 3 H) 3.99 - 4.12 (m, 3 H) 4.52 (td,  $J=10.3, 6.1$  Hz, 1 H) 5.58 (s, 1 H) 5.75 (s, 1 H) 5.95 (br d,  $J=6.6$  Hz, 2 H) 6.50 (br s, 1 H) 7.02 (br d,  $J=7.9$  Hz, 1 H) 7.34 (d,  $J=8.2$  Hz, 1 H) 7.44 (d,  $J=8.5$  Hz, 2 H) 7.55 (d,  $J=8.5$  Hz, 2 H) 8.04 (s, 1 H) 12.35 (br s, 1 H)

LC/MS (method LC-C):  $R_t$  2.83 min,  $MH^+$  565

$[\alpha]_D^{20}$ :  $+41.8^\circ$  (c 0.297, DMF)

Chiral SFC (method SFC-K):  $R_t$  4.34 min,  $MH^+$  565, chiral purity 99.1%.

**Example 13** : synthesis of 5-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)pentanoic acid (Compound **13**) and chiral separation into Enantiomers **13A** and **13B**



**Synthesis of intermediate 13a:**

To a stirred solution of methyl 5-bromo-valerate [CAS 5454-83-1] (1.06 mL, 7.19 mmol) in DMF (25 mL) was added 3-amino-5-methoxyphenol [CAS 162155-27-3] (1.0 g, 7.19 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (4.68 g, 14.4 mmol). The reaction was stirred at 60°C for 18 h, and allowed to reach room temperature. The mixture was poured out into H<sub>2</sub>O (125 mL). The product was extracted (2x) with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (25 g) using a gradient of heptane/EtOAc 100/0 to 50/50. The product fractions were combined, evaporated under reduced pressure and co-evaporated with CH<sub>3</sub>CN. The product were dried under vacuum at 45°C to provide methyl 5-(3-amino-5-methoxyphenoxy)pentanoate **13a** (200 mg).

**Synthesis of intermediate 13b:**

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (340 mg, 0.78 mmol), methyl 5-(3-amino-5-methoxyphenoxy)pentanoate **13a** (198 mg, 0.78 mmol) and diisopropylethylamine (270 µL, 1.56 mmol) in CH<sub>3</sub>CN (30 mL) was stirred at 60°C for 18 h. The mixture was allowed to reach room temperature, and was poured out into water (150 mL). The product was extracted (2x) with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (40 g) using a gradient of heptane/EtOAc/EtOH 100/0/0 to 40/45/15. The product fractions were combined and evaporated under reduced pressure, and co-evaporated with dioxane to provide methyl 5-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)pentanoate **13b** (475 mg).

**Synthesis of Compound 13 and separation into Enantiomers 13A and 13B:**

1M NaOH in water (1.96 mL, 1.96 mmol) was added to a stirring solution of methyl 5-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)pentanoate **13b** (475 mg, 0.78 mmol) in dioxane (5 mL). The reaction mixture was stirred at room temperature for 4.5 h. the reaction mixture was diluted with water (20 mL) 1N HCl (2.1 mL). After stirring for 10 min, the product was extracted with 2-Me-THF. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (40 g) with a gradient of heptane/EtOAc/EtOH/HOAc 100/0/0/0 to 40/45/14.7/0.3. The product fractions

were combined and evaporated under reduced pressure to a residual volume of ~7.5 mL, allowing precipitation of the reaction product. The solids were filtered off, washed (3x) with EtOAc/heptane 1/3 and dried under vacuum at 45°C to provide 5-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)pentanoic acid (Compound **13**, 139 mg) as a racemic mixture. The enantiomers of Compound **13** (112 mg) were separated via preparative chiral SFC (Stationary phase: Chiralpak<sup>®</sup> Diacel OD 20 x 250 mm, mobile phase: CO<sub>2</sub>, EtOH + 0.4% iPrNH<sub>2</sub>). The fractions containing the first eluted product were combined, evaporated under reduced pressure, and co-evaporated with CH<sub>3</sub>CN. The residue was lyophilized from a solvent mixture of CH<sub>3</sub>CN (1.5 mL) and water (1 mL) to provide Enantiomer **13A** (39 mg). The fractions containing the second eluted product were combined, evaporated under reduced pressure, and evaporated with CH<sub>3</sub>CN. The residue was lyophilized from CH<sub>3</sub>CN (1.75 mL) and water (1.25 mL) to provide Enantiomer **13B** (33 mg).

### Compound **13**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.55 - 1.69 (m, 4 H) 2.25 (t, *J*=7.0 Hz, 2 H) 3.07 - 3.26 (m, 2 H) 3.62 (s, 3 H) 3.83 (t, *J*=5.9 Hz, 2 H) 4.05 (td, *J*=10.4, 7.2 Hz, 1 H) 4.52 (td, *J*=10.3, 6.4 Hz, 1 H) 5.56 (d, *J*=8.8 Hz, 1 H) 5.75 (t, *J*=2.0 Hz, 1 H) 5.91 - 5.97 (m, 2 H) 6.42 (d, *J*=8.8 Hz, 1 H) 7.01 (dd, *J*=8.3, 1.7 Hz, 1 H) 7.33 (d, *J*=8.1 Hz, 1 H) 7.38 - 7.48 (m, 2 H) 7.55 (d, *J*=8.6 Hz, 2 H) 8.03 (br s, 1 H) 12.01 (s, 1 H)

LC/MS (method LC-A): R<sub>t</sub> 1.13 min, MH<sup>+</sup> 593

### Enantiomer **13A**:

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.55 - 1.69 (m, 4 H) 2.24 (t, *J*=7.0 Hz, 2 H) 3.07 - 3.26 (m, 2 H) 3.62 (s, 3 H) 3.83 (t, *J*=5.9 Hz, 2 H) 4.05 (td, *J*=10.5, 7.3 Hz, 1 H) 4.52 (td, *J*=10.3, 6.4 Hz, 1 H) 5.56 (d, *J*=8.8 Hz, 1 H) 5.75 (t, *J*=2.1 Hz, 1 H) 5.92 - 5.96 (m, 2 H) 6.42 (d, *J*=8.6 Hz, 1 H) 7.01 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.33 (d, *J*=8.1 Hz, 1 H) 7.39 - 7.48 (m, 2 H) 7.55 (d, *J*=8.6 Hz, 2 H) 8.03 (br s, 1 H) 12.02 (br s, 1 H)

LC/MS (method LC-B): R<sub>t</sub> 2.08 min, MH<sup>+</sup> 593

[α]<sub>D</sub><sup>20</sup>: -48.6° (c 0.43, DMF)

Chiral SFC (method SFC-D): R<sub>t</sub> 5.27 min, MH<sup>+</sup> 593 chiral purity 100%.

### Enantiomer **13B**:

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.55 - 1.69 (m, 4 H) 2.24 (t, *J*=7.2 Hz, 2 H) 3.04 - 3.25 (m, 2 H) 3.62 (s, 3 H) 3.83 (t, *J*=5.9 Hz, 2 H) 4.05 (td, *J*=10.4, 7.2 Hz, 1

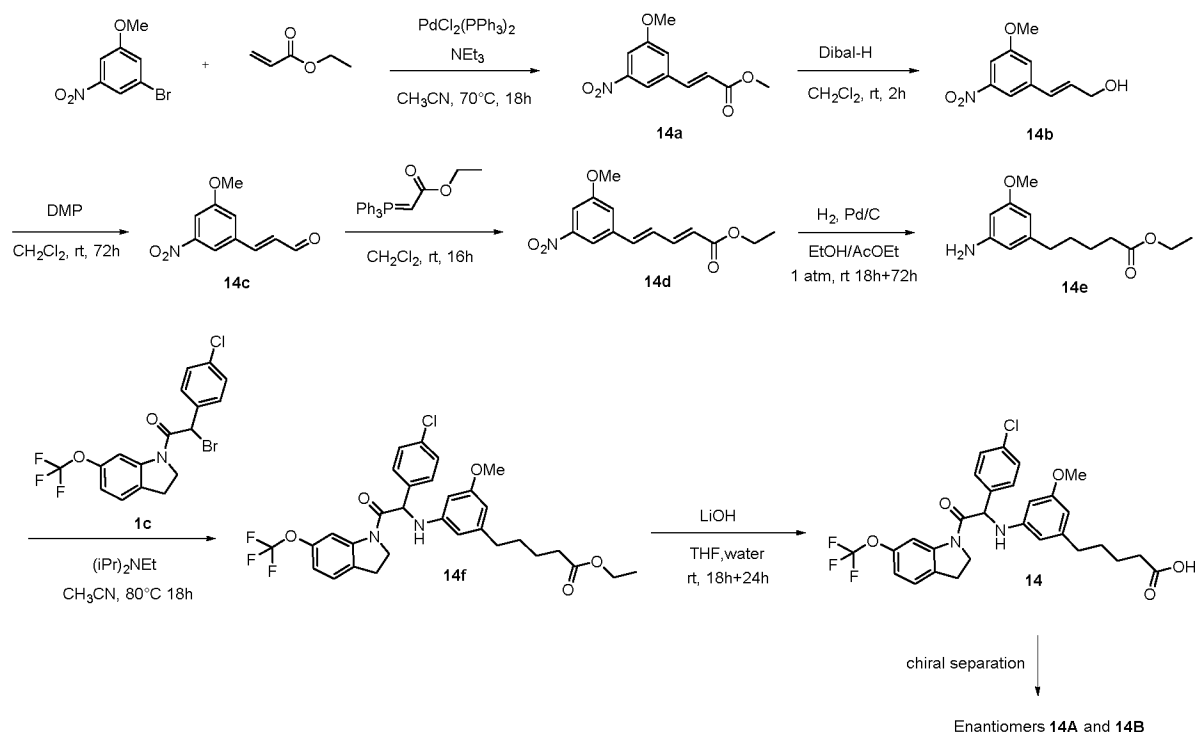
H) 4.52 (td,  $J=10.3, 6.2$  Hz, 1 H) 5.56 (d,  $J=8.8$  Hz, 1 H) 5.75 (t,  $J=2.0$  Hz, 1 H) 5.92 - 5.96 (m, 2 H) 6.42 (d,  $J=8.8$  Hz, 1 H) 7.01 (dd,  $J=8.1, 1.5$  Hz, 1 H) 7.33 (d,  $J=8.1$  Hz, 1 H) 7.42 - 7.46 (m, 2 H) 7.55 (d,  $J=8.6$  Hz, 2 H) 8.03 (br s, 1 H) 12.00 (br s, 1 H)

5 LC/MS (method LC-B):  $R_t$  2.08 min,  $MH^+$  593

$[\alpha]_D^{20}$ : +48.3° (c 0.42, DMF)

Chiral SFC (method SFC-D):  $R_t$  6.94 min,  $MH^+$  593 chiral purity 100%.

**Example 14** : synthesis of 5-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenyl)pentanoic acid (Compound 14) and chiral separation into Enantiomers 14A and 14B



### Synthesis of intermediate 14a:

15 In a sealed tube under  $N_2$  atmosphere,  $PdCl_2(PPh_3)_2$  (1.5 g, 2.2 mmol) was added to a degassed solution of 1-bromo-3-methoxy-5-nitrobenzene [CAS 16618-67-0] (5.0 g, 22 mmol), methyl acrylate (6.0 mL, 67 mmol) in  $CH_3CN$  (45 ml) and triethylamine (12 mL). The reaction was stirred at  $70^\circ C$  for 18 h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (30  $\mu m$ , 120 g, heptane/ $EtOAc$  gradient from 90/10 to 75/25) to give (*E*)-methyl 3-(3-methoxy-5-nitrophenyl)acrylate 14a (2.0 g).

**Synthesis of intermediate 14b:**

Under N<sub>2</sub> at 0°C, diisobutyl aluminumhydride (1M in CH<sub>2</sub>Cl<sub>2</sub>) (20 mL, 20 mmol) was added dropwise to a solution of (*E*)-methyl 3-(3-methoxy-5-nitrophenyl)acrylate **14a** (2.4 g, 10.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (65 ml). The reaction was slowly warmed to room temperature and stirred for 2 h. The mixture was quenched with HCl (3N) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give (*E*)-3-(3-methoxy-5-nitrophenyl)prop-2-en-1-ol **14b** (2.1 g). The compound was used as such in the next step.

10

**Synthesis of intermediate 14c:**

Under N<sub>2</sub> at 0°C, Dess-Martin Periodinane (24 mL, 11.04 mmol) was slowly added to a solution of (*E*)-3-(3-methoxy-5-nitrophenyl)prop-2-en-1-ol **14b** (2.1 g, 10.04 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (64 mL) and the mixture was stirred at room temperature for 72 h. Water was added and the mixture was filtered. The filtrate was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over MgSO<sub>4</sub> and evaporated until dryness to give (*E*)-3-(3-methoxy-5-nitrophenyl)acrylaldehyde **14c** (2.5 g). The compound was used as such in the next step.

15

**Synthesis of intermediate 14d:**

Under N<sub>2</sub>, (carbetoxymethylene)triphenylphosphorane (5.0 g, 14.48 mmol) was added in one portion to a mixture of (*E*)-3-(3-methoxy-5-nitrophenyl)acrylaldehyde **14c** (2.5 g, 9.65 mmol, 80% pure) in CH<sub>2</sub>Cl<sub>2</sub> (62 mL) and stirred at room temperature for 16 h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (30 μm, 80 g, heptane/EtOAc gradient from 85/15 to 60/30) to give (*2E,4E*)-ethyl 5-(3-methoxy-5-nitrophenyl)penta-2,4-dienoate **14d** (2.1 g). The compound was used as such in the next step.

25

**Synthesis of intermediate 14e:**

A mixture of (*2E,4E*)-ethyl 5-(3-methoxy-5-nitrophenyl)penta-2,4-dienoate **14d** (1.9 g, 6.85 mmol) in EtOH (40 mL) and EtOAc (6.7 mL) was hydrogenated under an atmospheric pressure of H<sub>2</sub> for 18 h with Pd/C (10%) (0.73 g, 0.69 mmol) as a catalyst. The catalyst was removed by filtration through a pad of Celite®. The Celite® was washed with EtOAc and the combined filtrates were concentrated under vacuum. The residue was hydrogenated again in EtOH (40 mL) and EtOAc (6.7 mL) under an atmospheric pressure of H<sub>2</sub> for 72 h with Pd/C (10%) (0.73 g, 0.69 mmol) as a catalyst. The catalyst was removed by filtration through a pad of

35

Celite<sup>®</sup>. The Celite<sup>®</sup> was washed with EtOAc and the combined filtrates were concentrated under vacuum to give ethyl 5-(3-amino-5-methoxyphenyl)pentanoate **14e** (1.4 g). The compound was used as such in the next step.

5 **Synthesis of intermediate 14f:**

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (1.6 g, 3.71 mmol), ethyl 5-(3-amino-5-methoxyphenyl)pentanoate **14e** (1.4 g, 5.57 mmol) and diisopropylethylamine (1.3 mL, 7.43 mmol) in CH<sub>3</sub>CN (19 mL) was stirred at 80°C for 18 h. The mixture was taken up with EtOAc, and  
10 washed with 0.5 N HCl (twice) and water. The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under vacuum. Purification was performed by flash chromatography on silica gel (30 μm, 40 g, heptane/EtOAc from 85/15 to 75/25) to give ethyl 5-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenyl)pentanoate **14f** (1.8  
15 g). The compound was used as such in the next step.

**Synthesis of Compound 14 and chiral separation into Enantiomers 14A and 14B:**

A solution of LiOH monohydrate (0.62 g, 15 mmol) in water (16 mL) was added to  
20 a solution of ethyl 5-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenyl)pentanoate **14f** (1.8 g, 2.98 mmol) in THF (36 mL). The mixture was stirred at room temperature for 18 h. LiOH monohydrate (0.62 g, 15 mmol) was added again and the mixture was stirred at room temperature for 24h. The solution was acidified with HCl (3N) and extracted with  
25 EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (30 μm, 40 g, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100/0 to 98/2) to give 5-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenyl)pentanoic acid (compound **14**, 920 mg). The enantiomers were separated via chiral SFC  
30 (Stationary phase: Chiralpak<sup>®</sup> AD-H 5 μm 250 x 30 mm, mobile phase: 55% CO<sub>2</sub>, 45% EtOH) to give, after solidification from pentane/Et<sub>2</sub>O, the first eluted Enantiomer **14A** (248 mg) and the second eluted Enantiomer **14B** (263 mg).

**Compound 14:**

35 <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.47 (br s, 4 H) 2.15 – 2.22 (m, 2 H) 2.34 – 2.43 (m, 2 H) 3.07 - 3.26 (m, 2 H) 3.62 (s, 3 H) 3.92 - 4.14 (m, 1 H) 4.40 - 4.64 (m, 1 H) 5.56 (br d, *J*=8.83 Hz, 1 H) 6.00 (s, 1 H) 6.13 (br s, 1 H) 6.20 (s, 1 H) 6.37 (br

d,  $J=8.51$  Hz, 1 H) 7.01 (br d,  $J=7.88$  Hz, 1 H) 7.33 (br d,  $J=7.88$  Hz, 1 H) 7.44 (br d,  $J=8.20$  Hz, 2 H) 7.56 (br d,  $J=8.20$  Hz, 2 H) 8.04 (br s, 1 H) 12.01 (br s, 1 H)  
LC/MS (method LC-C):  $R_t$  3.18 min,  $MH^+$  577

5 **Enantiomer 14A:**

$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.40 - 1.61 (m, 4 H) 2.14 - 2.24 (m, 2 H) 2.33 - 2.42 (m, 2 H) 3.06 - 3.23 (m, 2 H) 3.62 (s, 3 H) 3.92 - 4.18 (m, 1 H) 4.40 - 4.59 (m, 1 H) 5.40 - 5.69 (m, 1 H) 6.00 (s, 1 H) 6.13 (s, 1 H) 6.20 (s, 1 H) 6.30 - 6.47 (m, 1 H) 6.91 - 7.12 (m, 1 H) 7.28 - 7.38 (m, 1 H) 7.44 (d,  $J=8.20$  Hz, 2 H) 7.56 (d,  $J=8.51$  Hz, 2 H) 7.95 - 8.29 (m, 1 H) 11.99 (br s, 1 H)

10

LC/MS (method LC-C):  $R_t$  3.21 min,  $MH^+$  577

$[\alpha]_D^{20}$ : +55.8° (c 0.312, DMF)

Chiral SFC (method SFC-L):  $R_t$  1.32 min, no  $MH^+$ , chiral purity 100%.

15 **Enantiomer 14B:**

$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.40 - 1.53 (m, 4 H) 2.15 - 2.25 (m, 2 H) 2.32 - 2.44 (m, 2 H) 3.00 - 3.27 (m, 2 H) 3.62 (s, 3 H) 3.95 - 4.18 (m, 1 H) 4.44 - 4.79 (m, 1 H) 5.57 (d,  $J=8.83$  Hz, 1 H) 6.00 (s, 1 H) 6.13 (s, 1 H) 6.20 (s, 1 H) 6.37 (br d,  $J=8.83$  Hz, 1 H) 7.02 (br d,  $J=7.25$  Hz, 1 H) 7.34 (d,  $J=8.20$  Hz, 1 H) 7.44 (d,  $J=8.20$  Hz, 2 H) 7.56 (d,  $J=8.51$  Hz, 2 H) 8.04 (s, 1 H) 12.00 (m, 1 H)

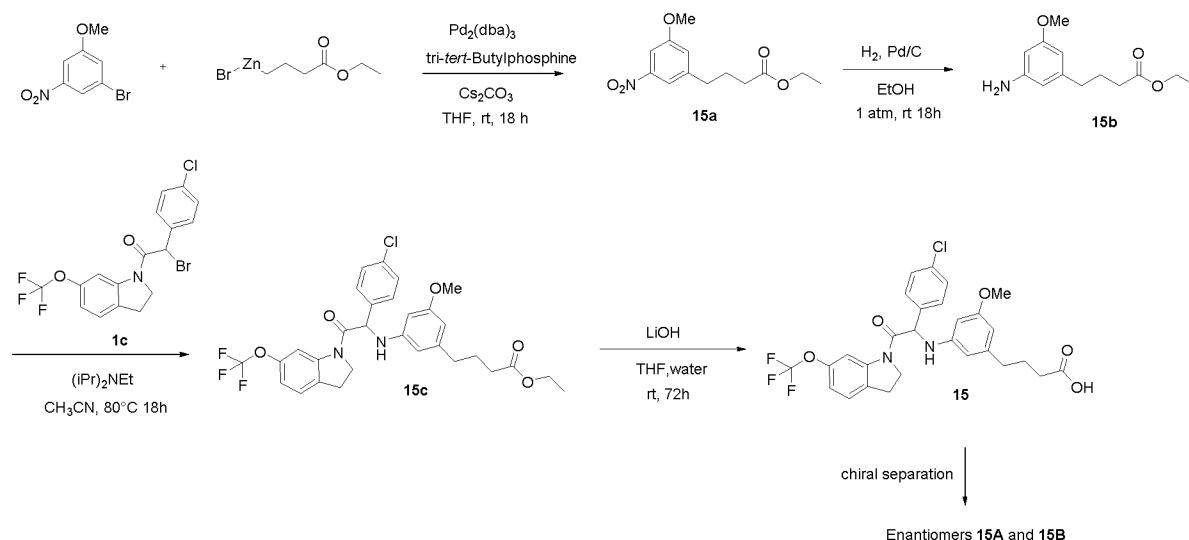
20

LC/MS (method LC-C):  $R_t$  3.20 min,  $MH^+$  577

$[\alpha]_D^{20}$ : -53.7° (c 0.326, DMF)

Chiral SFC (method SFC-L):  $R_t$  1.74 min, no  $MH^+$ , chiral purity 100%.

25 **Example 15** : synthesis of 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenyl)butanoic acid (Compound **15**) and chiral separation into Enantiomers **15A** and **15B**



**Synthesis of intermediate 15a:**

4-ethoxy-4-oxobutylzinc bromide (5.2 mL, 2.6 mmol) and Pd<sub>2</sub>(dba)<sub>3</sub> (0.20 g, 0.22 mmol) were added to a degassed solution of 1-bromo-3-methoxy-5-nitrobenzene [CAS 16618-67-0] (0.5 g, 2.2 mmol), tri-*tert*-butylphosphine (87 mg, 0.43 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.4 g, 4.3 mmol) in THF (8.8 mL). The reaction was stirred at room temperature for 18 h under N<sub>2</sub> atmosphere. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (30 μm, 80 g, heptane/EtOAc from 95/5 to 80/20) to give ethyl 4-(3-methoxy-5-nitrophenyl)butanoate **15a** (370 mg).

**Synthesis of intermediate 15b:**

A mixture of ethyl 4-(3-methoxy-5-nitrophenyl)butanoate **15a** (0.37 g, 1.38 mmol) in EtOH (8.1 mL) was hydrogenated under an atmospheric pressure of H<sub>2</sub> for 18 h with Pd/C (10%) (0.15 g, 0.14 mmol) as a catalyst. The catalyst was removed by filtration through a pad of Celite<sup>®</sup>. The Celite<sup>®</sup> was washed with EtOAc and the filtrate was concentrated under vacuum to give ethyl 4-(3-amino-5-methoxyphenyl)butanoate **15b** (350 mg). The compound was used as such in the next step.

**Synthesis of intermediate 15c:**

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (0.43 g, 0.98 mmol), ethyl 4-(3-amino-5-methoxyphenyl)butanoate **15b** (0.35 g, 1.48 mmol) and diisopropylethylamine (0.34 mL, 2.0 mmol) in CH<sub>3</sub>CN (5.1 mL) was stirred at 80°C for 18 h. The mixture was taken up with EtOAc, and washed with 0.5 N HCl (twice) and water. The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under vacuum. Purification was performed by flash chromatography on silica gel (30 μm, 40 g, heptane/EtOAc from 85/15 to 75/25) to give ethyl 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenyl)butanoate **15c** (340 mg).

**Synthesis of Compound 15 and chiral separation into Enantiomers 15A and 15B:**

Under N<sub>2</sub>, a solution of LiOH monohydrate (0.12 g, 2.9 mmol) in water (3.1 mL) was added to a solution of ethyl 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenyl)butanoate **15c** (0.34 g, 0.58 mmol) in THF (7 mL). The mixture was stirred at room temperature for 72 h. The solution was acidified with HCl (3N) and extracted with EtOAc. The organic



layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (30 μm, 24 g, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100/0 to 98/2) to give, after solidification from Et<sub>2</sub>O, 4-(3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenyl)butanoic acid (compound **15**, 285 mg). The enantiomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5 μm 250 x 30 mm, mobile phase: 65% CO<sub>2</sub>, 35% MeOH) to give, after solidification from Et<sub>2</sub>O, the first eluted Enantiomer **15A** (75 mg) and the second eluted Enantiomer **15B** (85 mg).

10

**Compound 15:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.66 - 1.86 (m, 2 H) 2.11 - 2.26 (m, 2 H) 2.32 - 2.44 (m, 2 H) 3.03 - 3.26 (m, 2 H) 3.62 (s, 3 H) 4.04 (td, *J*=10.32, 7.09 Hz, 1 H) 4.52 (td, *J*=10.32, 6.15 Hz, 1 H) 5.56 (d, *J*=8.83 Hz, 1 H) 6.00 (s, 1 H) 6.14 (s, 1 H) 6.21 (s, 1 H) 6.38 (d, *J*=8.83 Hz, 1 H) 7.01 (dd, *J*=8.20, 1.26 Hz, 1 H) 7.33 (d, *J*=8.20 Hz, 1 H) 7.38 - 7.50 (m, 2 H) 7.56 (d, *J*=8.20 Hz, 2 H) 8.03 (s, 1 H) 12.01 (s, 1 H)

15

LC/MS (method LC-D): R<sub>t</sub> 2.96 min, MH<sup>+</sup> 563

20 **Enantiomer 15A:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.56 - 1.87 (m, 2 H) 2.11 - 2.21 (m, 2 H) 2.35 - 2.42 (m, 2 H) 3.02 - 3.22 (m, 2 H) 3.62 (s, 3 H) 3.97 - 4.18 (m, 1 H) 4.39 - 4.61 (m, 1 H) 5.56 (d, *J*=8.59 Hz, 1 H) 5.99 (s, 1 H) 6.13 (s, 1 H) 6.20 (s, 1 H) 6.37 (br d, *J*=9.09 Hz, 1 H) 7.00 (br d, *J*=8.59 Hz, 1 H) 7.33 (d, *J*=8.08 Hz, 1 H) 7.43 (d, *J*=8.59 Hz, 2 H) 7.55 (d, *J*=8.59 Hz, 2 H) 8.03 (s, 1 H) 11.99 (br s, 1 H)

25

LC/MS (method LC-C): R<sub>t</sub> 3.08 min, MH<sup>+</sup> 563

[α]<sub>D</sub><sup>20</sup>: -59.0° (c 0.293, DMF)

Chiral SFC (method SFC-M): R<sub>t</sub> 2.19 min, no MH<sup>+</sup>, chiral purity 99.31%.

30 **Enantiomer 15B:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.60 - 1.86 (m, 2 H) 2.10 - 2.21 (m, 2 H) 2.35 - 2.42 (m, 2 H) 3.02 - 3.23 (m, 2 H) 3.62 (s, 3 H) 3.82 - 4.26 (m, 1 H) 4.36 - 4.71 (m, 1 H) 5.56 (d, *J*=9.09 Hz, 1 H) 5.99 (s, 1 H) 6.13 (s, 1 H) 6.20 (s, 1 H) 6.37 (d, *J*=9.09 Hz, 1 H) 7.00 (br d, *J*=8.59 Hz, 1 H) 7.33 (d, *J*=8.08 Hz, 1 H) 7.43 (d, *J*=8.59 Hz, 2 H) 7.55 (d, *J*=8.59 Hz, 2 H) 8.03 (s, 1 H) 11.97 (br s, 1 H)

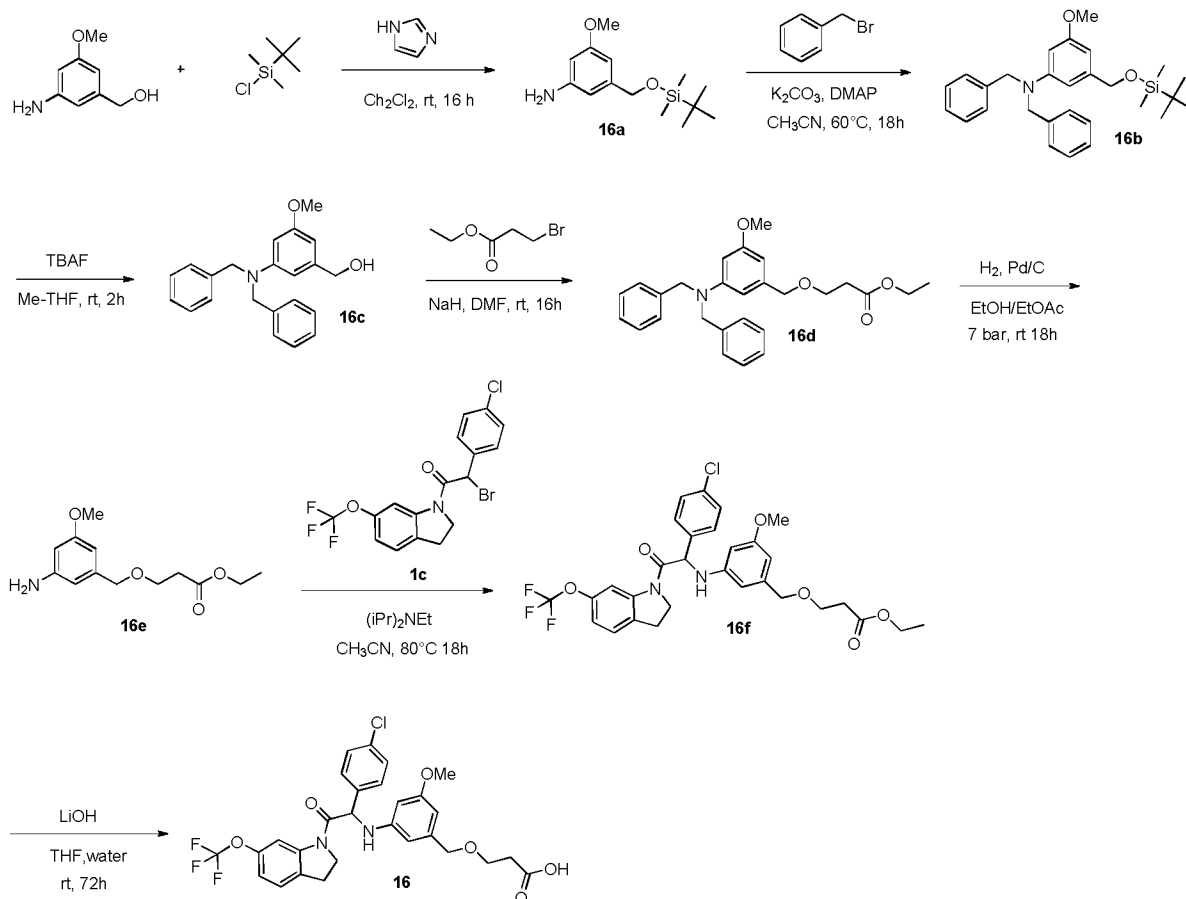
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LC/MS (method LC-C): R<sub>t</sub> 3.08 min, MH<sup>+</sup> 563

[α]<sub>D</sub><sup>20</sup>: +48.0° (c 0.225, DMF)

Chiral SFC (method SFC-M): R<sub>t</sub> 3.73 min, no MH<sup>+</sup>, chiral purity 99.61%.

**Example 16** : synthesis of 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)-indolin-1-yl)ethyl)amino)-5-methoxybenzyl)oxy)propanoic acid (Compound **16**)



### Synthesis of intermediate 16a:

*Tert*-butyldimethylsilyl chloride (6.1 g, 40.48 mmol) was added to a solution of (3-amino-5-methoxyphenyl)methanol [1261566-52-2] (3.1 g, 20.24 mmol) and imidazole (4.13 g, 60.71 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (130 mL) at room temperature. The reaction was stirred at room temperature for 16 h, quenched with water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was separated, washed with water and brine, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue was purified by flash chromatography on silica gel (30 μm, 120 g, heptane/EtOAc from 85/15 to 65/35). The pure fractions were combined and evaporated to dryness to give 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methoxyaniline **16a** (3.4 g). The compound was used as such in the next step.

**Synthesis of intermediate 16b:**

A mixture of benzyl bromide (3.8 mL, 31.8 mmol), 3-(((*tert*-butyldimethylsilyl)oxy)-methyl)-5-methoxyaniline **16a** (3.4 g, 12.71 mmol), K<sub>2</sub>CO<sub>3</sub> (5.27 g, 38.14 mmol) and DMAP (155 mg, 1.27 mmol) in CH<sub>3</sub>CN (66 mL) was stirred at 60°C for 18 h.

5 The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (30 μm, 120 g, heptane/EtOAc from 100/0 to 90/10). The pure fractions were combined and evaporated to dryness to give *N,N*-dibenzyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methoxyaniline **16b** (6 g).

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**Synthesis of intermediate 16c:**

TBAF (1M in THF) (15.3 mL, 15.3 mmol) was added to a solution of *N,N*-dibenzyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methoxyaniline **16b** (5.69 g, 12.71 mmol) in Me-THF (64 mL). The mixture was stirred at room temperature for 2 h. The

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mixture was diluted with EtOAc, washed 3 times with brine and with an aqueous saturated solution of NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (30 μm, 120 g, heptane/EtOAc from 85/15 to 75/25). The pure fractions were

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combined and evaporated to dryness to give (3-(dibenzylamino)-5-methoxyphenyl)methanol **16c** (4.1 g).

**Synthesis of intermediate 16d:**

Ethyl 3-bromopropionate (0.126 mL, 0.99 mmol) added dropwise to a solution of (3-(dibenzylamino)-5-methoxyphenyl)methanol **16c** (300 mg, 0.90 mmol), NaH (60% dispersion in mineral oil) (40 mg, 0.99 mmol) in DMF (7.0 ml). The reaction

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was stirred at room temperature for 16 h. After dilution with EtOAc, the crude material was washed with brine (5x). The organic layer was dried over MgSO<sub>4</sub> and evaporated to dryness. Purification was performed by flash chromatography on silica gel (30 μm, 24 g, heptane/EtOAc from 85/15 to 75/25). The pure fractions

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were combined and evaporated to dryness to give ethyl 3-((3-(dibenzylamino)-5-methoxybenzyl)oxy)propanoate **16d** (97 mg).

**Synthesis of intermediate 16e:**

A mixture of ethyl 3-((3-(dibenzylamino)-5-methoxybenzyl)oxy)propanoate **16d** (97 mg, 0.22 mmol) in EtOH (1.3 mL) and EtOAc (0.66 mL) was hydrogenated under a pressure of 7 bar of H<sub>2</sub> at room temperature for 18 h with Pd/C (10%) (24 mg, 0.022 mmol) as a catalyst. The catalyst was removed by filtration through a pad of Celite®. The Celite® was washed with EtOAc and the filtrate was concentrated

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under reduced pressure to give ethyl 3-((3-amino-5-methoxybenzyl)oxy)-propanoate **16e** (52 mg).

#### Synthesis of intermediate **16f**:

5 A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (74 mg, 0.17 mmol), ethyl 3-((3-amino-5-methoxybenzyl)oxy)-propanoate **16e** (52 mg, 0.21 mmol) and diisopropylethylamine (59  $\mu$ L, 0.34 mmol) in CH<sub>3</sub>CN (0.89 mL) was stirred at 80°C for 18 h. The mixture was concentrated under reduced pressure. Purification was performed by flash chromatography on  
10 silica gel (30  $\mu$ m, 12 g, heptane/EtOAc from 85/15 to 75/25). The pure fractions were combined and evaporated to dryness to give ethyl 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxybenzyl)oxy)propanoate **16f** (48 mg).

#### 15 Synthesis of Compound **16**:

A solution of LiOH monohydrate (33 mg, 0.79 mmol) in water (0.43 mL) was added to a solution of ethyl 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)-indolin-1-yl)ethyl)amino)-5-methoxybenzyl)oxy)propanoate **16f** (48 mg, 0.079  
20 mmol) in THF (0.97 mL). The mixture was stirred at room temperature for 72 h. The solution was acidified with HCl (3N) and extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (30  $\mu$ m, 12 g, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100/0 to 98/2). A second purification was performed via reverse  
25 phase chromatography (Stationary phase: YMC-actus Triart-C18 10  $\mu$ m 30 x 150 mm, mobile phase: Gradient from 65% NH<sub>4</sub>HCO<sub>3</sub> 0.2% , 35% CH<sub>3</sub>CN to 25% NH<sub>4</sub>HCO<sub>3</sub> 0.2% , 75% CH<sub>3</sub>CN). The pure fractions were combined and evaporated to dryness to give, after freeze-drying in CH<sub>3</sub>CN/water, 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxybenzyl)oxy)propanoic acid (compound **16**, 5 mg).

