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A novel selective PKR inhibitor restores cognitive deficits and neurodegeneration in Alzheimer's disease experimental models

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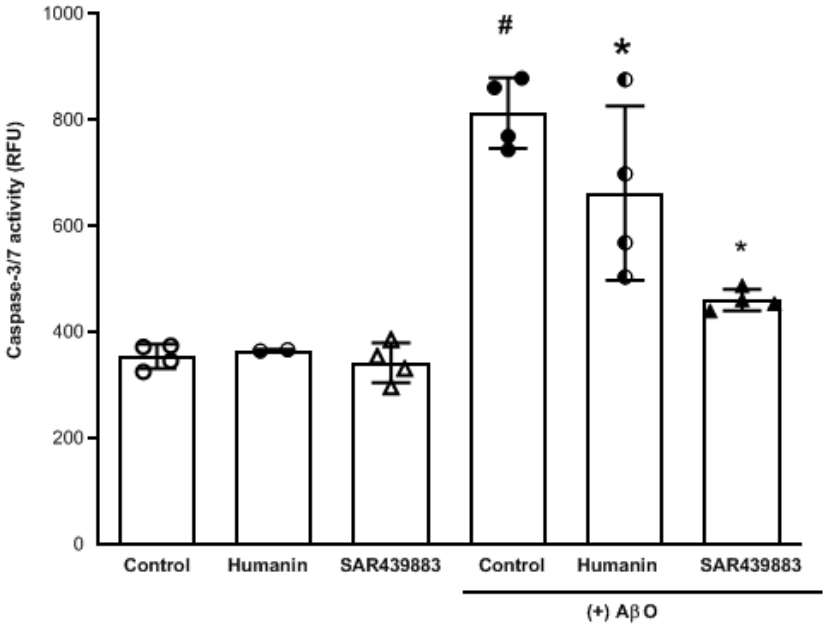
Supplemental Fig. 1

SAR439883 effect on Aβ42 oligomer (AβO)-induced neurotoxicity in vitro.

Effect of SAR439883 (3µM) on cell viability was measured by caspase-3/7 enzymatic activity induced by AβO (5µM) in mouse primary neuronal cultures. Humanin (1µM) was used as reference neuroprotective compound. Data are expressed as means ± S.D. from 4 biological replicates. P values are from Dunnett's test after a one-way ANOVA. # p <0.0001 versus Control; *p <0.0001 versus Control (+) AβO.

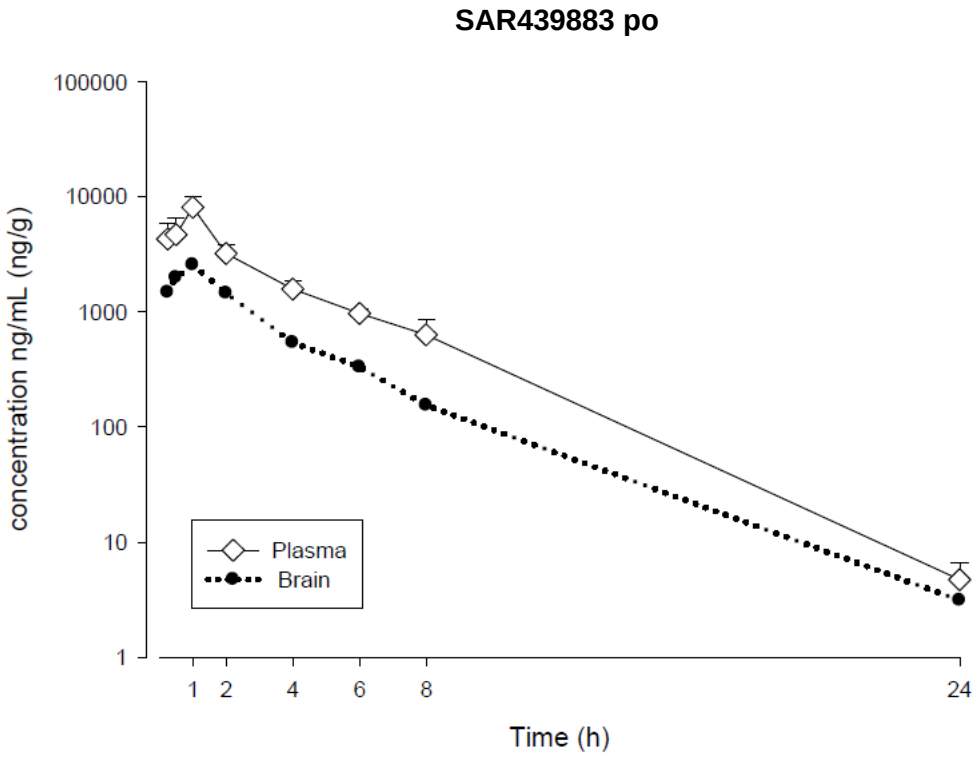

Caspase-3/7 activity (RFU)
1000
800
600
400
200
0
#
*
*
Control
Humanin
SAR439883
Control
Humanin
SAR439883
(+) AβO

Supplemental Fig. 2

Pharmacokinetic profile of SAR439883 in plasma and brain of WT mouse.

