The discovery of a potent analgesic NOP and opioid receptor agonist: Cebranopadol

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Supporting Information

Content

1 General methods

NMR spectral data were recorded on Bruker 300, 400 or 600 MHz or Varian Mercury 300 or 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6 (hexadeuteriodimethylsulfoxide) at room temperature. Chemical shifts are given in parts per million (δ) referenced to the NMR solvent. Assignments were obtained from 1D ^{1}H, 2D ^{13}C-HSQC and 2D ^{13}C-HMBC spectra. NOE distance information was measured by 2D NOESY with 500 ms mixing time.

Mass spectra were acquired either on UHPLC-MS (Agilent 1290 Infinity and 6530 Accurate-Mass-QTOF) on acidic conditions. Acidic condition is indicated by water (A)/acetonitrile(B) containing 0,1 % formic acid on Agilent Zorbax SB-C18 column (2.1 x 50 mm, 1.8 µm particle size). Signals were detected by photo diode array detector (Agilent 1290 DAD G4212A, store spectrum setting 190-400 nm) and QTOF-MS (Dual Electro Spray Ionisation source, mass range 100-1000 amu). Following gradient was used: Flow rate 1 ml/min, Wavelength 254 nm/bandwidth 4 nm. Gradient from 0 % B to 100 % B in 2 min

Otherwise, MS spectra were acquired on Agilent LC-MS 1200 Rapid Resolution with MSD6140, gradient from 0 min: (A) 95 % water (+ 1 % formic acid) / (B) 5 % methanol (+ 1 % formic acid). Fragmentor voltage: 100 V [pos/neg]; Signals were detected by photo diode array detector (254 nm) and MM-ES + APCI. Following gradient was used: Flow rate 0.8 mL/min from 0% B to 100% B in 5.4 min.

Flash column chromatography was performed on Biotage. MPLC was performed with LiChroprep Si_{60} (0.015–0.025 mm).

All the assayed compounds possess ≥ 90% purity determined using HPLC/MS analysis.

Silica gel 60 (0.040-0.063 mm) from E. Merck, Darmstadt, was used as stationary phase for the column chromatography. The thin layer chromatography investigations were carried out with HPTLC precoated plates, silica gel 60 F 254, from E. Merck, Darmstadt.

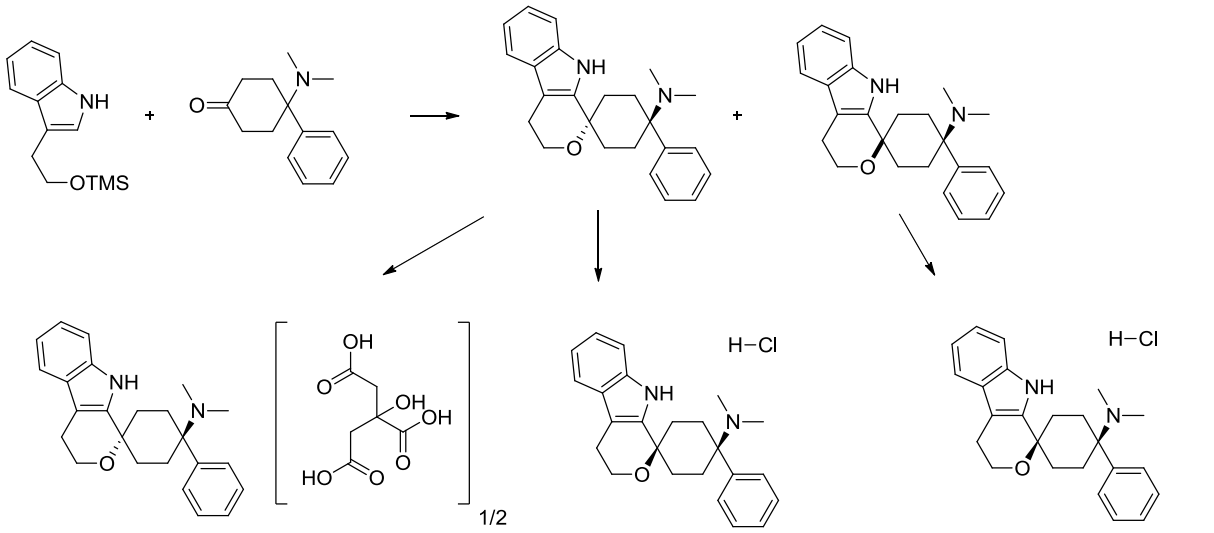
The mixture ratios of solvents for chromatographic investigations are always specified in volume/volume.