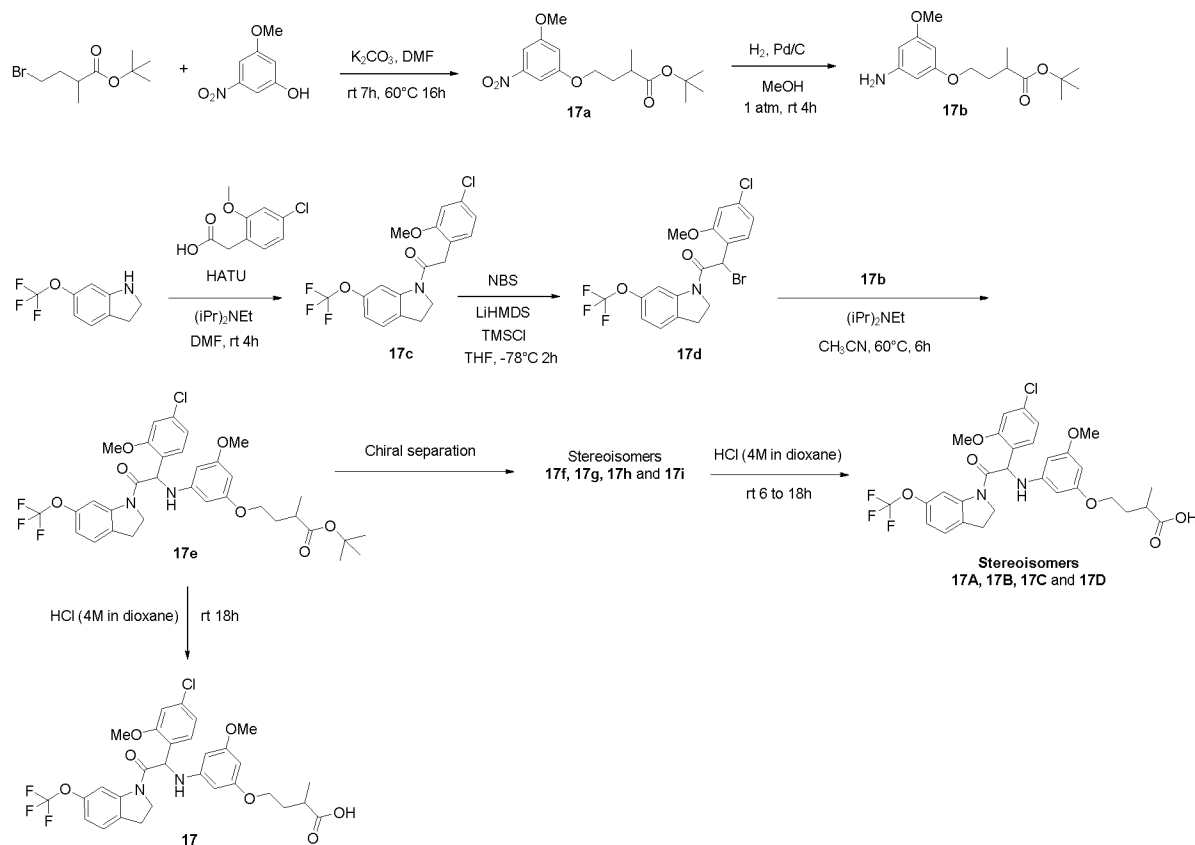
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#### Compound **16**:

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 2.34 - 2.42 (m, 2 H) 3.03 - 3.23 (m, 2 H) 3.49 - 3.59 (m, 2 H) 3.63 (s, 3 H) 3.97 - 4.21 (m, 2 H) 4.27 (s, 2 H) 4.49 - 4.57 (m, 1 H) 5.58 (d, *J*=8.59 Hz, 1 H) 6.11 (s, 1 H) 6.21 (s, 1 H) 6.33 (s, 1 H) 6.48 (br d, *J*=8.59  
35 Hz, 1 H) 7.00 (br d, *J*=8.59 Hz, 1 H) 7.33 (d, *J*=8.08 Hz, 1 H) 7.43 (d, *J*=8.59 Hz, 2 H) 7.56 (d, *J*=8.59 Hz, 2 H) 8.03 (s, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.84 min, MH<sup>+</sup> 579

**Example 17** : synthesis of 4-(3-((1-(4-chloro-2-methoxyphenoxy)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2-methylbutanoic acid (Compound **17**) and separation into Stereoisomers **17A**, **17B**, **17C** and **17D**.



### Synthesis of intermediate **17a**:

*Tert*-butyl 4-bromo-2-methylbutanoate [CAS 1210410-44-8 (3.9 g, 16.446 mmol) was added dropwise to a mixture of 3-methoxy-5-nitrophenol [7145-49-5] (2.78 g, 16.446 mmol) and  $K_2CO_3$  (3.409 g, 24.669 mmol) in DMF (25 mL). The mixture was stirred at room temperature for 7 h and at 60°C for 16 h. after cooling to 0°C, the mixture was diluted with water and ice and extracted with EtOAc. The organic layer was washed with water, dried over  $MgSO_4$ , filtered and the solvent was evaporated to dryness. The crude residue was purified by flash chromatography on silica gel (20-45  $\mu m$ , 80 g, mobile phase: heptane/EtOAc 75/25). The pure fractions were combined and the solvent was evaporated under reduced pressure to give *tert*-butyl 4-(3-methoxy-5-nitrophenoxy)-2-methylbutanoate **17a** (2.59 g).

### Synthesis of intermediate **17b**:

A mixture of *tert*-butyl 4-(3-methoxy-5-nitrophenoxy)-2-methylbutanoate **17a** (2.9 g, 8.913 mmol) in MeOH (50 mL) was hydrogenated under an atmospheric

pressure of H<sub>2</sub> for 4 h with Pd/C (10%) (1.52 g, 1.426 mmol) as a catalyst. The catalyst was removed by filtration through a pad of Celite®. The Celite® was washed with EtOAc and the filtrate was concentrated under reduced pressure. The mixture was purified by flash chromatography on silica gel (20-45 µm, 40 g, mobile phase: heptane/EtOAc 85/15). The pure fractions were combined and the solvent was evaporated until dryness to give *tert*-butyl 4-(3-amino-5-methoxyphenoxy)-2-methylbutanoate **17b** (2.29 g).

#### Synthesis of intermediate **17c**:

10 A mixture of 6-(trifluoromethoxy)indoline [CAS 959235-95-1] (2.5 g, 12.3 mmol), 2-(4-chloro-2-methoxyphenyl)acetic acid [CAS 170737-95-8] (2.47 g, 12.3 mmol), HATU (7 g, 18.5 mmol) and diisopropylethylamine (6.1 mL, 36.9 mmol) in DMF (40 mL) was stirred at room temperature for 4 h. Water and EtOAc were added. The organic layer was separated, washed with water, dried over MgSO<sub>4</sub>, filtered and  
15 the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (15-40 µm, 80 g, heptane/EtOAc 85/15). The pure fractions were combined and the solvent was concentrated under reduced pressure to give, after crystallization from CH<sub>3</sub>CN/heptane, 2-(4-chloro-2-methoxyphenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **17c** (4.3 g).

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#### Synthesis of intermediate **17d**:

At -78°C, under a N<sub>2</sub> flow, LiHMDS 1M in THF (19.7 mL, 19.7 mmol) was added dropwise to a mixture of 2-(4-chloro-2-methoxyphenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **17c** (3.8 g, 9.8 mmol) in THF (50 mL).  
25 TMSCl (1.5 mL, 11.8 mmol) was added dropwise. The mixture was stirred for 15 min at -78°C and a solution of *N*-bromosuccinimide (1.9 g, 10.8 mmol) in THF (35 mL) was added dropwise. After stirring for 2 h at -78°C, the reaction was quenched with a saturated solution of NH<sub>4</sub>Cl. The mixture was extracted with EtOAc. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and the  
30 solvent was evaporated under reduced pressure to give 2-bromo-2-(4-chloro-2-methoxyphenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **17d** (4.5 g). The compound was used as such in the next step.

#### Synthesis of intermediate **17e** and separation into Stereoisomers **17f**, **17g**, **17h** and **17i**:

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A mixture of 2-bromo-2-(4-chloro-2-methoxyphenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **17d** (2 g, 4.304 mmol), *tert*-butyl 4-(3-amino-5-methoxyphenoxy)-2-methylbutanoate **17b** (763 mg, 2.583 mmol) and diisopropylethylamine (1.5 mL,

8.608 mmol) in CH<sub>3</sub>CN (70 mL) was stirred at 60°C for 6 h. The mixture was cooled to 0°C, diluted water and ice, and extracted with EtOAc. The organic layer was washed with water, dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under reduced pressure. Purification was performed by flash chromatography on silica gel (25-30 μm, 40 g, heptane/EtOAc 80/20). A second purification was performed by flash chromatography on silica gel (25-30 μm, 40 g, heptane/EtOAc 85/15). The pure fractions were combined and evaporated to dryness to give *tert*-butyl 4-(3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2-methylbutanoate **17e** (787 mg). The stereoisomers were separated via chiral SFC (Stationary phase: Chiralpak® AD-H 5 μm 250 x 30 mm, mobile phase: 83% CO<sub>2</sub>, 17% EtOH) to give a mixture of **17f** and **17g** (348 mg), and pure **17h** (164 mg) and **17i** (184 mg). **17f** and **17g** were further separated via chiral SFC (Stationary phase: Chiralpak® AD-H 5 μm 250 x 30 mm, mobile phase: 88% CO<sub>2</sub>, 12% EtOH) to give **17f** (145 mg) and **17g** (140 mg).

#### Synthesis of Compound 17:

A mixture of *tert*-butyl 4-(3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2-methylbutanoate **17e** (180 mg, 0.265 mmol) in HCl (4M in dioxane) (3 mL) was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. 5 mL of triethylamine was added and the solution was evaporated under vacuum. Purification was performed by flash chromatography on silica gel (30 μm, 12 g, CH<sub>2</sub>Cl<sub>2</sub>/ MeOH from 99/1 to 96/4). The pure fractions were combined and evaporated to dryness (m = 115 mg). The residue was solidified in pentane/diisopropyl ether and few drops of CH<sub>3</sub>CN to give 4-(3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2-methylbutanoic acid (Compound **17**, 75 mg).

#### Synthesis of Stereoisomer 17A:

A mixture of **17f** (145 mg, 0.214 mmol) in HCl (4M in dioxane) (5 mL) was stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure. 5 mL of Et<sub>3</sub>N was added and the solution was evaporated under vacuum. Purification was performed by flash chromatography on silica gel (15-40 μm, 12 g, CH<sub>2</sub>Cl<sub>2</sub>/ MeOH from 99.5/0.5 to 95/5). The pure fractions were combined and evaporated to dryness (m = 93 mg). The residue was solidified from pentane/diisopropyl ether and few drops of CH<sub>3</sub>CN to give Stereoisomer **17A** (64 mg).

**Synthesis of Stereoisomer 17B:**

A mixture of **17g** (135 mg, 0.199 mmol) in HCl (4M in dioxane) (5 mL) was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. 5 mL of Et<sub>3</sub>N was added and the solution was evaporated under vacuum. Purification was performed by flash chromatography on silica gel (15-40 μm, 12 g, CH<sub>2</sub>Cl<sub>2</sub>/ MeOH from 99.5/0.5 to 95/5). The pure fractions were combined and evaporated to dryness (m = 65 mg). The residue was solidified from pentane/diisopropyl ether and few drops of CH<sub>3</sub>CN to give Stereoisomer **17B** (38 mg).

**Synthesis of Stereoisomer 17C:**

A mixture of **17h** (162 mg, 0.239 mmol) in HCl (4M in dioxane) (5 mL) was stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure. 5 mL of Et<sub>3</sub>N was added and the solution was evaporated under vacuum. Purification was performed by flash chromatography on silica gel (15-40 μm, 12 g, CH<sub>2</sub>Cl<sub>2</sub>/ MeOH from 99.5/0.5 to 95/5). The pure fractions were combined and evaporated to dryness (m = 85 mg). The residue was solidified from pentane/diisopropyl ether and few drops of CH<sub>3</sub>CN to give Stereoisomer **17C** (68 mg).

**Synthesis of Stereoisomer 17D:**

A mixture of **17i** (179 mg, 0.264 mmol) in HCl (4M in dioxane) (5 mL) was stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure. 5 mL of Et<sub>3</sub>N was added and the solution was evaporated under vacuum. Purification was performed by flash chromatography on silica gel (15-40 μm, 24 g, CH<sub>2</sub>Cl<sub>2</sub>/ MeOH from 99.5/0.5 to 95/5). The pure fractions were combined and evaporated to dryness (m = 98 mg). The residue was solidified from pentane/diisopropyl ether and few drops of CH<sub>3</sub>CN to give Stereoisomer **17D** (54 mg).

**Compound 17:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.11 (br d, *J*=6.62 Hz, 3 H) 1.54 - 1.82 (m, 1 H) 1.82 - 2.07 (m, 1 H) 3.10 - 3.22 (m, 2 H) 3.62 (s, 3 H) 3.77 - 3.87 (m, 2 H) 3.91 (s, 3 H) 3.96 - 4.18 (m, 1 H) 4.30 - 4.43 (m, 1 H) 5.60 (br d, *J*=8.20 Hz, 1 H) 5.76 (br s, 1 H) 5.87 (s, 1 H) 5.88 (s, 1 H) 6.46 (br d, *J*=8.51 Hz, 1 H) 6.98 - 7.6 (m, 2 H) 7.15 (br s, 1 H) 7.28 - 7.44 (m, 2 H) 8.03 (br s, 1 H) 12.20 (br s, 1 H) (1H missing CH CO<sub>2</sub>H under DMSO)



LC/MS (method LC-C):  $R_t$  3.16 min,  $MH^+$  623

**Stereoisomer 17A:**

$^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.10 (br d,  $J=7.07$  Hz, 3 H) 1.59 - 1.82 (m, 1 H) 1.82 - 2.04 (m, 1 H) 3.04 - 3.24 (m, 2 H) 3.61 (s, 3 H) 3.71 - 3.87 (m, 2 H) 3.90 (s, 3 H) 3.96 - 4.21 (m, 1 H) 4.32 - 4.56 (m, 1 H) 5.59 (br d,  $J=8.59$  Hz, 1 H) 5.75 (s, 1 H) 5.85 (s, 1 H) 5.87 (s, 1 H) 6.44 (br d,  $J=8.59$  Hz, 1 H) 6.98 - 7.05 (m, 2 H) 7.14 (s, 1 H) 7.22 - 7.53 (m, 2 H) 8.02 (br s, 1 H) 12.19 (br s, 1 H) (1H missing CH  $CO_2H$  under DMSO)

10 LC/MS (method LC-D):  $R_t$  3.07 min,  $MH^+$  623

$[\alpha]_D^{20}$ :  $-18.4^\circ$  (c 0.305, DMF)

Chiral SFC (method SFC-N):  $R_t$  4.75 min,  $MH^+$  623, chiral purity 99.3%.

**Stereoisomer 17B:**

15  $^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.09 (br d,  $J=6.57$  Hz, 3 H) 1.64 - 1.83 (m, 1 H) 1.83 - 2.09 (m, 1 H) 3.00 - 3.23 (m, 2 H) 3.61 (s, 3 H) 3.68 - 3.86 (m, 2 H) 3.90 (m, 3 H) 3.96 - 4.21 (m, 1 H) 4.26 - 4.56 (m, 1 H) 5.59 (br d,  $J=8.08$  Hz, 1 H) 5.75 (br s, 1 H) 5.86 (s, 1 H) 5.87 (s, 1 H) 6.44 (br d,  $J=8.59$  Hz, 1 H) 6.97 - 7.06 (m, 2 H) 7.14 (s, 1 H) 7.26 - 7.34 (m, 2 H) 8.02 (br s, 1 H) 12.20 (br s, 1 H) (1H missing CH  $CO_2H$  under DMSO)

20 LC/MS (method LC-D):  $R_t$  3.03 min,  $MH^+$  623

$[\alpha]_D^{20}$ :  $-51.0^\circ$  (c 0.298, DMF)

Chiral SFC (method SFC-N):  $R_t$  5.90 min,  $MH^+$  623, chiral purity 97.94%.

25 **Stereoisomer 17C:**

$^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.09 (d,  $J=6.57$  Hz, 3 H) 1.61 - 1.84 (m, 1 H) 1.88 - 2.02 (m, 1 H) 3.07 - 3.26 (m, 2 H) 3.61 (s, 3 H) 3.76 - 3.88 (m, 2 H) 3.90 (s, 3 H) 3.97 - 4.18 (m, 1 H) 4.27 - 4.45 (m, 1 H) 5.59 (br d,  $J=8.59$  Hz, 1 H) 5.75 (s, 1 H) 5.86 (br s, 1 H) 5.87 (br s, 1 H) 6.39 - 6.49 (m, 1 H) 6.97 - 7.02 (m, 1 H) 7.02 - 7.05 (m, 1 H) 7.14 (d,  $J=2.02$  Hz, 1 H) 7.29 - 7.32 (m, 1 H) 7.32 - 7.37 (m, 1 H) 8.02 (s, 1 H) 12.19 (br s, 1 H) (1H missing CH  $CO_2H$  under DMSO)

30 LC/MS (method LC-C):  $R_t$  3.16 min,  $MH^+$  623

$[\alpha]_D^{20}$ :  $+41.6^\circ$  (c 0.257, DMF)

Chiral SFC (method SFC-N):  $R_t$  6.86 min,  $MH^+$  623, chiral purity 98.89%.

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**Stereoisomer 17D:**

$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.11 (d,  $J=6.94$  Hz, 3 H) 1.70 (dq,  $J=13.44$ , 6.55 Hz, 1 H) 1.97 (dq,  $J=13.64$ , 6.80 Hz, 1 H) 3.09 - 3.26 (m, 2 H) 3.62 (s, 3 H)

3.85 (br t,  $J=6.31$  Hz, 2 H) 3.91 (s, 3 H) 3.97 - 4.09 (m, 1 H) 4.31 - 4.47 (m, 1 H) 5.60 (br d,  $J=8.51$  Hz, 1 H) 5.76 (s, 1 H) 5.86 (br s, 1 H) 5.88 (br s, 1 H) 6.45 (br d,  $J=8.51$  Hz, 1 H) 7.00 - 7.08 (m, 2 H) 7.15 (d,  $J=1.26$  Hz, 1 H) 7.32 (d,  $J=8.20$  Hz, 1 H) 7.34 (br d,  $J=8.20$  Hz, 1 H) 8.03 (br s, 1 H) 12.18 (br s, 1 H) (1H missing CH

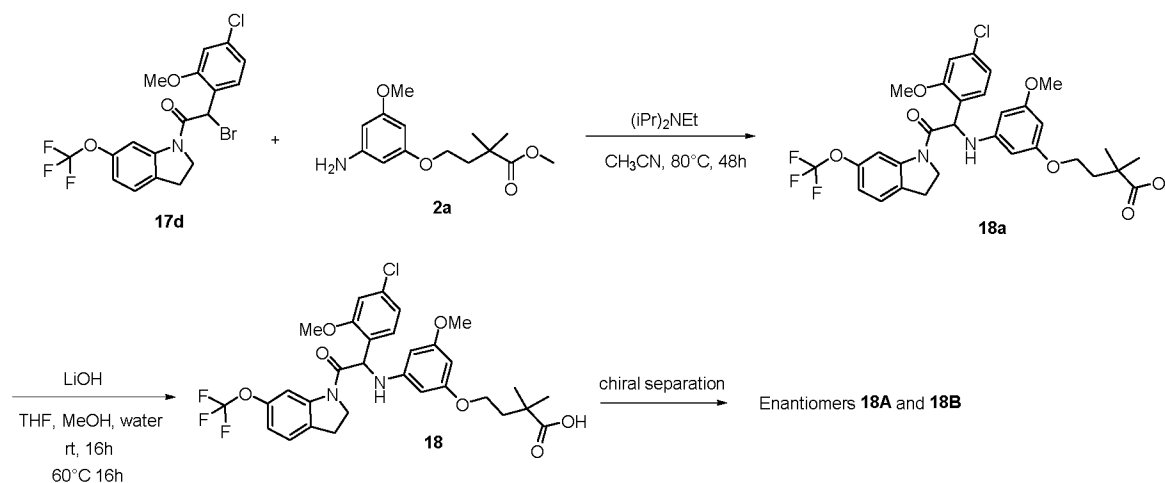
5 CO<sub>2</sub>H under DMSO)

LC/MS (method LC-C):  $R_t$  3.15 min,  $MH^+$  623

$[\alpha]_D^{20}$ : +15.8° (c 0.297, DMF)

Chiral SFC (method SFC-N):  $R_t$  8.14 min,  $MH^+$  623, chiral purity 98.6%.

- 10 **Example 18** : synthesis of 4-(3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2,2-dimethylbutanoic acid (Compound **18**) and chiral separation into Enantiomers **18A** and **18B**.



### Synthesis of intermediate 18a:

- A mixture of 2-bromo-2-(4-chloro-2-methoxyphenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **17d** (800 mg, 1.291 mmol), methyl 4-(3-amino-5-methoxyphenoxy)-2,2-dimethylbutanoate **2a** (518 mg, 1.937 mmol) and diisopropylethylamine (445  $\mu$ L, 2.583 mmol) in CH<sub>3</sub>CN (6 mL) was stirred at 80°C for 48 h. The mixture was concentrated to dryness. The residue was taken up with EtOAc, washed with 1N HCl (twice), and with water. The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under vacuum to give methyl 4-(3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2,2-dimethylbutanoate **18a** (950 mg). The compound was used as such in the next step.
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- 25

**Synthesis of Compound 18 and chiral separation into Enantiomers 18A and 18B:**

At 0°C, LiOH monohydrate (184 mg, 4.38 mmol) was added portionwise to a solution of methyl 4-(3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2,2-dimethylbutanoate **18a** (950 mg, 1.459 mmol) in THF/MeOH/water (1/1/1) (30 mL). The mixture was stirred at room temperature for 16 h, and then at 60°C for 16 h. The mixture was diluted with water and extracted with EtOAc. The aqueous layer was slowly acidified to pH 5-6 with 3N HCl and extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under vacuum. Purification was performed by flash chromatography on silica gel (15-40 μm, 40 g, CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH, from 100/0 to 99/1). The pure fractions were combined and evaporated to dryness (m = 350 mg). A small portion of the residue was crystallized from Et<sub>2</sub>O/diisopropyl ether. The precipitate was filtered off and dried to give 4-(3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)-2,2-dimethylbutanoic acid (Compound **18**, 25 mg). The remaining amount (290 mg) was used for chiral separation. The enantiomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5 μm 250 x 30 mm, mobile phase: 75% CO<sub>2</sub>, 25% MeOH) to give, after solidification from heptane/diisopropyl ether, the first eluted Enantiomer **18A** (68 mg) and the second eluted Enantiomer **18B** (70 mg).

**Compound 18:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.14 (d, *J*=2.2 Hz, 6 H) 1.87 (t, *J*=7.1 Hz, 2 H) 3.09 - 3.26 (m, 2 H) 3.61 (s, 3 H) 3.80 - 3.88 (m, 2 H) 3.90 (s, 3 H) 3.98 - 4.07 (m, 1 H) 4.33 - 4.42 (m, 1 H) 5.60 (d, *J*=8.5 Hz, 1 H) 5.74 (s, 1 H) 5.85 (s, 1 H) 5.87 (s, 1 H) 6.44 (d, *J*=8.5 Hz, 1 H) 6.98 - 7.06 (m, 2 H) 7.15 (d, *J*=1.6 Hz, 1 H) 7.33 (dd, *J*=11.7, 8.2 Hz, 2 H) 8.03 (s, 1 H) 12.23 (br s, 1 H)  
LC/MS (method LC-C): R<sub>t</sub> 3.40 min, MH<sup>+</sup> 637  
MP = 138°C

**Enantiomer 18A:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.14 (d, *J*=2.2 Hz, 6 H) 1.87 (br t, *J*=7.1 Hz, 2 H) 3.09 - 3.25 (m, 2 H) 3.61 (s, 3 H) 3.81 - 3.87 (m, 2 H) 3.90 (s, 3 H) 3.98 - 4.07 (m, 1 H) 4.33 - 4.42 (m, 1 H) 5.59 (d, *J*=8.5 Hz, 1 H) 5.74 (s, 1 H) 5.84 (s, 1 H) 5.87 (s, 1 H) 6.44 (br d, *J*=8.5 Hz, 1 H) 6.98 - 7.06 (m, 2 H) 7.14 (d, *J*=1.9 Hz, 1 H) 7.33 (dd, *J*=10.7, 8.5 Hz, 2 H) 8.02 (s, 1 H) 11.94 - 12.35 (m, 1 H)  
LC/MS (method LC-C): R<sub>t</sub> 3.40 min, MH<sup>+</sup> 637

$[\alpha]_D^{20}$ : -30.2° (c 0.315, DMF)

Chiral SFC (method SFC-O):  $R_t$  1.31 min, no  $MH^+$ , chiral purity 100%.

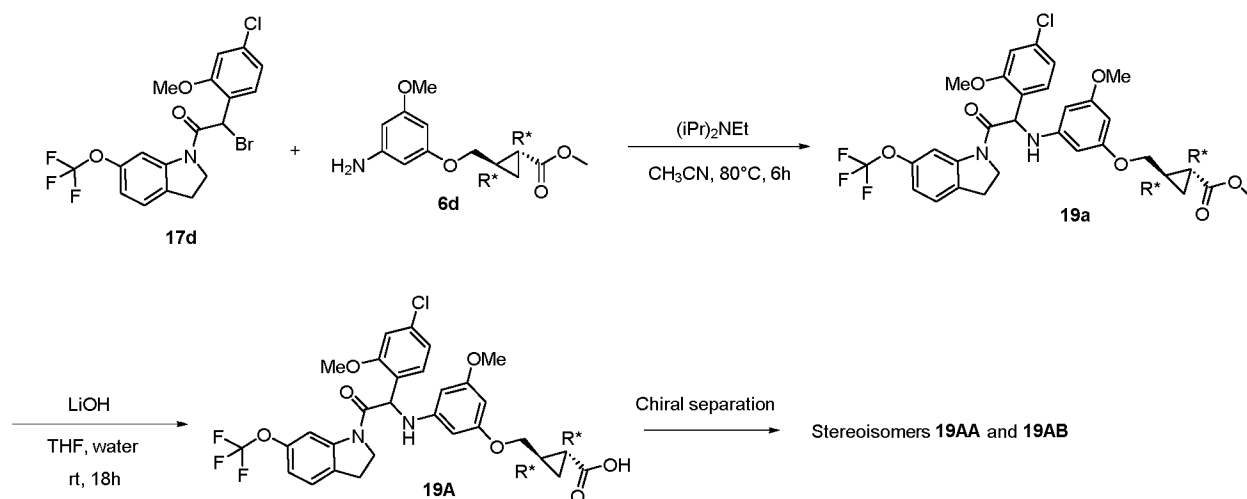
### Enantiomer 18B:

- 5  $^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.13 (d,  $J=2.5$  Hz, 6 H) 1.87 (t,  $J=7.3$  Hz, 2 H) 3.10 - 3.25 (m, 2 H) 3.61 (s, 3 H) 3.80 - 3.87 (m, 2 H) 3.90 (s, 3 H) 4.02 (td,  $J=10.2, 7.1$  Hz, 1 H) 4.33 - 4.41 (m, 1 H) 5.59 (d,  $J=8.8$  Hz, 1 H) 5.73 - 5.76 (m, 1 H) 5.84 (s, 1 H) 5.87 (s, 1 H) 6.44 (d,  $J=8.5$  Hz, 1 H) 6.97 - 7.08 (m, 2 H) 7.14 (d,  $J=1.9$  Hz, 1 H) 7.33 (dd,  $J=11.2, 8.4$  Hz, 2 H) 8.02 (s, 1 H) 11.92 - 12.44 (m, 1 H)
- 10 LC/MS (method LC-C):  $R_t$  3.40 min,  $MH^+$  637

$[\alpha]_D^{20}$ : +28.0° (c 0.354, DMF)

Chiral SFC (method SFC-O):  $R_t$  1.60 min, no  $MH^+$ , chiral purity 99.45%.

- Example 19A** : synthesis of (1*R*\*,2*R*\*)-2-((3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclopropanecarboxylic acid (Compound **19A**) and separation into Stereoisomers **19AA** and **19AB**.
- 15



### 20 Synthesis of intermediate 19a:

- A mixture of 2-bromo-2-(4-chloro-2-methoxyphenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **17d** (0.37 g, 0.796 mmol), (1*R*\*,2*R*\*)-methyl 2-((3-amino-5-methoxyphenoxy)methyl)cyclopropanecarboxylate methoxyphenoxy)methyl)cyclopropanecarboxylate **6d** (0.317 g, 1.194 mmol) and diisopropylethylamine (0.274 mL, 1.593 mmol) in  $CH_3CN$  (10 mL) was stirred at 80°C for 6 h. The reaction was cooled to 0°C and was diluted with water and ice. The mixture was extracted with EtOAc. The organic layer was washed with water, dried over  $MgSO_4$ , filtered and the solvent was evaporated to dryness. The compound was purified by flash chromatography on silica gel (25-30  $\mu m$ , 24 g, heptane/EtOAc 80/20). The pure
- 25

fractions were combined and the solvent was removed under reduced pressure to give (1*R*\*,2*R*\*)-methyl 2-((3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylate **19a** (306 mg).

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### Synthesis of Compound **19A** and separation into Stereoisomers **19AA** and **19AB**:

A solution of LiOH monohydrate (77 mg, 1.826 mmol) in water (5 mL) was added to a solution of (1*R*\*,2*R*\*)-methyl 2-((3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylate **19a** (237 mg, 0.365 mmol) in THF (5 mL). The mixture was stirred at room temperature for 18 h and concentrated under vacuum. The compound was purified by flash chromatography on silica gel (20-45  $\mu$ m, 24 g, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 99.5/0.5 to 98/2). The pure fractions were combined and concentrated under reduced pressure to give (1*R*\*,2*R*\*)-2-((3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)cyclopropanecarboxylic acid (Compound **19A**, 170 mg). The stereoisomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5  $\mu$ m 250 x 30 mm, mobile phase: 65% CO<sub>2</sub>, 35% MeOH) to give, after solidification from CH<sub>3</sub>CN/diisopropyl ether/heptane the first eluted Stereoisomer **19AA** (67 mg) and the second eluted Stereoisomer **19AB** (59 mg).

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### Stereoisomer **19AA**:

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 0.85 - 0.95 (m, 1 H) 0.99 - 1.08 (m, 1 H) 1.55 (dt, *J*=8.12, 4.30 Hz, 1 H) 1.57 - 1.67 (m, 1 H) 3.10 - 3.25 (m, 2 H) 3.61 (s, 3 H) 3.64 - 3.73 (m, 1 H) 3.83 (br dd, *J*=10.40, 6.31 Hz, 1 H) 3.90 (s, 3 H) 3.98 - 4.08 (m, 1 H) 4.29 - 4.44 (m, 1 H) 5.60 (br d, *J*=8.51 Hz, 1 H) 5.76 (s, 1 H) 5.87 (s, 2 H) 6.45 (br d, *J*=8.83 Hz, 1 H) 6.96 - 7.07 (m, 2 H) 7.14 (d, *J*=1.26 Hz, 1 H) 7.31 (d, *J*=8.51 Hz, 1 H) 7.32 - 7.38 (m, 1 H) 8.02 (br s, 1 H) 12.23 (br s, 1 H)

LC/MS (method LC-D): R<sub>t</sub> 2.84 min, MH<sup>+</sup> 621

[ $\alpha$ ]<sub>D</sub><sup>20</sup>: -65.6° (c 0.25, DMF)

Chiral SFC (method SFC-P): R<sub>t</sub> 1.44 min, no MH<sup>+</sup>, chiral purity 100%.

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### Stereoisomer **19AB**:

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 0.87 - 0.95 (m, 1 H) 0.99 - 1.07 (m, 1 H) 1.50 - 1.57 (m, 1 H) 1.59 - 1.70 (m, 1 H) 3.09 - 3.24 (m, 2 H) 3.61 (s, 3 H) 3.63 - 3.72 (m, 1 H) 3.85 (br dd, *J*=10.40, 6.31 Hz, 1 H) 3.90 (s, 3 H) 3.99 - 4.09 (m, 1 H) 4.30 - 4.44 (m, 1 H) 5.60 (br d, *J*=8.51 Hz, 1 H) 5.76 (s, 1 H) 5.87 (s, 2 H) 6.45 (br d,

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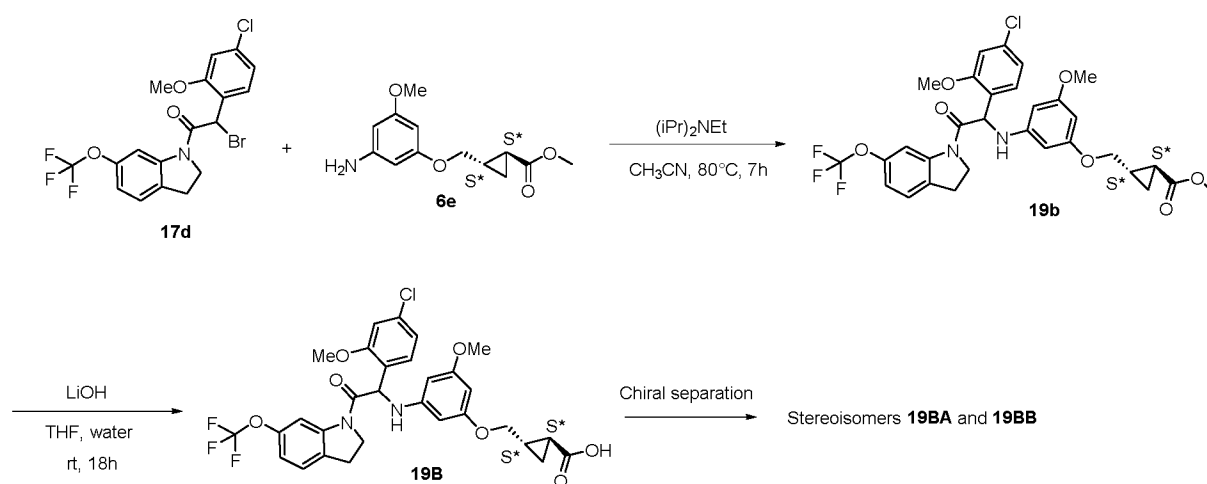
$J=8.51$  Hz, 1 H) 7.00 - 7.09 (m, 2 H) 7.14 (d,  $J=1.26$  Hz, 1 H) 7.30 (d,  $J=8.51$  Hz, 1 H) 7.34 (br d,  $J=8.20$  Hz, 1 H) 8.02 (br s, 1 H) 12.26 (br s, 1 H)

LC/MS (method LC-D):  $R_t$  2.85 min,  $MH^+$  621

$[\alpha]_D^{20}$ :  $+37.1^\circ$  (c 0.28, DMF)

- 5 Chiral SFC (method SFC-P):  $R_t$  2.20 min, no  $MH^+$ , chiral purity 99.84%.

**Example 19B** : synthesis of (1*S*\*,2*S*\*)-2-((3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylic acid (Compound **19B**) and separation into Stereoisomers **19BA** and **19BB**.



### Synthesis of intermediate 19b:

- 15 A mixture of 2-bromo-2-(4-chloro-2-methoxyphenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **17d** (0.39 g, 0.839 mmol), (1*S*\*,2*S*\*)-methyl 2-((3-amino-5-methoxyphenoxy)methyl)cyclopropanecarboxylate (6e) (0.334 g, 1.259 mmol) and diisopropylethylamine (0.289 mL, 1.679 mmol) in  $CH_3CN$  (10 mL) was stirred at  $80^\circ C$  for 7 h. The reaction was cooled to  $0^\circ C$  and was diluted with water and ice. The mixture was extracted with EtOAc.
- 20 The organic layer was washed with water, dried over  $MgSO_4$ , filtered and the solvent was evaporated to dryness. The compound was purified by flash chromatography on silica gel (25-30  $\mu m$ , 24 g, heptane/EtOAc 80/20). The pure fractions were combined and the solvent was removed under reduced pressure to give (1*S*\*,2*S*\*)-methyl 2-((3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylate **19b** (308 mg).
- 25

**Synthesis of Compound 19B and separation into Stereoisomers 19BA and 19BB:**

A solution of LiOH monohydrate (98 mg, 2.334 mmol) in water (5 mL) was added to a solution of (1*S*\*,2*S*\*)-methyl 2-((3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylate **19b** (303 mg, 0.467 mmol) in THF (5 mL). The mixture was stirred at room temperature for 18 h and then concentrated under vacuum. The compound was purified by flash chromatography on silica gel (20-45  $\mu$ m, 24 g, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100/0 to 98/2). The pure fractions were combined and concentrated under reduced pressure to give (1*S*\*,2*S*\*)-2-((3-((1-(4-chloro-2-methoxyphenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylic acid (Compound **19B**, 250 mg). The stereoisomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5  $\mu$ m 250 x 30 mm, mobile phase: 65% CO<sub>2</sub>, 35% MeOH) to give, after solidification from CH<sub>3</sub>CN/diisopropyl ether/heptane the first eluted Stereoisomer **19BA** (97 mg) and the second eluted Stereoisomer **19BB** (103 mg).

**Stereoisomer 19BA:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 0.85 - 0.95 (m, 1 H) 0.95 - 1.09 (m, 1 H) 1.54 (dt, *J*=8.34, 4.42 Hz, 1 H) 1.55 - 1.66 (m, 1 H) 3.09 - 3.25 (m, 2 H) 3.61 (s, 3 H) 3.66 (dd, *J*=10.36, 7.33 Hz, 1 H) 3.85 (dd, *J*=10.61, 6.06 Hz, 1 H) 3.89 (s, 3 H) 3.96 - 4.12 (m, 1 H) 4.26 - 4.43 (m, 1 H) 5.59 (d, *J*=8.59 Hz, 1 H) 5.76 (s, 1 H) 5.87 (s, 1 H) 5.88 (s, 1H) 6.44 (d, *J*=9.09 Hz, 1 H) 6.93 - 7.06 (m, 2 H) 7.14 (d, *J*=2.02 Hz, 1 H) 7.30 (d, *J*=8.08 Hz, 1 H) 7.34 (d, *J*=8.08 Hz, 1 H) 8.02 (s, 1 H) 12.20 (br s, 1 H)

LC/MS (method LC-D): R<sub>t</sub> 2.84 min, MH<sup>+</sup> 621

[ $\alpha$ ]<sub>D</sub><sup>20</sup>: -47.6° (c 0.271, DMF)

Chiral SFC (method SFC-P): R<sub>t</sub> 1.48 min, no MH<sup>+</sup>, chiral purity 100%.