Pharmacokinetic parameters were determined following a single intravenous (3 mg/kg) or oral (30 mg/kg) administration of SAR439883 to male C57Bl6 mice (n=3).

Formulations used: iv Glycofurol/PS80/G5 (10%/5%/85%); po MC/Tween (0.6%/0.5%) pH=6.



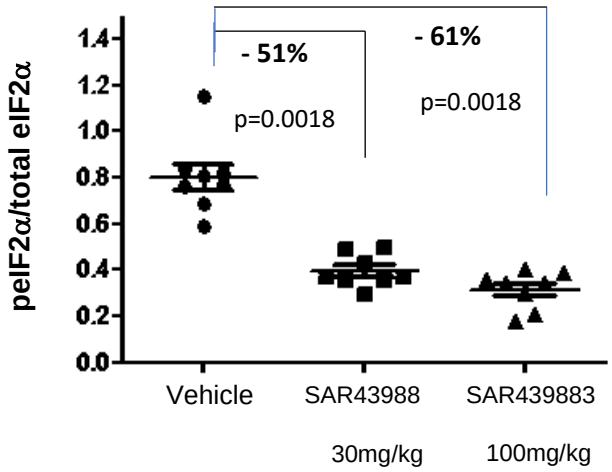
Route	Dose (mg/kg)	Matrix	C_0 or C_{max} (ng/mL or /g)	t_{max} (h)	AUC_{last} (ng.h/mL or /g)	t_{last} (h)	AUC (ng.h/mL or /g)	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2z}$ (h)	Brain/Plasma AUC ratio
i.v.	3	Plasma	2190	-	1560	8	1610	1.86	3.23	1.68	-
p.o.	30	Plasma	8130	1	24600	24	24600	-	-	2.35	-
		Brain	2560	1	8370	24	8380	-	-	2.59	0.340

Supplemental Fig. 3

Effect of SAR439883 on peIF2α levels in hippocampus of C57Bl6 mouse

SAR439883 was administered at 30 (■) and 100 (▲) mg/kg by gavage to C57Bl6 mice and peIF2α levels were measured in the hippocampus by WB and compared to vehicle group (●).

Data are presented as individual data point for each animal sample (n=8 per group). The pons/cerebellum from the same animals were used to evaluate compound exposure (mean values are indicated for each dose in the table below).



Supplemental Fig. 4

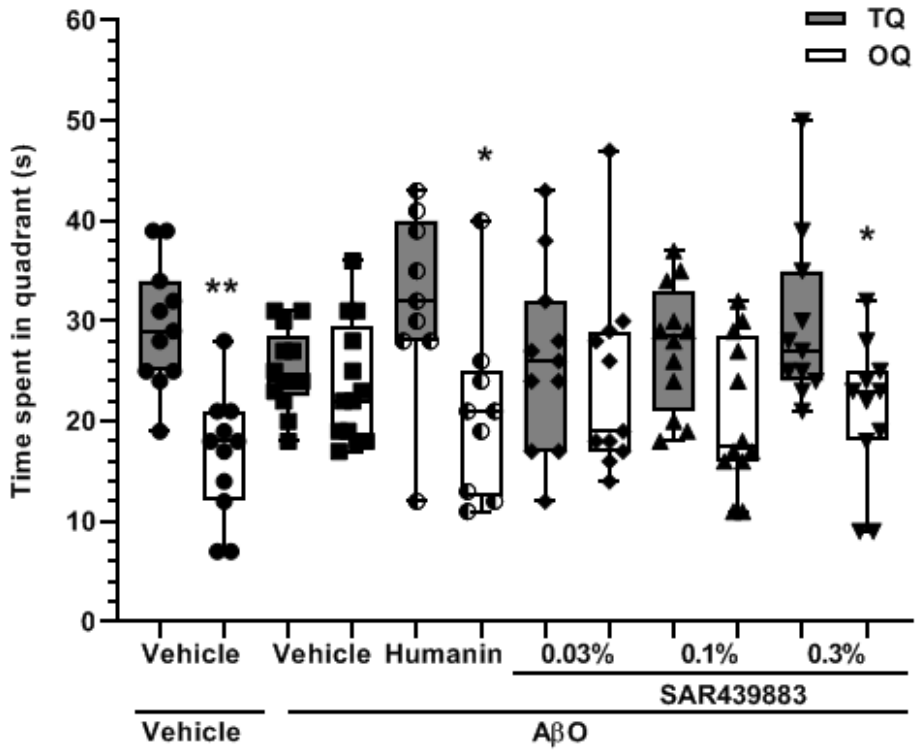
Effect of SAR439883 on memory impairment in AβO i.c.v. mouse (MWM).