Abbreviations: DCM = dichloromethane; DCE = 1,2-dichloroethane; DEA = diethylamine; EtOAc = ethyl acetate; Et_2O = diethylether; TMSOMs= trimethylsilyl methanesulfonate; NaOH = sodium hydroxide; TMSOTf = trimethylsilyl trifluoromethanesulfonate;

2 SYNTHESIS OF COMPOUNDS 2-49

2.1 Synthesis of Compound 2a and 2b [1]

Step 1: 4',9'-Dihydro-*N,N*-dimethyl-4-phenyl-3'H-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine, trans- (**2a**) and 4',9'-Dihydro-*N,N*-dimethyl-4-phenyl-3'H-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine, cis (**2b**)



2a hemicitrate **2a hydrochloride** **2b hydrochloride**

TMSOTf (1 ml, 5 mmol) was added under argon to a solution of 4-dimethylamino-4-phenylcyclohexanone (1.1 g, 5.07 mmol) and 3-(2-((trimethylsilyl)oxy)ethyl)-1*H*-indole (1.4 g, 6.01 mmol) in DCM (30 ml) at -78 °C in the course of 5 min, while stirring. The mixture was stirred at -78 °C for 1 h. The mixture was then brought to rt over a period of 4 h and stirred at rt for a further 10 h. For working up, 1N NaOH (30 ml) was added to the reaction mixture and the mixture was stirred for 30 min. The organic phase was separated off and the aqueous phase which remained was extracted with DCM (2 x 30 ml). The combined organic phases were washed with 1N NaOH (1 x 30 ml) and water (2 x 30 ml) and dried over sodium sulfate. After the solvent had been distilled off, a yellow solid was obtained, which was washed with

EtOAc. After recrystallization of the crude product which remained from toluene, the trans isomer of the spiroether, which had an mp of 279 - 284 °C, was isolated in a yield of 0.8 g. The mother liquor which remained and the EtOAc wash solution were concentrated. By means of purification by column chromatography on silica gel, first with EtOAc/ethanol (volume ratio 8 : 2) then with EtOAc/ethanol (volume ratio 1 : 1), it was possible isolate additional material of the trans diastereomer (150 mg) and the cis diastereomer.
After recrystallization from toluene, the cis product **2b** was obtained in a yield of 60 mg with an mp of 230-235 °C.

4',9'-Dihydro-*N,N*-dimethyl-4-phenyl-3'H-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine, trans-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1) (**2a hemicitrate)**:

For preparation of the hemicitrate, the trans diastereoisomer of 4',9'-Dihydro-*N,N*-dimethyl-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine (1.2 g, 3.33 mmol) was dissolved in hot ethanol (350 ml), and a hot solution of citric acid (1.2 g, 6.25 mmol) in ethanol (30 ml) was added. After cooling, the mixture was left at approx. 10 °C for 4 h. The solid formed was filtered with suction. The hemicitrate was obtained in a yield of 1.05 g as a white solid with an mp of 259-265 °C.

^{1}H-NMR (600 MHz, DMSO-d6) δ ppm: 1.77, 1.83 (d, t, 2 H, 2 H); 2.14 (s, 6 H); 2.28 (t, 2 H); 2.58, (m, 2 H); 2.67 (m, 4 H); 3.89 (s, 4 H); 6.96 (m, 1 H); 7.03 (m, 1 H); 7.30, 7.35, 7.36-7.45 (t, d, m, 1 H, 1 H, 5 H); 10.78 (1 H); ca. 11-12.5 (br, < 1.5 H
1.85, 2.59 (CH_2-2, CH_2-4 Cy); 2.68 (Indole-CH_2); 2.29, 1.78 (CH_2-1, CH_2-5 Cy); 2.15 ($N(CH_3)_2$); 3.89 (CH_2O); 6.96 (CH-26Indole); 7.04 (CH-25 Indole); 7.30 (CH_p Ph); 7.36 (CH-24 Indole) ; 7.38 (CH-27 Indole); 7.40 (2 CH_m Ph); 7.43 (2 CH_o Ph); 10.74 (NH Indole).

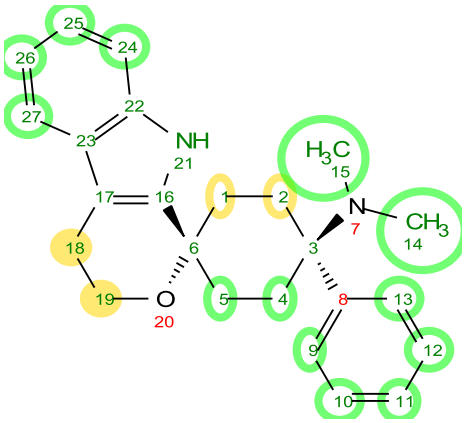


Fig. 1. **(B)** Atom numbering of **2a** with ^{1}H and ^{13}C chemical shift assignments. Syntax: (atom number: 1H shift [ppm], 13C shift [ppm];).

^{13}C-NMR (150 MHz, DMSO-d6) δ ppm: 22.7 (Indole-CH_2); 28.3 (Cy CH_2-2, CH_2-4); 30.9 (Cy CH_2-1, CH_2-5); 38.6 ($N(CH_3)_2$); 59.3 (CH_2O); 59.4 (Cy C-3); 72.6 (Cy C-6); 105.7 (C-17 Indole); 111.8 (CH-24 Indole); 117.8 (CH-27 Indole); 118.7 (CH-26 Indole); 120.8 (CH-25 Indole));127.0 (C-23 Indole); 127.2 (CH_p Ph); 127.30 (2 CH_o Ph); 127.98 (2 CH_m Ph136.3 (C-22 Indole).; 139.9 (C-16 Indole)