**Stereoisomer 19BB:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 0.85 - 0.97 (m, 1 H) 0.98 - 1.07 (m, 1 H) 1.51 - 1.58 (m, 1 H) 1.55 - 1.67 (m, 1 H) 3.07 - 3.25 (m, 2 H) 3.61 (s, 3 H) 3.65 - 3.74 (m, 1 H) 3.83 (br dd, *J*=10.36, 5.81 Hz, 1 H) 3.90 (s, 3 H) 3.97 - 4.14 (m, 1 H) 4.30 - 4.42 (m, 1 H) 5.60 (br d, *J*=8.59 Hz, 1 H) 5.76 (s, 1 H) 5.87 (s, 2 H) 6.44 (br d, *J*=8.59 Hz, 1 H) 6.98 - 7.07 (m, 2 H) 7.14 (d, *J*=1.52 Hz, 1 H) 7.30 (d, *J*=8.08 Hz, 1 H) 7.33 (br d, *J*=8.08 Hz, 1 H) 8.02 (s, 1 H) 12.24 (br s, 1 H)

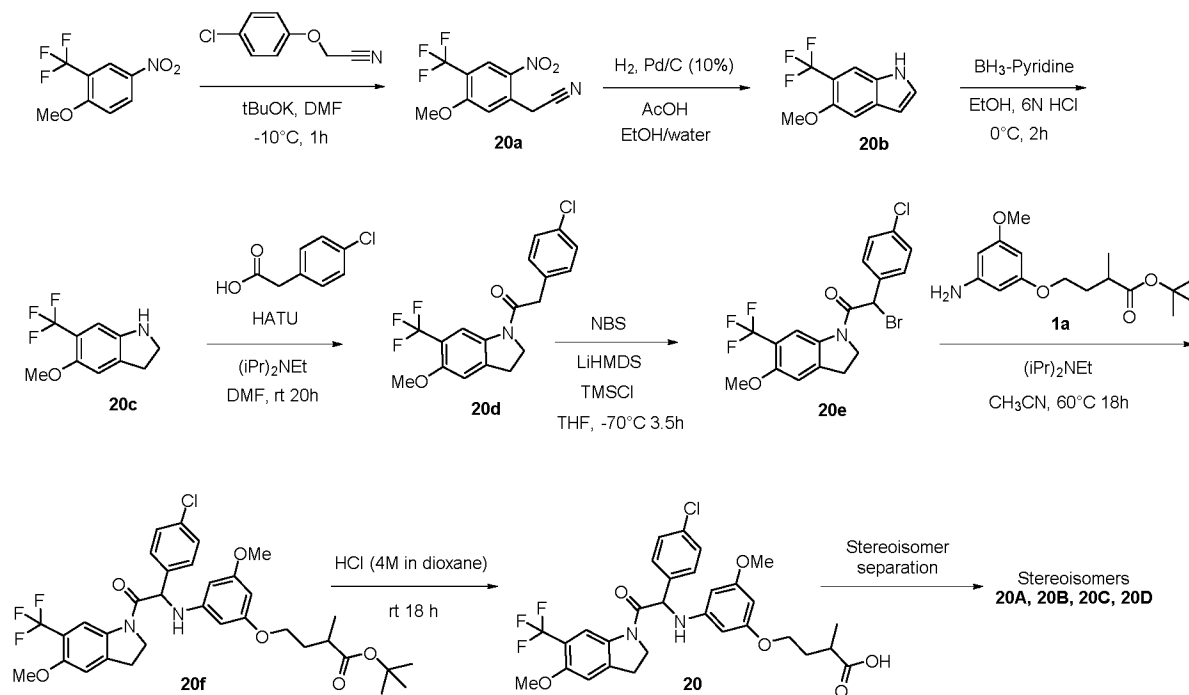
LC/MS (method LC-D): R<sub>t</sub> 2.84 min, MH<sup>+</sup> 621

[ $\alpha$ ]<sub>D</sub><sup>20</sup>: +56.8° (c 0.264, DMF)

Chiral SFC (method SFC-P): R<sub>t</sub> 2.12 min, no MH<sup>+</sup>, chiral purity 99.59%.

**Example 20** : synthesis of 4-(3-((1-(4-chlorophenyl)-2-(5-methoxy-6-(trifluoromethyl)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)-2-methylbutanoic acid (Compound **20**) and separation into Stereoisomers **20A**, **20B**, **20C** and **20D**

5



### Synthesis of intermediate **20a**:

A mixture of 1-methoxy-4-nitro-2-(trifluoromethyl)benzene [CAS 654-76-2] (24.5 g, 110.8 mmol) and 4-chlorophenoxyacetonitrile [CAS 3598-13-8] (20.4 g, 121.9 mmol) in DMF (100 mL) was added dropwise over 30 min to a stirred solution of tBuOK (27.35 g, 243.7 mmol) in DMF (100 mL) at -10°C. After addition, the purple solution was maintained at -10°C for 1 h. 500 mL of ice-water and 500 mL of 6N HCl were added and the precipitate was filtered off, washed with water and dried under reduced pressure to afford 40.4 g of 2-(5-methoxy-2-nitro-4-(trifluoromethyl)phenyl)acetonitrile **20a** (used as such in the next step).

### Synthesis of intermediate **20b**:

A solution of 2-(5-methoxy-2-nitro-4-(trifluoromethyl)phenyl)acetonitrile **20a** (26 g, 99.9 mmol) in ethanol/water (9/1) (500 mL) and AcOH (5.2 mL) was hydrogenated for 1 h under a pressure of 3.5 Bar with 10% Pd/C (15.3 g) as the catalyst. The reaction mixture was filtered through a pad of Celite<sup>®</sup> and the filter cake was washed with a solvent mixture of CH<sub>2</sub>Cl<sub>2</sub> and CH<sub>3</sub>OH. The combined filtrates were concentrated under reduced pressure. The residue was filtered through a glass filter charged with silica 60-200 μm using heptane/EtOAc 80/20 as the eluent. The



fractions containing the expected compound were combined and the solvent was concentrated under reduced pressure to give 5-methoxy-6-(trifluoromethyl)-1*H*-indole **20b** (15.6 g).

5 **Synthesis of intermediate 20c:**

At 0°C, BH<sub>3</sub>-Pyridine (23.5 mL, 232.4 mmol) was added dropwise to a solution of 5-methoxy-6-(trifluoromethyl)-1*H*-indole **20b** (10 g, 46.5 mmol) in EtOH (60 mL). 6N HCl (140 mL) was slowly added while maintaining the temperature below 10°C. The mixture was stirred at 0°C for 2 h. Water (200 mL) was added and the mixture  
10 was basified to pH 8-9 with a concentrated aqueous solution of NaOH (the reaction temperature was kept below 20°C). The precipitate was filtered off, washed with water (twice) and co-evaporated under reduced pressure with toluene to give 5-methoxy-6-(trifluoromethyl)indoline **20c** (9 g).

15 **Synthesis of Compound 20 and separation into Stereoisomers 20A, 20B, 20C and 20D:**

Compound **20** (330 mg) was obtained following the procedures described for the synthesis of Compound **1** starting from intermediate **20c**. The 4 Stereoisomers **20A** (50 mg), **20B** (18 mg), **20C** (68 mg) and **20D** (32 mg) were obtained, in this  
20 elution order, via two subsequent chiral SFC separations: (Stationary phase: Chiralpak® AD-H 5 µm 250 x 30 mm, mobile phase: 40% CO<sub>2</sub>, 60% iPrOH) and (Stationary phase: Chiralcel® OJ-H 5 µm 250 x 20mm, mobile phase: 60% CO<sub>2</sub>, 40% MeOH); followed by individual purification by flash chromatography on silica gel (15-40 µm, 12 g, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 99.5/0.5 to 90/10) and subsequent  
25 solidification from CH<sub>3</sub>CN/diisopropyl ether/heptane.

**Stereoisomer 20A:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.10 (d, *J*=7.07 Hz, 3 H) 1.60 – 1.72 (m, 1 H) 1.90 – 2.01 (m, 1 H) 3.20 – 3.32 (m, 2 H) 3.61 (s, 3 H) 3.79 - 3.90 (m, 5 H) 3.93 -  
30 4.09 (m, 1 H) 4.42 – 4.53 (m, 1 H) 5.53 (br d, *J*=8.59 Hz, 1 H) 5.74 (s, 1 H) 5.93 (br s, 1 H) 5.95 (br s, 1 H) 6.38 (br d, *J*=9.09 Hz, 1 H) 7.23 (s, 1 H) 7.43 (br d, *J*=8.08 Hz, 2 H) 7.55 (br d, *J*=8.08 Hz, 2 H) 8.33 (s, 1 H) 12.16 (br s 1 H) (1H missing CH CO<sub>2</sub>H under DMSO)

LC/MS (method LC-C): R<sub>t</sub> 2.95 min, MH<sup>+</sup> 607

35 [α]<sub>D</sub><sup>20</sup>: -40.9° (c 0.257, DMF)

Chiral SFC (method SFC-Q): R<sub>t</sub> 1.07 min, MH<sup>+</sup> 607, chiral purity 100%.

**Stereoisomer 20B:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.09 (d, *J*=6.94 Hz, 3 H) 1.69 (dq, *J*=13.52, 6.53 Hz, 1 H) 1.88 - 2.11 (m, 1 H) 3.08 - 3.28 (m, 2 H) 3.53 - 3.66 (m, 3 H) 3.79 - 3.90 (m, 5 H) 3.92 - 4.11 (m, 1 H) 3.92 - 4.11 (m, 1 H) 4.32 - 4.67 (m, 1 H) 5.54 (d, *J*=8.51 Hz, 1 H) 5.75 (s, 1 H) 5.93 (s, 1 H) 5.95 (s, 1H) 6.30 - 6.45 (m, 1 H) 7.23 (s, 1 H) 7.43 (d, *J*=8.20 Hz, 2 H) 7.55 (d, *J*=8.20 Hz, 2 H) 8.33 (s, 1 H) 12.05 (br s, 1 H) (1H missing CH CO<sub>2</sub>H under DMSO)

LC/MS (method LC-C): R<sub>t</sub> 2.95 min, MH<sup>+</sup> 607

[α]<sub>D</sub><sup>20</sup>: -50.0° (c 0.266, DMF)

Chiral SFC (method SFC-Q): R<sub>t</sub> 1.07 min, MH<sup>+</sup> 607, chiral purity 100%.

10

**Stereoisomer 20C:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.09 (br d, *J*=6.94 Hz, 3 H) 1.52 - 1.83 (m, 1 H) 1.86 - 2.06 (m, 1 H) 3.07 - 3.28 (m, 2 H) 3.61 (s, 3 H) 3.73 - 3.91 (m, 5 H) 3.94 - 4.04 (m, 1 H) 4.37 - 4.58 (m, 1 H) 5.54 (br d, *J*=8.51 Hz, 1 H) 5.75 (s, 1 H) 5.93 (s, 1 H) 5.95 (s, 1H) 6.39 (br d, *J*=8.51 Hz, 1 H) 7.23 (s, 1H) 7.43 (br d, *J*=8.20 Hz, 2 H) 7.55 (br d, *J*=8.20 Hz, 2 H) 8.33 (s, 1 H) 12.13 (br s, 1 H) (1H missing CH CO<sub>2</sub>H under DMSO)

LC/MS (method LC-C): R<sub>t</sub> 2.95 min, MH<sup>+</sup> 607

[α]<sub>D</sub><sup>20</sup>: +26.0° (c 0.288, DMF)

Chiral SFC (method SFC-Q): R<sub>t</sub> 1.56 min, MH<sup>+</sup> 607, chiral purity 99.68%.

20

**Stereoisomer 20D:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.09 (d, *J*=7.07 Hz, 3 H) 1.60 - 1.75 (m, 1 H) 1.85 - 1.99 (m, 1 H) 3.11 - 3.27 (m, 2 H) 3.61 (s, 3 H) 3.77 - 3.91 (m, 5 H) 3.93 - 4.05 (m, 1 H) 4.44 - 4.56 (m, 1 H) 5.54 (br d, *J*=8.59 Hz, 1 H) 5.74 (s, 1 H) 5.93 (br s, 1 H) 5.95 (br s, 1 H) 6.38 (br d, *J*=8.59 Hz, 1 H) 7.23 (s, 1 H) 7.43 (d, *J*=8.59 Hz, 2 H) 7.55 (br d, *J*=8.08 Hz, 2 H) 8.33 (s, 1 H) 12.22 (br s, 1 H) (1H missing CH CO<sub>2</sub>H under DMSO)

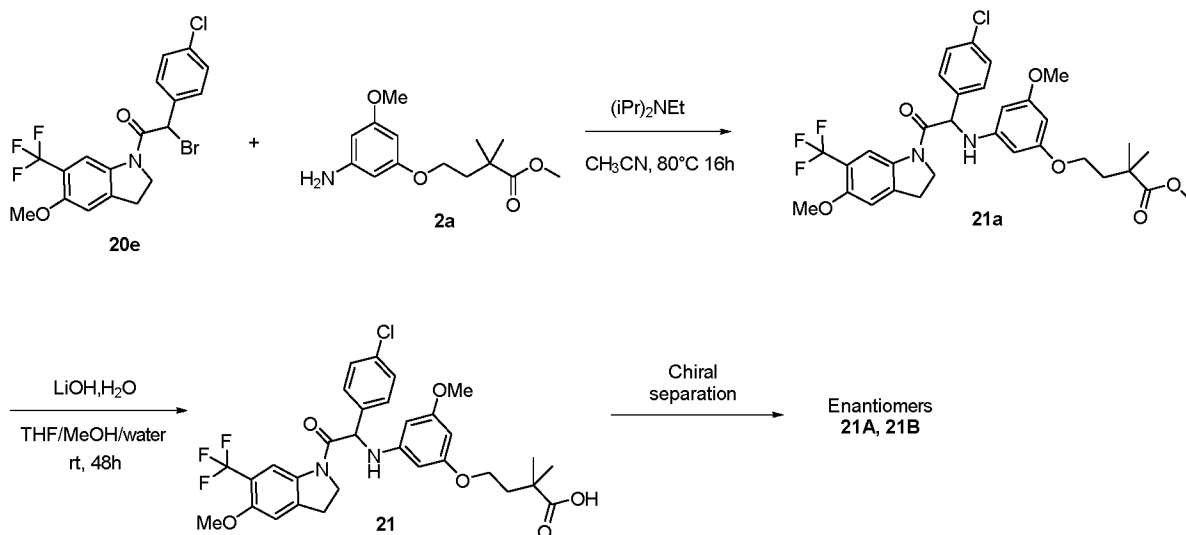
LC/MS (method LC-C): R<sub>t</sub> 2.96 min, MH<sup>+</sup> 607

[α]<sub>D</sub><sup>20</sup>: +57.4° (c 0.27, DMF)

Chiral SFC (method SFC-Q): R<sub>t</sub> 2.19 min, MH<sup>+</sup> 607, chiral purity 100%.

30

**Example 21** : synthesis of 4-(3-((1-(4-chlorophenyl)-2-(5-methoxy-6-(trifluoromethyl)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)-2,2-dimethylbutanoic acid (Compound **21**) and chiral separation into Enantiomers **21A** and **21B**



#### Synthesis of intermediate **21a**:

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(5-methoxy-6-(trifluoromethyl)indolin-1-yl)ethanone **20e** (904 mg, 2.014 mmol), methyl 4-(3-amino-5-methoxyphenoxy)-2,2-dimethylbutanoate **2a** (700 mg, 2.619 mmol) and diisopropylethylamine (694  $\mu$ L, 4.029 mmol) in  $\text{CH}_3\text{CN}$  (10 mL) was stirred at 80°C for 16 h. The mixture was concentrated under reduced pressure. The residue was taken up with EtOAc. The organic layer was dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated to give methyl 4-(3-((1-(4-chlorophenyl)-2-(5-methoxy-6-(trifluoromethyl)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)-2,2-dimethylbutanoate **21a** (1.58 g), which was used as such in the next step.

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#### Synthesis of Compound **21** and chiral separation into Enantiomers **21A** and **21B**:

At 0°C, LiOH monohydrate (254 mg, 6.046 mmol) was added to a solution of methyl 4-(3-((1-(4-chlorophenyl)-2-(5-methoxy-6-(trifluoromethyl)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)-2,2-dimethylbutanoate **21a** (1.28 g, 2.015 mmol) in THF/MeOH/water (15 mL). The mixture was warmed to room temperature and stirred for 48 h. The mixture was cooled to 0°C and water was added. The mixture was acidified to pH 4-5 with 3N HCl and extracted with EtOAc. The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and the solvent was evaporated. Purification was performed by flash chromatography on silica gel (15-40  $\mu$ m, 40 g,  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ : 100/0 to 98/2). The fractions containing expected

20  
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compound were combined and evaporated to dryness. A second purification was performed via Reverse phase (Stationary phase: YMC-actus Triart-C18 10  $\mu$ m 30 x 150 mm, mobile phase: Gradient from 70% aqueous  $\text{NH}_4\text{HCO}_3$  0.2%, 30%  $\text{CH}_3\text{CN}$  to 0% aqueous  $\text{NH}_4\text{HCO}_3$  0.2%, 100%  $\text{CH}_3\text{CN}$ ). The pure fractions were combined and concentrated under vacuum to give 4-(3-((1-(4-chlorophenyl)-2-(5-methoxy-6-(trifluoromethyl)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)-2,2-dimethylbutanoic acid (Compound **21**, 455 mg). The enantiomers were separated via chiral SFC (Stationary phase: Chiralcel<sup>®</sup> OD-H 5  $\mu$ m 250 x 30 mm, mobile phase: 55%  $\text{CO}_2$ , 45% MeOH) to give, after solidification from heptane/diisopropyl ether, the first eluted Enantiomer **21A** (106 mg) and the second eluted Enantiomer **21B** (103 mg).

**Compound 21:**

$^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.13 (d,  $J=3.8$  Hz, 6 H) 1.87 (t,  $J=7.3$  Hz, 2 H) 3.14 - 3.30 (m, 2 H) 3.61 (s, 3 H) 3.84 (m, 5 H) 3.98 (td,  $J=10.4$ , 7.3 Hz, 1 H) 4.51 (td,  $J=10.3$ , 6.1 Hz, 1 H) 5.52 (d,  $J=8.5$  Hz, 1 H) 5.73 (t,  $J=1.9$  Hz, 1 H) 5.92 (s, 1 H) 5.94 (s, 1 H) 6.39 (d,  $J=8.5$  Hz, 1 H) 7.23 (s, 1 H) 7.43 (d,  $J=8.5$  Hz, 2 H) 7.55 (d,  $J=8.5$  Hz, 2 H) 8.33 (s, 1 H) 12.23 (br s, 1 H)  
LC/MS (method LC-C):  $R_t$  3.19 min,  $\text{MH}^+$  621

**Enantiomer 21A:**

$^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.08 - 1.15 (m, 6 H) 1.85 (t,  $J=7.3$  Hz, 2 H) 3.13 - 3.30 (m, 2 H) 3.55 - 3.65 (m, 3 H) 3.80 - 3.89 (m, 5 H) 3.98 (td,  $J=10.4$ , 7.3 Hz, 1 H) 4.52 (td,  $J=10.4$ , 6.3 Hz, 1 H) 5.54 (d,  $J=8.8$  Hz, 1 H) 5.73 (t,  $J=1.9$  Hz, 1 H) 5.92 (s, 1 H) 5.95 (s, 1 H) 6.38 (d,  $J=8.5$  Hz, 1 H) 7.23 (s, 1 H) 7.43 (d,  $J=8.5$  Hz, 2 H) 7.56 (d,  $J=8.5$  Hz, 2 H) 8.34 (s, 1 H)  
LC/MS (method LC-C):  $R_t$  3.21 min,  $\text{MH}^+$  621

$[\alpha]_D^{20}$ :  $-41.7^\circ$  (c 0.254, DMF)

Chiral SFC (method SFC-H):  $R_t$  1.23 min,  $\text{MH}^+$  621, chiral purity 100%.

**Enantiomer 21B:**

$^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.08 - 1.16 (m, 6 H) 1.86 (t,  $J=7.1$  Hz, 2 H) 3.15 - 3.29 (m, 2 H) 3.61 (s, 3 H) 3.80 - 3.90 (m, 5 H) 3.98 (td,  $J=10.2$ , 7.3 Hz, 1 H) 4.52 (td,  $J=10.4$ , 6.3 Hz, 1 H) 5.53 (d,  $J=8.5$  Hz, 1 H) 5.70 - 5.75 (m, 1 H) 5.92 (s, 1 H) 5.95 (s, 1 H) 6.38 (d,  $J=8.5$  Hz, 1 H) 7.23 (s, 1 H) 7.43 (d,  $J=8.5$  Hz, 2 H) 7.56 (d,  $J=8.5$  Hz, 2 H) 8.34 (s, 1 H)

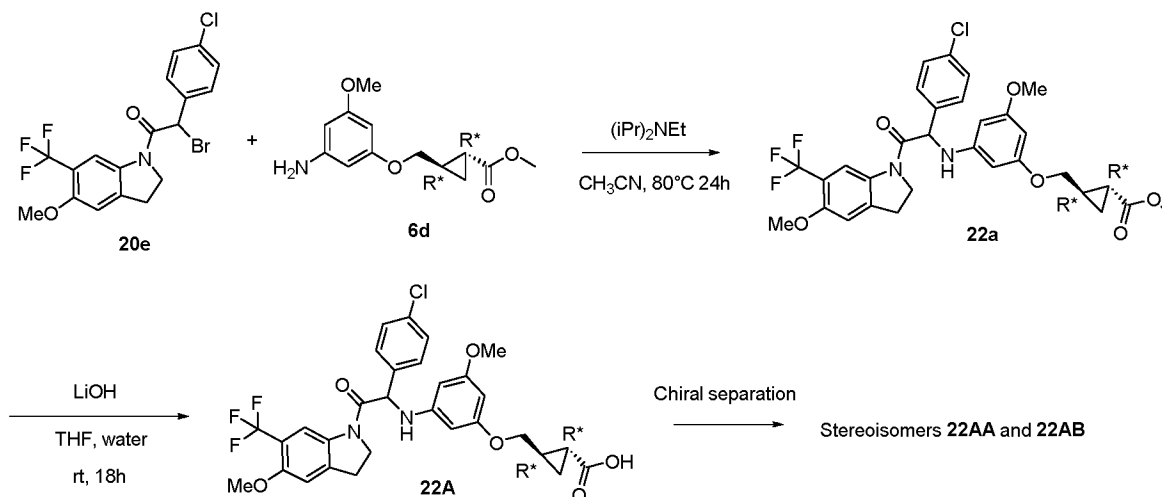
LC/MS (method LC-C):  $R_t$  3.21 min,  $\text{MH}^+$  621

$[\alpha]_D^{20}$ :  $+44.0^\circ$  (c 0.275, DMF)

Chiral SFC (method SFC-H):  $R_t$  2.38 min,  $\text{MH}^+$  621, chiral purity 100%.

**Example 22A** : synthesis of (1*R*\*,2*R*\*)-2-(((1-(4-chlorophenyl)-2-(5-methoxy-6-(trifluoromethyl)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylic acid (Compound **22A**) and separation into Stereoisomers

5 **22AA and 22AB**



10 **Synthesis of Compound 22A and separation into Stereoisomers 22AA and 22AB:**

Compound **22A** (284 mg) was synthesized from intermediate **20e** using the procedures described for the synthesis of Compound **6A**. The two stereoisomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5 μm 250 x 30 mm, mobile phase: 50% CO<sub>2</sub>, 50% EtOH) to give, after solidification from pentane/diisopropyl ether, the first eluted Stereoisomers **22AA** (79 mg) and the second eluted Stereoisomers **22AB** (74 mg).

15 **Stereoisomers 22AA:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.85 – 0.93 (m, 1 H) 1.00 - 1.08 (m, 1 H)  
 20 1.54 (dt, *J*=8.12, 4.30 Hz, 1 H) 1.60 -1.68 (m, 1 H) 3.12 - 3.26 (m, 2 H) 3.61 (s, 3 H) 3.68 (dd, *J*=10.40, 7.57 Hz, 1 H) 3.79 - 3.90 (m, 4 H) 3.93 - 4.05 (m, 1 H) 4.50 (td, *J*=10.40, 6.31 Hz, 1 H) 5.55 (d, *J*=8.51 Hz, 1 H) 5.75 (s, 1 H) 5.94 (s, 1 H) 5.96 (s, 1 H) 6.39 (d, *J*=8.83 Hz, 1 H) 7.23 (s, 1 H) 7.43 (d, *J*=8.51 Hz, 2 H) 7.55 (d, *J*=8.51 Hz, 2 H) 8.33 (s, 1 H) 12.23 (br s, 1 H)

25 LC/MS (method LC-C): *R*<sub>t</sub> 2.80 min, MH<sup>+</sup> 605

[α]<sub>D</sub><sup>20</sup>: -75.0° (c 0.3, DMF)

Chiral SFC (method SFC-R): *R*<sub>t</sub> 0.86 min, no MH<sup>+</sup>, chiral purity 100%.

**Stereoisomers 22AB:**

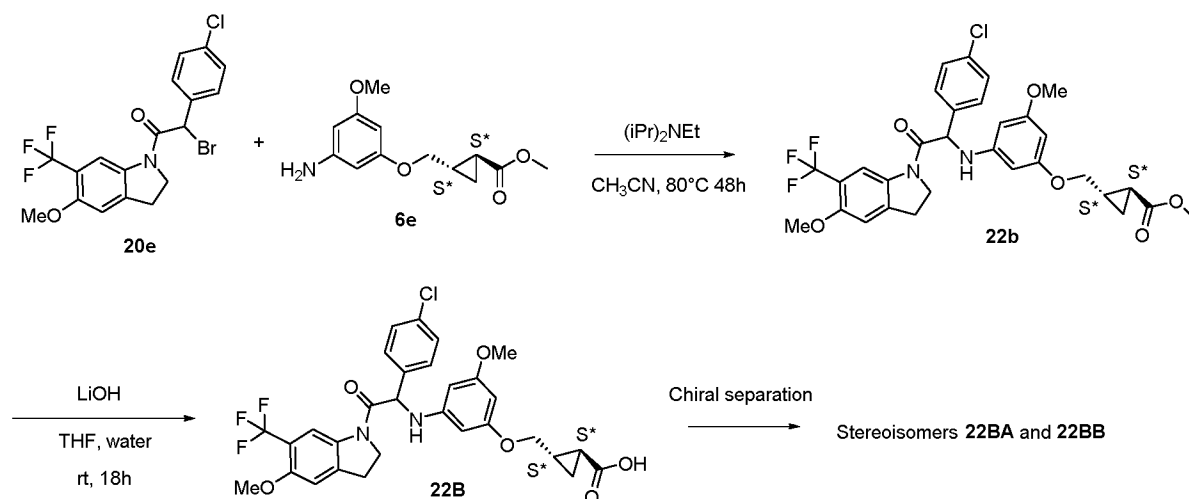
<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.88 (br t, *J*=9.30 Hz, 1 H) 1.02 (dt, *J*=8.43, 4.45 Hz, 1 H) 1.47 - 1.58 (m, 1 H) 1.59 - 1.68 (m, 1 H) 3.13 - 3.28 (m, 2 H) 3.61 (s, 3 H) 3.64 - 3.72 (m, 1 H) 3.84 (s, 4 H) 3.92 - 4.06 (m, 1 H) 4.50 (td, *J*=10.32, 6.15 Hz, 1 H) 5.55 (d, *J*=8.83 Hz, 1 H) 5.75 (s, 1 H) 5.95 (s, 1 H) 5.96 (s, 1 H) 6.39 (d, *J*=8.83 Hz, 1 H) 7.23 (s, 1 H) 7.43 (d, *J*=8.51 Hz, 2 H) 7.55 (d, *J*=8.51 Hz, 2 H) 8.33 (s, 1 H) 12.08 (br s, 1 H)

LC/MS (method LC-D): *R*<sub>t</sub> 2.69 min, MH<sup>+</sup> 605

[α]<sub>D</sub><sup>20</sup>: +10.0° (c 0.281, DMF)

Chiral SFC (method SFC-R): *R*<sub>t</sub> 1.84 min, no MH<sup>+</sup>, chiral purity 100%.

**Example 22B** : synthesis of (1*S*\*,2*S*\*)-2-(((1-(4-chlorophenyl)-2-(5-methoxy-6-(trifluoromethyl)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylic acid (Compound **22B**) and separation into Stereoisomers **22BA** and **22BB**

**Synthesis of Compound 22B and separation into Stereoisomers 22BA and 22BB:**

Compound **22B** (257 mg) was synthesized from intermediate **20e** using the procedure described for the synthesis of Compound **6B**. The two stereoisomers were separated via chiral SFC (Stationary phase: Chiralcel<sup>®</sup> OD-H 5 μm 250 x 30 mm, mobile phase: 50% CO<sub>2</sub>, 50% EtOH) to give, after solidification from pentane/diisopropyl ether, the first eluted stereoisomers **22BA** (49 mg) and the second eluted stereoisomers **22BB** (61 mg).

**Stereoisomers 22BA:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.83 - 1.00 (m, 1 H) 0.98 - 1.09 (m, 1 H) 1.54 (dt, *J*=8.35, 4.33 Hz, 1 H) 1.58 - 1.70 (m, 1 H) 3.13 - 3.28 (m, 2 H) 3.61 (s, 3 H) 3.68 (dd, *J*=10.09, 7.57 Hz, 1 H) 3.78 - 3.89 (m, 4 H) 3.95 - 4.05 (m, 1 H) 4.50 (td, *J*=10.25, 6.31 Hz, 1 H) 5.55 (d, *J*=8.83 Hz, 1 H) 5.75 (s, 1 H) 5.95 (br s, 1 H) 5.96 (br s, 1 H) 6.39 (br d, *J*=8.83 Hz, 1 H) 7.23 (s, 1 H) 7.43 (d, *J*=8.51 Hz, 2 H) 7.55 (d, *J*=8.51 Hz, 2 H) 8.33 (s, 1 H) 12.24 (br s, 1 H)

LC/MS (method LC-D): *R*<sub>t</sub> 2.68 min, MH<sup>+</sup> 605

[α]<sub>D</sub><sup>20</sup>: -9.3° (c 0.291, DMF)

10 Chiral SFC (method SFC-S): *R*<sub>t</sub> 1.48 min, MH<sup>+</sup> 605, chiral purity 100%.

**Stereoisomers 22BB:**

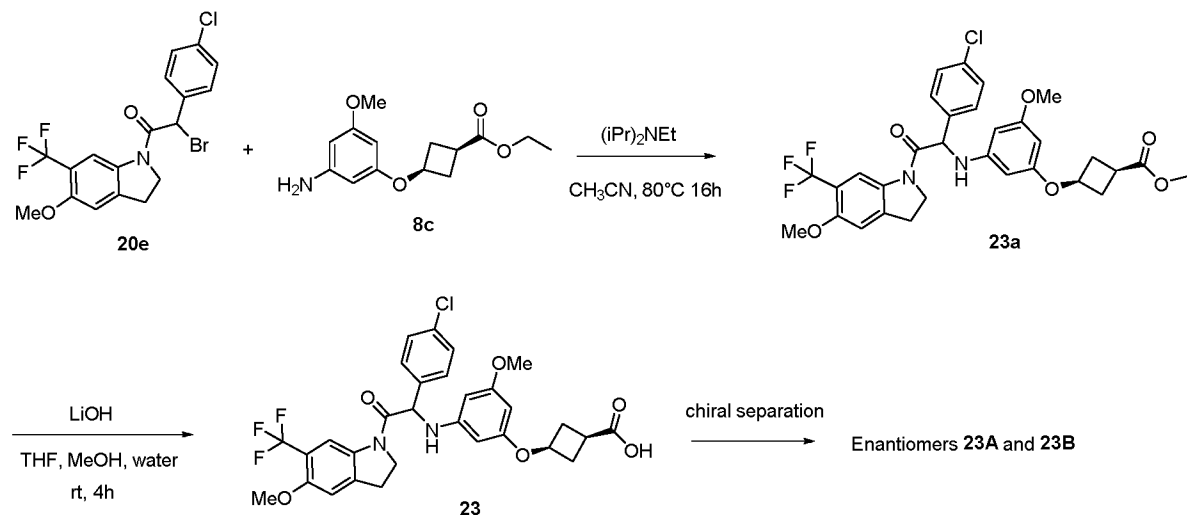
<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.82 - 0.95 (m, 1 H) 1.04 - 1.06 (m, 1 H) 1.55 (dt, *J*=8.28, 4.22 Hz, 1 H) 1.58 - 1.68 (m, 1 H) 3.13 - 3.28 (m, 2 H) 3.61 (s, 3 H) 3.68 (dd, *J*=10.40, 7.25 Hz, 1 H) 3.81 - 3.88 (m, 4 H) 3.95 - 4.02 (m, 1 H) 4.46 - 4.55 (m, 1 H) 5.54 (d, *J*=8.83 Hz, 1 H) 5.75 (s, 1 H) 5.94 (s, 1 H) 5.96 (s, 1 H) 6.39 (d, *J*=9.14 Hz, 1 H) 7.23 (s, 1 H) 7.43 (d, *J*=8.51 Hz, 2 H) 7.55 (d, *J*=8.51 Hz, 2 H) 8.33 (s, 1 H) 12.20 (br s, 1 H)

LC/MS (method LC-C): *R*<sub>t</sub> 2.80 min, MH<sup>+</sup> 605

20 [α]<sub>D</sub><sup>20</sup>: +80.0° (c 0.275, DMF)

Chiral SFC (method SFC-S): *R*<sub>t</sub> 3.12 min, MH<sup>+</sup> 605, chiral purity 99.55%.

**Example 23** : synthesis of (1*s*,3*s*)-3-(3-((1-(4-chlorophenyl)-2-(5-methoxy-6-(trifluoromethyl)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)cyclobutene-carboxylic acid (Compound **23**) and chiral separation into Enantiomers **23A** and **23B**



**Synthesis of Compound 23 and chiral separation into enantiomers 23A and 23B:**

Compound **23A** (280 mg) was synthesized from intermediate **20e** using the procedures described for the synthesis of Compound **8**. The two enantiomers  
5 were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5 µm 250 x 30 mm, mobile phase: 45% CO<sub>2</sub>, 55% EtOH) to give, after solidification from heptane/diisopropyl ether, the first eluted Enantiomer **23A** (60 mg) and the second eluted Enantiomer **23B** (71 mg).

**Compound 23:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.02 - 2.15 (m, 2 H) 2.58 - 2.65 (m, 2 H) 2.66 - 2.75 (m, 1 H) 3.14 - 3.29 (m, 2 H) 3.61 (s, 3 H) 3.84 (s, 3 H) 3.98 (td, *J*=10.4, 7.3 Hz, 1 H) 4.42 - 4.57 (m, 2 H) 5.51 (d, *J*=8.5 Hz, 1 H) 5.65 (t, *J*=1.9 Hz, 1 H) 5.86 (s, 1 H) 5.93 (s, 1 H) 6.42 (d, *J*=8.5 Hz, 1 H) 7.23 (s, 1 H) 7.44 (d, *J*=8.5 Hz, 2 H)  
15 7.55 (d, *J*=8.5 Hz, 2 H) 8.34 (s, 1 H) 12.11 - 12.40 (m, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.76 min, MH<sup>+</sup> 605

**Enantiomer 23A:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.02 - 2.15 (m, 2 H) 2.57 - 2.65 (m, 2 H) 2.66 - 2.75 (m, 1 H) 3.14 - 3.28 (m, 2 H) 3.61 (s, 3 H) 3.84 (s, 3 H) 3.98 (td, *J*=10.3, 7.1 Hz, 1 H) 4.42 - 4.56 (m, 2 H) 5.51 (d, *J*=8.5 Hz, 1 H) 5.65 (t, *J*=2.0 Hz, 1 H) 5.86 (s, 1 H) 5.93 (s, 1 H) 6.42 (d, *J*=8.5 Hz, 1 H) 7.23 (s, 1 H) 7.44 (d, *J*=8.5 Hz, 2 H) 7.55 (d, *J*=8.5 Hz, 2 H) 8.34 (s, 1 H) 12.02 - 12.49 (m, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.75 min, MH<sup>+</sup> 605

[α]<sub>D</sub><sup>20</sup>: -38.1° (c 0.307, DMF)

Chiral SFC (method SFC-R): R<sub>t</sub> 0.84 min, MH<sup>+</sup> 605, chiral purity 100%.