SAR439883 was administered at 0.03, 0.1 and 0.3% in diet for 18 days to AβO i.c.v. injected C57B6/J mice.

Probe test was performed 72h after the last training day: time spent in the Target Quadrant (TQ) versus Opposite Quadrant (OQ). Individual data and boxplot by group present Medians, [Q1; Q3], maximum and minimum values per group. p-value are from a post hoc Student test after a repeated two-way ANOVA, * p=0.0378; ** p=0.0220;

*** p=0.0153 TQ versus OQ in the same treatment group,

All analysis steps and the sample size per group have been decided before we performed the experiment. Sample size was unequal for one group (N=9) at the beginning of the experiment N=13 for the rest.



Supplemental Fig. 5

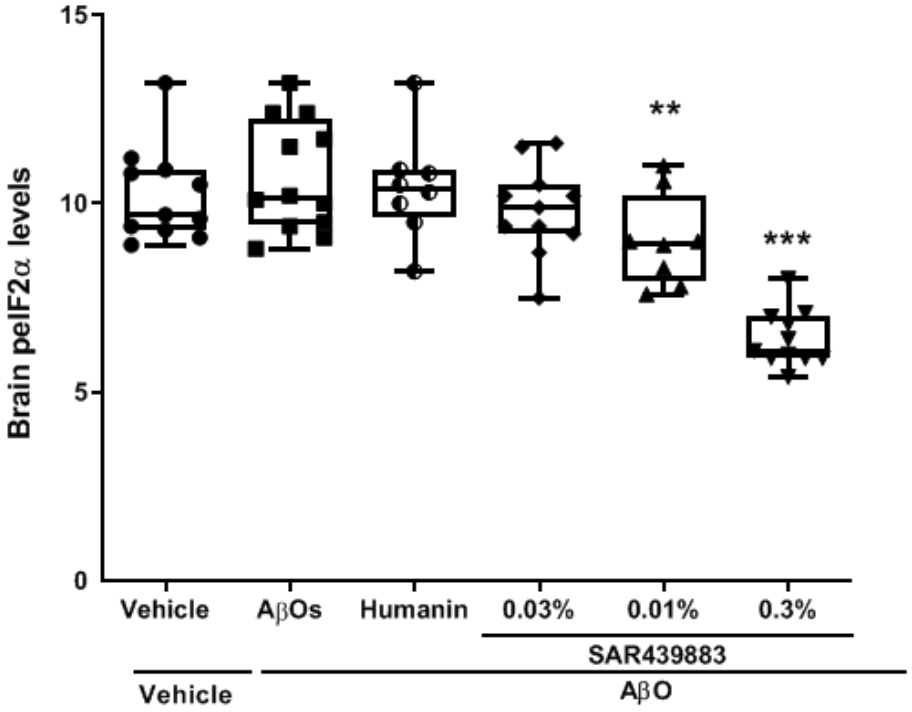
Effect of SAR439883 18-day diet treatment on peIF2α levels in AβO i.c.v. injection model

SAR439883 was administered at 0.03, 0.1 and 0.3% in diet for 18 days to AβO- i.c.v. -injected mice. At the end of the treatment period, peIF2α levels were measured in the individual brain homogenates by WB.

Data are presented as individual data point for each animal sample and as means ± S.D. from 8 to 12 individual brain homogenates.

P values are from Dunnett's test versus AβO after a one-way ANOVA

**p<0.01 ***p<0.0001



Supplemental Table 1

SAR439883 selectivity profile using KiNativ™ technology (ActivX Biosciences, San Diego, CA) in in vitro cells or in vivo 2h after oral treatment in ApoE4 mice.

a.Data are from lysates of PC3 cell treated at 6 concentrations for IC_{50} determination

b.Data are mean ± S.E.M. from 5 pooled brain homogenates (3 brains per pool) from ApoE4 mice

* NT: not tested

	SAR439883	
	PC3 cells [a]	**Brain tissue 30 mg/kg [b]**
Kinase	**IC_{50} (µM)**	**% inhibition**
PKR	**0.073**	**74.1** ± 1.8
GCN2	**8-12**	**8.8** ± 5.2
PERK	**8.8**	NT*
CDC2	NT*	**28.8** ± 4.8
SRPK1, SRPK2	**>30**	**28.1** ± 4.3
RSK2	**>30**	**26.4** ± 4.3
RSKL1	NT*	**22.4** ± 4.7
ULK3	NT*	**20.1** ± 3.3
other 111 kinases	**>30**	
other 194 kinases		**<20**

Supplemental Table 2

Kinetics and associated pharmacodynamic response to SAR439883 treatment in diet in WT mice.