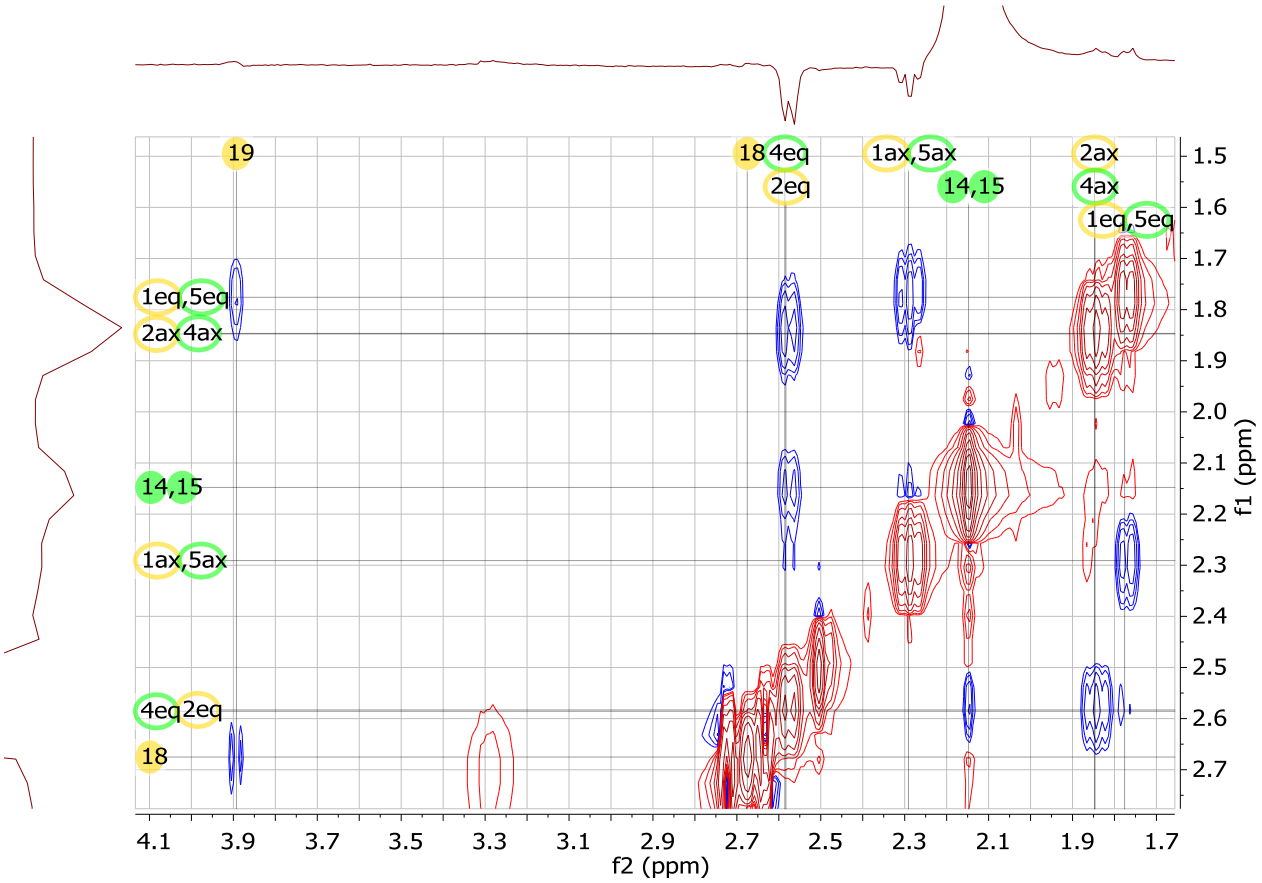
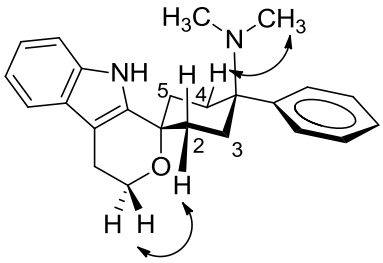


Fig. 1. **(A)** 2D NOESY of **2a**. NOE cross-peaks between the dimethylamino protons (14,15) and the equatorial but not the axial protons of atoms 2 and 4 indicate an axial configuration of the dimethylamino group. NOE cross-peaks between the methylene protons of 19 and the equatorial but not the axial protons of atoms of atoms 1 and 5 indicate an axial configuration of the methylene group 19. In conclusion, for **2a** a trans-configuration of the spiroether is indicated.
The 1D traces on the top and left of the 2D spectrum show the intensity slices through the cross-peak (2eq,4eq)/(14,15). The strong geminal NOEs between H1eq and H1ax as well as H2eq and H2ax are well resolved.

HRMS (ESI) m/z+H+ calcd. for $C_{24}H_{28}N_2O \cdot H^+$: 361.22744; found: 361.2270.

Fig. 2: Illustration of spatial orientation of atoms involved in observed cross peaks in **2a**



cis-diastereomer **2b**:

Step 2a hydrochloride: 4',9'-Dihydro-*N,N*-dimethyl-4-phenyl-3'H-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine, trans-, hydrochloride

For preparation of the hydrochloride, the trans diastereoisomer of the spiroether (500 mg, 1.38 mmol) was dissolved in 2-butanone (40 ml), chlorotrimethylsilane (250 µl, 1.98 mmol) was added and the mixture was stirred at rt for 3 h. The solid formed was filtered off with suction. The hydrochloride of the more non-polar diastereoisomer was obtained in a yield of 420 mg as a white solid with an mp of 278-280 °C.