**Enantiomer 23B:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.02 - 2.15 (m, 2H) 2.56 - 2.75 (m, 3 H) 3.14 - 3.27 (m, 2 H) 3.61 (s, 3 H) 3.84 (s, 3 H) 3.93 - 4.04 (m, 1 H) 4.43 - 4.57 (m, 2 H) 5.51 (br d, *J*=8.5 Hz, 1 H) 5.65 (s, 1 H) 5.86 (s, 1 H) 5.93 (s, 1 H) 6.42 (br d, *J*=8.5 Hz, 1 H) 7.23 (s, 1 H) 7.44 (br d, *J*=8.5 Hz, 2 H) 7.55 (br d, *J*=8.5 Hz, 2 H) 8.34 (s, 1 H) 12.07 - 12.47 (m, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.76 min, MH<sup>+</sup> 605

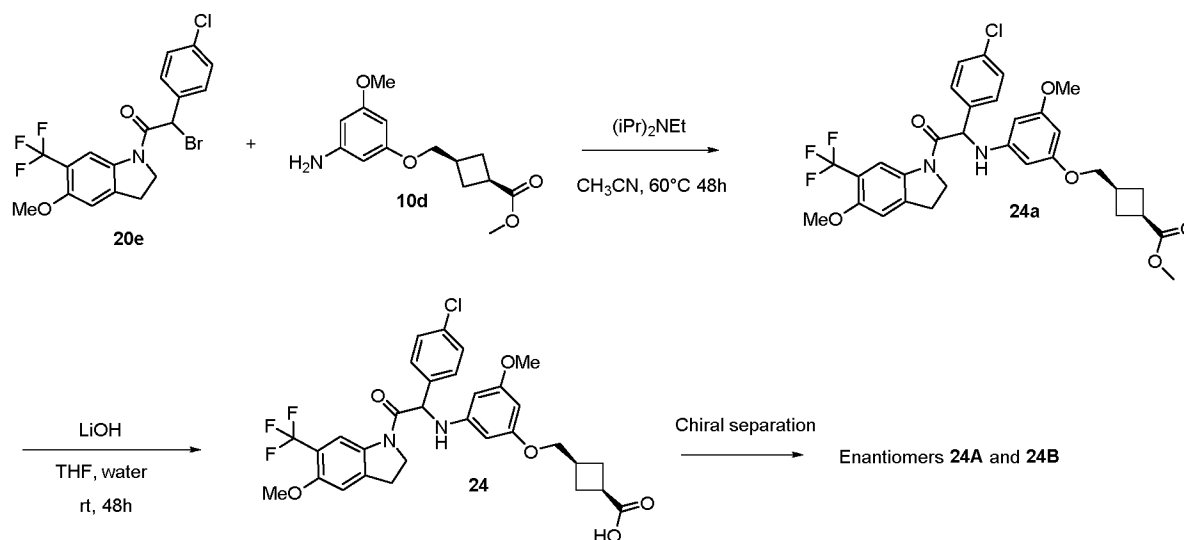
[α]<sub>D</sub><sup>20</sup>: +36.9° (c 0.309, DMF)

Chiral SFC (method SFC-R): R<sub>t</sub> 1.86 min, MH<sup>+</sup> 605, chiral purity 100%.



**Example 24** : synthesis of (1*s*,3*s*)-3-((3-((1-(4-chlorophenyl)-2-(5-methoxy-6-(trifluoromethyl)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)methyl)cyclobutanecarboxylic acid (Compound **24**) and chiral separation into Enantiomers **24A** and **24B**

5



**Synthesis of Compound 24 and chiral separation into Enantiomers 24A and 24B:**

10 Compound **24** (550 mg) was synthesized from intermediate **20e** using the procedures described for the synthesis of Compound **10**. The two enantiomers were separated via chiral SFC (Stationary phase:  $Whelk^{\circ} O1$  (S,S) 5  $\mu m$  250 x 21.1 mm, mobile phase: 50%  $CO_2$ , 50% MeOH) to give, after solidification from  $Et_2O$ , the first eluted Enantiomer **24A** (190 mg) and the second eluted Enantiomer **24B** (177 mg).

**Compound 24:**

$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.93 (br q,  $J=9.77$  Hz, 2 H) 2.11 - 2.32 (m, 2 H) 2.53 - 2.60 (m, 1 H) 2.97 (quin,  $J=8.91$  Hz, 1 H) 3.16 - 3.30 (m, 2 H) 3.62 (s, 3 H) 3.74 - 3.82 (m, 2 H) 3.85 (s, 3 H) 3.96 - 4.06 (m, 1 H) 4.51 (td,  $J=10.25, 5.99$  Hz, 1 H) 5.55 (d,  $J=8.83$  Hz, 1 H) 5.74 (s, 1 H) 5.94 (br s, 2 H) 6.39 (d,  $J=8.51$  Hz, 1 H) 7.23 (s, 1 H) 7.44 (d,  $J=8.51$  Hz, 2 H) 7.55 (d,  $J=8.51$  Hz, 2 H) 8.34 (s, 1 H) 12.07 (br s, 1 H)

LC/MS (method LC-C):  $R_t$  2.91 min,  $MH^+$  619

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**Enantiomer 24A:**

$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.87 - 2.02 (m, 2 H) 2.15 - 2.30 (m, 2 H) 2.52 - 2.59 (m, 1 H) 2.95 (qt  $J = 8.83$  Hz, 1 H) 3.07 - 3.29 (m, 2 H) 3.61 (s, 3 H) 3.77 (br

d,  $J=6.31$  Hz, 2 H) 3.84 (s, 3 H) 3.95 – 4.07 (m, 1 H) 4.42 – 4.56 (m, 1 H) 5.54 (d,  $J=8.83$  Hz, 1 H) 5.74 (t,  $J=2.05$  Hz, 1 H) 5.81 - 6.01 (m, 2 H) 6.38 (d,  $J=8.83$  Hz, 1 H) 7.23 (s, 1 H) 7.43 (d,  $J=8.51$  Hz, 2 H) 7.55 (d,  $J=8.51$  Hz, 2 H) 8.33 (s, 1 H) 12.11 (br s, 1 H)

5 LC/MS (method LC-C):  $R_t$  2.89 min,  $MH^+$  619

$[\alpha]_D^{20}$ :  $-41.5^\circ$  (c 0.224, DMF)

Chiral SFC (method SFC-T):  $R_t$  1.81 min, no  $MH^+$ , chiral purity 100%.

### Enantiomer 24B:

10  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.91 (q,  $J=9.35$  Hz, 2 H) 2.17 - 2.26 (m, 2 H) 2.53 - 2.61 (m, 1 H) 2.94 (quin,  $J=8.91$  Hz, 1 H) 3.13 - 3.27 (m, 2 H) 3.61 (s, 3 H) 3.72 - 3.79 (m, 2 H) 3.84 (s, 3 H) 3.90 - 4.06 (m, 1 H) 4.50 (td,  $J=10.32, 6.46$  Hz, 1 H) 5.54 (d,  $J=8.83$  Hz, 1 H) 5.72 - 5.75 (m, 1 H) 5.91 - 5.95 (m, 2 H) 6.38 (d,  $J=8.83$  Hz, 1 H) 7.23 (s, 1 H) 7.43 (d,  $J=8.51$  Hz, 2 H) 7.55 (d,  $J=8.20$  Hz, 2 H)

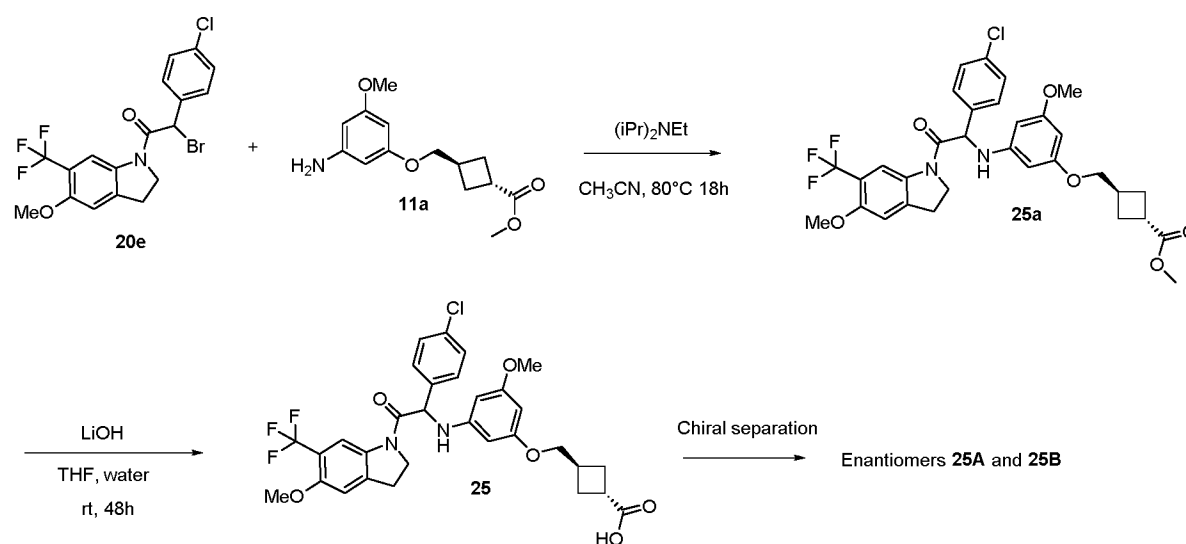
15 8.33 (s, 1 H) 12.07 (br s, 1 H)

LC/MS (method LC-C):  $R_t$  2.89 min,  $MH^+$  619

$[\alpha]_D^{20}$ :  $+36.6^\circ$  (c 0.232, DMF)

Chiral SFC (method SFC-T):  $R_t$  2.26 min, no  $MH^+$ , chiral purity 98.71%.

20 **Example 25** : synthesis of (1*r*,3*r*)-3-((3-((1-(4-chlorophenyl)-2-(5-methoxy-6-(trifluoromethyl)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)methyl)-cyclobutanecarboxylic acid (Compound **25**) and chiral separation into Enantiomers **25A** and **25B**



**Synthesis of Compound 25 and chiral separation into Enantiomers 25A and 25B:**

Compound **25** (310 mg) was synthesized from intermediate **20e** using the procedures described for the synthesis of Compound **11**. The two enantiomers were separated via chiral SFC (Stationary phase: Whelk<sup>®</sup> O1 (S,S) 5  $\mu$ m 250 x 21.1 mm, mobile phase: 50% CO<sub>2</sub>, 50% MeOH) to give, after solidification from Et<sub>2</sub>O/pentane, the first eluted Enantiomer **25A** (94 mg) and the second eluted Enantiomer **25B** (105 mg).

**Compound 25:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.80 - 2.04 (m, 2 H) 2.22 - 2.31 (m, 2 H) 2.56 - 2.64 (m, 1 H) 3.09 (br qt, *J*=7.33 Hz, 1 H) 3.14 - 3.28 (m, 2 H) 3.62 (s, 3 H) 3.84 (s, 3 H) 3.87 (d, *J*=6.57 Hz, 2 H) 3.93 - 4.06 (m, 1 H) 4.45 - 4.56 (m, 1 H) 5.54 (d, *J*=8.59 Hz, 1 H) 5.77 (s, 1 H) 5.94 (s, 1 H) 5.96 (s, 1 H) 6.38 (d, *J*=9.09 Hz, 1 H) 7.23 (s, 1H) 7.43 (d, *J*=8.59 Hz, 2 H) 7.55 (d, *J*=8.59 Hz, 2 H) 8.33 (s, 1 H) 12.10 (br s, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.87 min, MH<sup>+</sup> 619

**Enantiomer 25A:**

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.91 - 2.03 (m, 2 H) 2.18 - 2.29 (m, 2 H) 2.55 - 2.62 (m, 1 H) 3.01 - 3.11 (m, 1 H) 3.14 - 3.28 (m, 2 H) 3.62 (s, 3 H) 3.84 (s, 3 H) 3.86 (d, *J*=7.07 Hz, 2 H) 3.93 - 4.05 (m, 1 H) 4.42 - 4.58 (m, 1 H) 5.54 (d, *J*=8.59 Hz, 1 H) 5.77 (s, 1 H) 5.92 - 5.95 (m, 1 H) 5.95 - 5.98 (m, 1 H) 6.38 (d, *J*=8.59 Hz, 1 H) 7.23 (s, 1 H) 7.43 (d, *J*=8.08 Hz, 2 H) 7.55 (d, *J*=8.08 Hz, 2 H) 8.33 (s, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.90 min, MH<sup>+</sup> 619

$[\alpha]_D^{20}$ : -41.1° (c 0.28, DMF)

Chiral SFC (method SFC-T): R<sub>t</sub> 1.91 min, no MH<sup>+</sup>, chiral purity 100%.

**Enantiomer 25B:**

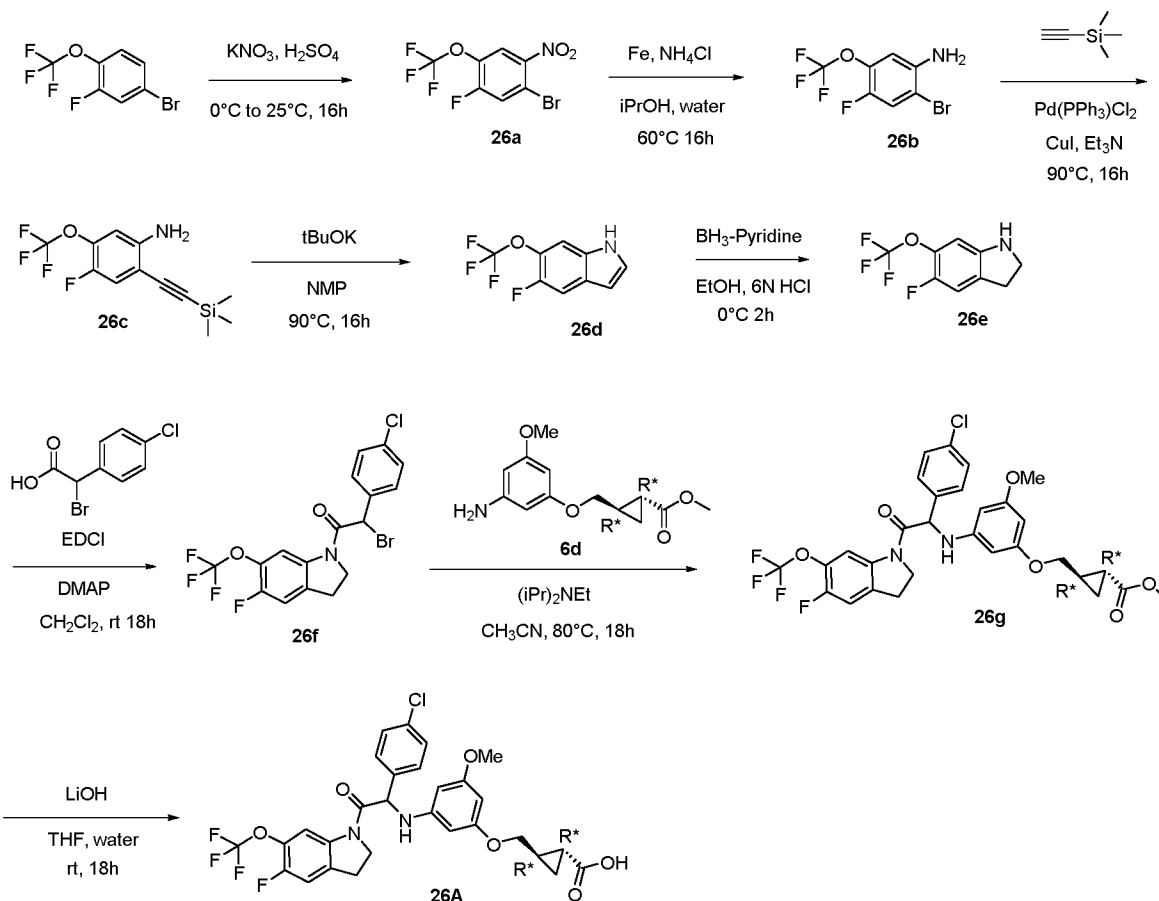
<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.90 - 2.04 (m, 2 H) 2.19 - 2.29 (m, 2 H) 2.55 - 2.60 (m, 1 H) 3.00 - 3.30 (m, 3 H) 3.62 (s, 3 H) 3.84 (s, 3 H) 3.86 (br d, *J*=7.07 Hz, 2 H) 3.94 - 4.04 (m, 1 H) 4.45 - 4.55 (m, 1 H) 5.54 (d, *J*=8.59 Hz, 1 H) 5.77 (s, 1 H) 5.88 - 5.95 (m, 1 H) 5.95 - 5.98 (m, 1 H) 6.38 (br d, *J*=8.59 Hz, 1 H) 7.23 (s, 1 H) 7.43 (d, *J*=8.59 Hz, 2 H) 7.55 (d, *J*=8.08 Hz, 2 H) 8.33 (s, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.90 min, MH<sup>+</sup> 619

$[\alpha]_D^{20}$ : +40.6° (c 0.32, DMF)

Chiral SFC (method SFC-T): R<sub>t</sub> 2.48 min, no MH<sup>+</sup>, chiral purity 98.68%.

**Example 26A** : synthesis of (1*R*\*,2*R*\*)-2-((3-((1-(4-chlorophenyl)-2-(5-fluoro-6-(trifluoromethoxy)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylic acid (Compound **26A**)



5

### Synthesis of intermediate **26a**:

A solution of 4-bromo-2-fluoro-1-(trifluoromethoxy)benzene [CAS 105529-58-6] (98.7 g, 381.1 mmol) in concentrated  $\text{H}_2\text{SO}_4$  (98%, 200 mL), was cooled to  $0^\circ\text{C}$  with an ice-bath.  $\text{KNO}_3$  (43.0 g, 425.3 mmol) was added in portions. After addition, the ice-bath was removed and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured out into ice-water (2 L) while stirring. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3x 500 mL). The combined organic layers were washed with a saturated aqueous  $\text{NaHCO}_3$  solution (2x 500 mL), brine (500 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford 1-bromo-5-fluoro-2-nitro-4-(trifluoromethoxy)benzene **26a** (117.2 g), which was used in the next step without further purification.

**Synthesis of intermediate 26b:**

To a stirred suspension of 1-bromo-5-fluoro-2-nitro-4-(trifluoromethoxy)benzene **26a** (70.0 g, 230 mmol) and NH<sub>4</sub>Cl (123.2 g, 2.30 mol) in iPrOH (1 L) and water (330 mL) was added reductive iron powder (64.3 g, 1.15 mol) under N<sub>2</sub>-atmosphere. The reaction mixture was stirred at 60°C for 16 h. The reaction mixture was diluted with EtOAc (1 L) and filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was partitioned between EtOAc (1 L) and water (800 mL). The layers were separated and the organic phase was washed with brine (1 L), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by distillation under reduced pressure (oil pump, b.p. 60~64°C). 2-Bromo-4-fluoro-5-(trifluoromethoxy)aniline **26b** (47.3 g) was obtained as a yellow oil.

**Synthesis of intermediate 26c:**

To a mixture of 2-bromo-4-fluoro-5-(trifluoromethoxy)aniline **26b** (18.4 g, 67.2 mmol) and ethynyl(trimethyl)silane (19.9 g, 202.4 mmol, 28.00 mL) in Et<sub>3</sub>N (300 mL) was added CuI (1.28 g, 6.72 mmol) and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2.40 g, 3.42 mmol). The reaction mixture was heated under N<sub>2</sub>-atmosphere at 90°C for 16 h. After cooling to room temperature, the mixture was diluted with MTBE (300 mL) and filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ISCO®, 220 g SepaFlash® Silica Flash Column, eluent: gradient of 0 to 5% EtOAc in petroleum ether @100mL/min). 4-Fluoro-5-(trifluoromethoxy)-2-((trimethylsilyl)ethynyl)aniline **26c** (16.1 g, 90% purity) was obtained as a brown oil.

**Synthesis of intermediate 26d:**

A mixture of 4-fluoro-5-(trifluoromethoxy)-2-((trimethylsilyl)ethynyl)aniline **26c** (16.1 g, 55.3 mmol) and tBuOK (18.6 g, 165.8 mmol) in NMP (220.00 mL) was heated at 90°C for 16 h under N<sub>2</sub>-atmosphere. After cooling to room temperature, the reaction mixture was poured out into ice-water (1 L) and extracted with MTBE (3x 300mL). The combined organic phases were washed with water (2x 200 mL), brine (300 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ISCO®, 120 g SepaFlash® Silica Flash Column, eluent: gradient of 0 to 5% EtOAc in petroleum ether, flow rate = 85 mL/min) to afford 5-fluoro-6-(trifluoromethoxy)-1*H*-indole **26d** (11 g) product as a dark-green oil. The residue was combined with another fraction (total amount = 17.2 g) and further purified by distillation under

reduced pressure (oil pump, b.p. 60~64°C) to provide 5-fluoro-6-(trifluoromethoxy)-1*H*-indole **26d** (14.7 g, 95% purity) as a colorless oil.

#### Synthesis of intermediate **26e**:

- 5 At 0°C, BH<sub>3</sub>-Pyridine (1.2 mL, 11 mmol) was added slowly to a solution of 5-fluoro-6-(trifluoromethoxy)-1*H*-indole **26d** (500 mg, 2.3 mmol) in EtOH (3.2 mL). 6N HCl (7.6 mL) was slowly added while maintaining the temperature below 10°C. The mixture was stirred at 0°C for 2 h. Water (100 mL) was added and the mixture was basified to pH 14 with concentrated NaOH (temperature was kept below 20°C).
- 10 CH<sub>2</sub>Cl<sub>2</sub> was added. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under reduced pressure to give 5-fluoro-6-(trifluoromethoxy)indoline **26e** (550 mg). The compound was used in the next step without further purification.

#### 15 Synthesis of intermediate **26f**:

- To a mixture of 2-bromo-2-(4-chlorophenyl)acetic acid [CAS 3381-73-5] (0.61 g, 2.4 mmol), 5-fluoro-6-(trifluoromethoxy)indoline **26e** (0.55 g, 2.2 mmol, 89% purity) and DMAP (0.027 g, 0.22 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (14 mL) was added EDCI (0.51 g, 2.7 mmol). The mixture was stirred at room temperature for 18 h. The mixture
- 20 was diluted with a 10% K<sub>2</sub>CO<sub>3</sub> solution in water. The layers were decanted. The organic layer was washed with water, dried over MgSO<sub>4</sub>, filtered and the solvent was concentrated under reduced pressure to give 2-bromo-2-(4-chlorophenyl)-1-(5-fluoro-6-(trifluoromethoxy)indolin-1-yl)ethanone **26f** (1.1 g, purple oil). The compound was used in the next step without further purification.

25

#### Synthesis of Compound **26A**:

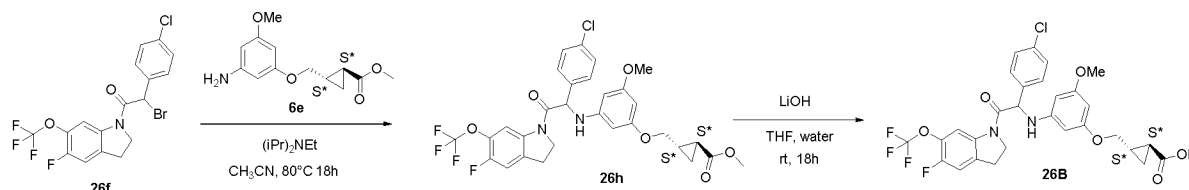
Compound **26A** (135 mg) was synthesized from intermediate **26f** using the procedures described for the synthesis of Compound **6A**.

#### 30 Compound **26A**:

- <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.87 - 0.94 (m, 1 H) 1.01 - 1.07 (m, 1 H) 1.55 (dq, *J*=8.55, 4.40 Hz, 1 H) 1.60 - 1.68 (m, 1 H) 3.12 - 3.30 (m, 2 H) 3.61 (s, 3 H) 3.68 (dd, *J*=10.40, 7.57 Hz, 1 H) 3.85 (dd, *J*=10.40, 6.31 Hz, 1 H) 4.01 - 4.08 (m, 1 H) 4.48 - 4.55 (m, 1 H) 5.57 (d, *J*=8.83 Hz, 1 H) 5.75 (s, 1 H) 5.94 (br s, 1 H) 5.95 (br s, 1 H) 6.46 (br d, *J*=8.83 Hz, 1 H) 7.40 - 7.48 (m, 3 H) 7.54 (d, *J*=8.51 Hz, 2 H) 8.16 (br d, *J*=6.94 Hz, 1 H) 12.22 (br s, 1 H)
- LC/MS (method LC-C): R<sub>t</sub> 2.97 min, MH<sup>+</sup> 609
- MP = 120°C

**Example 26B** : synthesis of (1*S*\*,2*S*\*)-2-((3-((1-(4-chlorophenyl)-2-(5-fluoro-6-(trifluoromethoxy)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)methyl)-cyclopropanecarboxylic acid (Compound **26B**)

5



### Synthesis of Compound 26B:

Compound **26B** (150 mg) was synthesized from intermediate **26f** using the procedure described for for the synthesis of Compound **6B**.

### Compound 26B:

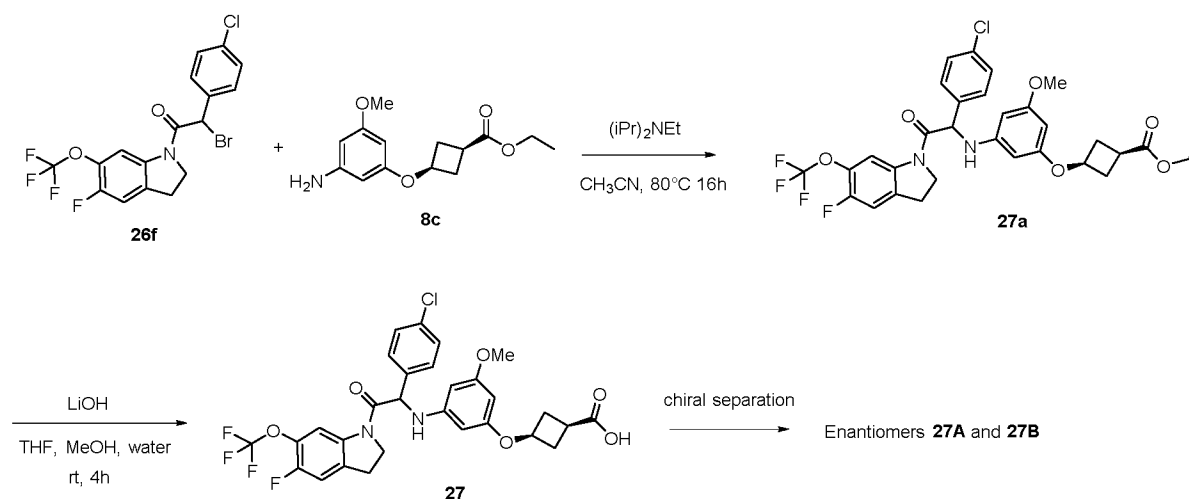
<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.86 – 0.94 (m, 1 H) 1.04 (dq, *J*=8.20, 4.31 Hz, 1 H) 1.55 (dq, *J*=8.43, 4.33 Hz, 1 H) 1.58 - 1.67 (m, 1 H) 3.12 - 3.30 (m, 2 H) 3.61 (s, 3 H) 3.68 (dd, *J*=10.40, 7.57 Hz, 1 H) 3.85 (dd, *J*=10.25, 6.15 Hz, 1 H) 4.04 (q, *J*=8.72 Hz, 1 H) 4.47 - 4.55 (m, 1 H) 5.57 (d, *J*=8.83 Hz, 1 H) 5.75 (s, 1 H) 5.94 (br s, 1 H) 5.95 (br s, 1 H) 6.46 (br d, *J*=8.51 Hz, 1 H) 7.40 - 7.48 (m, 3 H) 7.54 (d, *J*=8.51 Hz, 2 H) 8.16 (br d, *J*=6.94 Hz, 1 H) 12.21 (br s, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.97 min, MH<sup>+</sup> 609

MP = 126°C

**Example 27** : synthesis of ((1*s*,3*s*)-3-(3-((1-(4-chlorophenyl)-2-(5-fluoro-6-(trifluoromethoxy)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)cyclobutene-carboxylic acid (Compound **27**) and separation into Enantiomers **27A** and **27B**

25



**Synthesis of Compound 27 and chiral separation into Enantiomers 27A and 27B:**

Compound **27** (175 mg) was synthesized from intermediate **26f** using the procedure described for the synthesis of Compound **8**. The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5  $\mu$ m 250 x 20 mm, mobile phase: 55% CO<sub>2</sub>, 45% EtOH) to give, after solidification from heptane/diisopropyl ether, the first eluted Enantiomer **27A** (33 mg) and the second eluted Enantiomer **27B** (35 mg).

**Compound 27:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 2.01 - 2.17 (m, 2 H) 2.57 - 2.65 (m, 2 H) 2.66 - 2.77 (m, 1 H) 3.08 - 3.28 (m, 2 H) 3.61 (s, 3 H) 3.99 - 4.10 (m, 1 H) 4.43 - 4.57 (m, 2 H) 5.54 (d, *J*=8.5 Hz, 1 H) 5.66 (s, 1 H) 5.86 (s, 1 H) 5.93 (s, 1 H) 6.49 (br d, *J*=8.5 Hz, 1 H) 7.45 (d, *J*=8.5 Hz, 3 H) 7.55 (d, *J*=8.5 Hz, 2 H) 8.16 (br d, *J*=6.9 Hz, 1 H) 12.06 - 12.47 (m, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.88 min, MH<sup>+</sup> 609

**Enantiomer 27A:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 2.00 - 2.12 (m, 2 H) 2.57 - 2.65 (m, 3 H) 3.11 - 3.25 (m, 2 H) 3.60 (s, 3 H) 4.04 (br d, *J*=7.3 Hz, 1 H) 4.40 - 4.48 (m, 1 H) 4.48 - 4.57 (m, 1 H) 5.53 (br d, *J*=8.5 Hz, 1 H) 5.65 (s, 1 H) 5.85 (s, 1 H) 5.92 (s, 1 H) 6.48 (br d, *J*=8.5 Hz, 1 H) 7.44 (br d, *J*=8.5 Hz, 3 H) 7.54 (br d, *J*=8.5 Hz, 2 H) 8.16 (br d, *J*=6.9 Hz, 1 H)

LC/MS (method LC-D): R<sub>t</sub> 2.79 min, MH<sup>+</sup> 609

[ $\alpha$ ]<sub>D</sub><sup>20</sup>: -40.5° (c 0.252, DMF)

Chiral SFC (method SFC-I): R<sub>t</sub> 1.18 min, no MH<sup>+</sup>, chiral purity 100%.

**Enantiomer 27B:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 2.00 - 2.13 (m, 2 H) 2.54 - 2.67 (m, 3 H) 3.10 - 3.27 (m, 2 H) 3.60 (s, 3 H) 3.99 - 4.10 (m, 1 H) 4.40 - 4.48 (m, 1 H) 4.48 - 4.56 (m, 1 H) 5.54 (br d, *J*=8.5 Hz, 1 H) 5.66 (s, 1 H) 5.86 (s, 1 H) 5.92 (s, 1 H) 6.48 (br d, *J*=8.5 Hz, 1 H) 7.44 (br d, *J*=8.5 Hz, 3 H) 7.54 (br d, *J*=8.5 Hz, 2 H) 8.16 (br d, *J*=6.9 Hz, 1 H)

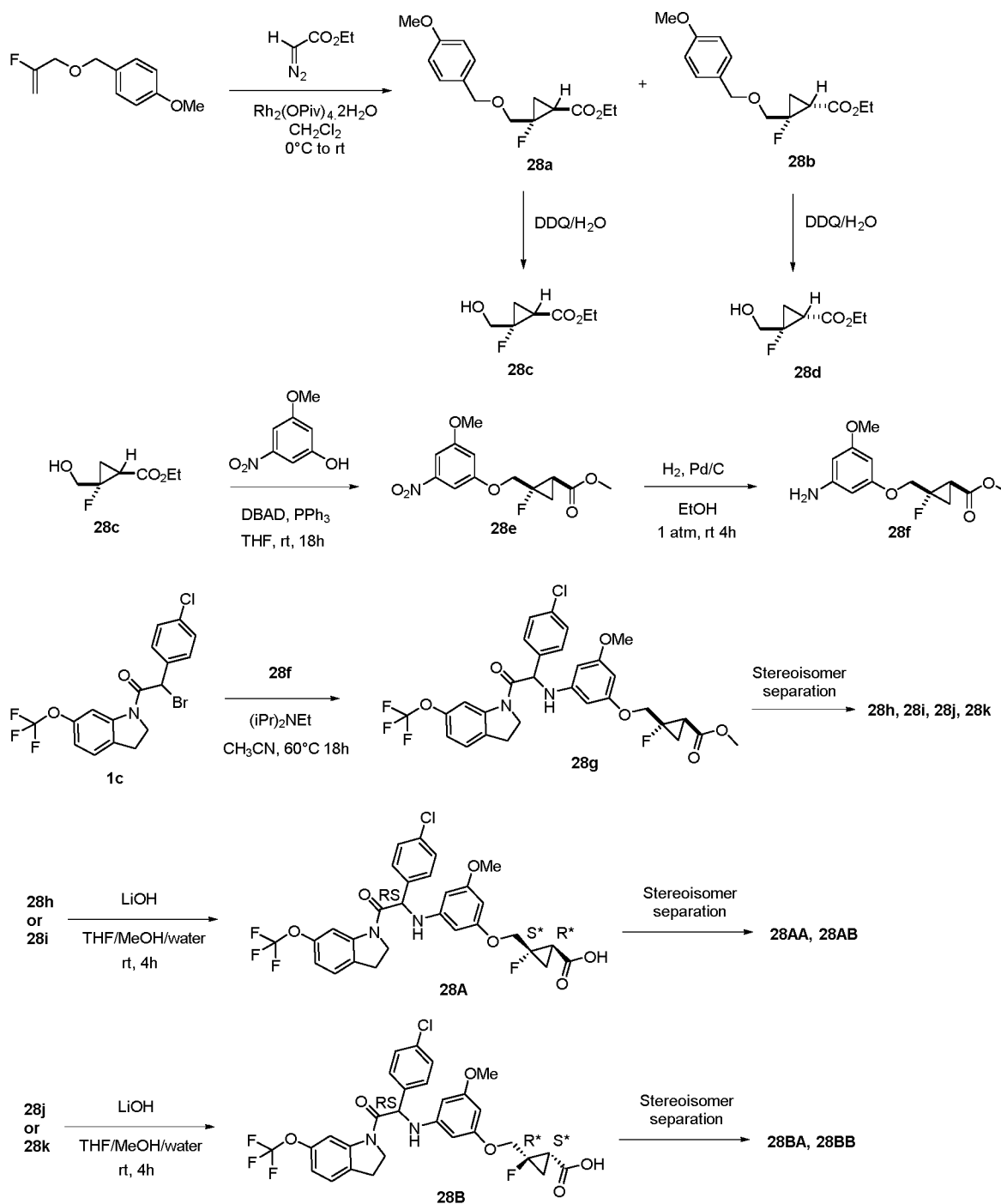
LC/MS (method LC-D): R<sub>t</sub> 2.79 min, MH<sup>+</sup> 609

[ $\alpha$ ]<sub>D</sub><sup>20</sup>: +37.5° (c 0.333, DMF)

Chiral SFC (method SFC-I): R<sub>t</sub> 2.56 min, no MH<sup>+</sup>, chiral purity 100%.



**Example 28** : synthesis of (1*R*\*,2*S*\*)-2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-2-fluorocyclopropanecarboxylic acid (Compound **28A**) and separation into Stereoisomers **28AA** and **28AB** and synthesis of (1*S*\*,2*R*\*)-2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-2-fluorocyclopropanecarboxylic acid (Compound **28B**) and separation into Stereoisomers **28BA** and **28BB**



**Synthesis of intermediates 28a and 28b:**

Rh<sub>2</sub>(OPiv)<sub>4</sub>·2H<sub>2</sub>O (2 mol%, 0.599 mmol, 387 mg) was added to a solution of 1-(((2-fluoroallyl)oxy)methyl)-4-methoxybenzene [CAS 1673563-84-2] (29.9 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (86 mL) in a three-necked round bottom flask equipped with a bubble room. After cooling the solution to 0°C, a solution of the commercially available diazo ethylacetate 83% in dichloromethane (3 equiv., 89.85 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (86 mL) was slowly added using a micro pump with a flow rate of 24 mL/h. The mixture was stirred at room temperature until completion of the reaction (indicated by TLC and <sup>19</sup>F NMR analysis) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 9/1 to 7/3) to give in 60% yield a mixture of diastereomers (dr 53:47). The diastereomers were separated by column chromatography on silica gel (petroleum ether/EtOAc, from 100/0 to 80/20) to give *trans*-ethyl 2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)cyclopropanecarboxylate **28a** and *cis*-ethyl 2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)cyclopropanecarboxylate **28b**.

**Synthesis of intermediate 28c:**

DDQ (1.5 equiv., 27.9 mmol, 6.33 g) was added to a solution of *trans*-ethyl 2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)cyclopropanecarboxylate **28a** (1 equiv., 18.6 mmol, 5.25 g) in dichloromethane (340 mL) and water (30 mL) at 0 °C. The mixture was stirred for 20 h. A solution of saturated aqueous NaHCO<sub>3</sub> was added and the mixture was stirred for 30 minutes. The aqueous layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with a saturated NaHCO<sub>3</sub> solution and brine. The organic layer was evaporated under reduced pressure and the crude residue was purified by chromatography on silica gel (petroleum ether/EtOAc, 9/1 to 6/4) to give *trans*-ethyl 2-fluoro-2-(hydroxymethyl)-cyclopropanecarboxylate **28c** (876 mg).

**Synthesis of intermediate 28d:**

DDQ (1.5 equiv., 15.8 mmol, 3.6 g) was added to a solution of *cis*-ethyl 2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)cyclopropanecarboxylate **28b** (1 equiv., 10.6 mmol, 2.98 g) in dichloromethane (193 mL) and water (17 mL) at 0°C. The mixture was stirred for 20 h. A solution of saturated aqueous NaHCO<sub>3</sub> was added and the mixture was stirred for 30 minutes. The aqueous layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with a saturated NaHCO<sub>3</sub> solution and brine. The organic layer was evaporated under reduced pressure and the crude residue was purified by chromatography on silica gel (petroleum

ether/EtOAc, 9/1 to 6/4) to give *cis*-ethyl 2-fluoro-2-(hydroxymethyl)cyclopropanecarboxylate (876 mg).