Data are means +/- S.D. from 10 individual animals for exposure data or means from 8 to 10 animals expressed as % of inhibition vs. vehicle group for peIF2α data.

SAR439883 dose	**readout**	**7 PM**	**8 PM**	**2 AM**	**8 AM**	**2 PM**
0.1%	Plasma exposure (µM)	3.7 ± 0.8	6.1 ± 1.1	8.4 ± 2.0	5.8 ± 1.4	2.8 ± 1.1
	Brain exposure (µM)	**0.8 ± 0.2**	**1.4 ± 0.3**	**1.6 ± 0.3**	**1.2 ± 0.2**	**0.6 ± 0.2**
	Brain peIF2α/eIF2α decrease (%vehicle)	**21**	**24**	**27**	**25**	**10**
0.3%	Plasma exposure (µM)	6.7 ± 2.9	10 ± 3.6	16.4 ± 3.8	8.6 ± 2.2	4.3 ± 1.4
	Brain exposure (µM)	**1.4 ± 0.5**	**2.1 ± 0.9**	**3.2 ± 0.6**	**1.7 ± 0.4**	**0.8 ± 0.3**
	Brain peIF2α/eIF2α decrease (% vehicle)	**47**	**40**	**53**	**27**	**22**

Supplemental Table 3

SAR439883 effect on Aβ42 oligomers (AβO)-induced neurotoxicity in vitro: Effect on peIF2α levels.

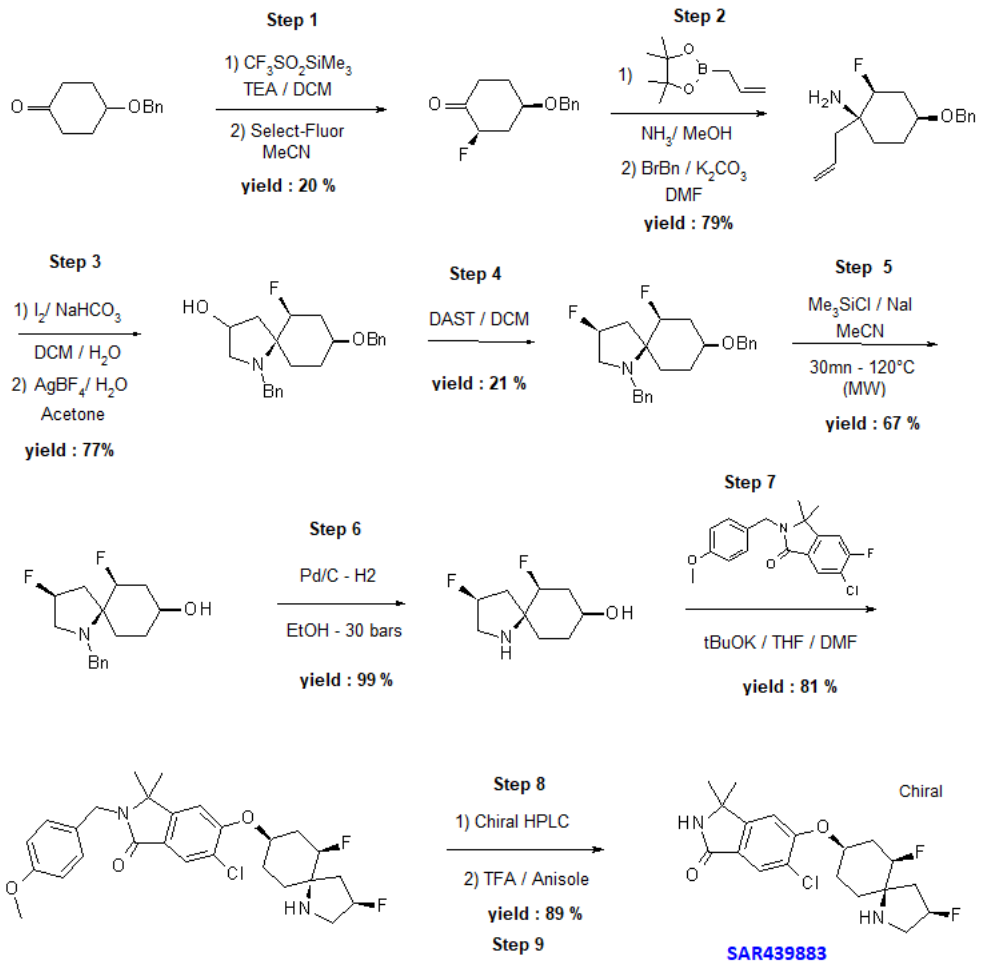
Data are means from pooled samples from one exploratory study.