Step 2b hydrochloride: 4',9'-Dihydro-*N,N*-dimethyl-4-phenyl-3'H-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine, cis-, hydrochloride

Chlorotrimethylsilane (25 µl, 0.198 mmol) was added to a solution of the cis diastereoisomer of 4',9'-Dihydro-*N,N*-dimethyl-4-phenyl-3'H-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine (50 mg, 0.138 mmol) in 2-butanone (10 ml). After a reaction time of 2 h, it was possible to isolate the precipitated hydrochloride of the cis diastereoisomer in a yield of 36 mg with an mp of 271-272 °C.

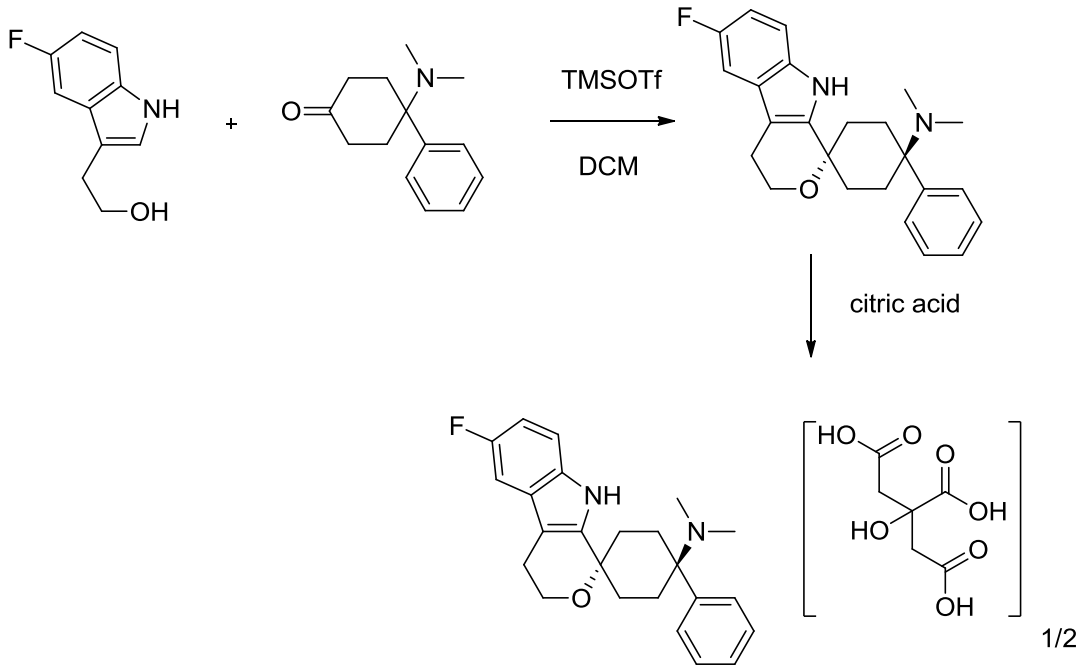
^{1}H-NMR (600 MHz, DMSO-d_6) δ ppm: 1.65 (t, 2 H); 1.94 (d, 2 H); 2,36 (t, 2 H); 2.69 (t, 2 H); 2.84 (d, 2 H); 3.97 (t, 2 H); 6.92 (t, 2 H); 6.96 (t, 2 H); 7.17 (d, 1 H); 7.36 (d, 1 H); 7.63 (m, 3 H); 7.80 (m, 2 H); 10.15 (br, 1 H); 10.57 (s, 1 H).
Some signals are obscured by the DMSO signal.

The 2D NOESY shows a cis-relationship of the azole NH and the phenyl ring in the head position. Thereby, **2b** was shown to be the cis-spiroether.

HRMS (ESI) m/z+H^+ calcd. for $C_{24}H_{28}N_2O \cdot H^+$: 361.2274, found: 361.2270.

2.2 Synthesis of Compound 3a [2]

6'-Fluoro-4',9'-dihydro-*N,N*-dimethyl-4-phenyl-spiro[cyclohexane-1,1'(3'*H*)-pyrano[3,4-b]indol]-4-amine, trans-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1)



Step 1: 6'-Fluoro-4',9'-dihydro-*N,N*-dimethyl-4-phenyl-spiro[cyclohexane-1,1'(3'*H*)-pyrano[3,4-b]indol]-4-amine, trans-

4-Dimethylamino-4-phenylcyclohexanone (651 mg, 3 mmol) and 2-(5-fluoro-1*H*-indol-3-yl)-ethanol (37 mg, 3 mmol) were initially introduced into abs. DCM (20 ml) under argon. Trifluoromethanesulfonic acid trimethylsilyl ester (0.6 ml, 3.1 mmol) was then added very rapidly. The mixture was stirred at RT for 20 h. For working up, 1 N NaOH (30 ml) was added to the reaction mixture and the mixture was stirred for 30 min. The organic phase was separated off and the aqueous phase which remained was extracted with DCM (3 x 60 ml). The combined organic phases were washed with water (2 x 30 ml) and dried over sodium sulfate. Methanol (30 ml) was added to the solid residue obtained after the solvent had been distilled off, and the mixture was heated, and stirred for 15 h. The solid contained in the suspension was filtered off with suction and dried. 955 mg of the trans diastereoisomer of the spiroether were obtained (mp 284-292 °C).