#### Synthesis of intermediate 28e:

5 Under a N<sub>2</sub> flow at 10°C, di-*tert*-butyl azodicarboxylate (948 mg, 4.118 mmol) was added portionwise to a solution of 3-methoxy-5-nitrophenol [7145-49-5] (633 mg, 3.743 mmol), *trans*-ethyl 2-fluoro-2-(hydroxymethyl)cyclopropanecarboxylate **28c** (607 mg, 3.743 mmol), and PPh<sub>3</sub> (1.08 g; 4.118 mmol) in THF (30 mL). The reaction was stirred at room temperature under N<sub>2</sub> for 18 h. The solution was  
10 concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (15-40 μm, 80 g, heptane/EtOAc from 95/5 to 80/20). The pure fractions were combined and concentrated under reduced pressure to give *trans*-methyl 2-fluoro-2-((3-methoxy-5-nitrophenoxy)methyl)cyclopropanecarboxylate **28e** (930 mg).

15

#### Synthesis of intermediate 28f:

A solution of *trans*-methyl 2-fluoro-2-((3-methoxy-5-nitrophenoxy)methyl)cyclopropanecarboxylate **28e** (810 mg, 2.586 mmol) in EtOH (20 mL) and THF (10 mL) containing a catalytic amount of 10% Pd/C (275 mg, 0.259 mmol) was  
20 hydrogenated under atmospheric pressure of H<sub>2</sub> at room temperature for 4 h. The catalyst was removed by filtration over a short pad of Celite<sup>®</sup> and the filter cake was rinsed several times with EtOH. The combined filtrates were evaporated under reduced pressure to give *trans*-methyl 2-((3-amino-5-methoxyphenoxy)methyl)-2-fluorocyclopropanecarboxylate **28f** (710 mg), which was used in the next  
25 step without further purification.

#### Synthesis of intermediate 28g and separation into Stereoisomers 28h, 28i, 28j and 28k:

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (927 mg, 2.133 mmol), *trans*-methyl 2-((3-amino-5-methoxyphenoxy)methyl)-2-fluorocyclopropanecarboxylate **28f** (725 mg, 2.559 mmol) and diisopropylethylamine (735 μL, 4.265 mmol) in CH<sub>3</sub>CN (4 mL) was stirred at 80°C for 12 h. The solvent was concentrated under reduced pressure. The residue was taken up with EtOAc. The organic layer was washed with 1N HCl,  
35 water, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (15-40 μm, 40 g, heptane/EtOAc from 95/5 to 80/20). The pure fractions were combined and evaporated under reduced pressure to give methyl 2-((3-((1-(4-chlorophenyl)-2-

oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-*trans*-2-fluorocyclopropanecarboxylate **28g** (550 mg). The four stereoisomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5 µm 250 x 20mm, mobile phase: 70% CO<sub>2</sub>, 30% EtOH) to give **28h** (118 mg), **28i** (114 mg), **28j** (158 mg) and **28k** (165 mg).

#### Synthesis of Compound **28A** and separation into Stereoisomers **28AA** and **28AB**:

LiOH monohydrate (23.3 mg, 0.556 mmol) was added dropwise to a solution of stereoisomer **28h** (118 mg, 0.185 mmol) in THF/MeOH/water (1/1/1) (2 mL). The reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with water and ice, slowly acidified with 1N HCl and extracted with EtOAc. The combined organic layers were washed with water, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to give, after crystallization from heptane/diisopropyl ether, (1*R*\*,2*S*\*)-2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-2-fluorocyclopropanecarboxylic acid **28A** (110 mg) (during this reaction, full racemization occurred on the central chiral center).

A second batch of Compound **28A** (100 mg) was obtained similarly starting from stereoisomer **28i**. The two batches were combined. The two stereoisomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5 µm 250 x 20 mm, mobile phase: 65% CO<sub>2</sub>, 35% EtOH) to give the first eluted stereoisomer (94 mg) and the second eluted stereoisomer (80 mg). The first eluted stereoisomer was solidified from diisopropyl ether to give Stereoisomer **28AA** (47 mg). The second eluted stereoisomer was solidified from heptane to give Stereoisomer **28AB** (37 mg).

#### Synthesis of Compound **28B** and separation into Stereoisomers **28BA** and **28BB**:

LiOH monohydrate (31.2 mg, 0.744 mmol) was added dropwise to a solution of stereoisomer **28j** (158 mg, 0.248 mmol) in THF/MeOH/water (1/1/1) (2 mL). The reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with water and ice, slowly acidified with 1N HCl and extracted with EtOAc. The combined organic layers were washed with water, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to give, after crystallization from MeOH/water, (1*S*\*,2*R*\*)-2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-2-fluorocyclopropane-

carboxylic acid **28B** (100 mg) (during this reaction, full racemization occurred on the central chiral center).

A second batch of **28A** (105 mg) was obtained similarly starting from stereoisomer **28k**.

- 5 The two stereoisomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5 µm 250 x 30mm, mobile phase: 60% CO<sub>2</sub>, 30% MeOH) to give the first eluted stereoisomer (88 mg) and the second eluted stereoisomer (78 mg). The first eluted stereoisomer was solidified from heptane/diisopropyl ether to give Stereoisomer **28BA** (54 mg). The second eluted stereoisomer was solidified from  
10 heptane/diisopropyl ether to give Stereoisomer **28BB** (60 mg).

**Stereoisomer 28AA:**

- <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.37 (dt, *J*=11.7, 7.1 Hz, 1 H) 1.62 - 1.76 (m, 1 H) 2.18 - 2.31 (m, 1 H) 3.07 - 3.23 (m, 2 H) 3.62 (s, 3 H) 3.98 - 4.10 (m, 1 H)  
15 4.15 - 4.29 (m, 1 H) 4.43 (dd, *J*=18.9, 12.0 Hz, 1 H) 4.48 - 4.57 (m, 1 H) 5.58 (d, *J*=8.8 Hz, 1 H) 5.78 (s, 1 H) 5.97 (s, 1 H) 5.99 (s, 1 H) 6.49 (br d, *J*=8.8 Hz, 1 H) 7.01 (br d, *J*=7.9 Hz, 1 H) 7.33 (d, *J*=8.2 Hz, 1 H) 7.44 (d, *J*=8.5 Hz, 2 H) 7.55 (d, *J*=8.2 Hz, 2 H) 8.03 (s, 1 H) 12.71 (br s, 1 H)  
LC/MS (method LC-C): R<sub>t</sub> 2.83 min, MH<sup>+</sup> 609  
20 [α]<sub>D</sub><sup>20</sup>: -43.3° (c 0.3, DMF)  
Chiral SFC (method SFC-F): R<sub>t</sub> 1.98 min, no MH<sup>+</sup>, chiral purity 100%.

**Stereoisomer 28AB:**

- <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32 - 1.42 (m, 1 H) 1.62 - 1.75 (m, 1 H) 2.24  
25 (dt, *J*=18.5, 9.2 Hz, 1 H) 3.08 - 3.25 (m, 2 H) 3.62 (s, 3 H) 3.99 - 4.08 (m, 1 H) 4.13 - 4.26 (m, 1 H) 4.39 - 4.57 (m, 2 H) 5.58 (br d, *J*=8.8 Hz, 1 H) 5.78 (s, 1 H) 5.96 (br s, 1 H) 5.99 (br s, 1 H) 6.49 (br d, *J*=8.8 Hz, 1 H) 7.01 (br d, *J*=7.6 Hz, 1 H) 7.33 (br d, *J*=8.2 Hz, 1 H) 7.44 (br d, *J*=8.2 Hz, 2 H) 7.55 (br d, *J*=8.2 Hz, 2 H) 8.03 (br s, 1 H) 12.71 (br s, 1 H)  
30 LC/MS (method LC-C): R<sub>t</sub> 2.84 min, MH<sup>+</sup> 609  
[α]<sub>D</sub><sup>20</sup>: +52.5° (c 0.301, DMF)  
Chiral SFC (method SFC-F): R<sub>t</sub> 3.29 min, no MH<sup>+</sup>, chiral purity 100%.

**Stereoisomer 28BA:**

- 35 <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32 - 1.42 (m, 1 H) 1.62 - 1.72 (m, 1 H) 2.18 - 2.29 (m, 1 H) 3.08 - 3.23 (m, 2 H) 3.62 (s, 3 H) 4.04 (td, *J*=10.4, 7.3 Hz, 1 H) 4.15 - 4.26 (m, 1 H) 4.45 (dd, *J*=18.8, 11.8 Hz, 1 H) 4.52 (td, *J*=10.5, 6.1 Hz, 1 H) 5.58 (d, *J*=8.8 Hz, 1 H) 5.78 (t, *J*=2.0 Hz, 1 H) 5.96 (s, 1 H) 5.99 (s, 1 H) 6.49 (d, *J*=9.1

Hz, 1 H) 7.01 (dd,  $J=8.2, 1.6$  Hz, 1 H) 7.33 (d,  $J=8.2$  Hz, 1 H) 7.44 (d,  $J=8.5$  Hz, 2 H) 7.55 (d,  $J=8.5$  Hz, 2 H) 8.03 (s, 1 H) 12.76 (br s, 1 H)

LC/MS (method LC-D):  $R_t$  2.71 min,  $MH^+$  609

$[\alpha]_D^{20}$ :  $-57.1^\circ$  (c 0.31, DMF)

5 Chiral SFC (method SFC-F):  $R_t$  2.26 min, no  $MH^+$ , chiral purity 100%.

**Stereoisomer 28BB:**

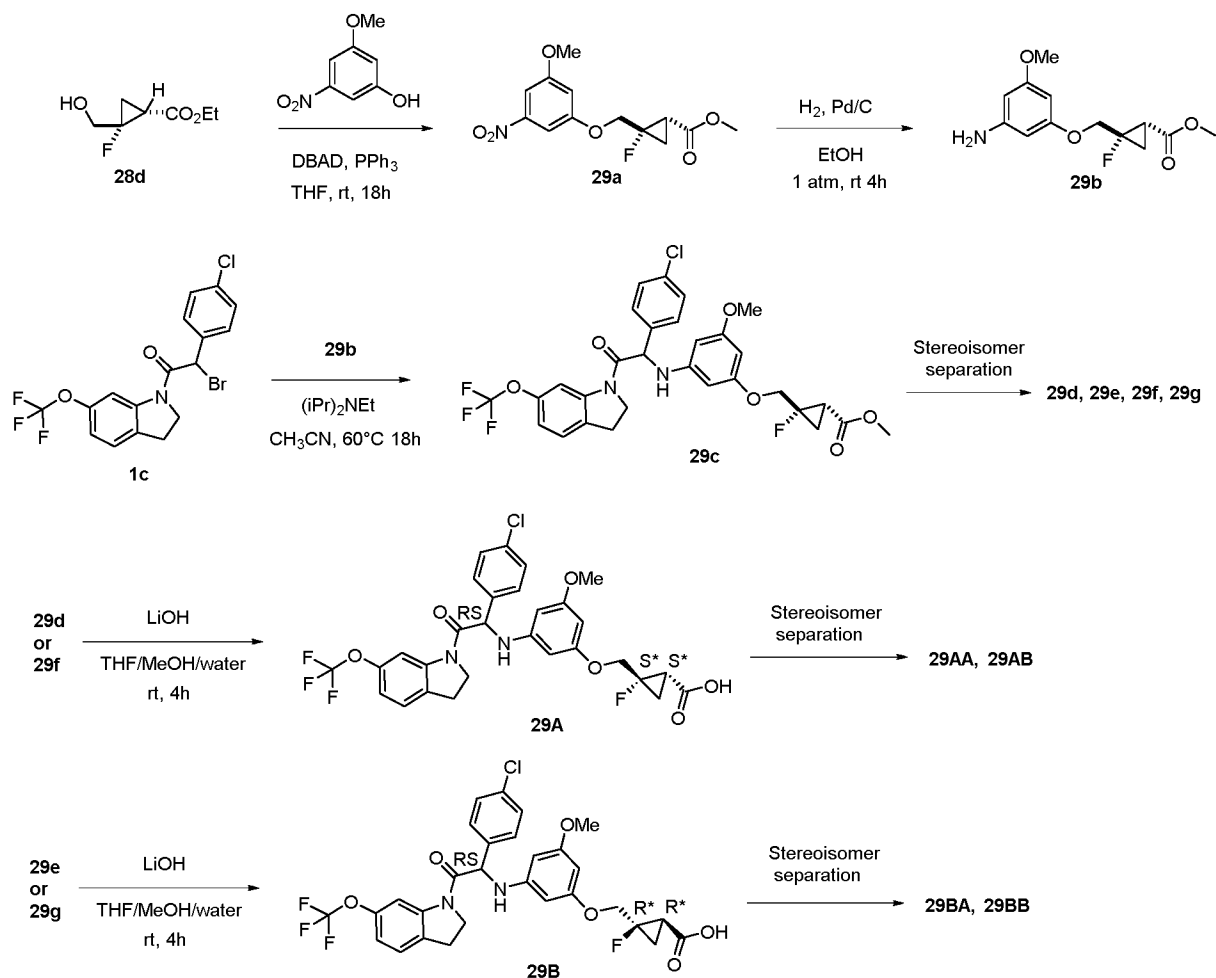
$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.35 (dt,  $J=11.7, 7.1$  Hz, 1 H) 1.59 - 1.71 (m, 1 H) 2.17 - 2.28 (m, 1 H) 3.08 - 3.25 (m, 2 H) 3.62 (s, 3 H) 4.04 (td,  $J=10.5, 7.1$  Hz, 1 H) 4.17 - 4.29 (m, 1 H) 4.43 (dd,  $J=19.5, 11.7$  Hz, 1 H) 4.52 (td,  $J=10.4, 6.3$  Hz, 1 H) 5.59 (d,  $J=9.1$  Hz, 1 H) 5.78 (t,  $J=1.9$  Hz, 1 H) 5.96 (s, 1 H) 5.99 (s, 1 H) 6.49 (d,  $J=8.8$  Hz, 1 H) 7.01 (dd,  $J=8.0, 1.4$  Hz, 1 H) 7.33 (d,  $J=8.2$  Hz, 1 H) 7.44 (d,  $J=8.5$  Hz, 2 H) 7.55 (d,  $J=8.2$  Hz, 2 H) 8.03 (s, 1 H) 12.79 (br s, 1 H)

LC/MS (method LC-D):  $R_t$  2.70 min,  $MH^+$  609

$[\alpha]_D^{20}$ :  $+38.1^\circ$  (c 0.289, DMF)

15 Chiral SFC (method SFC-F):  $R_t$  3.68 min, no  $MH^+$ , chiral purity 100%.

**Example 29** : synthesis of (1*S*\*,2*S*\*)-2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-2-fluorocyclopropanecarboxylic acid (Compound **29A**) and separation into Stereoisomers **29AA** and **29AB** and synthesis of (1*R*\*,2*R*\*)-2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-2-fluorocyclopropanecarboxylic acid (Compound **29B**) and separation into Stereoisomers **29BA** and **29BB**



### Synthesis of intermediate 29a:

Under a N<sub>2</sub> flow at 10°C, di-*tert*-butyl azodicarboxylate (750 mg, 3.256 mmol) was added portionwise to a solution of 3-methoxy-5-nitrophenol [7145-49-5] (501 mg, 2.96 mmol), *cis*-ethyl 2-fluoro-2-(hydroxymethyl)cyclopropanecarboxylate **28d** (480 mg, 2.96 mmol), and PPh<sub>3</sub> (854 mg, 3.256 mmol) in THF (23 mL). The reaction was stirred at room temperature under N<sub>2</sub> for 18 h. The solution was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (15-40 μm, 80 g, heptane/EtOAc 70/30). The pure fractions were combined and concentrated under reduced pressure to give *cis*-methyl 2-fluoro-2-((3-methoxy-5-nitrophenoxy)methyl)cyclopropanecarboxylate **29a** (660 mg).

### 15 Synthesis of intermediate 29b:

A solution of *cis*-methyl 2-fluoro-2-((3-methoxy-5-nitrophenoxy)methyl)cyclopropanecarboxylate **29a** (610 mg, 1.947 mmol) in EtOH (15 mL) and THF (7.5 mL) containing a catalytic amount of 10% Pd/C (207 mg, 0.195 mmol) was

hydrogenated under atmospheric pressure of H<sub>2</sub> at room temperature for 4 h. The catalyst was removed by filtration over a short pad of Celite® and the filter cake was rinsed several times with EtOH. The combined filtrates were evaporated to give *cis*-methyl 2-((3-amino-5-methoxyphenoxy)methyl)-2-fluorocyclopropanecarboxylate **29b** (560 mg), which was used in the next step without further purification.

**Synthesis of intermediate 29c and separation into Stereoisomers 29d, 29e, 29f and 29g:**

10 A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (716 mg, 1.647 mmol), *cis*-methyl 2-((3-amino-5-methoxyphenoxy)methyl)-2-fluorocyclopropanecarboxylate **29b** (560 mg, 1.977 mmol) and diisopropylethylamine (568 µL, 3.295 mmol) in CH<sub>3</sub>CN (3.5 mL) was stirred at 80°C for 12 h. The solvent was concentrated under reduced pressure. The residue  
15 was taken up with EtOAc. The organic layer was washed with 1N HCl, water, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (15-40 µm, 40 g, heptane/EtOAc from 95/5 to 80/20). The pure fractions were combined and evaporated under reduced pressure to give methyl 2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-  
20 (trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-*cis*-2-fluorocyclopropanecarboxylate **29c** (500 mg). The four stereoisomers were separated via chiral SFC (Stationary phase: Chiralpak® AD-H 5 µm 250 x 30 mm, mobile phase: 65% CO<sub>2</sub>, 35% EtOH) to give a mixture of **29d+29e** (250 mg), **29f** (125 mg), and **29g** (114 mg). The mixture of **29d+29e** was further separated via  
25 chiral SFC (Stationary phase: Chiralpak® AD-H 5 µm 250 x 30mm, mobile phase: 75% CO<sub>2</sub>, 25% EtOH) to give **29d** (88 mg) and **29e** (66 mg).

**Synthesis of Compound 29A and separation into Stereoisomers 29AA and 29AB:**

30 LiOH monohydrate (17.4 mg, 0.414 mmol) was added dropwise to a solution of stereoisomers **29d** (88 mg, 0.138 mmol) in THF/MeOH/water (1/1/1) (1 mL). The reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with water and ice, slowly acidified with 1N HCl and extracted with EtOAc. The combined organic layers were washed with water, dried over MgSO<sub>4</sub>, filtered, and  
35 concentrated under reduced pressure to give, (1*S*\*,2*S*\*)-2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-2-fluorocyclopropanecarboxylic acid **29A** (80 mg) (during this reaction, full racemization occurred on the central chiral center).



A second batch of **29A** (90 mg) was obtained similarly starting from stereoisomer **29f**. The two batches were combined. The two stereoisomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5 µm 250 x 20 mm, mobile phase: 65% CO<sub>2</sub>, 35% MeOH) and further purified by flash chromatography on silica gel (15-40 µm, 4 g, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 99/1) to give the first eluted stereoisomer (43 mg) and the second eluted stereoisomer (40 mg). The first eluted stereoisomer was solidified in heptane/diisopropyl ether to give stereoisomer **29AA** (29 mg). The second eluted stereoisomer was solidified in heptane/diisopropyl ether to give stereoisomer **29AB** (27 mg).

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### Synthesis of Compound **29B** and separation into Stereoisomers **29BA** and **29BB**:

LiOH monohydrate (13 mg, 0.311 mmol) was added dropwise to a solution of stereoisomer **29e** (66 mg, 0.104 mmol) in THF/MeOH/water (1/1/1) (1 mL). The reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with water and ice, slowly acidified with 1N HCl and extracted with EtOAc. The combined organic layers were washed with water, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to give, after crystallization from MeOH/water, (1*R*\*,2*R*\*)-2-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)-indolin-1-yl)ethyl)amino)-5-methoxyphenoxy)methyl)-2-fluorocyclopropane-carboxylic acid **29B** (60 mg) (during this reaction, full racemization occurred on the central chiral center).

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A second batch of **29A** (100 mg) was obtained similarly starting from stereoisomer **29g**. The two batches were combined. The two stereoisomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5 µm 250 x 20 mm, mobile phase: 70% CO<sub>2</sub>, 30% MeOH) and further purified by flash chromatography on silica gel (15-40 µm, 4 g, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 99/1) to give the first eluted stereoisomer (38 mg) and the second eluted stereoisomer (31 mg). The first eluted stereoisomer was solidified in heptane/diisopropyl ether to give stereoisomer **29BA** (24 mg). The second eluted stereoisomer was solidified in heptane/diisopropyl ether to give stereoisomer **29BB** (20 mg).

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### Stereoisomer **29AA**:

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.30 - 1.37 (m, 1 H) 1.69 (dt, *J*=19.7, 6.9 Hz, 1 H) 1.98 - 2.06 (m, 1 H) 3.08 - 3.24 (m, 2 H) 3.63 (s, 3 H) 4.01 - 4.09 (m, 1 H) 4.10 - 4.23 (m, 2 H) 4.48 - 4.57 (m, 1 H) 5.59 (d, *J*=8.8 Hz, 1 H) 5.81 (s, 1 H) 5.99 (br d, *J*=5.7 Hz, 2 H) 6.49 (br d, *J*=8.8 Hz, 1 H) 7.01 (br d, *J*=7.9 Hz, 1 H) 7.33 (d,

35

$J=7.9$  Hz, 1 H) 7.44 (d,  $J=8.5$  Hz, 2 H) 7.55 (d,  $J=8.2$  Hz, 2 H) 8.03 (br s, 1 H)  
12.58 (br s, 1 H)

LC/MS (method LC-D):  $R_t$  2.67 min,  $MH^+$  609

$[\alpha]_D^{20}$ :  $-15.7^\circ$  (c 0.242, DMF)

5 Chiral SFC (method SFC-P):  $R_t$  2.53 min, no  $MH^+$ , chiral purity 100%.

#### Stereoisomer 29AB:

$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.29 - 1.38 (m, 1 H) 1.69 (dt,  $J=19.5$ , 6.5 Hz, 1 H) 1.97 - 2.10 (m, 1 H) 3.08 - 3.25 (m, 2 H) 3.63 (s, 3 H) 4.00 - 4.10 (m, 1 H)

10 4.10 - 4.23 (m, 2 H) 4.52 (br d,  $J=6.0$  Hz, 1 H) 5.60 (br d,  $J=8.8$  Hz, 1 H) 5.82 (br s, 1 H) 6.00 (br d,  $J=6.6$  Hz, 2 H) 6.50 (br d,  $J=8.5$  Hz, 1 H) 7.01 (br d,  $J=7.6$  Hz, 1 H) 7.34 (br d,  $J=7.9$  Hz, 1 H) 7.44 (br d,  $J=8.2$  Hz, 2 H) 7.55 (br d,  $J=8.2$  Hz, 2 H) 8.04 (br s, 1 H) 12.58 (br s, 1 H)

LC/MS (method LC-D):  $R_t$  2.67 min,  $MH^+$  609

15  $[\alpha]_D^{20}$ :  $+77.4^\circ$  (c 0.323, DMF)

Chiral SFC (method SFC-P):  $R_t$  4.47 min, no  $MH^+$ , chiral purity 99.20%.

#### Stereoisomer 29BA:

$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.33 (td,  $J=9.8$ , 6.6 Hz, 1 H) 1.69 (dt,  $J=19.9$ , 6.9 Hz, 1 H) 2.03 (ddd,  $J=9.5$ , 7.1, 3.0 Hz, 1 H) 3.08 - 3.25 (m, 2 H) 3.63 (s, 3 H) 4.05 (td,  $J=10.3$ , 7.1 Hz, 1 H) 4.10 - 4.23 (m, 2 H) 4.52 (td,  $J=10.2$ , 6.3 Hz, 1 H) 5.59 (d,  $J=8.8$  Hz, 1 H) 5.80 - 5.84 (m, 1 H) 6.00 (br d,  $J=7.6$  Hz, 2 H) 6.49 (br d,  $J=8.8$  Hz, 1 H) 7.01 (dd,  $J=8.0$ , 1.4 Hz, 1 H) 7.33 (d,  $J=8.2$  Hz, 1 H) 7.44 (d,  $J=8.5$  Hz, 2 H) 7.55 (d,  $J=8.2$  Hz, 2 H) 8.03 (s, 1 H) 12.58 (br s, 1 H)

25 LC/MS (method LC-D):  $R_t$  2.67 min,  $MH^+$  609

$[\alpha]_D^{20}$ :  $-74.2^\circ$  (c 0.302, DMF)

Chiral SFC (method SFC-P):  $R_t$  2.37 min, no  $MH^+$ , chiral purity 100%.

#### Stereoisomer 29BB:

30  $^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.34 (td,  $J=9.8$ , 6.6 Hz, 1 H) 1.69 (dt,  $J=19.9$ , 6.9 Hz, 1 H) 2.02 (ddd,  $J=9.5$ , 7.1, 3.0 Hz, 1 H) 3.09 - 3.25 (m, 2 H) 3.63 (s, 3 H) 4.05 (td,  $J=10.4$ , 7.3 Hz, 1 H) 4.10 - 4.22 (m, 2 H) 4.52 (td,  $J=10.3$ , 6.5 Hz, 1 H) 5.59 (d,  $J=8.8$  Hz, 1 H) 5.81 (t,  $J=2.0$  Hz, 1 H) 5.96 - 6.03 (m, 2 H) 6.49 (d,  $J=8.8$  Hz, 1 H) 7.01 (dd,  $J=8.2$ , 1.6 Hz, 1 H) 7.33 (d,  $J=8.2$  Hz, 1 H) 7.44 (d,  $J=8.5$  Hz, 2 H) 7.55 (d,  $J=8.2$  Hz, 2 H) 8.03 (s, 1 H) 12.58 (br s, 1 H)

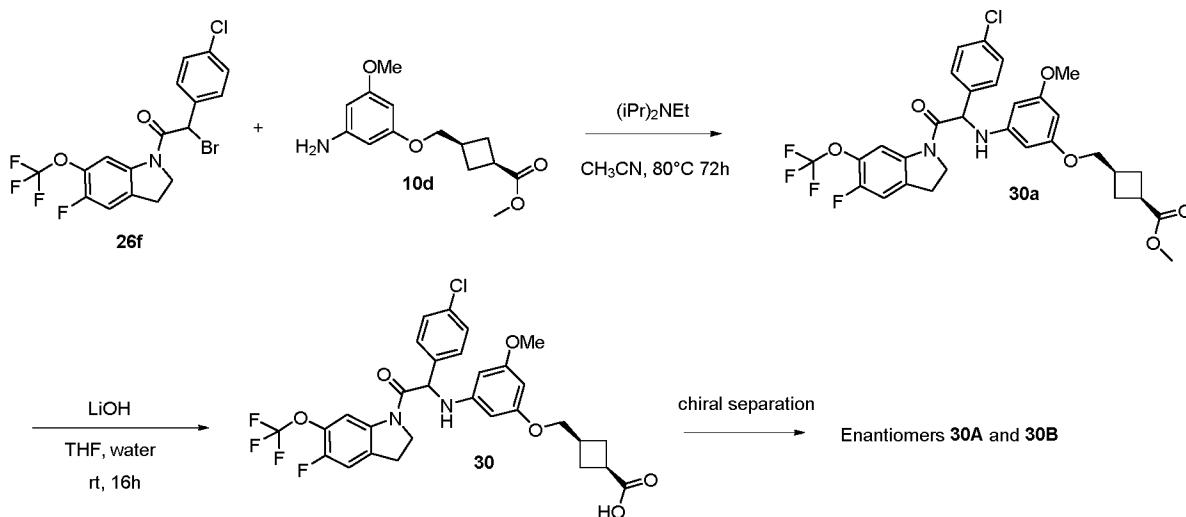
LC/MS (method LC-D):  $R_t$  2.70 min,  $MH^+$  609

35  $[\alpha]_D^{20}$ :  $+12.0^\circ$  (c 0.3, DMF)

Chiral SFC (method SFC-P):  $R_t$  3.73 min, no  $MH^+$ , chiral purity 99.14%.

**Example 30** : synthesis of (1*s*,3*s*)-3-((3-((1-(4-chlorophenyl)-2-(5-fluoro-6-(trifluoromethoxy)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)methyl)cyclobutanecarboxylic acid (Compound **30**) and chiral separation into Enantiomers

5 **30A** and **30B**



**Synthesis of Compound 30 and chiral separation into Enantiomers 30A and 30B:**

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Compound **30** (105 mg) was synthesized from intermediate **26f** using the procedures described for the synthesis of Compound **10**. The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel<sup>®</sup> OJ-H 5  $\mu m$  250 x 20 mm, mobile phase: 70%  $CO_2$ , 30% MeOH) to give, after lyophilization in  $CH_3CN$ /water, the first eluted Enantiomer **30A** (43 mg) and the second eluted Enantiomer **30B** (47 mg).

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**Enantiomer 30A:**

$^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.85 - 1.98 (m, 2 H) 2.17 - 2.28 (m, 2 H) 2.53 - 2.59 (m, 1 H) 2.96 (quin,  $J=8.9$  Hz, 1 H) 3.09 - 3.23 (m, 2 H) 3.61 (s, 3 H) 3.72 - 3.81 (m, 2 H) 4.05 (td,  $J=10.3, 7.4$  Hz, 1 H) 4.51 (td,  $J=10.2, 6.5$  Hz, 1 H) 5.56 (d,  $J=8.8$  Hz, 1 H) 5.74 (s, 1 H) 5.93 (s, 2 H) 6.45 (br d,  $J=8.5$  Hz, 1 H) 7.44 (d,  $J=8.5$  Hz, 3 H) 7.54 (d,  $J=8.5$  Hz, 2 H) 8.16 (br d,  $J=6.9$  Hz, 1 H) 11.24 - 13.06 (m, 1 H) LC/MS (method LC-C):  $R_t$  3.08 min,  $MH^+$  623

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$[\alpha]_D^{20}$ : +42.6° (c 0.298, DMF)

Chiral SFC (method SFC-F):  $R_t$  2.91 min, no  $MH^+$ , chiral purity 100%.

**Enantiomer 30B:**

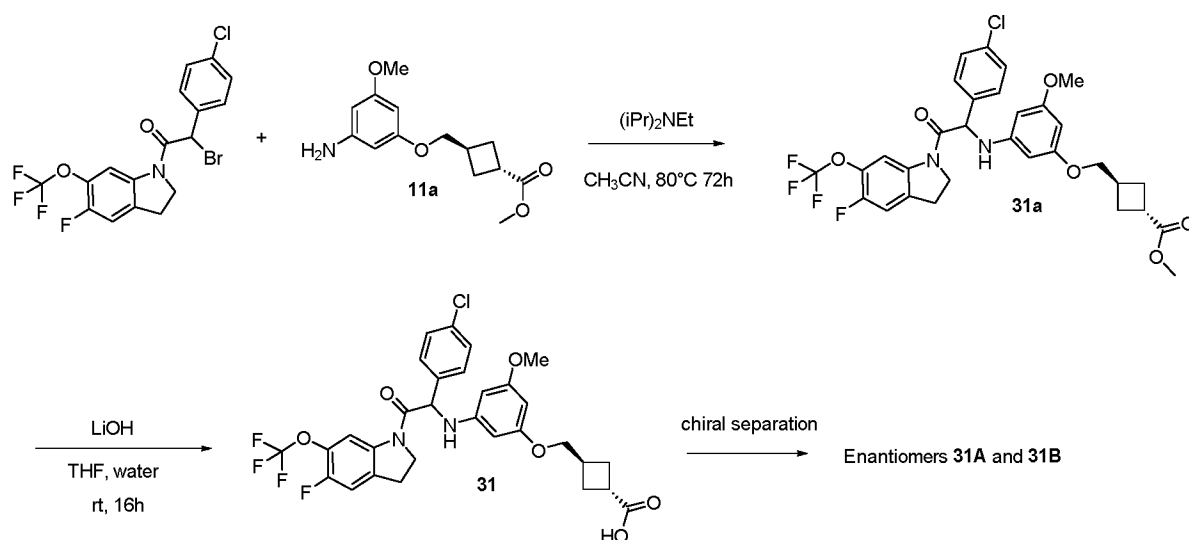
<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.87 - 1.99 (m, 2 H) 2.16 - 2.29 (m, 2 H) 2.53 - 2.59 (m, 1 H) 2.96 (br t, *J*=8.8 Hz, 1 H) 3.11 - 3.23 (m, 2 H) 3.61 (s, 3 H) 3.77 (br d, *J*=6.0 Hz, 2 H) 4.05 (td, *J*=10.2, 7.3 Hz, 1 H) 4.51 (td, *J*=10.3, 6.5 Hz, 1 H) 5.56 (d, *J*=8.8 Hz, 1 H) 5.74 (s, 1 H) 5.93 (s, 2 H) 6.45 (br d, *J*=8.8 Hz, 1 H) 7.44 (br d, *J*=8.2 Hz, 3 H) 7.54 (d, *J*=8.5 Hz, 2 H) 8.16 (br d, *J*=6.9 Hz, 1 H) 11.43 - 12.72 (m, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 3.07 min, MH<sup>+</sup> 623

[α]<sub>D</sub><sup>20</sup>: -44.2° (c 0.217, DMF)

Chiral SFC (method SFC-F): R<sub>t</sub> 4.10 min, no MH<sup>+</sup>, chiral purity 99.09%.

**Example 31** : synthesis of (1*r*,3*r*)-3-((3-((1-(4-chlorophenyl)-2-(5-fluoro-6-(trifluoromethoxy)indolin-1-yl)-2-oxoethyl)amino)-5-methoxyphenoxy)methyl)cyclobutanecarboxylic acid (Compound **31**) and chiral separation into Enantiomers **31A** and **31B**



**Synthesis of Compound 31 and chiral separation into Enantiomers 31A and 31B:**

Compound **31** (75 mg) was synthesized from intermediate **26f** using the procedure described for the synthesis of Compound **11**. The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel<sup>®</sup> OJ-H 5 μm 250 x 20 mm, mobile phase: 70% CO<sub>2</sub>, 30% MeOH) to give, after lyophilization in CH<sub>3</sub>CN/water, the first eluted Enantiomer **31A** (23 mg) and the second eluted Enantiomer **31B** (24 mg).

**Enantiomer 31A:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.90 - 2.03 (m, 2 H) 2.20 - 2.30 (m, 2 H) 2.55 - 2.62 (m, 1 H) 3.07 (br t, *J*=7.7 Hz, 1 H) 3.12 - 3.24 (m, 2 H) 3.62 (s, 3 H) 3.87 (br d, *J*=6.9 Hz, 2 H) 4.05 (td, *J*=10.3, 7.1 Hz, 1 H) 4.51 (td, *J*=10.4, 6.6 Hz, 1 H) 5.57 (d, *J*=8.8 Hz, 1 H) 5.78 (s, 1 H) 5.94 (s, 1 H) 5.96 (s, 1 H) 6.45 (d, *J*=8.8 Hz, 1 H) 7.44 (d, *J*=8.5 Hz, 3 H) 7.54 (d, *J*=8.5 Hz, 2 H) 8.16 (br d, *J*=6.9 Hz, 1 H)

LC/MS (method LC-C): *R*<sub>t</sub> 3.07 min, MH<sup>+</sup> 623

[α]<sub>D</sub><sup>20</sup>: +43.1° (c 0.255, DMF)

Chiral SFC (method SFC-F): *R*<sub>t</sub> 3.25 min, no MH<sup>+</sup>, chiral purity 100%.

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**Enantiomer 31B:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.90 - 2.03 (m, 2 H) 2.19 - 2.31 (m, 2 H) 2.55 - 2.62 (m, 1 H) 3.01 - 3.10 (m, 1 H) 3.12 - 3.23 (m, 2 H) 3.62 (s, 3 H) 3.86 (br d, *J*=6.9 Hz, 2 H) 4.05 (td, *J*=10.2, 7.3 Hz, 1 H) 4.51 (td, *J*=10.3, 6.5 Hz, 1 H) 5.57 (d, *J*=8.8 Hz, 1 H) 5.78 (s, 1 H) 5.94 (s, 1 H) 5.95 (s, 1 H) 6.45 (br d, *J*=8.8 Hz, 1 H) 7.44 (d, *J*=8.5 Hz, 3 H) 7.54 (d, *J*=8.2 Hz, 2 H) 8.15 (br d, *J*=6.6 Hz, 1 H)

LC/MS (method LC-C): *R*<sub>t</sub> 3.07 min, MH<sup>+</sup> 623

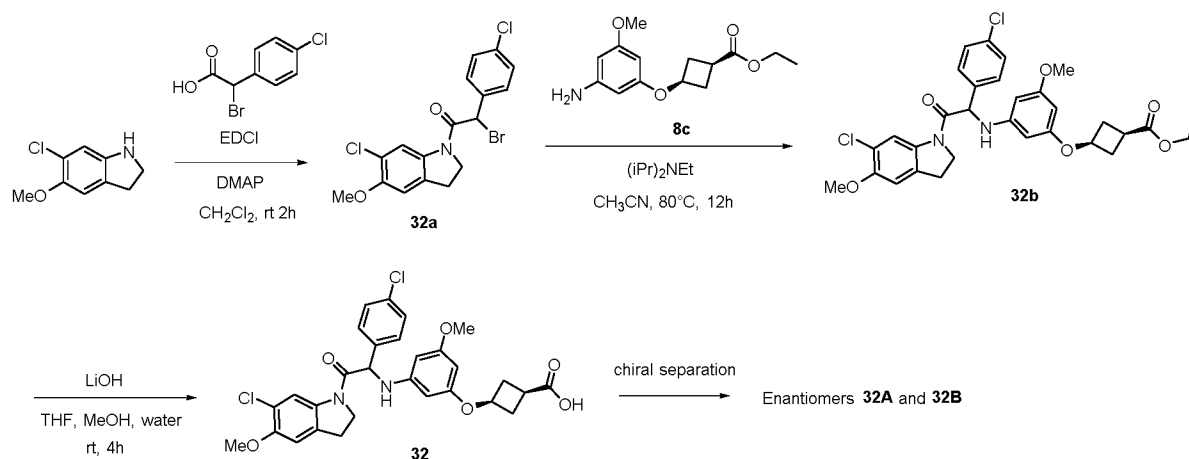
[α]<sub>D</sub><sup>20</sup>: -43.4° (c 0.244, DMF)

Chiral SFC (method SFC-F): *R*<sub>t</sub> 4.85 min, no MH<sup>+</sup>, chiral purity 99.09%.