Cell treatment	peIF2α levels (% control)
AβO	177
AβO + SAR439883 3 µM	97

Supplementary information:

Synthesis of SAR439883 compound

Reagents were purchased from commercial suppliers and were used without purification unless otherwise noted. Normal-phase column chromatography was performed on silica gel using prepacked cartridges. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker 400MHz spectrometer. Chemical shifts for ^{1}H NMR spectra are reported in ppm (d) relative to residue protium in the solvent (DMSO); the multiplicities are presented as follows: s = singlet, d = doublet, t = triplet, m = multiplet, coupling constants *J* in Hertz (Hz), integration. Mass spectra (MS) were obtained on a SQD Waters spectrometer using electrospray ionization (ESI) in positive mode. Calculated (calcd.) mass corresponds to the exact mass. Chemical names were generated using BIOVIA Draw 18.1 (Dassault Systèmes).



Step 1: rac-(2R,4R)-4-benzyloxy-2-fluoro-cyclohexanone

To a mechanically stirred solution of 4-benzyloxycyclohexanone (500 g, 2.45 mol) and triethylamine (997 mL, 7.17 mol, 2.9 equiv.) in dichloromethane (DCM) (7 L) at -5°C under nitrogen was dropwise added a solution of trimethylsilyl trifluoromethanesulfonate (491 mL, 2.78 mol, 1.1 equiv.) in DCM (1.5 L) over 3 hours while maintaining the temperature below 0°C. The mixture was mechanically stirred for 15 minutes at 0°C and then a saturated auqueous $NaHCO_3$ solution (10 L) was added. After stirring for 5 minutes the layers were separated. The aqueous layer was extracted with DCM (1 L). The combined organic layers were washed with brine (2.5 L), dried over sodium sulfate and concentrated under reduced pressure to give the corresponding trimethylsilyl enol ether (816.7 g) as a brown oil. To a solution of the resulting intermediate (816.7 g, 2.45 mol) in acetonitrile (7.5 L) was portionwise added Selectfluor (1101 g, 3.11 mol, 1.3 eq) in 1 hour while maintaining the temperature below 25°C with an ice-bath. The mixture was stirred for 2 hours allowing the temperature to warm up to room temperature. Diethylether (10 L) was added, and the precipitate was filtered through Celite and washed with diethylether (3 L). The filtrate was concentrated under reduced pressure to give 1198 g of a crude mixture of diastereomers as a brown oil. This mixture was separated by column chromatography on silica gel eluting with a gradient of 0.05% to 5% methanol in dichloromethane. The second eluting product was collected and concentrated under reduced pressure then taken into ethyl acetate (220 mL) followed by heptane (880 mL). After stirring for 45 minutes, the product was filtered, washed with heptane (100 mL) and dried under vacuum to give 110 g (20%) of rac-(2R,4R)-4-benzyloxy-2-fluoro-cyclohexanone as a white solid. MS (EI): mass calcd. for $C_{13}H_{15}FO_2$, 222; m/z found, 222 [M+]. ^{1}H NMR (400 MHz, $CDCl_3$): d 7.32-7.43 (m, 5 H), 4.90 (ddd, *J* = 48.0, 12.4, 6.8 Hz, 1 H), 4.62 (s, 2 H), 3.83-3.90 (m, 1 H), 2.80-2.83 (m, 1 H), 2.52-2.54 (m, 1 H), 2.28-2.32 (m, 2 H), 1.94-2.00 (m, 1H), 1.75-1.79 (m, 1 H).