Step 2: 6'-Fluoro-4',9'-dihydro-*N,N*-dimethyl-4-phenyl-spiro[cyclohexane-1,1'(3'*H*)-pyrano[3,4-b]indol]-4-amine, trans-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1)

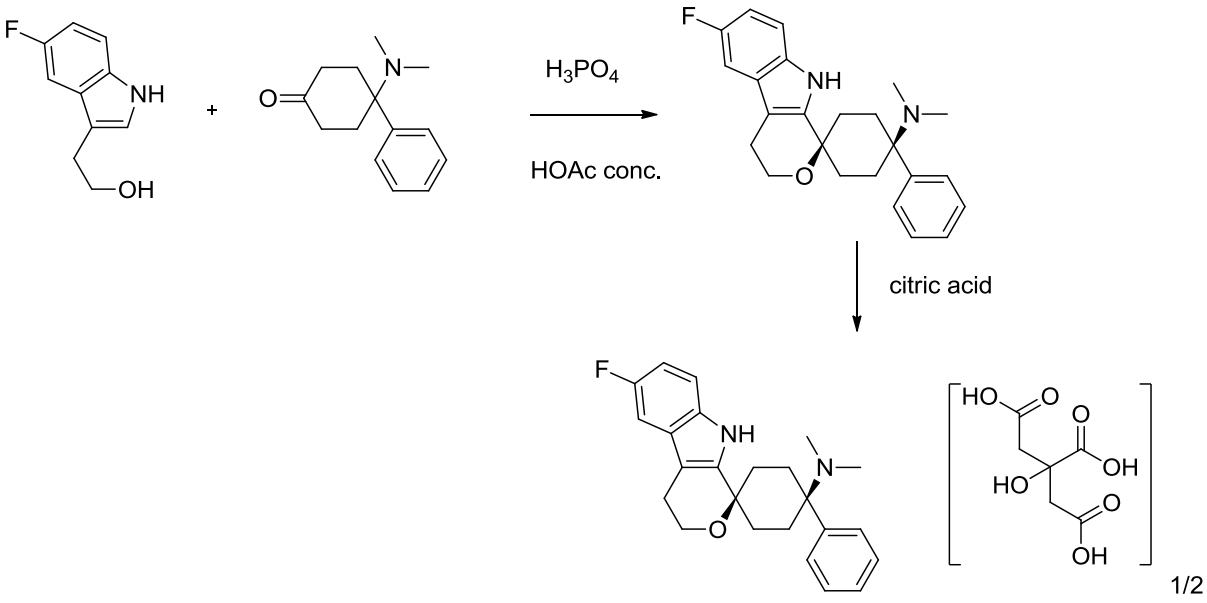
850 mg of the free base were dissolved in hot ethanol (900 ml), and a hot solution of citric acid (1 g, 5.2 mmol) in ethanol (20 ml) was added. After approx. 15 minutes, crystals precipitated out at the boiling point. After cooling to approx. 5 °C, the mixture was left to stand for 2 h. The solid formed was filtered off with suction. 640 mg of the hemicitrate were obtained as a white solid (mp 258-282 °C).

1H-NMR (300 MHz; DMSO-d_6): 1.75-1.87 (m, 4 H); 2.14 (s, 6 H); 2.27 (t, 2 H); 2.61-2.76 (m,6 H); 3.88 (t, 2 H); 6.86 (dt, 1 H); 7.10 (dd, 1 H); 7.30-7.43 (m, 6 H); 10.91 (br s, 1 H).
^{13}C-NMR (75.47 MHz; DMSO-d_6): 22.1; 27.6; 30.2 (2 C); 38.0 (2 C); 43.1; 58.8 (2 C, overlap); 71.5; 72.2; 102.3 ($^{2}J_{C,F}$ = 23 Hz); 105.6 ($^{3}J_{C,F}$ = 4 Hz); 108.3 ($^{2}J_{C,F}$ = 26 Hz); 112.0 ($^{3}J_{C,F}$ = 10 Hz); 126.5; 126.6; 126.7 (2 C); 127.4 (2 C); 132.4; 138.7; 141.5; 156,7 ($^{1}J_{C,F}$ = 231 Hz); 171.3 (2 C), 175.3.