20

**Example 32** : synthesis of (1*s*,3*s*)-3-(3-((2-(6-chloro-5-methoxyindolin-1-yl)-1-(4-chlorophenyl)-2-oxoethyl)amino)-5-methoxyphenoxy)cyclobutanecarboxylic acid (Compound **32**) and chiral separation into Enantiomers **32A** and **32B**.

25



**Synthesis of intermediate 32a:**

Intermediate **32a** (3.58 g) was synthesized from 6-chloro-5-methoxyindoline [CAS 1369041-89-3] using the procedure described for the synthesis of intermediate **26f**.

5

**Synthesis of intermediate 32b:**

Intermediate **32b** (210 mg) was synthesized from intermediate **32a** using the procedure described for the synthesis of intermediate **8d**.

10 **Synthesis of Compound 32 and chiral separation into Enantiomers 32A and 32B:**

Compound **32** (165 mg) was synthesized from intermediate **32b** using the procedure described for the synthesis of Compound **28**. The two enantiomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5 µm 250 x 30 mm, mobile phase: 50% CO<sub>2</sub>, 50% EtOH) to give, after purification via flash chromatography on silica gel (15-40 µm; 4 g, CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 97/3) and solidification from heptane/diisopropyl ether, the first eluted Enantiomer **32A** (26 mg) and the second eluted Enantiomer **32B** (31 mg).

20 **Compound 32:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.03 - 2.15 (m, 2 H) 2.57 - 2.66 (m, 2 H) 2.66 - 2.75 (m, 1 H) 3.06 - 3.23 (m, 2 H) 3.61 (s, 3 H) 3.80 (s, 3 H) 3.95 (td, *J*=10.4, 7.3 Hz, 1 H) 4.43 - 4.52 (m, 2 H) 5.50 (d, *J*=8.5 Hz, 1 H) 5.65 (t, *J*=1.9 Hz, 1 H) 5.86 (s, 1 H) 5.93 (s, 1 H) 6.40 (d, *J*=8.5 Hz, 1 H) 7.10 (s, 1 H) 7.44 (d, *J*=8.5 Hz, 2 H) 7.54 (d, *J*=8.5 Hz, 2 H) 8.11 (s, 1 H) 12.26 (br s, 1 H)  
LC/MS (method LC-C): R<sub>t</sub> 2.66 min, MH<sup>+</sup> 569

**Enantiomer 32A:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.03 - 2.15 (m, 2 H) 2.57 - 2.66 (m, 2 H) 2.66 - 2.76 (m, 1 H) 3.04 - 3.24 (m, 2 H) 3.57 - 3.64 (m, 3 H) 3.80 (s, 3 H) 3.89 - 4.00 (m, 1 H) 4.42 - 4.54 (m, 2 H) 5.50 (br d, *J*=8.8 Hz, 1 H) 5.65 (s, 1 H) 5.86 (s, 1 H) 5.93 (s, 1 H) 6.40 (br d, *J*=8.5 Hz, 1 H) 7.10 (s, 1 H) 7.44 (d, *J*=8.2 Hz, 2 H) 7.54 (br d, *J*=8.2 Hz, 2 H) 8.11 (s, 1 H) 12.26 (br s, 1 H)  
LC/MS (method LC-D): R<sub>t</sub> 2.56 min, MH<sup>+</sup> 569  
[α]<sub>D</sub><sup>20</sup>: -55.4° (c 0.332, DMF)  
Chiral SFC (method SFC-R): R<sub>t</sub> 1.73 min, no MH<sup>+</sup>, chiral purity 100%.

35

**Enantiomer 32B:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.02 - 2.14 (m, 2 H) 2.58 - 2.65 (m, 2 H) 2.66 - 2.74 (m, 1 H) 3.04 - 3.24 (m, 2 H) 3.61 (s, 3 H) 3.80 (s, 3 H) 3.95 (td, *J*=10.4, 7.3 Hz, 1 H) 4.42 - 4.53 (m, 2 H) 5.50 (d, *J*=8.5 Hz, 1 H) 5.65 (t, *J*=2.0 Hz, 1 H) 5.86 (s, 1 H) 5.93 (s, 1 H) 6.40 (d, *J*=8.5 Hz, 1 H) 7.10 (s, 1 H) 7.44 (d, *J*=8.5 Hz, 2 H) 7.54 (d, *J*=8.5 Hz, 2 H) 8.11 (s, 1 H) 12.26 (br s, 1 H)

LC/MS (method LC-D): R<sub>t</sub> 2.56 min, MH<sup>+</sup> 569

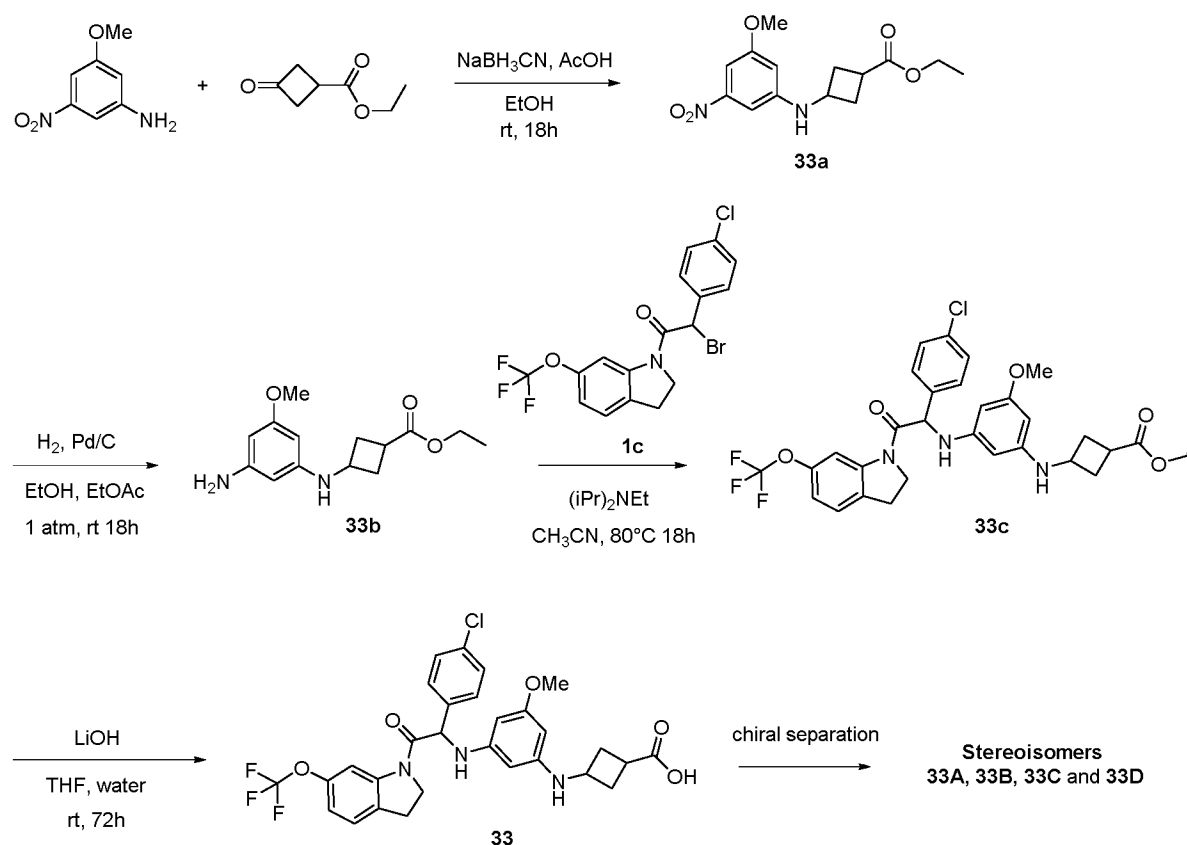
[α]<sub>D</sub><sup>20</sup>: +53.4° (c 0.35, DMF)

Chiral SFC (method SFC-R): R<sub>t</sub> 3.16 min, no MH<sup>+</sup>, chiral purity 99.59%.

10

**Example 33** : synthesis of 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenyl)amino)-cyclobutanecarboxylic acid (Compound **33**) and chiral separation into Stereoisomers **33A**, **33B**, **33C** and **33D**.

15

**Synthesis of intermediate 33a:**

Under nitrogen, a mixture of 3-methoxy-5-nitroaniline [CAS 586-10-7] (0.50 g, 2.973 mmol), ethyl 3-oxocyclobutanecarboxylate [CAS 87121-89-9] (1.27 g, 8.92 mmol), and acetic acid (0.34 mL, 5.947 mmol) in dry EtOH (26 mL) was stirred at

20

room temperature for 30 min. NaBH<sub>3</sub>CN (0.374 g, 5.947 mmol) was added and the mixture was stirred at room temperature for 18 h. Brine was added and the mixture was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (30 μm, 24 g, heptane/EtOAc from 85/15 to 75/25). The pure fractions were combined and concentrated under reduced pressure to give ethyl 3-((3-methoxy-5-nitrophenyl)amino)cyclobutanecarboxylate **33a** (820 mg). The compound was used in the next step without further purification.

10

**Synthesis of intermediate 33b:**

A solution of ethyl 3-((3-methoxy-5-nitrophenyl)amino)cyclobutanecarboxylate **33a** (820 mg, 2.8 mmol) in EtOH (16 mL) and EtOAc (14 mL) containing a catalytic amount of 10% Pd/C (300 mg, 0.28 mmol) was hydrogenated under atmospheric pressure of H<sub>2</sub> at room temperature for 18 h. The catalyst was removed by filtration over a short pad of Celite® and the filter cake was rinsed several times with EtOAc. The combined filtrates were evaporated under reduced pressure to give ethyl 3-((3-amino-5-methoxyphenyl)amino)cyclobutanecarboxylate **33b** (800 mg), which was used in the next step without further purification.

20

**Synthesis of intermediate 33c:**

A mixture of 2-bromo-2-(4-chlorophenyl)-1-(6-(trifluoromethoxy)indolin-1-yl)ethanone **1c** (0.936 g, 2.154 mmol), ethyl 3-((3-amino-5-methoxyphenyl)amino)cyclobutanecarboxylate **33b** (0.74 g, 2.8 mmol) and diisopropylethylamine (0.742 mL, 4.307 mmol) in CH<sub>3</sub>CN (11 mL) was stirred at 80°C for 18 h. The mixture was concentrated under reduced pressure. Purification was performed by flash chromatography on silica gel (30 μm, 40 g, heptane/EtOAc from 85/15 to 70/30) The pure fractions were combined and evaporated to dryness to give ethyl 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenyl)amino)cyclobutanecarboxylate **33c** (600 mg).

30

**Synthesis of Compound 33 and chiral separation into Stereisomers 33A, 33B, 33C and 33D:**

A solution of LiOH monohydrate (0.407 g, 9.71 mmol) in water (5.3 mL) was added to a solution of ethyl 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenyl)amino)cyclobutanecarboxylate **33c** (600 mg, 0.971 mmol) in THF (12 mL). The mixture was stirred at room temperature for 72 h, acidified with AcOH, concentrated under reduced pressure,

35



and co-evaporated twice with toluene. Purification was performed by flash chromatography on silica gel (30  $\mu$ m, 24 g, CH<sub>2</sub>Cl<sub>2</sub>/MeOH from 99/1 to 96/4). The pure fractions were combined and evaporated to dryness. A second purification was performed via Reverse Phase chromatography (Stationary phase: YMC-actus  
5 Triart-C18 10  $\mu$ m 30 x 150 mm, mobile phase: Gradient from 65% aqueous NH<sub>4</sub>HCO<sub>3</sub> 0.2%, 35% CH<sub>3</sub>CN to 25% aqueous NH<sub>4</sub>HCO<sub>3</sub> 0.2%, 75% CH<sub>3</sub>CN). The pure fractions were combined and evaporated to dryness to give 3-((3-((1-(4-chlorophenyl)-2-oxo-2-(6-(trifluoromethoxy)indolin-1-yl)ethyl)amino)-5-methoxyphenyl)amino)cyclobutanecarboxylic acid (Compound **33**, 80 mg). The  
10 stereoisomers were separated via chiral SFC (Stationary phase: Chiralcel® OD-H 5  $\mu$ m 250 x 20 mm, mobile phase: 60% CO<sub>2</sub>, 40% EtOH) to give 4 fractions which were freeze-dried from CH<sub>3</sub>CN/water to give Stereoisomer **33A** (19 mg), Stereoisomer **33B** (24 mg), Stereoisomer **33C** (19 mg) and Stereoisomer **33D** (26 mg).

15

**Stereoisomer 33A:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.94 - 2.02 (m, 2 H) 2.43 (ddd, *J*=11.8, 7.7, 4.1 Hz, 2 H) 2.91 (dt, *J*=9.5, 4.7 Hz, 1 H) 3.07 - 3.21 (m, 2 H) 3.56 (s, 3 H) 3.78 - 3.88 (m, 1 H) 4.05 (td, *J*=10.4, 7.3 Hz, 1 H) 4.50 (td, *J*=10.3, 6.8 Hz, 1 H) 5.38 (d, *J*=1.9 Hz, 1 H) 5.43 (d, *J*=8.5 Hz, 1 H) 5.46 (s, 1 H) 5.60 (s, 1 H) 5.63 (d, *J*=6.3 Hz, 1 H) 6.19 (d, *J*=8.5 Hz, 1 H) 7.00 (dd, *J*=8.2, 1.6 Hz, 1 H) 7.33 (d, *J*=8.2 Hz, 1 H) 7.43 (d, *J*=8.5 Hz, 2 H) 7.54 (d, *J*=8.5 Hz, 2 H) 8.03 (s, 1 H)

20 LC/MS (method LC-C): R<sub>t</sub> 2.86 min, MH<sup>+</sup> 590[ $\alpha$ ]<sub>D</sub><sup>20</sup>: -26.2° (c 0.248, DMF)25 Chiral SFC (method SFC-I): R<sub>t</sub> 1.48 min, no MH<sup>+</sup>, chiral purity 100%.**Stereoisomer 33B:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.82 - 1.95 (m, 2 H) 2.41 - 2.47 (m, 2 H) 2.68 (br t, *J*=8.5 Hz, 1 H) 3.08 - 3.21 (m, 2 H) 3.56 (s, 3 H) 3.62 (br dd, *J*=15.4, 8.2 Hz, 1 H) 4.06 (td, *J*=10.3, 7.1 Hz, 1 H) 4.46 - 4.56 (m, 1 H) 5.41 (s, 1 H) 5.43 (br d, *J*=8.5 Hz, 1 H) 5.50 (s, 1 H) 5.60 (s, 2 H) 6.14 (br d, *J*=8.8 Hz, 1 H) 7.01 (br d, *J*=8.2 Hz, 1 H) 7.33 (d, *J*=8.2 Hz, 1 H) 7.43 (d, *J*=8.5 Hz, 2 H) 7.54 (d, *J*=8.5 Hz, 2 H) 8.03 (s, 1 H)

30 LC/MS (method LC-C): R<sub>t</sub> 2.84 min, MH<sup>+</sup> 590[ $\alpha$ ]<sub>D</sub><sup>20</sup>: -27.9° (c 0.248, DMF)35 Chiral SFC (method SFC-I): R<sub>t</sub> 2.20 min, no MH<sup>+</sup>, chiral purity 100%.

**Stereoisomer 33C:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.93 - 2.03 (m, 2 H) 2.41-2.46 (m, 2 H) 2.82 - 2.95 (m, 1 H) 3.07 - 3.21 (m, 2 H) 3.56 (s, 3 H) 3.78 - 3.88 (m, 1 H) 4.00 - 4.11 (m, 1 H) 4.45 - 4.56 (m, 1 H) 5.37 (s, 1 H) 5.40 - 5.49 (m, 2 H) 5.58 - 5.66 (m, 2 H) 6.19 (br d, *J*=8.5 Hz, 1 H) 7.00 (br d, *J*=6.6 Hz, 1 H) 7.32 (br d, *J*=8.2 Hz, 1 H) 7.43 (d, *J*=8.5 Hz, 2 H) 7.54 (d, *J*=8.2 Hz, 2 H) 8.02 (br s, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.86 min, MH<sup>+</sup> 590

[α]<sub>D</sub><sup>20</sup>: +26.7° (c 0.221, DMF)

Chiral SFC (method SFC-I): R<sub>t</sub> 2.91 min, no MH<sup>+</sup>, chiral purity 100%.

10

**Stereoisomer 33D:**

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.78 - 1.96 (m, 2 H) 2.40 - 2.47 (m, 2 H) 2.65 - 2.71 (m, 1 H) 3.08 - 3.21 (m, 2 H) 3.56 (s, 3 H) 3.58 - 3.67 (m, 1 H) 4.06 (td, *J*=10.2, 7.3 Hz, 1 H) 4.44 - 4.56 (m, 1 H) 5.38 - 5.46 (m, 2 H) 5.50 (s, 1 H) 5.60 (s, 2 H) 6.14 (br d, *J*=8.8 Hz, 1 H) 7.00 (br d, *J*=6.9 Hz, 1 H) 7.33 (d, *J*=8.2 Hz, 1 H) 7.43 (d, *J*=8.5 Hz, 2 H) 7.54 (d, *J*=8.5 Hz, 2 H) 8.03 (s, 1 H)

LC/MS (method LC-C): R<sub>t</sub> 2.84 min, MH<sup>+</sup> 590

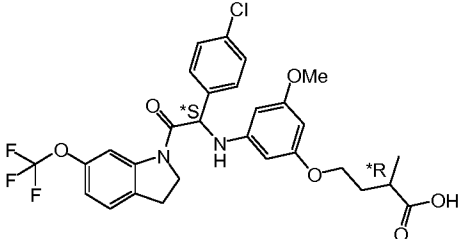
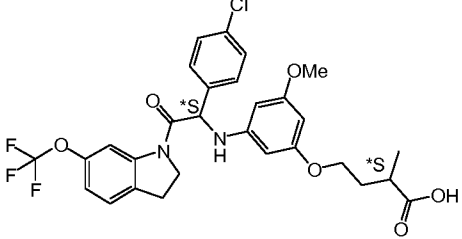
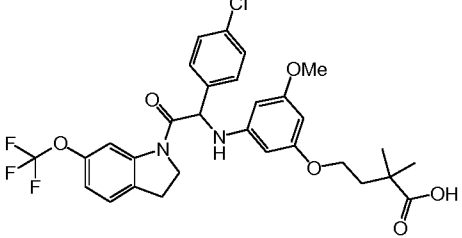
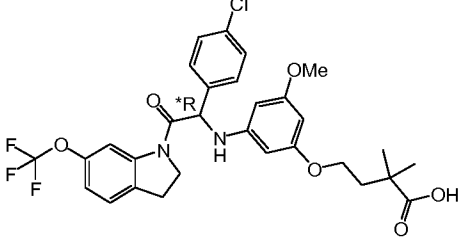
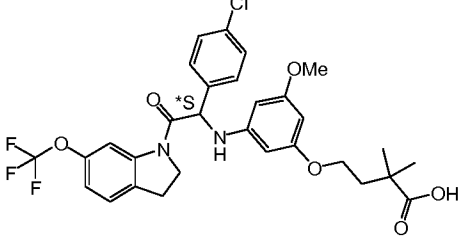
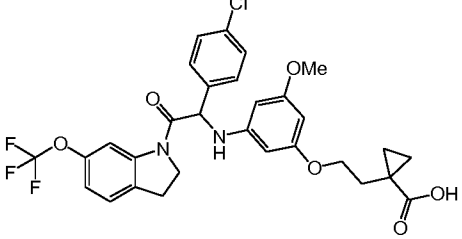
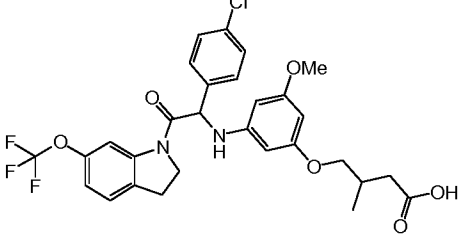
[α]<sub>D</sub><sup>20</sup>: +23.4° (c 0.295, DMF)

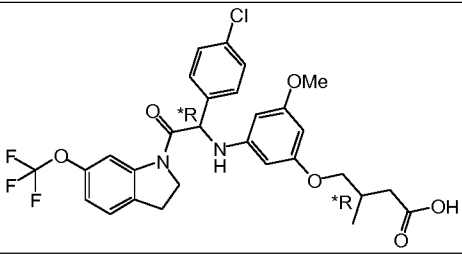
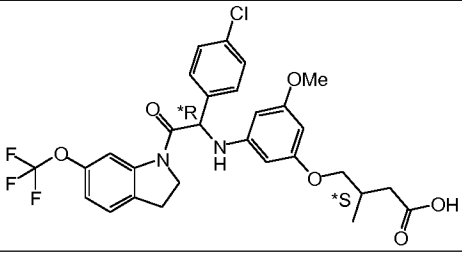
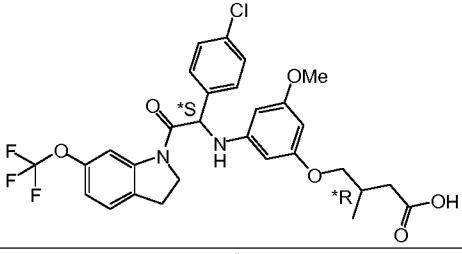
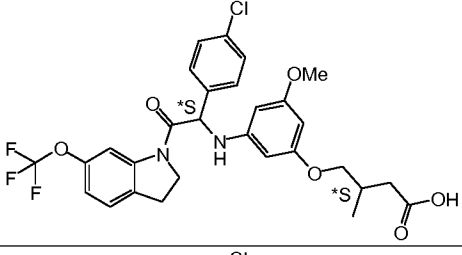
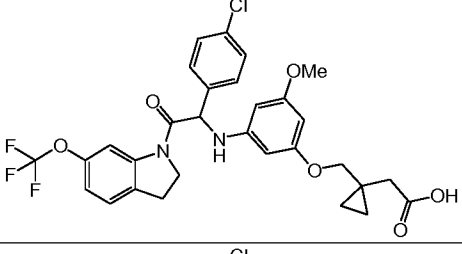
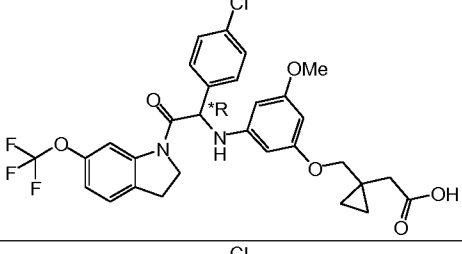
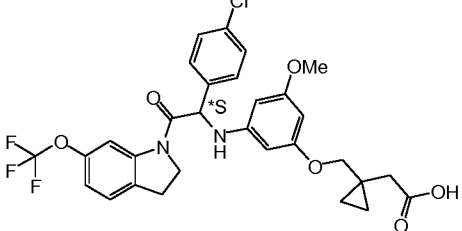
Chiral SFC (method SFC-I): R<sub>t</sub> 5.35 min, no MH<sup>+</sup>, chiral purity 100%.

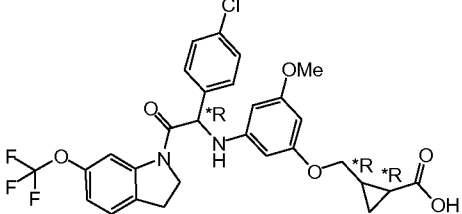
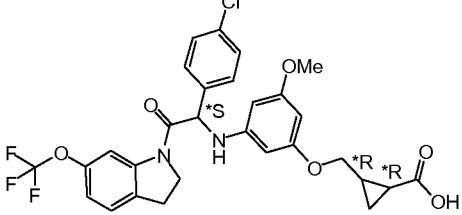
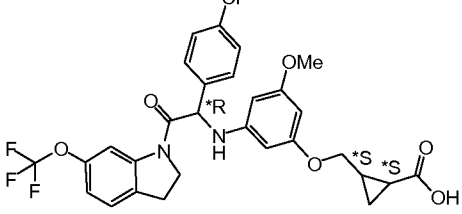
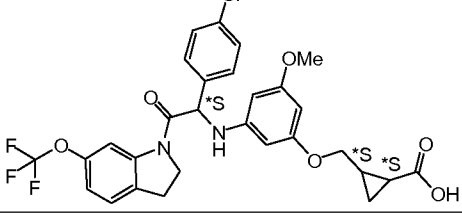
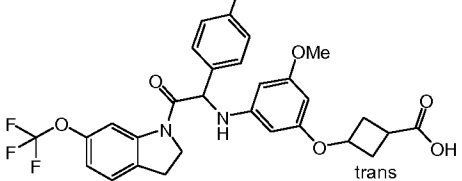
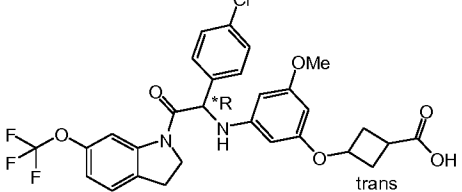
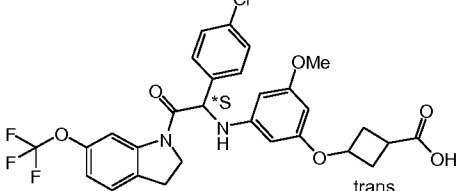
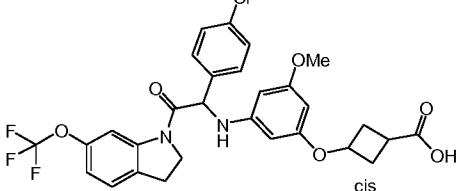
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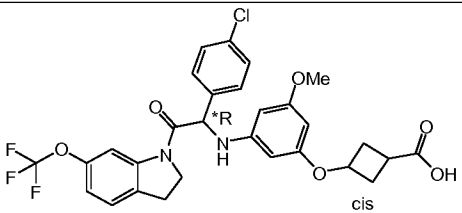
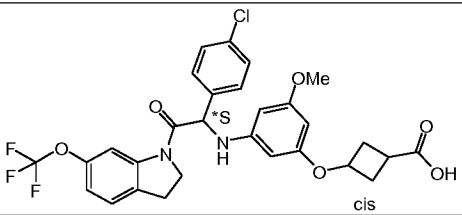
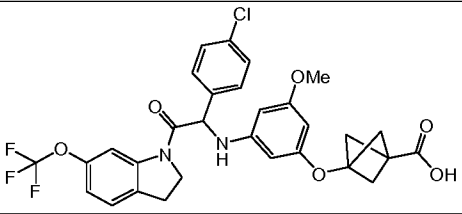
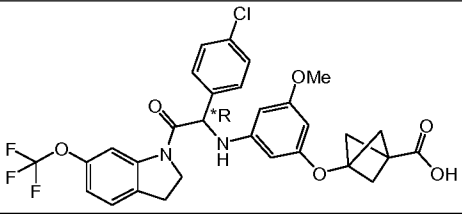
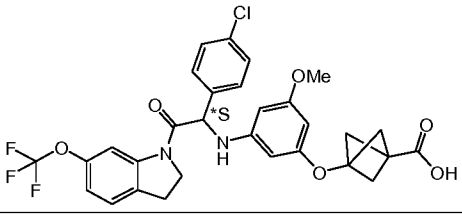
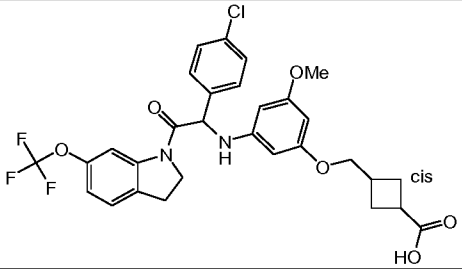
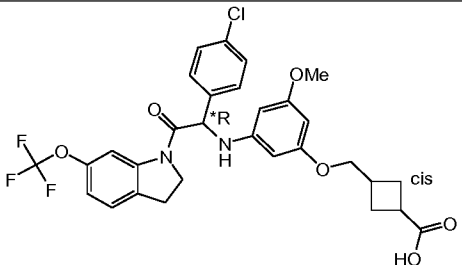
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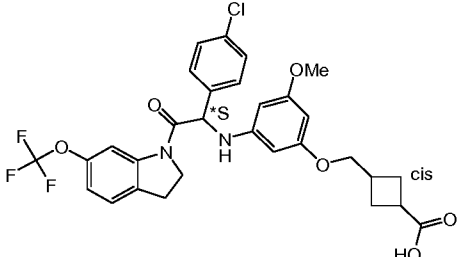
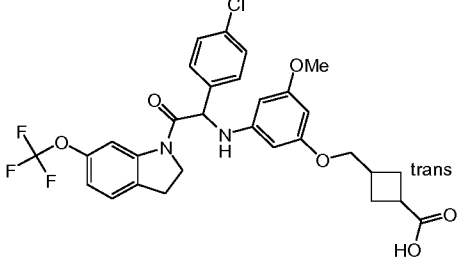
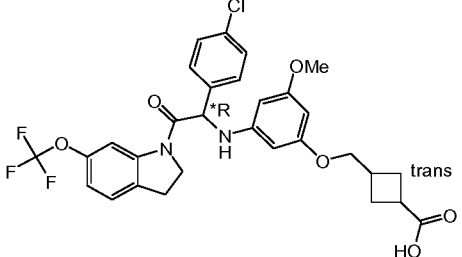
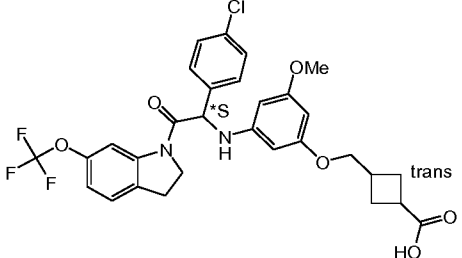
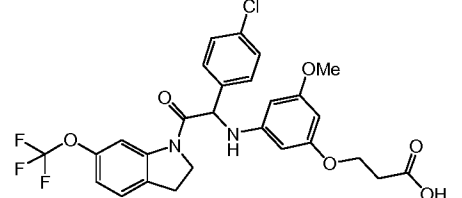
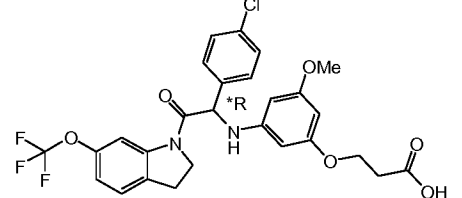
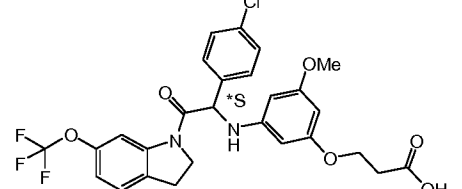
Compound	Structure	Optical rotation
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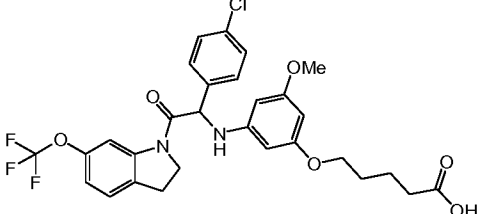
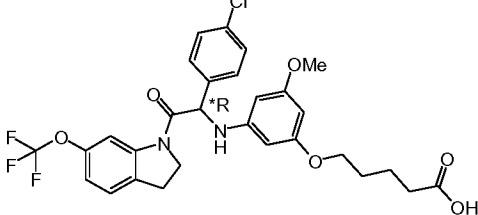
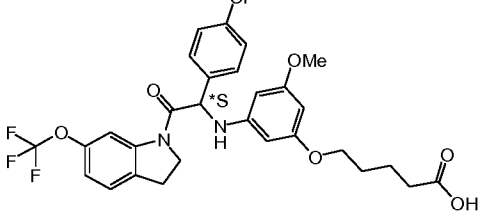
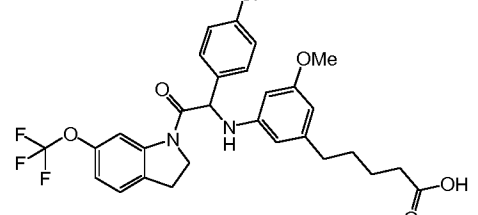
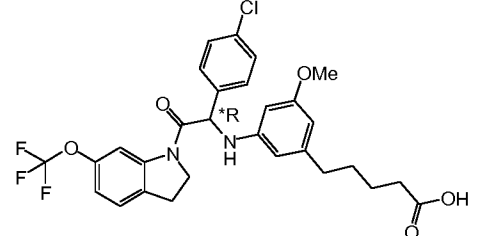
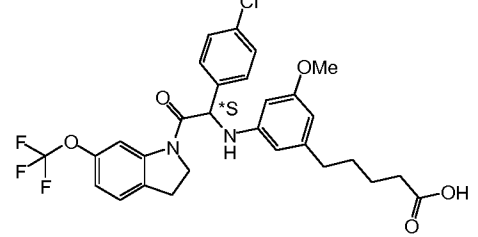
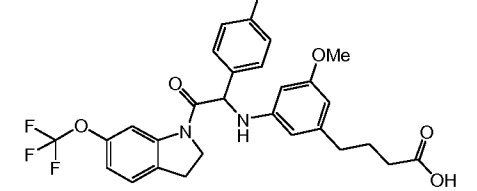
Compound	Structure	Optical rotation
1C		$[\alpha]_D^{20} = +35.2^\circ$
1D		$[\alpha]_D^{20} = +64.3^\circ$
2		racemic
2A		$[\alpha]_D^{20} = +49.6^\circ$
2B		$[\alpha]_D^{20} = -49.2^\circ$
3		racemic
4		racemic

Compound	Structure	Optical rotation
4A		$[\alpha]_D^{20} = -59.6^\circ$
4B		$[\alpha]_D^{20} = -47.5^\circ$
4C		$[\alpha]_D^{20} = +47.7^\circ$
4D		$[\alpha]_D^{20} = +60.7^\circ$
5		racemic
5A		$[\alpha]_D^{20} = +37.0^\circ$
5B		$[\alpha]_D^{20} = -48.8^\circ$

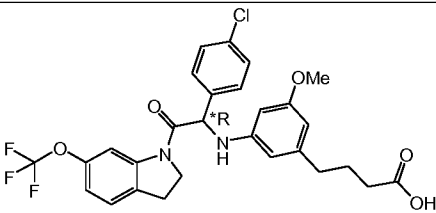
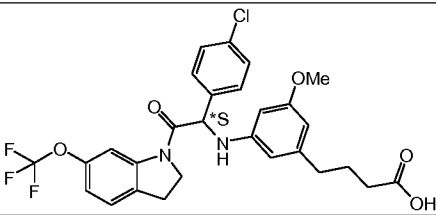
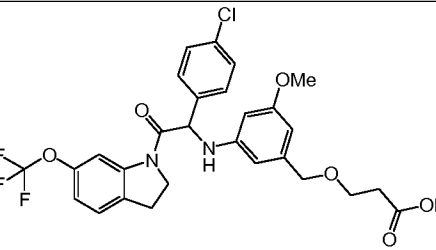
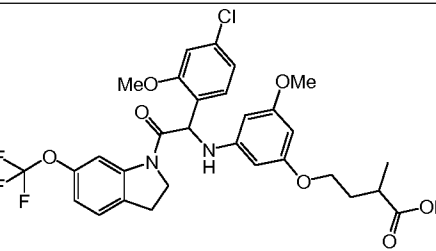
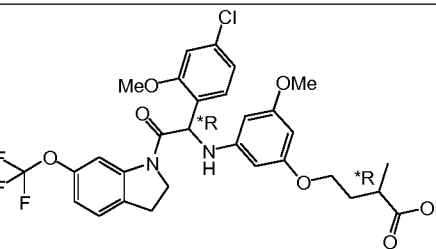
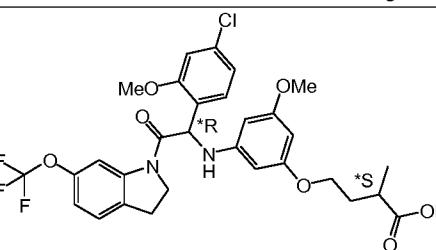
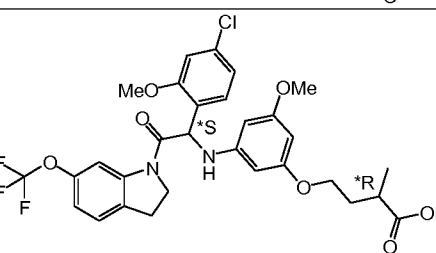
Compound	Structure	Optical rotation
6AA		$[\alpha]_D^{20} = -78.0^\circ$
6AB		$[\alpha]_D^{20} = +12.9^\circ$
6BA		$[\alpha]_D^{20} = -12.5^\circ$
6BB		$[\alpha]_D^{20} = +81.4^\circ$
7		-
7A		$[\alpha]_D^{20} = -41.6^\circ$
7B		$[\alpha]_D^{20} = +43.7^\circ$
8		-