Step 2: rac-(1S,2S,4S)-1-allyl-N-benzyl-4-benzyloxy-2-fluoro-cyclohexanamine

To a solution of rac-(2R,4R)-4-benzyloxy-2-fluoro-cyclohexanone (25 g, 112.48 mmol) in 7N methanolic ammonia solution (170 mL, 1.19 mol, 10 equiv.) was added 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (27 mL, 143 mmol, 1.27 equiv.). The mixture was stirred for

24 hours at room temperature and then concentrated under reduced pressure. To a mixture of the crude product and potassium carbonate (47 g, 340 mmol) in dimethylformamide (DMF, 200 mL) was added benzyl bromide (27 mL, 227 mmol). The mixture was stirred at room temperature for 20 hours then poured onto water (1 L) and extracted with diisopropyl ether (1 L). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of 0 to 10% diisopropyl ether in heptane to give 30.9 g (79%) of rac-(1S,2S,4S)-1-allyl-N-benzyl-4-benzyloxy-2-fluoro-cyclohexanamine as a colorless oil. MS (ESI): mass calcd. for $C_{23}H_{28}FNO$, 353.4; m/z found, 354.3 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6): d 7.21-7.36 (m, 10 H), 5.84-5.94 (m, 1 H), 5.08-5.14 (m, 2 H), 4.40-4.55 (m, 3 H), 3.63-3.74 (m, 2 H), 3.37-3.40 (m, 1 H), 2.33-2.47 (m, 2 H), 1.11-1.76 (m, 7 H).

Step 3: rac-(5S,6S,8S)-1-benzyl-8-benzyloxy-6-fluoro-1-azaspiro[4.5]decan-3-ol

To a vigorously stirred mixture of rac-(1S,2S,4S)-1-allyl-N-benzyl-4-benzyloxy-2-fluoro-cyclohexanamine (30.9 g, 87.4 mmol) in a 5% aqueous solution of sodium bicarbonate (900 mL) and dichloromethane (600 mL) was dropwise added a solution of iodine (31 g, 122.1 mmol, 1.4 equiv.) in dichloromethane (1200 mL) over 45 minutes. The mixture was vigorously stirred overnight. The organic layer was separated, washed with brine (200 mL) and concentrated under reduced pressure to give crude rac-(5S,6S,8S)-1-benzyl-8-benzyloxy-6-fluoro-3-iodo-1-azaspiro[4.5]decane as a deep red oil that was used directly in the next step without further purification. MS (ESI): mass calcd. for $C_{23}H_{27}FINO$, 479.1; m/z found, 480.1 [M+H]+. To a solution of the resulting product (41.91 g) in acetone (730 mL) was added a solution of silver tetrafluoroborate (19 g, 96.6 mmol) in water (90 mL) over 10 minutes. The yellow suspension was stirred for 45 minutes at room temperature. The reaction mixture was then poured onto diluted aqueous Na_2CO_3 solution (700 mL) and extracted with ethyl acetate (500 mL). The whole mixture was filtered on dicalite. The organic layer was separated and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of 0 to 5% methanol in dichloromethane to give 24.7 g (77**%** over 2 steps) of rac-(5S,6S,8S)-1-benzyl-8-

benzyloxy-6-fluoro-1-azaspiro[4.5]decan-3-ol as a deep orange solid. MS (ESI): mass calcd. for $C_{23}H_{28}FNO_2$, 369.2; m/z found, 370.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6): d 7.06-7.38 (m, 10 H), 4.39-4.89 (m, 4H), 4.01-4.09 (m, 2 H),vvvv 3.50-3.60 (m, 2 H), 2.60-2.86 (m, 1 H), 2.26-2.37 (m, 2 H), 1.13-1.61 (m, 6 H).

Step 4: rac-(3S,5S,6S,8S)-1-benzyl-8-benzyloxy-3,6-difluoro-1-azaspiro[4.5]decane

To a solution of rac-(5S,6S,8S)-1-benzyl-8-benzyloxy-6-fluoro-1-azaspiro[4.5]decan-3-ol (18.61 g, 50.37 mmol) in dry dichloromethane (300 mL) at -10°C under a dry argon atmosphere was dropwise added diethylaminosulfur trifluoride DAST (10.4 mL, 78.71 mmol, 1.5 equiv.). The mixture was stirred for 2 hours allowing the temperature to warm up to room temperature then poured onto saturated aqueous $NaHCO_3$ solution (500 mL) and dichloromethane (200 mL). The pH was slowly made basic with careful solid $NaHCO_3$ addition. The layers were separated and the auqeous layer extracted with dichloromethane (200 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of 20 to 100% dichloromethane in heptane to give 3.9 g (21%) of rac-(3S,5S,6S,8S)-1-benzyl-8-benzyloxy-3,6-difluoro-1-azaspiro[4.5]decane. ^{1}H NMR (400 MHz, DMSO-d6): d 7.11-7.41 (m, 10 H), 4.98 (d, *J* = 56.0 Hz, 1 H), 4.79 (d, *J* = 52.0 Hz, 1 H), 4.48 (dd, *J* = 48.0, 12.0 Hz, 2 H), 3.70-4.18 (m, 2 H), 3.60 (s, 1 H), 2.91-3.02 (m, 2H), 2.42-2.47 (m, 2H), 1.88-2.09 (m, 3H), 1.47-1.70 (m, 2H), 1.14-1.18 (m, 1 H).