HPLC-MS: m/z 378.9 [M + H]+

2.3 Synthesis of Compound 3b [3]

6'-Fluoro-4',9'-dihydro-*N,N*-dimethyl-4-phenyl-spiro[cyclohexane-1,1'(3'*H*)-pyrano[3,4-b]indol]-4-amine, cis-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1)



Step 1: 6'-Fluoro-4',9'-dihydro-*N,N*-dimethyl-4-phenyl-spiro[cyclohexane-1,1'(3'*H*)-pyrano[3,4-b]indol]-4-amine, cis-

4-Dimethylamino-4-phenylcyclohexanone (217 mg, 1 mmol) and 2-(5-fluoro-1*H*-indol-3-yl)-ethanol (179 mg, 1 mmol) were dissolved in conc. acetic acid (4 ml). Phosphoric acid (1 ml, 85 weight-%) was slowly added dropwise to this mixture. The mixture was stirred at RT for 16 h. For working up, the mixture was diluted with water (20 ml), brought to pH 11 with 5 N NaOH and extracted with DCM (3 x 20 ml). The combined organic phases were dried with sodium sulfate and evaporated.

Step 2: 6'-Fluoro-4',9'-dihydro-*N,N*-dimethyl-4-phenyl-spiro[cyclohexane-1,1'(3'*H*)-pyrano[3,4-b]indol]-4-amine, cis-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1)

The residue (364 mg of white solid) was suspended in hot ethanol (20 ml), and a hot solution of citric acid (185 mg, 0.96 mmol) in ethanol (5 ml) was added. The residue thereby dissolved completely and no longer precipitated out even on cooling to approx. 5 °C. Ethanol was removed in vacuo, giving rise to the hemicitrate of the cis

diastereoisomer of the spiroether in a yield of 548 mg as a white solid (mp 148-155 °C).

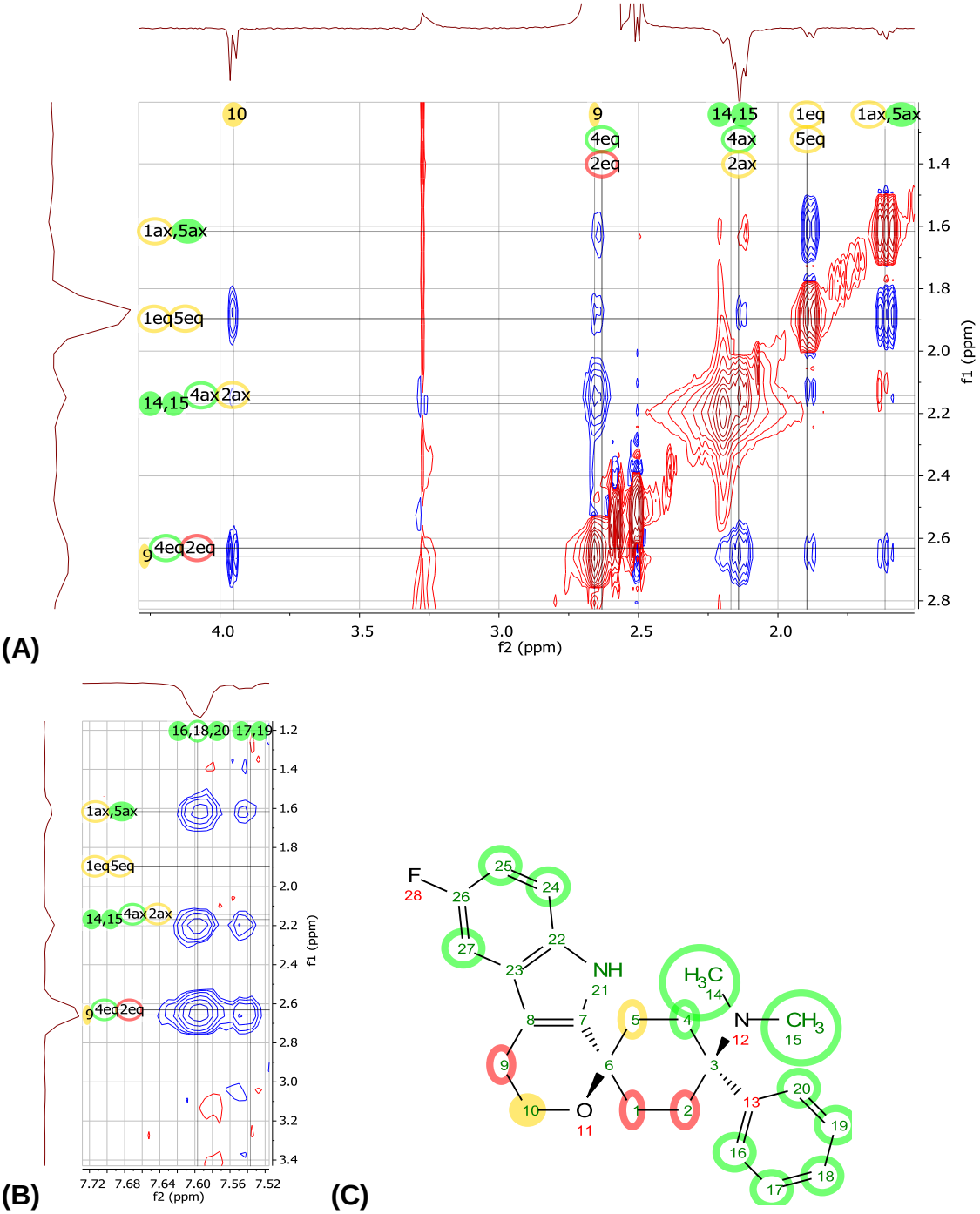


Fig. 1: **(A)** 2D NOESY of **3b**. NOE cross-peaks between the methylene protons of atom 10 and the equatorial but not the axial protons of atoms 1 and 5 indicate an axial configuration of methylene 10. The 1D traces on the top and left of the 2D spectrum show the intensity slices through the cross-peak (2eq, 4eq)/(10). The strong geminal NOEs between $H1_{eq}$ and $H1_{ax}$ as well as $H2_{eq}$ and $H2_{ax}$ are well