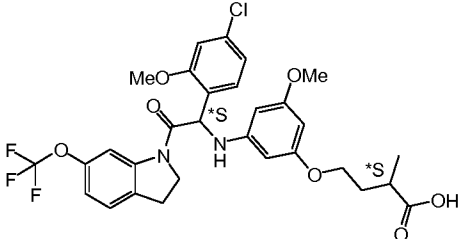
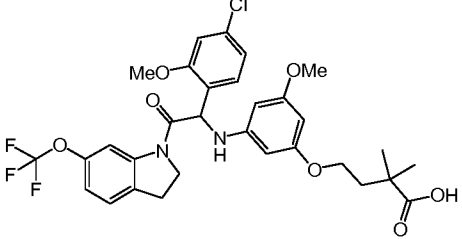
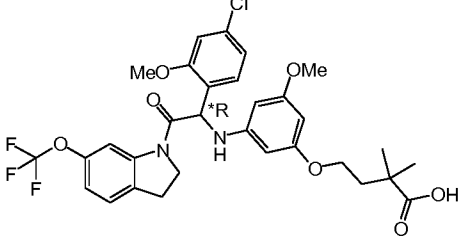
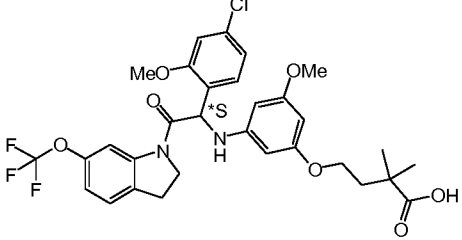
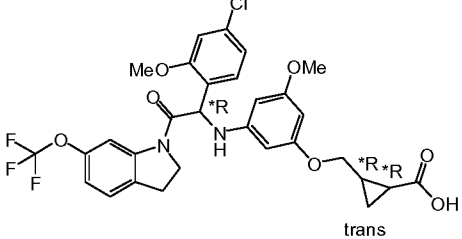
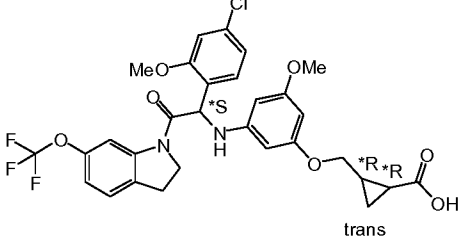
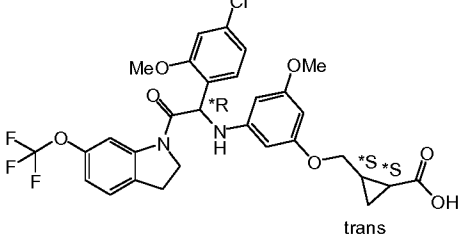
Compound	Structure	Optical rotation
8A		$[\alpha]_D^{20} = -47.1^\circ$
8B		$[\alpha]_D^{20} = +40.0^\circ$
9		racemic
9A		$[\alpha]_D^{20} = -43.6^\circ$
9B		$[\alpha]_D^{20} = +42.2^\circ$
10		-
10A		$[\alpha]_D^{20} = -44.0^\circ$

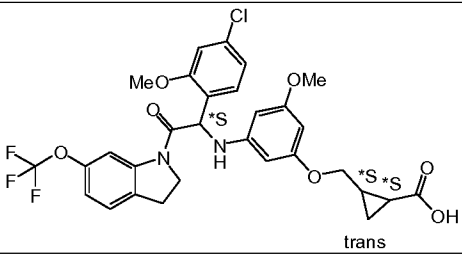
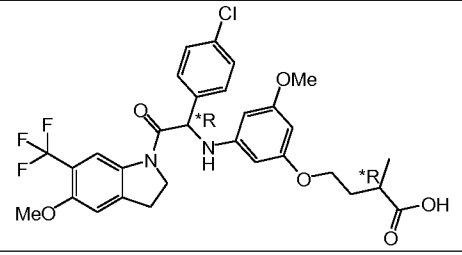
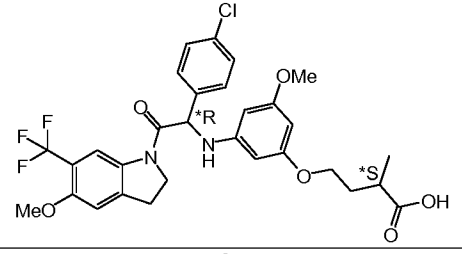
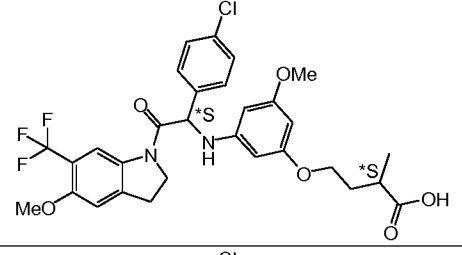
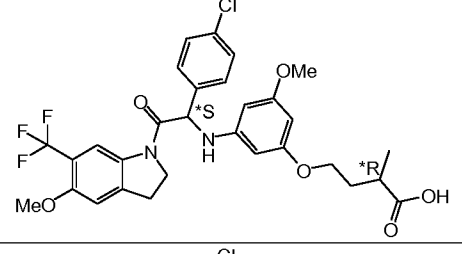
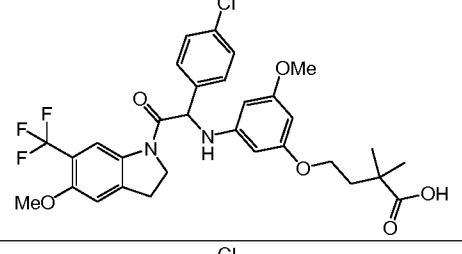
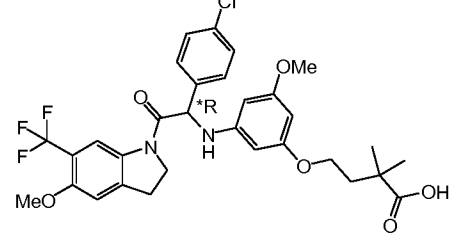
Compound	Structure	Optical rotation
10B		$[\alpha]_D^{20} = +45.5^\circ$
11		-
11A		$[\alpha]_D^{20} = -43.3^\circ$
11B		$[\alpha]_D^{20} = +45.5^\circ$
12		racemic
12A		$[\alpha]_D^{20} = -47.3^\circ$
12B		$[\alpha]_D^{20} = +41.8^\circ$

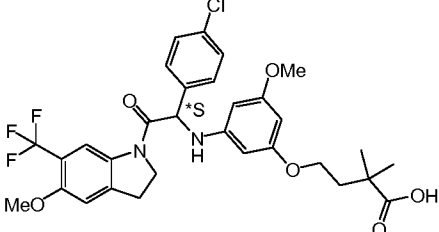
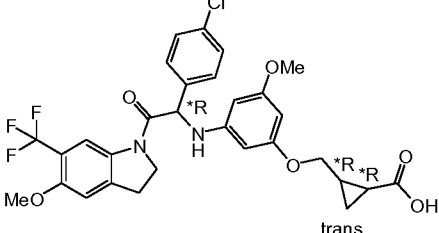
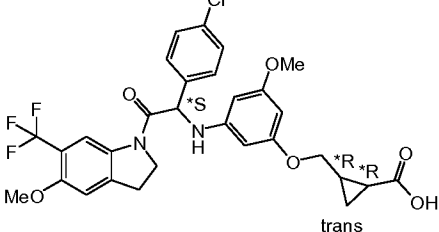
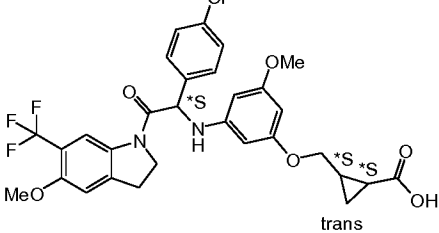
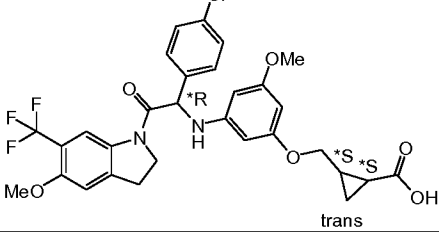
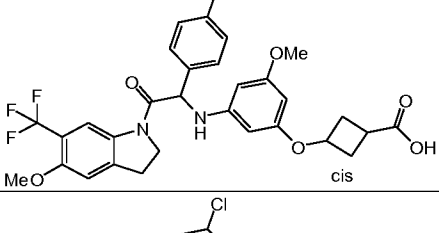
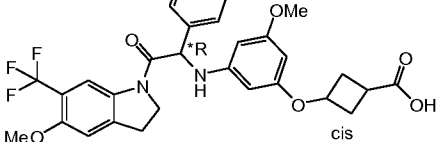
Compound	Structure	Optical rotation
13		racemic
13A		$[\alpha]_D^{20} = -48.6^\circ$
13B		$[\alpha]_D^{20} = +48.3^\circ$
14		racemic
14A		$[\alpha]_D^{20} = +55.8^\circ$
14B		$[\alpha]_D^{20} = -53.7^\circ$
15		racemic

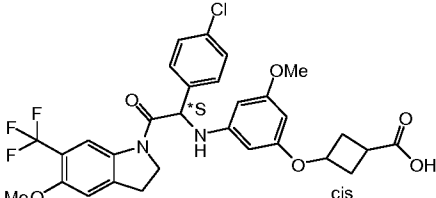
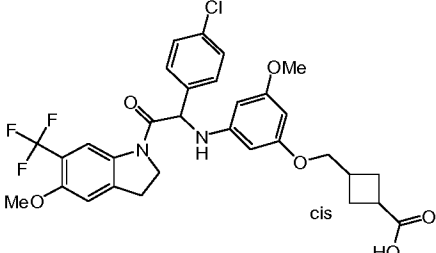
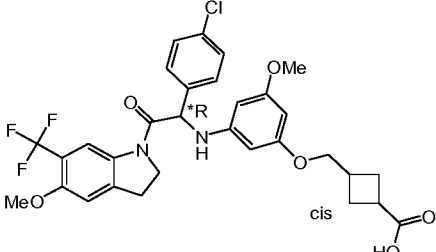
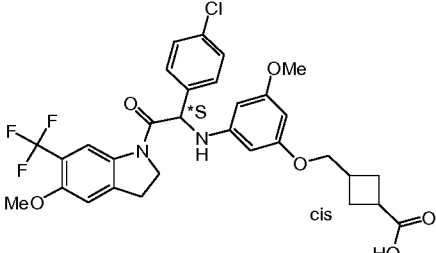
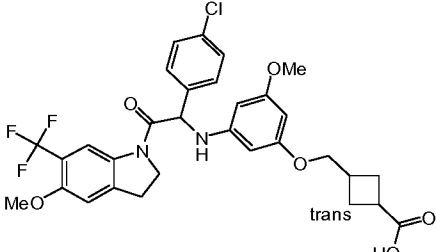
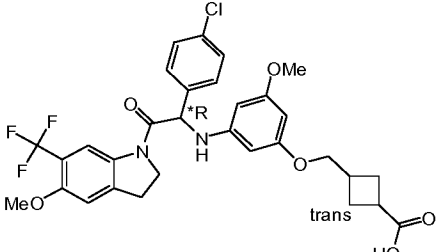


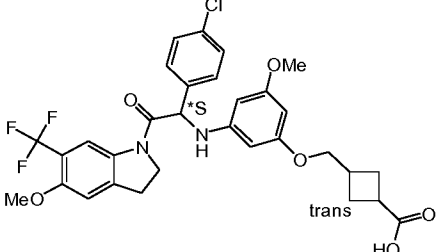
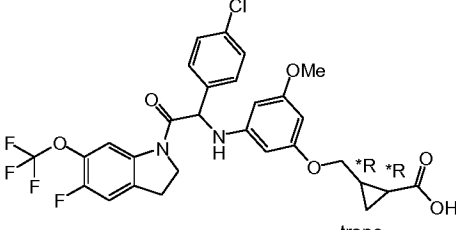
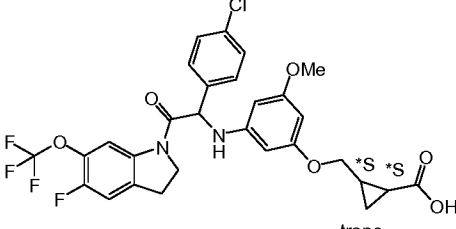
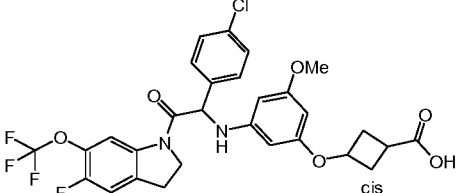
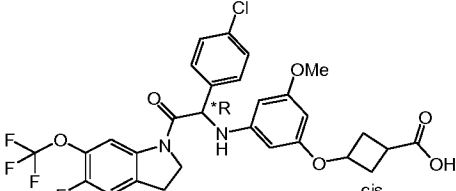
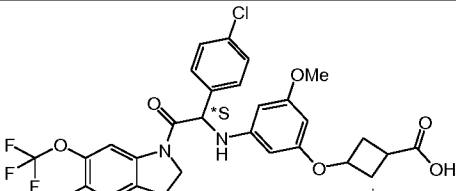
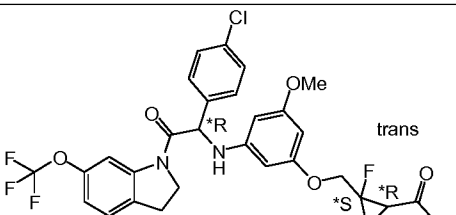
Compound	Structure	Optical rotation
15A		$[\alpha]_D^{20} = -59.0^\circ$
15B		$[\alpha]_D^{20} = +48.0^\circ$
16		racemic
17		racemic
17A		$[\alpha]_D^{20} = -18.4^\circ$
17B		$[\alpha]_D^{20} = -51.0^\circ$
17C		$[\alpha]_D^{20} = +41.6^\circ$

Compound	Structure	Optical rotation
17D		$[\alpha]_D^{20} = +15.8^\circ$
18		racemic
18A		$[\alpha]_D^{20} = -30.2^\circ$
18B		$[\alpha]_D^{20} = +28.0^\circ$
19AA		$[\alpha]_D^{20} = -65.6^\circ$
19AB		$[\alpha]_D^{20} = +37.1^\circ$
19BA		$[\alpha]_D^{20} = -47.6^\circ$

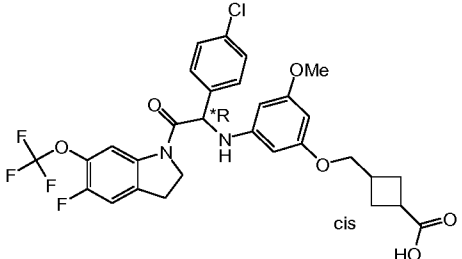
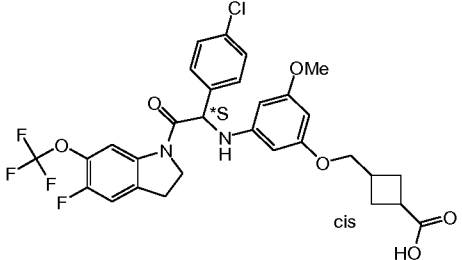
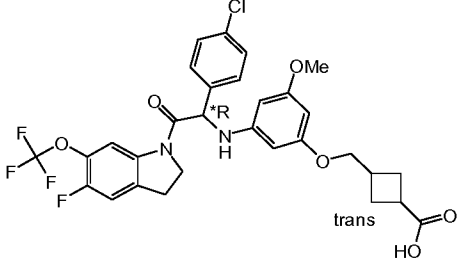
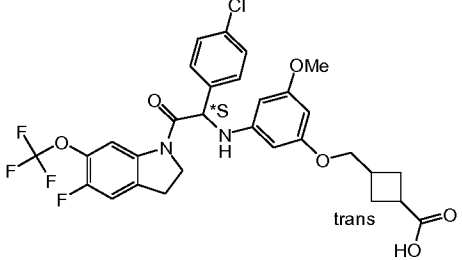
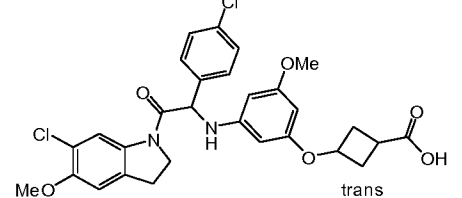
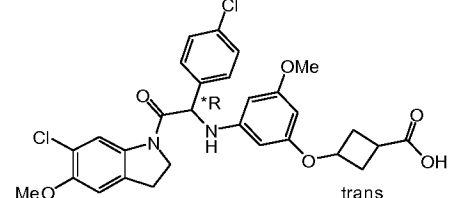
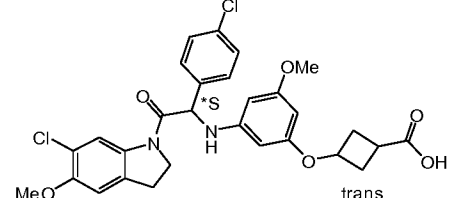
Compound	Structure	Optical rotation
19BB		$[\alpha]_D^{20} = +56.8^\circ$
20A		$[\alpha]_D^{20} = -40.9^\circ$
20B		$[\alpha]_D^{20} = -50.0^\circ$
20C		$[\alpha]_D^{20} = +26.0^\circ$
20D		$[\alpha]_D^{20} = +57.4^\circ$
21		racemic
21A		$[\alpha]_D^{20} = -41.7^\circ$

Compound	Structure	Optical rotation
21B		$[\alpha]_D^{20} = +44.0^\circ$
22AA		$[\alpha]_D^{20} = -75.0^\circ$
22AB		$[\alpha]_D^{20} = +10.0^\circ$
22BA		$[\alpha]_D^{20} = -9.3^\circ$
22BB		$[\alpha]_D^{20} = +80.0^\circ$
23		-
23A		$[\alpha]_D^{20} = -38.1^\circ$

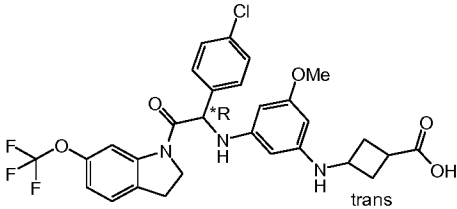
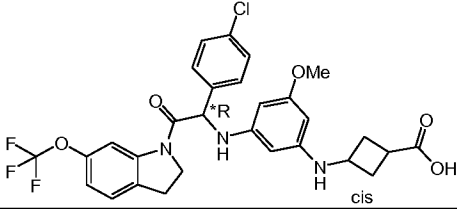
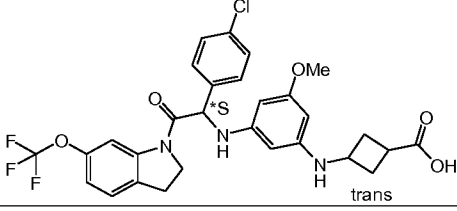
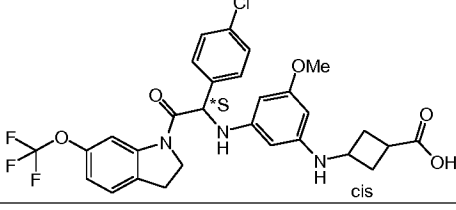
Compound	Structure	Optical rotation
23B		$[\alpha]_D^{20} = +36.9^\circ$
24		-
24A		$[\alpha]_D^{20} = -41.5^\circ$
24B		$[\alpha]_D^{20} = +36.6^\circ$
25		-
25A		$[\alpha]_D^{20} = -41.1^\circ$

Compound	Structure	Optical rotation
25B		$[\alpha]_D^{20} = +40.6^\circ$
26A		-
26B		-
27		-
27A		$[\alpha]_D^{20} = -40.5^\circ$
27B		$[\alpha]_D^{20} = +37.5^\circ$
28AA		$[\alpha]_D^{20} = -43.3^\circ$



Compound	Structure	Optical rotation
30A		$[\alpha]_D^{20} = +42.6^\circ$
30B		$[\alpha]_D^{20} = -44.2^\circ$
31A		$[\alpha]_D^{20} = +43.1^\circ$
31B		$[\alpha]_D^{20} = -43.4^\circ$
32		-
32A		$[\alpha]_D^{20} = -55.4^\circ$
32B		$[\alpha]_D^{20} = +53.4^\circ$



Compound	Structure	Optical rotation
33A		$[\alpha]_D^{20} = -26.2^\circ$
33B		$[\alpha]_D^{20} = -27.9^\circ$
33C		$[\alpha]_D^{20} = +26.7^\circ$
33D		$[\alpha]_D^{20} = +23.4^\circ$

## ANTIVIRAL ACTIVITY OF THE COMPOUNDS OF THE INVENTION

### *DENV-2 antiviral assay*

The antiviral activity of all the compounds of the invention was tested against the

5 DENV-2 16681 strain which was labeled with enhanced green fluorescent protein (eGFP). The culture medium consists of minimal essential medium supplemented with 2% of heat-inactivated fetal calf serum, 0.04% gentamycin (50mg/mL) and 2mM of L-glutamine. Vero cells, obtained from ECACC, were suspended in culture medium and 25 $\mu$ L was added to 384-well plates (2500 cells/well), which already

10 contain the antiviral compounds. Typically, these plates contain a 5-fold serial dilution of 9 dilution steps of the test compound at 200 times the final concentration in 100% DMSO (200nL). In addition, each compound concentration is tested in quadruplicate (final concentration range: 25 $\mu$ M – 0.000064 $\mu$ M or 2.5 $\mu$ M – 0.0000064 $\mu$ M for the most active compounds). Finally, each plate

15 contains wells which are assigned as virus controls (containing cells and virus in the absence of compound), cell controls (containing cells in the absence of virus and compound) and medium controls (containing medium in the absence of cells, virus and compounds). To the wells assigned as medium control, 25 $\mu$ L of culture medium was added instead of Vero cells. Once the cells are added to the plates,

the plates were incubated for 30 minutes at room temperature to allow the cells to distribute evenly within the wells. Next, the plates were incubated in a fully humidified incubator (37°C, 5% CO<sub>2</sub>) until the next day. Then, DENV-2 strain 16681, labeled with eGFP, was added at a multiplicity of infection (MOI) of 0.5.

5 Therefore, 15µL of virus suspension was added to all the wells containing test compound and to the wells assigned as virus control. In parallel, 15µL of culture medium was added to the medium and cell controls. Next, the plates were incubated for 3 days in a fully humidified incubator (37°C, 5% CO<sub>2</sub>). At the day of the read out, the eGFP fluorescence was measured using an automated  
10 fluorescence microscope at 488 nm (blue laser). Using an in-house LIMS system, inhibition dose response curves for each compound were calculated and the half maximal effective concentration (EC<sub>50</sub>) was determined. Therefore, the percent inhibition (I) for every test concentration is calculated using the following formula:  $I = 100 \cdot (S_T - S_{CC}) / (S_{VC} - S_{CC})$ ; S<sub>T</sub>, S<sub>CC</sub> and S<sub>VC</sub> are the amount of eGFP signal in the  
15 test compound, cell control and virus control wells, respectively. The EC<sub>50</sub> represents the concentration of a compound at which the virus replication is inhibited with 50%, as measured by a 50% reduction of the eGFP fluorescent intensity compared to the virus control. The EC<sub>50</sub> is calculated using linear interpolation (Table 1).

20 In parallel, the toxicity of the compounds was assessed on the same plates. Once the read-out for the eGFP signal was done, 40µL of ATPlite, a cell viability stain, was added to all wells of the 384-well plates. ATP is present in all metabolically active cells and the concentration declines very rapidly when the cells undergo necrosis or apoptosis. The ATPlite assay system is based on the production of  
25 light caused by the reaction of ATP with added luciferase and D-luciferin. The plates were incubated for 10 minutes at room temperature. Next, the plates were measured on a ViewLux. The half maximal cytotoxic concentration (CC<sub>50</sub>) was also determined, defined as the concentration required to reduce the luminescent signal by 50% compared to that of the cell control wells. Finally, the selectivity  
30 index (SI) was determined for the compounds, which was calculated as followed:  $SI = CC_{50} / EC_{50}$ .

Table 1: EC<sub>50</sub>, CC<sub>50</sub>, and SI for the compounds of the invention in the DENV-2 antiviral assay

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compound#	EC <sub>50</sub> (µM)	N	CC <sub>50</sub> (µM)	N	SI	N
1	0.00050	3	11	3	24400	3
1A	0.018	3	9.6	3	523	3
1B	0.018	4	10	4	579	4

compound#	EC <sub>50</sub> (μM)	N	CC <sub>50</sub> (μM)	N	SI	N
1C	0.000094	3	12	3	131193	3
1D	0.00023	3	12	3	57700	3
2	0.00062	3	12	3	19200	3
2A	0.00038	3	13	3	34500	3
2B	0.019	3	11	4	565	3
3	0.00050	3	10	3	17700	3
4	0.00014	3	10	3	73900	3
4A	0.0029	3	9.0	3	3090	3
4B	0.011	3	10	3	935	3
4C	0.00011	4	13	4	121878	4
4D	0.00017	3	13	3	81200	3
5	0.00092	3	9.7	3	11300	3
5A	0.00051	3	12	3	26300	3
5B	0.011	3	10	3	921	3
6AA	0.00074	3	8.3	3	8870	3
6AB	0.000016	6	12	7	>199223	6
6BA	0.012	3	8.7	3	703	3
6BB	0.00018	3	12	3	83800	3
7	0.00049	3	12	3	14600	3
7A	0.0091	3	10	3	1130	3
7B	0.00012	3	13	3	121027	3
8	0.000048	5	13	5	>126733	5
8A	0.00086	3	12	3	11600	3
8B	0.000023	10	14	10	>102836	10
9	0.00070	3	9.8	3	14700	3
9A	0.090	3	11	3	125	3
9B	0.00039	3	12	4	32500	3
10	0.00027	3	12	3	44900	3
10A	0.0027	3	10	3	3790	3
10B	0.00011	3	11	3	109987	3
11	0.00013	4	12	4	97100	4
11A	0.0038	3	10	3	2710	3
11B	0.00011	4	11	4	118692	4
12	0.0011	3	11	3	9440	3
12A	0.038	3	10	3	267	3
12B	0.00069	3	14	3	21500	3
13	0.00025	3	12	4	38100	3
13A	0.0014	6	9.1	7	5720	6
13B	0.00013	4	12	4	88200	4

compound#	EC <sub>50</sub> (μM)	N	CC <sub>50</sub> (μM)	N	SI	N
14	0.00023	3	9.6	3	50200	3
14A	0.00011	3	16	3	151558	3
14B	0.060	3	9.3	3	156	3
15	0.00042	3	8.3	3	25500	3
15A	0.049	3	8.4	3	171	3
15B	0.00045	3	12	5	24900	3
16	0.00033	4	16	5	56100	4
17	0.00018	3	13	3	100043	3
17A	0.076	3	11	3	147	3
17B	0.18	3	11	3	59	3
17C	0.00023	3	12	3	39300	3
17D	0.00012	4	14	4	>9720	4
18	0.00049	3	11	3	26100	3
18A	0.0099	3	12	4	1160	3
18B	0.00028	3	12	3	62700	3
19AA	0.010	3	11	4	1030	3
19AB	0.000012	8	12	9	>390600	8
19BA	0.016	3	11	3	707	3
19BB	0.000038	5	8.8	5	>148612	5
20A	0.44	3	12	3	27	3
20B	0.18	3	12	3	69	3
20C	0.00017	3	12	3	59500	3
20D	0.00023	3	13	3	53400	3
21	0.0011	3	15	3	11000	3
21A	0.016	3	11	3	687	3
21B	0.00032	3	12	3	45200	3
22AA	0.016	4	13	4	798	4
22AB	0.000034	6	12	7	>196427	6
22BA	0.015	3	12	3	786	3
22BB	0.00046	3	14	3	27600	3
23	0.000093	4	12	4	116424	4
23A	0.034	3	11	3	321	3
23B	0.000062	7	12	8	>88755	7
24	0.00064	4	12	4	18300	4
24A	0.024	3	11	3	469	3
24B	0.00034	3	12	3	43100	3
25	0.00045	4	12	4	26800	4
25A	0.0071	3	12	3	1640	3
25B	0.00028	3	13	3	52900	3

compound#	EC <sub>50</sub> (μM)	N	CC <sub>50</sub> (μM)	N	SI	N
26A	0.00010	4	14	4	>12200	4
26B	0.00094	4	12	4	10600	4
27	0.000067	4	13	4	149640	4
27A	0.00041	3	11	3	14300	3
27B	0.000022	6	13	7	>205482	6
28AA	0.33	3	11	3	34	3
28AB	0.00068	3	13	3	19000	3
28BA	0.017	3	10.0	3	574	3
28BB	0.00020	3	12	3	70600	3
29AA	0.061	3	9.2	3	151	3
29AB	0.00053	3	12	3	22300	3
29BA	0.0034	3	9.8	3	2890	3
29BB	0.000069	3	12	4	124722	3
30A	0.00024	3	13	4	47400	3
30B	0.0059	3	11	3	1800	3
31A	0.00020	3	12	3	70300	3
31B	0.0026	3	12	3	4400	3
32	0.00013	3	15	3	130935	3
32A	0.063	3	13	3	205	3
32B	0.000081	5	14	5	>230623	5
33A	0.013	3	17	4	1110	3
33B	0.0079	3	14	3	1760	3
33C	0.0032	3	19	3	5930	3
33D	0.00052	3	18	3	39000	3

N= the number of independent experiments in which the compounds were tested.

#### *Tetravalent reverse transcriptase quantitative-PCR (RT-qPCR) assay*

The antiviral activity of the compounds of the invention was tested against DENV-1 strain TC974#666 (NCPV), DENV-2 strain 16681, DENV-3 strain H87 (NCPV) and DENV-4 strain H241 (NCPV) in a RT-qPCR assay. Therefore, Vero cells were infected with either DENV-1, or -2, or -3, or -4 in the presence or absence of test compounds. At day 3 post-infection, the cells were lysed and cell lysates were used to prepare cDNA of both a viral target (the 3'UTR of DENV; Table 2) and a cellular reference gene ( $\beta$ -actin, Table 2). Subsequently, a duplex real time PCR was performed on a Lightcycler480 instrument. The generated Cp value is inversely proportional to the amount of RNA expression of these targets. Inhibition of DENV replication by a test compound results in a shift of Cp's for the 3'UTR gene. On the other hand, if a test compound is toxic to the cells, a similar effect on

$\beta$ -actin expression will be observed. The comparative  $\Delta\Delta C_p$  method is used to calculate  $EC_{50}$ , which is based on the relative gene expression of the target gene (3'UTR) normalized with the cellular housekeeping gene ( $\beta$ -actin). In addition,  $CC_{50}$  values are determined based on the  $C_p$  values acquired for the housekeeping gene  $\beta$ -actin.

Table 2: Primers and probes used for the real-time, quantitative RT-PCR .

Primer/probe	Target	Sequence <sup>a, b</sup>
F3utr258	DENV 3'-UTR	5'-CGGTTAGAGGAGACCCCTC-3'
R3utr425	DENV 3'-UTR	5'-GAGACAGCAGGATCTCTGGTC-3'
P3utr343	DENV 3'-UTR	<b>FAM-5'-AAGGACTAG-ZEN-AGGTTAGAGGAGACCCCCC-3'-IABkFQ</b>
Factin743	$\beta$ -actin	5'-GGCCAGGTCATCACCATT-3'
Ractin876	$\beta$ -actin	5'-ATGTCCACGTCACACTTCATG-3'
Pactin773	$\beta$ -actin	<b>HEX-5'-TTCCGCTGC-ZEN-CCTGAGGCTCTC-3'-IABkFQ</b>

<sup>a</sup> Reporter dyes (FAM, HEX) and quenchers (ZEN and IABkFQ) elements are indicated in bold and italics.

<sup>b</sup> The nucleotide sequence of the primers and probes were selected from the conserved region in the 3'UTR region of the dengue virus genome, based on the alignment of 300 nucleotide sequences of the four dengue serotypes deposited in Genbank (Gong et al., 2013, Methods Mol Biol, Chapter 16).

The culture medium consisted of minimal essential medium supplemented with 2% of heat-inactivated fetal calf serum, 0.04% gentamycin (50mg/mL) and 2mM of L-glutamine. Vero cells, obtained from ECACC, were suspended in culture medium and 75 $\mu$ L/well was added in 96-well plates (10000 cells/well), which already contain the antiviral compounds. Typically, these plates contain a 5-fold serial dilution of 9 dilution steps of the test compound at 200 times the final concentration in 100% DMSO (500nL; final concentration range: 25 $\mu$ M – 0.000064 $\mu$ M or 2.5 $\mu$ M – 0.000064 $\mu$ M for the most active compounds). In addition, each plate contains wells which are assigned as virus controls (containing cells and virus in the absence of compound) and cell controls (containing cells in the absence of virus and compound). Once the cells were

added in the plates, the plates were incubated in a fully humidified incubator (37°C, 5% CO<sub>2</sub>) until the next day. Dengue viruses serotype-1, 2, 3 and 4 were diluted in order to obtain a Cp of ~22-24 in the assay. Therefore, 25µL of virus suspension was added to all the wells containing test compound and to the wells assigned as virus control. In parallel, 25µL of culture medium was added to the cell controls. Next, the plates were incubated for 3 days in a fully humidified incubator (37°C, 5% CO<sub>2</sub>). After 3 days, the supernatant was removed from the wells and the cells were washed twice with ice-cold PBS (~100µL). The cell pellets within the 96-well plates were stored at -80°C for at least 1 day. Next, RNA was extracted using the Cells-to-CT™ lysis kit, according to the manufacturer's guideline (Life Technologies). The cell lysates can be stored at -80°C or immediately used in the reverse transcription step.

In preparation of the reverse transcription step, mix A (table 3A) was prepared and 7.57µL/well was dispensed in a 96-well plate. After addition of 5µL of the cell lysates, a five minute denaturation step at 75°C was performed (table 3B). Afterwards, 7.43µL of mix B was added (table 3C) and the reverse transcription step was initiated (table 3D) to generate cDNA.

Finally, a RT-qPCR mix was prepared, mix C (table 4A), and 22.02 µL/well was dispensed in 96-well LightCycler qPCR plates to which 3µL of cDNA was added and the qPCR was performed according to the conditions in table 4B on a LightCycler 480.

Using the LightCycler software and an in-house LIMS system, dose response curves for each compound were calculated and the half maximal effective concentration (EC<sub>50</sub>) and the half maximal cytotoxic concentration (CC<sub>50</sub>) were determined (Tables 5-8).

Table 3: cDNA synthesis using Mix A, denaturation, Mix B and reverse transcription.

**A**

Mix A					
Plates	8				
Samples	828		Reaction Vol. (µl)		20
Mix Item	Concentration			Volume for (µl)	
	Unit	Stock	Final	1 sample	x samples
Milli-Q H <sub>2</sub> O				7.27	6019.56
R3utr425	µM	20	0.27	0.15	124.20
Ractin876	µM	20	0.27	0.15	124.20
Volume mix/well (µl)				7.57	
Cell lysates				5.00	

**B Denaturation step:**

Step	Temp	Time
Denaturation	75°C	5'
Hold	4°C	hold

**C Mix B**

Samples	864				
Mix Item	Concentration			Volume for (µl)	
	Unit	Stock	Final	1 sample	x samples
Expand HIFI buffer 2	X	10.00	1.00	2.00	1728.0
MgCl <sub>2</sub>	mM	25.00	3.50	2.80	2419.2
dNTPs	mM	10.00	1.00	2.00	1728.0
Rnase inhibitor	U/µl	40.00	1.00	0.50	432.0
Expand RT	U/µl	50.00	0.33	0.13	112.3
Total Volume Mix (µl)				7.43	

**D Protocol cDNA synthesis**

Step	Temp	Time
Rev transc	42°C	30'
Denaturation	99°C	5'
Hold	4°C	hold



Table 4: qPCR mix and protocol.

**A** **Mix C**

Samples	833			Reaction Vol. ( $\mu$ l)	25
Mix Item	Concentration			Volume for ( $\mu$ l)	
	Unit	Stock	Final	1 sample	x samples
H <sub>2</sub> O PCR grade Roche				7.74	6447.42
Roche 2xMM mix	X	2	1	12.50	10412.50
F3utr258	$\mu$ M	20	0.3	0.38	316.54
R3utr425	$\mu$ M	20	0.3	0.38	316.54
P3utr343	$\mu$ M	20	0.1	0.13	108.29
Factin743	$\mu$ M	20	0.3	0.38	316.54
Ractin876	$\mu$ M	20	0.3	0.38	316.54
Pactin773	$\mu$ M	20	0.1	0.13	108.29
<b>Volume Mix / Tube (<math>\mu</math>l)</b>				<b>22.02</b>	
<b>cDNA</b>				<b>3.00</b>	

**B** **Protocol qPCR3**

Step	Temp	Time	Ramp rate
preincub/denat	95°C	10 min	4.4
Denaturation	95°C	10 sec	4.4
annealing	58°C	1 min	2.2
Elongation	72°C	1 sec	4.4
Cooling	40°C	10 sec	1.5

40 cycles

Table 5: EC<sub>50</sub>, CC<sub>50</sub>, and SI for the compounds against serotype 1 in the RT-qPCR assays

compound#	RT-qPCR serotype 1 TC974#666					
	EC <sub>50</sub> ( $\mu$ M)	N	CC <sub>50</sub> ( $\mu$ M)	N	SI	N
1C	0.00023	3	>2.5	3	>11000	3
1D	0.00027	3	>2.5	3	>11400	3
2A	0.00057	3	>2.5	3	>7920	3
4C	0.000066	4	>1.0	4	>61000	4
4D	0.00023	4	>1.0	4	>7140	4
5A	0.00058	3	>1.0	3	>1930	3

compound#	RT-qPCR serotype 1 TC974#666					
	EC <sub>50</sub> ( $\mu$ M)	N	CC <sub>50</sub> ( $\mu$ M)	N	SI	N
6AB	0.000022	3	>2.5	3	>133413	3
6BB	0.00013	3	>2.5	2	>24100	2
7B	0.00015	3	>2.5	3	>23200	3
8B	0.000032	3	>1.0	3	>38900	3
9B	0.00081	3	>1.0	3	>2080	3
10B	0.00027	3	>2.5	3	>18700	3
11B	0.00020	4	>2.5	4	>11800	4
12B	0.00047	3	>2.5	3	>8660	3
13B	0.00019	3	>2.5	3	>10400	3
14A	0.00026	3	>1.0	3	>6140	3
15B	0.00024	3	>1.0	2	>6280	2
17C	0.00019	3	>1.0	3	>8230	3
17D	0.00021	3	>1.0	3	>15400	3
18B	0.00055	3	>1.0	3	>2220	3
19AB	0.000021	3	>1.0	3	>56300	3
19BB	0.000091	3	>1.0	3	>13300	3
20C	0.00030	4	>1.0	4	>4540	4
20D	0.00089	4	>1.0	4	>1820	4
21B	0.0010	3	>2.5	3	>1950	3
22AB	0.000091	3	>1.0	3	>15700	3
22BB	0.0015	3	>2.5	1	>1740	1
23B	0.000092	5	>1.0	5	>18200	5
24B	0.0022	4	>1.0	4	>898	4
25B	0.0013	4	>1.0	4	>1210	4
27B	0.000013	4	>1.0	4	>114234	4
28AB	0.00041	4	>1.0	4	>4260	4
28BB	0.00011	4	>1.0	4	>29800	4
29AB	0.00023	4	>1.0	4	>5680	4
29BB	0.000048	4	>1.0	4	>30400	4
30A	0.000094	5	>1.0	5	>54900	5
31A	0.00019	3	>1.0	3	>6090	3
32B	0.00011	4	>1.0	4	>10300	4
33C	0.00097	4	>1.0	4	>3500	4

compound#	RT-qPCR serotype 1 TC974#666					
	EC <sub>50</sub> ( $\mu$ M)	N	CC <sub>50</sub> ( $\mu$ M)	N	SI	N
33D	0.00048	4	>1.0	4	>7130	4

N= the number of independent experiments in which the compounds were tested.