Step 5: rac-(3S,5S,6S,8S)-1-benzyl-3,6-difluoro-1-azaspiro[4.5]decan-8-ol

To a solution of rac-(3S,5S,6S,8S)-1-benzyl-8-benzyloxy-3,6-difluoro-1-azaspiro[4.5]decane (3.82 g, 10.28 mmol) in acetonitrile (39 mL) equally partitioned in three 30 mL microwave vials (Anton Paar apparatus) was added a suspension from equally partitioned sodium iodide (7.70 g, 51.37 mmol, 5 equiv.) and trimethylsilyl chloride (6.6 mL, 51.64 mmol, 5 equiv.) in acetonitrile (15 mL). The 3 mixture were placed in the microwave apparatus and heated to 120°C under microwave irradiation (MW) for 30 minutes. The reaction mixtures were combined and concentrated not to complete dryness under reduced pressure, taken-up into ethyl acetate (100 mL), washed with a saturated Na_2CO_3 aqueous solution then with a

2N aqueous sodium thiosulfate solution (100 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of 0 to 10% ethyl acetate in dichloromethane to give 1.94 g (67%) of rac-(3S,5S,6S,8S)-1-benzyl-3,6-difluoro-1-azaspiro[4.5]decan-8-ol as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d6): d 7.16-7.38 (m, 5 H), 5.09 (dt, *J* = 55, 5 Hz, 1 H), 4.60 (dt, *J* = 49, 3Hz, 1 H), 4.19 (d, *J* = 8 Hz, 1 H), 4.17 (s, 1 H), 3.82 (m, 1 H), 3.52 (d, *J* = 14 Hz, 1 H), 2.70-2.92 (m, 2 H), 2.31 (td, *J* = 13, 4 Hz, 1 H), 2.15 (m, 1 H), 1.82-2.10 (m, 3 H), 1.77 (m, 1 H), 1.57 (tt, *J* = 14, 3 Hz, 1 H), 1.20 (m, 1 H).

Step 6: rac-(3S,5S,6S,8S)-3,6-difluoro-1-azaspiro[4.5]decan-8-ol

A solution of rac-(3S,5S,6S,8S)-1-benzyl-8-benzyloxy-3,6-difluoro-1-azaspiro[4.5]decane (1.92 g, 6.82 mmol) in ethanol (250 mL) is hydrogenated at 60°C under 30 bars of hydrogen with a H-Cube Pro apparatus (Thales) using a 10% Pd/C cartridge (140 mg) and a 1 mL/minute flowrate. The solution is concentrated under reduced pressure to give 1.3 g (99%) of rac-(3S,5S,6S,8S)-3,6-difluoro-1-azaspiro[4.5]decan-8-ol. MS (ESI): mass calcd. for $C_9H_{15}F_2NO$, 191.1; m/z found, 192.1 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6): d 5.19 (d, *J* = 52.0 Hz, 1 H), 4.78 (br.s., 1H), 4.52 (ddd, *J* = 47.2, 13.2, 4.4 Hz, 1H), 3.49-3.53 (m, 1H), 3.01-3.15 (m, 2H), 1.99-2.07 (m, 3H), 1.48-1.69 (m, 4H), 1.13-1.19 (m, 1H).

Step 7: 6-chloro-2-[(4-methoxyphenyl)methyl]-3,3-dimethyl-5-[[rac-(3R,5R,6R,8R)-3,6-difluoro-1-azaspiro[4.5]decan-8-yl]oxy]isoindolin-1-one

To a solution of rac-(3S,5S,6S,8S)-3,6-difluoro-1-azaspiro[4.5]decan-8-ol (900 mg, 4.71 mmol) and 6-chloro-5-fluoro-2-(4-methoxybenzyl)-3,3-dimethylisoindolin-1-one (1.7 g, 5.09 mmol, 1.08 equiv.) in N,N-dimethylformamide DMF (25 mL) was added over 10 minutes a 1M solution of potassium tert-butoxide in tetrahydrofuran THF (5.4 mL, 5.40 mmol, 1.1 equiv.). The reaction mixture was stirred for 20 minutes at room temperature then poured onto a non-saturated KH_2PO_4 aqueous solution and extracted with ethyl acetate (150 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a