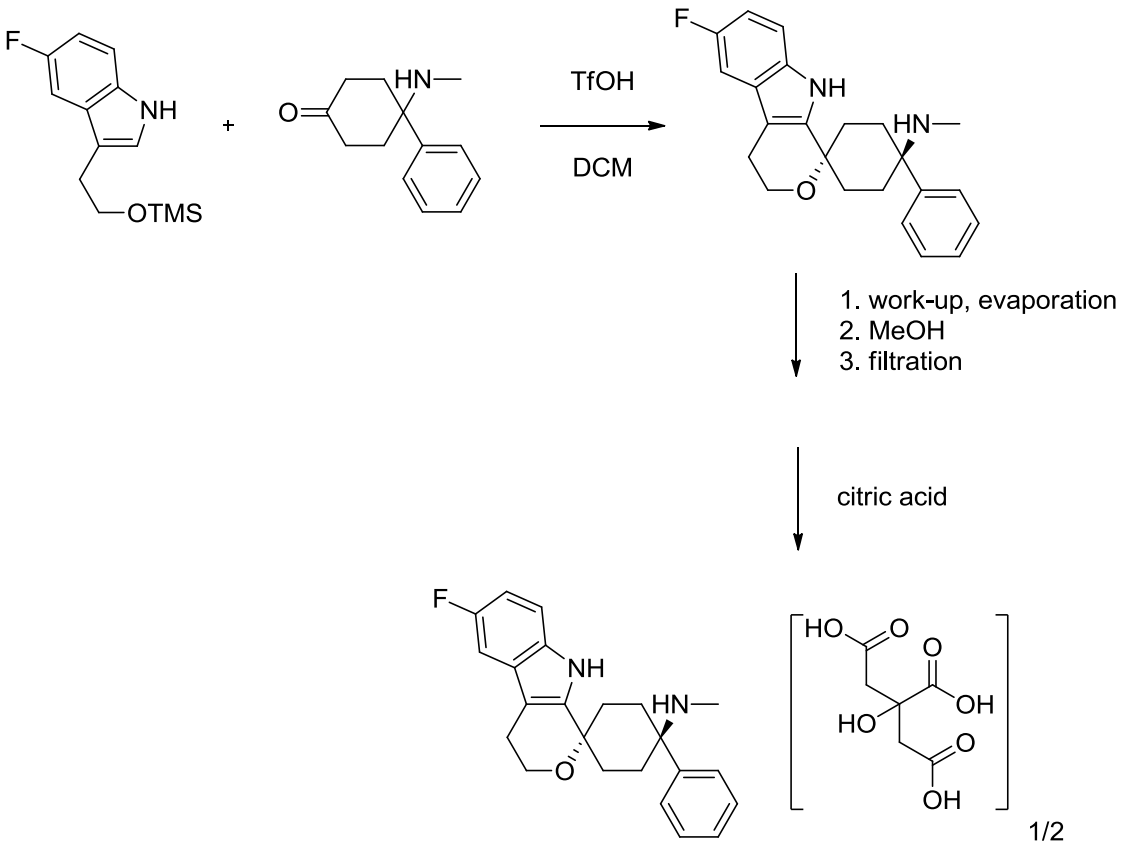
resolved. **(B**) The NOE cross-peaks between the phenyl protons (16, 20) and the axial but not the equatorial protons of atoms 1 and 5 indicate an axial configuration of the phenyl ring. The 1D traces are taken from the cross-peak (2eq, 4eq)/(16,20). **(C)** Atom numbering of **3b** with ^{1}H and ^{13}C chemical shift assignments.

^{1}H-NMR (600 MHz, DMSO-d6) δ ppm: 1.62 (t, 2 H, CH-1, CH-5 Cy); 1.90 (d, 2 H, CH´-1, CH´-5 Cy); 2.14-2.22 (t, s, 2 H, 6 H, CH-2, CH-4 Cy, $N(CH_3)_2$); 2.50- 2.63 (m, 6 H, CH´-2, CH´-4 Cy, 2 CH_2 citrate, obscured by DMSO signal); 2.66 (t, 2 H, Indole-CH_2); 3.95 (t, 2 H, CH_2O); 6.81 (app td, 1 H, J = 2.7, 8.8, 10 Hz, CH-25 Indole); 7.11 (dd, 1 H, $^{3}J_{H,H}$ = 2.7, $^{3}J_{H,F}$ = 10 Hz, CH-27 Indole); 7.15 (dd, 1 H, J = 4.5, 8.8 Hz, CH-24 Indole); 7.46-7.54 (m, 3 H, CH_{m+p} Ph); 7.60 (m, 2 H, CH_o Ph); 10.78 (1 H, NH Indole); ca. 11-12.5 (very br, COOH).
^{13}C-NMR (150.94 MHz; DMSO-d_6): 22.7 (Indole-CH_2); 27.1 (CH_2-2, CH_2-4 Cy); 32.1 (CH_2-1, CH_2-5 Cy); 38.3 ($N(CH_3)_2$); 59.4 (CH_2O); 59.9 (CN-3); 71.7; 102.8 (d, $^{2}J_{H,F}$ = 23 Hz, CH-27 Indole); 106.3 (d, $^{3}J_{H,F}$ = 3 Hz, C-8 Indole); 108.8 (d, $^{2}J_{H,F}$ = 26 Hz, CH-25 Indole); 112.2 (d, $^{3}J_{H,F}$ = 10 Hz, CH-24 Indole); 127.0 (C-23 Indole); 128.2, 128.6; 128.7 (Ph); 132.9 (C-22 Indole); 141.0 (C-7 Indole); 156.4 (d; $^{1}J_{C,F}$ = 230 Hz, CF-26 Indole).