Table 6: EC<sub>50</sub>, CC<sub>50</sub>, and SI for the compounds against serotype 2 in the RT-qPCR assays

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compound#	RT-qPCR serotype 2 16681					
	EC <sub>50</sub> ( $\mu$ M)	N	CC <sub>50</sub> ( $\mu$ M)	N	SI	N
1C	0.00018	3	>2.5	3	>15300	3
1D	0.00023	3	>2.5	3	>9200	3
2A	0.00048	3	>2.5	3	>6500	3
4C	0.000060	4	>1.0	4	>51900	4
4D	0.00013	4	>1.0	4	>15600	4
5A	0.00042	3	>1.0	3	>3220	3
6AB	0.000017	3	>2.5	3	>187753	3
6BB	0.00012	3	>2.5	3	>23700	3
7B	0.00012	3	>2.5	3	>30600	3
8B	0.000025	3	>1.0	3	>54100	3
9B	0.00050	3	>1.0	3	>2680	3
10B	0.00011	3	>2.5	3	>27400	3
11B	0.00010	3	>2.5	3	>22400	3
12B	0.00053	3	>2.5	3	>8920	3
13B	0.00012	3	>2.5	3	>23900	3
14A	0.00020	3	>1.0	3	>5890	3
15B	0.00023	4	>1.0	3	>4310	3
17C	0.00011	3	>1.0	3	>13700	3
17D	0.00010	3	>1.0	3	>24100	3
18B	0.00034	4	>1.0	3	>4590	3
19AB	0.000014	3	>1.0	3	>92300	3
19BB	0.000078	3	>1.0	3	>14100	3
20C	0.000071	4	>1.0	4	>19200	4
20D	0.00019	4	>1.0	4	>7660	4

compound#	RT-qPCR serotype 2 16681					
	EC <sub>50</sub> ( $\mu$ M)	N	CC <sub>50</sub> ( $\mu$ M)	N	SI	N
21B	0.00016	3	>2.5	3	>12700	3
22AB	0.000029	4	>1.0	3	>46400	3
22BB	0.00033	3	>2.5	2	>9450	2
23B	0.000034	5	>1.0	4	>51700	4
24B	0.00026	4	>1.0	4	>11300	4
25B	0.00027	4	>1.0	3	>6080	3
27B	0.000014	4	>1.0	4	>92800	4
28AB	0.00031	4	>1.0	4	>5530	4
28BB	0.00010	4	>1.0	4	>19900	4
29AB	0.00025	3	>1.0	3	>5180	3
29BB	0.000025	4	>1.0	4	>60200	4
30A	0.000076	4	>1.0	4	>65700	4
31A	0.00011	3	>1.0	3	>11600	3
32B	0.000033	4	>1.0	3	>35800	3
33C	0.0010	4	>1.0	4	>4630	4
33D	0.00066	4	>1.0	4	>6620	4

N= the number of independent experiments in which the compounds were tested.

Table 7: EC<sub>50</sub>, CC<sub>50</sub>, and SI for the compounds against serotype 3 in the RT-qPCR assays

5

compound#	RT-qPCR serotype 3 H87					
	EC <sub>50</sub> ( $\mu$ M)	N	CC <sub>50</sub> ( $\mu$ M)	N	SI	N
1C	0.0024	4	>2.5	4	>1300	4
1D	0.0034	4	>2.5	4	>949	4
2A	0.0061	4	>2.5	4	>390	4
4C	0.00077	4	>1.0	3	>1660	3
4D	0.0023	4	>1.0	4	>727	4
5A	0.0081	3	>1.0	3	>170	3
6AB	0.00013	3	>2.5	3	>15300	3
6BB	0.0016	3	>2.5	3	>1320	3
7B	0.0018	3	>2.5	3	>1810	3
8B	0.00016	3	>1.0	3	>7020	3

compound#	RT-qPCR serotype 3 H87					
	EC <sub>50</sub> ( $\mu$ M)	N	CC <sub>50</sub> ( $\mu$ M)	N	SI	N
9B	0.0080	3	>1.0	3	>203	3
10B	0.0029	3	>2.5	3	>1370	3
11B	0.0018	3	>2.5	3	>1650	3
12B	0.0047	4	>2.5	4	>401	4
13B	0.0019	4	>2.5	4	>1350	4
14A	0.0028	3	>1.0	3	>584	3
15B	0.0028	3	>1.0	2	>525	2
17C	0.0036	3	>1.0	3	>401	3
17D	0.0027	3	>1.0	3	>541	3
18B	0.0043	3	>1.0	3	>281	3
19AB	0.00014	3	>1.0	3	>8790	3
19BB	0.00085	5	>1.0	5	>1910	5
20C	0.0034	4	>1.0	3	>249	3
20D	0.0089	4	>1.0	4	>178	4
21B	0.0065	3	>2.5	3	>357	3
22AB	0.00049	3	>1.0	3	>4430	3
22BB	0.0090	3	>2.5	3	>245	3
23B	0.00033	5	>1.0	5	>6770	5
24B	0.014	5	>1.0	5	>123	5
25B	0.0063	5	>1.0	5	>190	5
27B	0.000091	4	>1.0	4	>22600	4
28AB	0.0053	3	>1.0	3	>277	3
28BB	0.0012	3	>1.0	3	>1680	3
29AB	0.0046	4	>1.0	4	>264	4
29BB	0.00039	3	>1.0	3	>3050	3
30A	0.0019	3	>1.0	3	>840	3
31A	0.0015	4	>1.0	4	>791	4
32B	0.00057	3	>1.0	3	>2870	3
33C	0.011	4	>1.0	4	>185	4
33D	0.0023	4	>1.0	4	>732	4

N= the number of independent experiments in which the compounds were tested.

Table 8:  $EC_{50}$ ,  $CC_{50}$ , and SI for the compounds against serotype 4 in the RT-qPCR assays

compound#	RT-qPCR serotype 4 H241					
	$EC_{50}$ ( $\mu$ M)	N	$CC_{50}$ ( $\mu$ M)	N	SI	N
1C	0.016	3	8.7	3	427	3
1D	0.024	3	7.3	3	280	3
2A	0.027	3	2.2	3	125	3
4C	0.015	3	>1.0	2	>73	2
4D	0.026	3	3.2	3	73	3
5A	0.058	3	8.0	3	206	3
6AB	0.0029	3	>1.0	2	>425	2
6BB	0.020	3	5.4	3	205	3
7B	0.013	3	8.8	2	582	2
8B	0.0013	3	8.7	2	8240	2
9B	0.036	3	6.7	3	372	3
10B	0.022	3	>1.0	2	>57	2
11B	0.017	3	5.7	3	273	3
12B	0.039	3	9.2	2	318	2
13B	0.015	3	3.7	2	323	2
14A	0.015	3	8.9	3	510	3
15B	0.035	3	10.0	3	456	3
17C	0.016	3	1.7	2	95	2
17D	0.015	3	2.9	3	168	3
18B	0.033	3	3.0	2	148	2
19AB	0.00069	3	6.4	3	8200	3
19BB	0.0068	3	5.2	3	905	3
20C	0.020	3	>1.0	2	>60	2
20D	0.055	3	>1.0	1	>21	1
21B	0.048	3	9.0	3	115	3
22AB	0.0033	3	9.1	2	2890	2
22BB	0.071	3	8.2	3	126	3
23B	0.0027	3	6.0	2	2230	2
24B	0.066	3	7.8	3	115	3
25B	0.055	3	9.9	3	202	3
27B	0.00081	3	8.3	3	9330	3
28AB	0.069	3	9.0	3	158	3
28BB	0.018	3	>1.0	2	>58	2
29AB	0.035	3	8.0	2	118	2
29BB	0.0028	3	8.3	3	2790	3

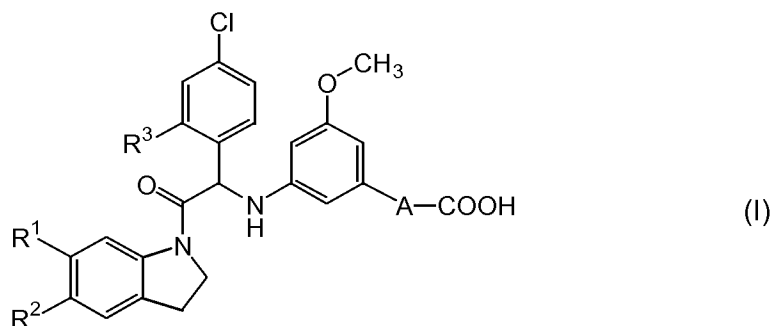
compound#	RT-qPCR serotype 4 H241					
	EC <sub>50</sub> ( $\mu$ M)	N	CC <sub>50</sub> ( $\mu$ M)	N	SI	N
30A	0.018	3	7.3	3	399	3
31A	0.017	4	7.3	4	445	4
32B	0.010	3	4.3	3	295	3
33C	0.34	3	4.2	3	9.8	3
33D	0.022	3	5.4	3	256	3

N= the number of independent experiments in which the compounds were tested.

### Claims

1. A compound of formula (I), including any stereochemically isomeric form thereof,

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wherein

R<sup>1</sup> is trifluoromethyl, trifluoromethoxy, or chloro;

10 R<sup>2</sup> is hydrogen, fluoro, or methoxy;

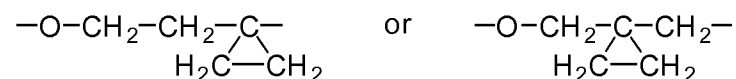
R<sup>3</sup> is hydrogen, or methoxy;

A represents  $-(CH_2)_n-$  wherein n is 3 or 4;

$-O-(CH_2)_n-$  wherein n is 2 or 4;

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$-O-(CH_2)_n-$  wherein n is 3 and one or two CH<sub>2</sub> are substituted with one or two CH<sub>3</sub>;



$-CH_2-O-(CH_2)_n-$  wherein n is 2; or

$-X-Y-$  wherein X is a  $-O-$ ,  $-OCH_2-$ , or  $-NH-$ ; and

20

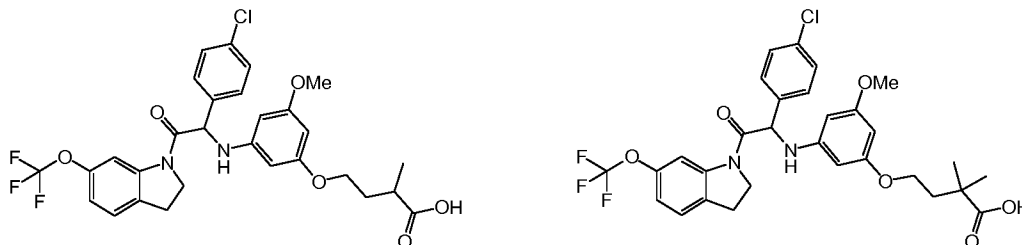
Y is C<sub>3-4</sub>cycloalkyl optionally substituted with fluoro, or

Y is bicyclo[1.1.1]pentanyl;

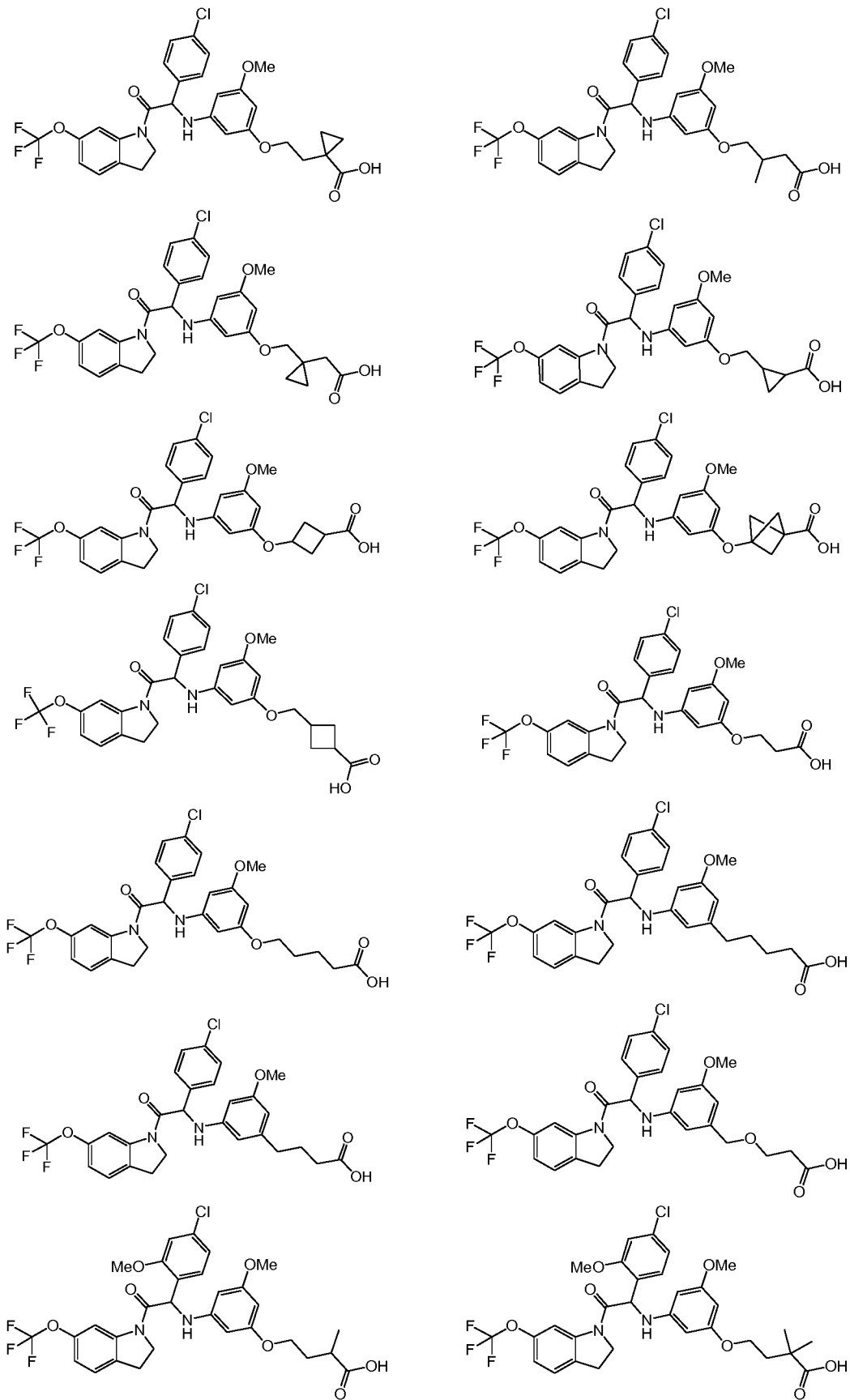
or a pharmaceutically acceptable salt, solvate or polymorph thereof.

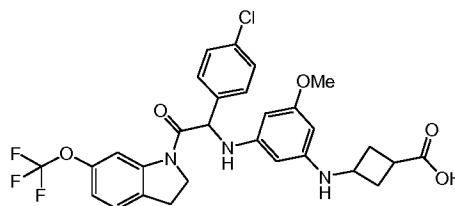
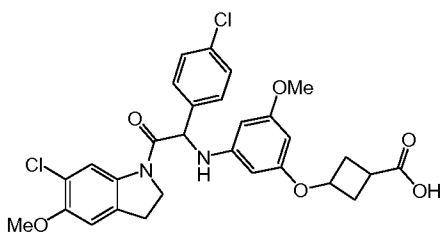
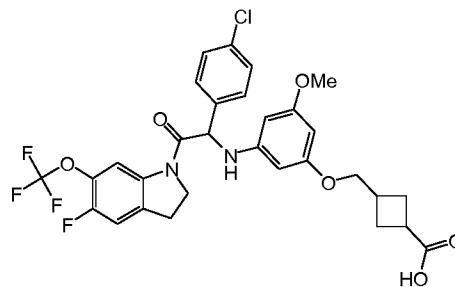
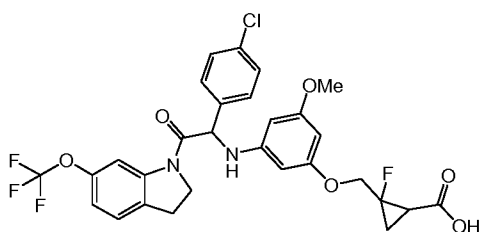
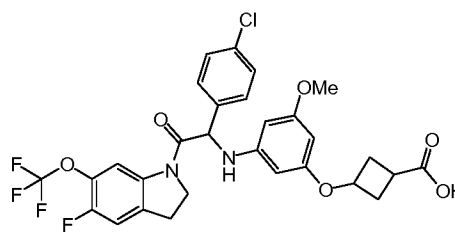
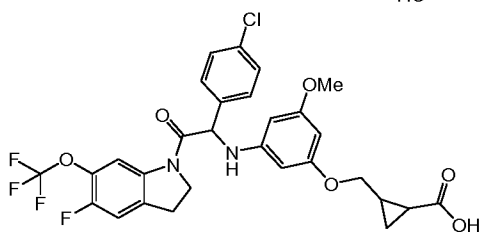
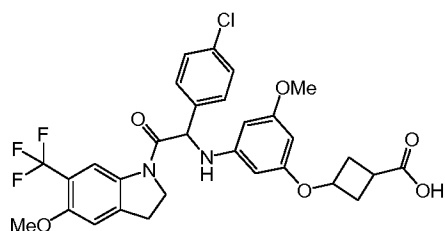
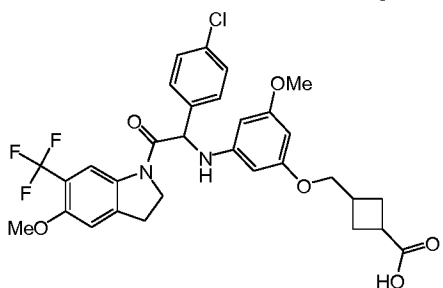
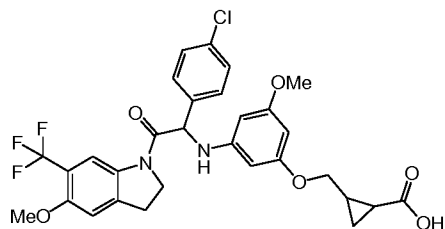
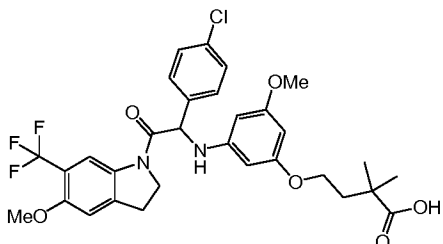
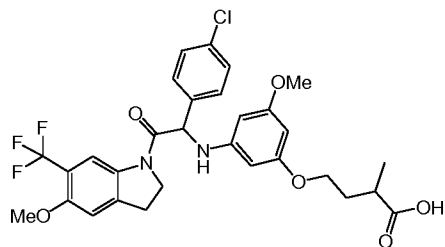
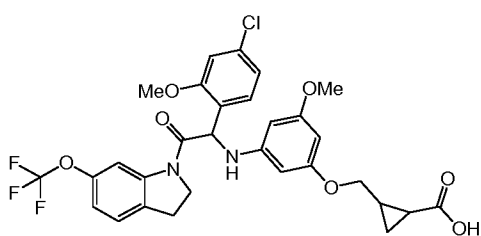
2. The compound according to claim 1 wherein said compound is selected from

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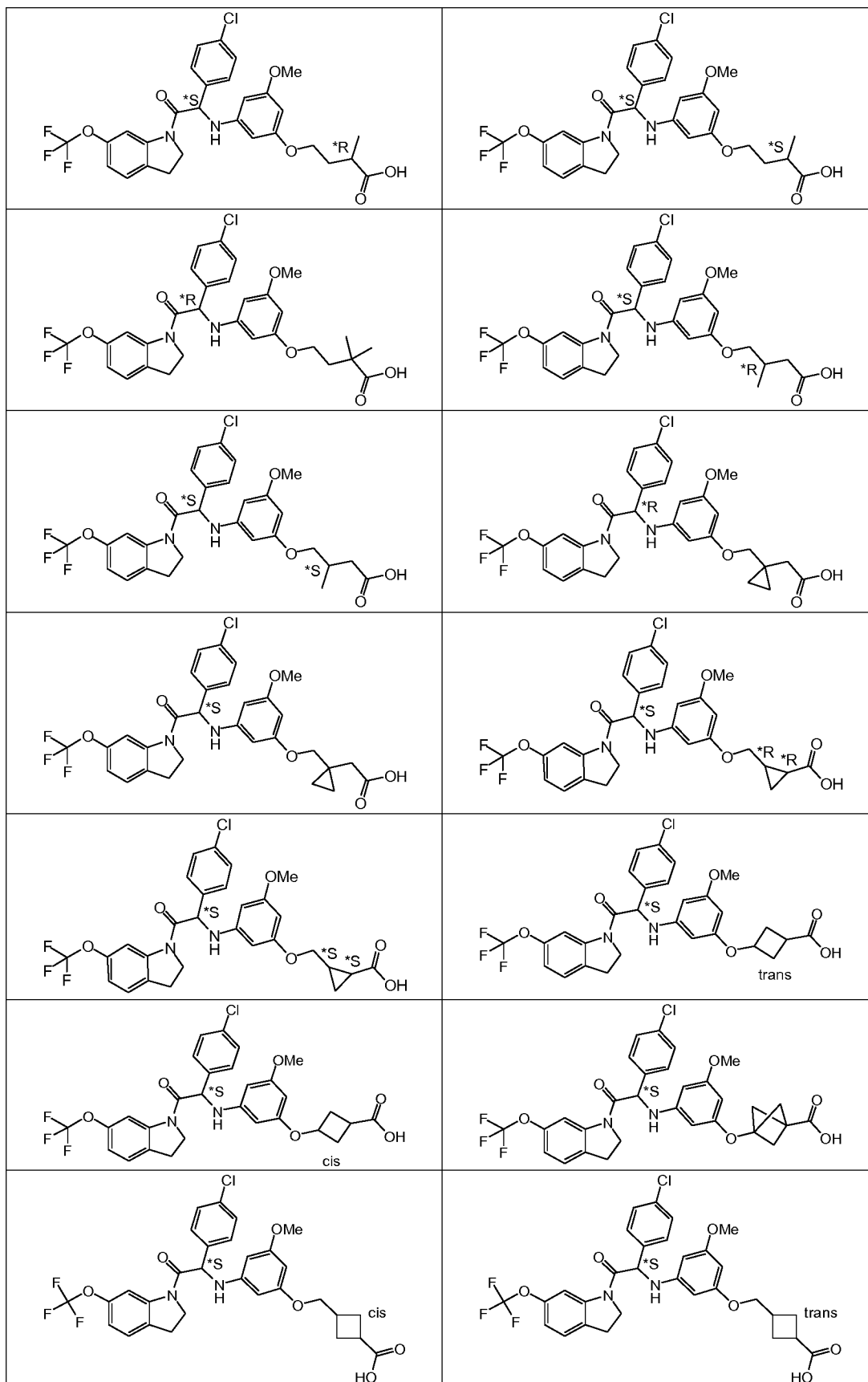


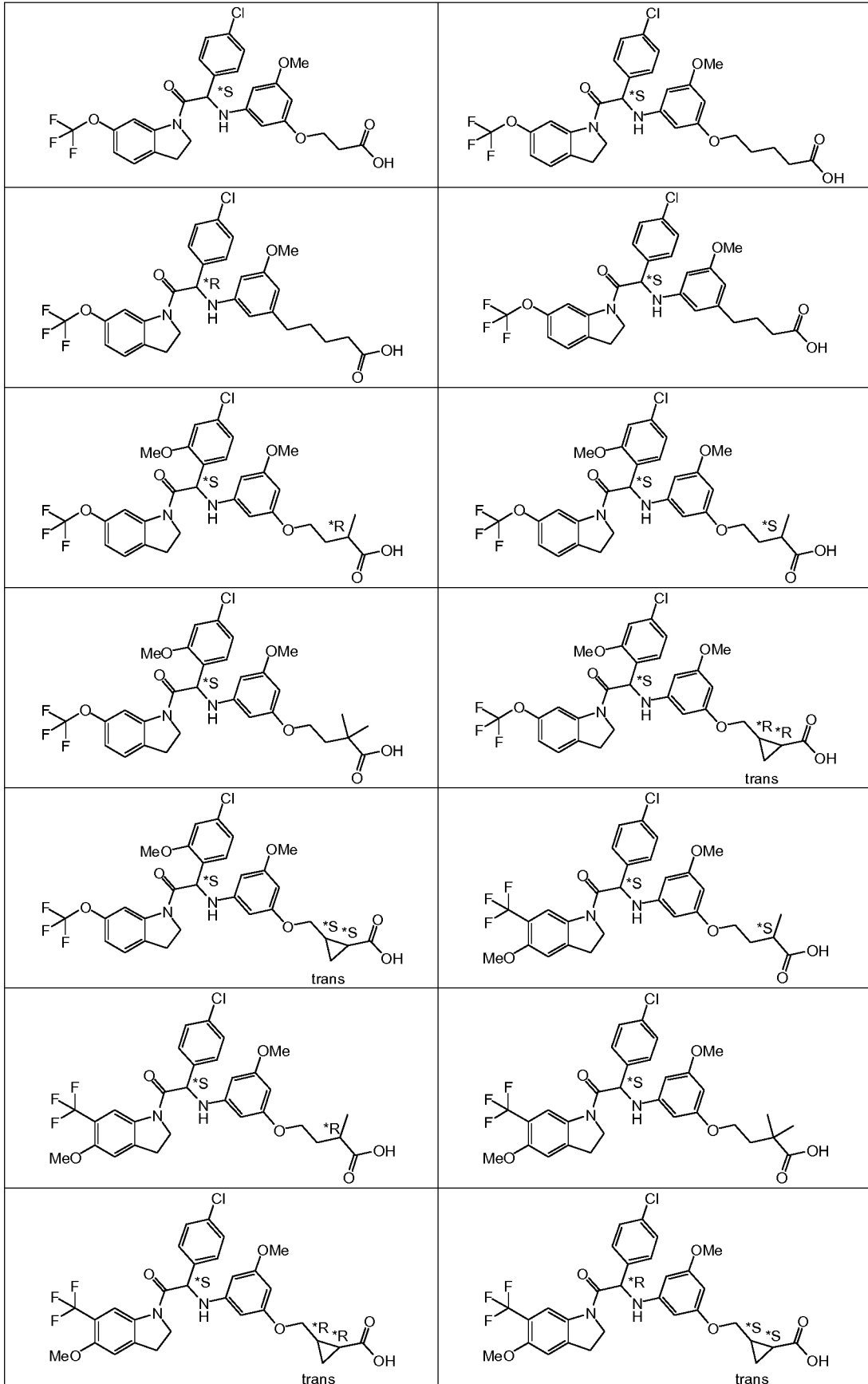


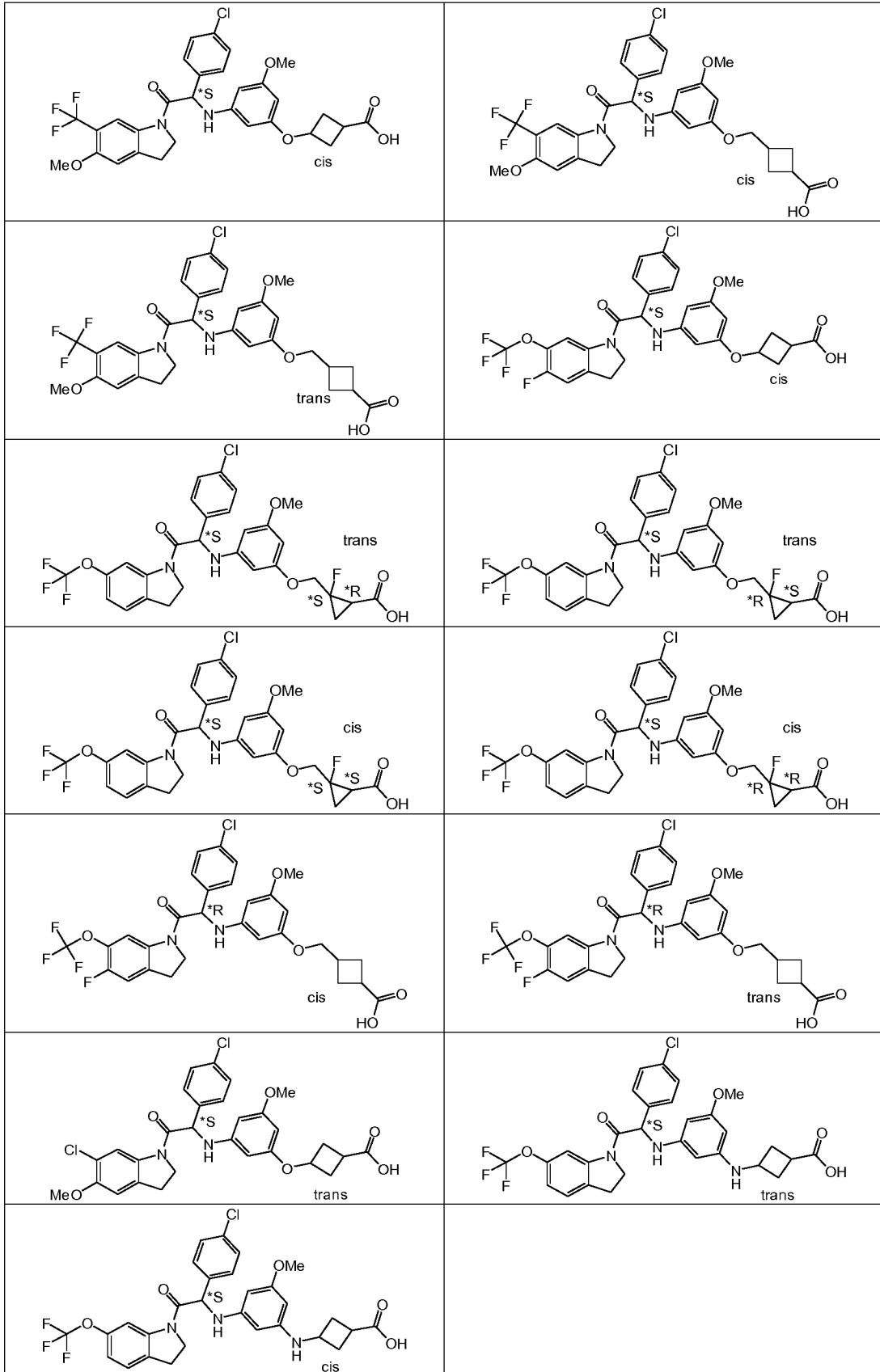


3. The compound according to claim 1 wherein said compound has the (+) specific rotation measured in DMF as solvent.

4. The compound according to claim 3 wherein said compound is selected from :







5. The compound as claimed in claim 1 wherein wherein R<sup>1</sup> is trifluoromethoxy, R<sup>2</sup> is hydrogen, and R<sup>3</sup> is hydrogen.
6. The compound as claimed in claim 1 wherein A represents -(CH<sub>2</sub>)<sub>n</sub>- wherein n is 3 or 4.
7. The compound as claimed in claim 1 wherein A represents -O-(CH<sub>2</sub>)<sub>n</sub>- wherein n is 2 or 4.
8. The compound as claimed in claim 1 wherein A represents -O-(CH<sub>2</sub>)<sub>n</sub>- wherein n is 3 and one or two CH<sub>2</sub> are substituted with one or two CH<sub>3</sub>; or A represents 
$$\begin{array}{c} \text{---O---CH}_2\text{---CH}_2\text{---C---} \\ | \quad \quad | \\ \text{H}_2\text{C} \quad \text{---CH}_2 \end{array} \quad \text{or} \quad \begin{array}{c} \text{---O---CH}_2\text{---C---CH}_2\text{---} \\ | \quad \quad | \\ \text{H}_2\text{C} \quad \text{---CH}_2 \end{array} .$$
9. The compound as claimed in claim 1 wherein A represents -X-Y- wherein X is a -O-, -OCH<sub>2</sub>-, or -NH-; and Y is C<sub>3-4</sub>cycloalkyl optionally substituted with fluoro.
10. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 together with one or more pharmaceutically acceptable excipients, diluents or carriers.
11. The pharmaceutical composition according to claim 10 which comprises a second or further active ingredient.
12. The pharmaceutical composition according to claim 11 wherein the second or further active ingredient is an antiviral agent.
13. A compound of formula (I) according to any one of claims 1 to 9 for use as a medicine.
14. A compound of formula (I) according to any one of claims 1 to 9 for use in the treatment of Dengue infection and for the prevention or treatment of disease associated with Dengue infection.
15. A compound of formula (I) for use according to claim 14 wherein the Dengue infection is infection by viruses of the DENV-1, DENV-2, DENV-3 or DENV-4 strain.

**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/EP2018/063028

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. C07D209/08 A61K31/403 A61P31/12  
 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 A61K A61P

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, EMBASE, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/045516 A1 (UNIV LEUVEN KATH [BE]) 4 April 2013 (2013-04-04) cited in the application page 113; claims 1, 13, 15, 17; compounds CPD-056	1-15
X	WO 2016/050841 A1 (JANSSEN PHARMACEUTICALS INC [US]; UNIV LEUVEN KATH [BE]) 7 April 2016 (2016-04-07) claims 1, 2, 3, 6	1-15
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Further documents are listed in the continuation of Box C.       See patent family annex.

\* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&amp;" document member of the same patent family</p>
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Date of the actual completion of the international search <b>14 August 2018</b>	Date of mailing of the international search report <b>21/08/2018</b>
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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 <b>Moriggi, J</b>
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2018/063028

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	PRASAD L. POLAVARAPU ET AL: "Intrinsic rotation and molecular structure", CHIRALITY., vol. 15, no. S1, 1 January 2003 (2003-01-01), pages S143-S149, XP055490973, US ISSN: 0899-0042, DOI: 10.1002/chir.10255 figure 1; table C	3
A,P	----- WO 2017/167951 A1 (JANSSEN PHARMACEUTICALS INC [US]; UNIV LEUVEN KATH [BE]) 5 October 2017 (2017-10-05) claims 1, 2, 5, 8	1-15
A,P	----- WO 2017/167953 A1 (JANSSEN PHARMACEUTICALS INC [US]; UNIV LEUVEN KATH [BE]) 5 October 2017 (2017-10-05) claims 1, 2, 4, 8 -----	1-15



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2018/063028

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO 2013045516	A1	04-04-2013	AU 2012314498 A1	03-04-2014
			AU 2017221865 A1	21-09-2017
			BR 112014007134 A2	19-12-2017
			CA 2848604 A1	04-04-2013
			CL 2014000732 A1	26-09-2014
			CL 2016001580 A1	13-01-2017
			CN 104024223 A	03-09-2014
			CO 7010824 A2	31-07-2014
			CR 20140147 A	04-08-2014
			EA 201490654 A1	28-11-2014
			EC SP14013315 A	30-06-2014
			EP 2760831 A1	06-08-2014
			JP 6266521 B2	24-01-2018
			JP 2014527978 A	23-10-2014
			JP 2018095646 A	21-06-2018
			KR 20140069209 A	09-06-2014
			NZ 622588 A	27-01-2017
			PE 12802014 A1	03-10-2014
			SG 10201705974P A	30-08-2017
			SG 11201400927W A	28-04-2014
			UA 115537 C2	27-11-2017
US 2014213586 A1	31-07-2014			
WO 2013045516 A1	04-04-2013			
-----				
WO 2016050841	A1	07-04-2016	AU 2015326930 A1	16-03-2017
			BR 112017006299 A2	16-01-2018
			CA 2959573 A1	07-04-2016
			CL 2017000782 A1	03-11-2017
			CN 107001264 A	01-08-2017
			EP 3201176 A1	09-08-2017
			JP 2017531619 A	26-10-2017
			KR 20170063802 A	08-06-2017
			PH 12017500571 A1	30-08-2017
			SG 11201702463Y A	27-04-2017
			TW 201630879 A	01-09-2016
			US 2017298017 A1	19-10-2017
			UY 36340 A	01-04-2016
			WO 2016050841 A1	07-04-2016
			-----	
WO 2017167951	A1	05-10-2017	AR 108046 A1	11-07-2018
			TW 201808898 A	16-03-2018
			UY 37182 A	29-09-2017
			WO 2017167951 A1	05-10-2017
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WO 2017167953	A1	05-10-2017	NONE	
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