gradient of 50 to 100% ethyl acetate in heptane to give 1.93 g (81%) of 6-chloro-2-[(4-methoxyphenyl)methyl]-3,3-dimethyl-5-[[rac-(3R,5R,6R,8R)-3,6-difluoro-1-azaspiro[4.5]decan-8-yl]oxy]isoindolin-1-one as a white foam. MS (ESI): mass calcd. for $C_{27}H_{31}ClF_2N_2O_3$, 504.1; m/z found, 505.1 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6): d 7.69 (s, 1 H), 7.57 (s, 1 H), 7.30 (d, *J* = 9 Hz, 2 H), 6.87 (d, *J* = 9 Hz, 2 H), 5.20 (dtd, *J* = 56, 4, 2 Hz, 1 H), 4.50-4.76 (m, 4 H), 3.73 (s, 3 H), 3.03 (m, 2 H), 2.35 (m, 1 H), 1.65-2.15 (m, 6 H), 1.38 (s, 3 H), 1.36 (s, 3 H), 1.28 (m, 1 H).

Step 8: 6-chloro-5-[[(3R,5R,6R,8R)-3,6-difluoro-1-azaspiro[4.5]decan-8-yl]oxy]-2-[(4-methoxyphenyl)methyl]-3,3-dimethyl-isoindolin-1-one

The racemic mixture of 6-chloro-2-[(4-methoxyphenyl)methyl]-3,3-dimethyl-5-[[rac-(3R,5R,6R,8R)-3,6-difluoro-1-azaspiro[4.5]decan-8-yl]oxy]isoindolin-1-one (1.9 g) was separated by chiral HPLC with a Chiralcel OD-I column 20µm (7.65 x 35cm) using heptane 70%/ ethanol 30%/ triethylamine 0.1% as mobile phase, a flowrate of 350 mL/min and a UV detector at 254 nm to give 916 mg (48%) of 6-chloro-5-[[(3R,5R,6R,8R)-3,6-difluoro-1-azaspiro[4.5]decan-8-yl]oxy]-2-[(4-methoxyphenyl)methyl]-3,3-dimethyl-isoindolin-1-one as second eluting dextrogyre enantiomer. $[\alpha]_D$ = +15.2° (c= 0.0043, DMSO, 25°C). MS (ESI): mass calcd. for $C_{27}H_{31}ClF_2N_2O_3$, 504.1; m/z found, 505.1 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6): d 7.69 (s, 1 H), 7.57 (s, 1 H), 7.30 (d, *J* = 9 Hz, 2 H), 6.87 (d, *J* = 9 Hz, 2 H), 5.20 (dtd, *J* = 56, 4, 2 Hz, 1 H), 4.50-4.76 (m, 4 H), 3.73 (s, 3 H), 3.03 (m, 2 H), 2.35 (m, 1 H), 1.65-2.15 (m, 6 H), 1.38 (s, 3 H), 1.36 (s, 3 H), 1.28 (m, 1 H).

Step 9: 6-chloro-5-[[(3R,5R,6R,8R)-3,6-difluoro-1-azaspiro[4.5]decan-8-yl]oxy]-3,3-dimethyl-isoindolin-1-one

A solution of 6-chloro-5-[[(3R,5R,6R,8R)-3,6-difluoro-1-azaspiro[4.5]decan-8-yl]oxy]-2-[(4-methoxyphenyl)methyl]-3,3-dimethyl-isoindolin-1-one (915 mg, 1.81 mmol) and anisole (4 ml, 36.62 mmol) in trifluoroacetic acid (20 mL) was heated to 140°C for 45 minutes under microwave irradiation (Anton Paar apparatus). The reaction mixture was poured onto

saturated Na_2CO_3 aqueous solution (200 mL) and extracted with ethyl acetate (200 mL). The organic layer was separated, washed with 1N aqueous sodium hydroxyde solution (100 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate to give 622 mg (89%) of 6-chloro-5-[[(3R,5R,6R,8R)-3,6-difluoro-1-azaspiro[4.5]decan-8-yl]oxy]-3,3-dimethyl-isoindolin-1-one as a white foam. MS (ESI): mass calcd. for $C_{19}H_{23}ClF_2N_2O_2$, 384.1; m/z found, 385.2 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d6): d 8.54 (s, 1 H), 7.55 (s, 1 H), 7.50 (s, 1 H), 5.19 (dtd, *J* = 56, 4, 2 Hz, 1 H), 4.52-4.74 (m, 2 H), 2.82-3.13 (m, 2 H), 2.34 (m, 1 H), 1.63-2.16 (m, 6 H), 1.45 (s, 3 H), 1.44 (s, 3 H), 1.29 (m, 1 H).