The 2D NOESY shows a cis-relationship of the azole NH and the phenyl group in the head position. Thereby, **3b** was shown to be the cis-spiroether.

2.4 Synthesis of Compound 4a [4]

6'-Fluoro-4',9'-dihydro-*N*-methyl-4-phenyl-spiro[cyclohexane-1,1'(3'*H*)-pyrano[3,4-b]indol]-4-amine, trans-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1)



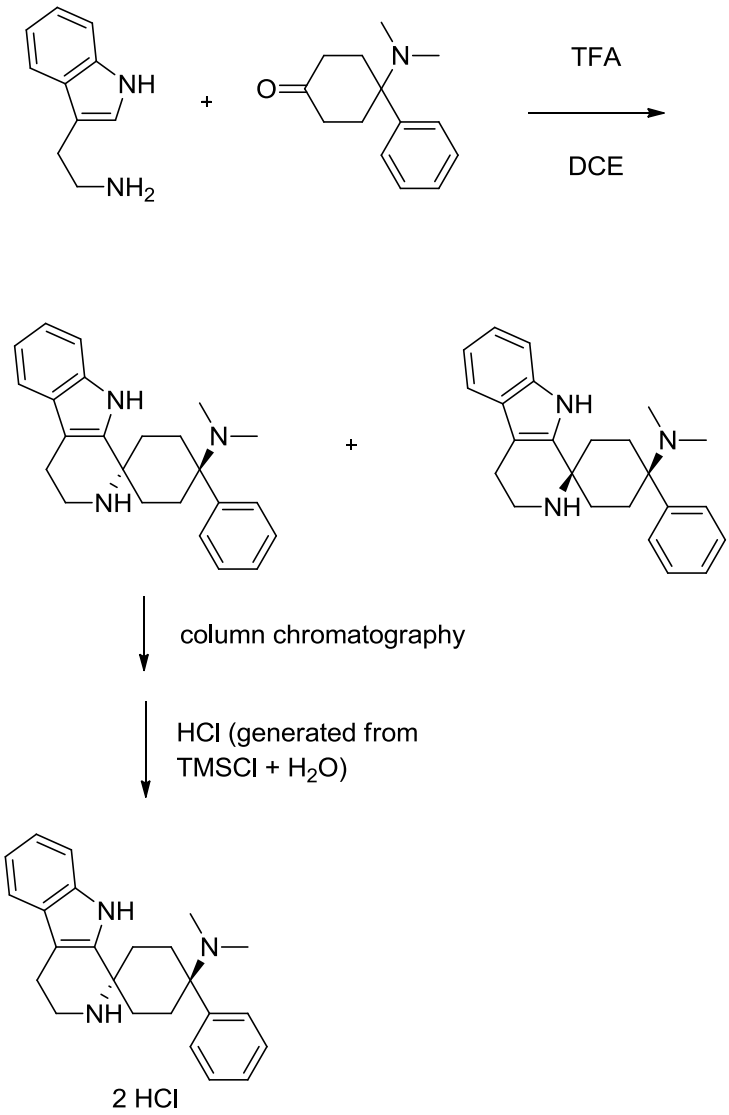
^{1}H-NOESY:

The NOESY shows a cis-relationship of the azole NH and the methylamino group in the head position. Thereby, **4a** was shown to be the trans-spiroether.

HRMS (ESI) m/z calcd. for $C_{23}H_{25}FN_2O + H^+$: 365.2024, found: 365.2022.

2.5 Synthesis of Compound 5a [5]

2',3',4',9'-Tetrahydro- *N,N*-dimethyl-4-phenyl-spiro[cyclohexane-1,1'-pyrido[3,4-b]indol]-4-amine, trans-, dihydrochloride



Step 1: 2',3',4',9'-Tetrahydro- *N,N*-dimethyl-4-phenyl-spiro[cyclohexane-1,1'-pyrido-[3,4-b]indol]-4-amine, trans-,

The trans spiroamine was obtained in a yield of 557 mg (31 %) as a white solid.

Step 2: 2',3',4',9'-Tetrahydro- *N,N*-dimethyl-4-phenyl-spiro[cyclohexane-1,1'-pyrido[3,4-b]indol]-4-amine, trans-, dihydrochloride

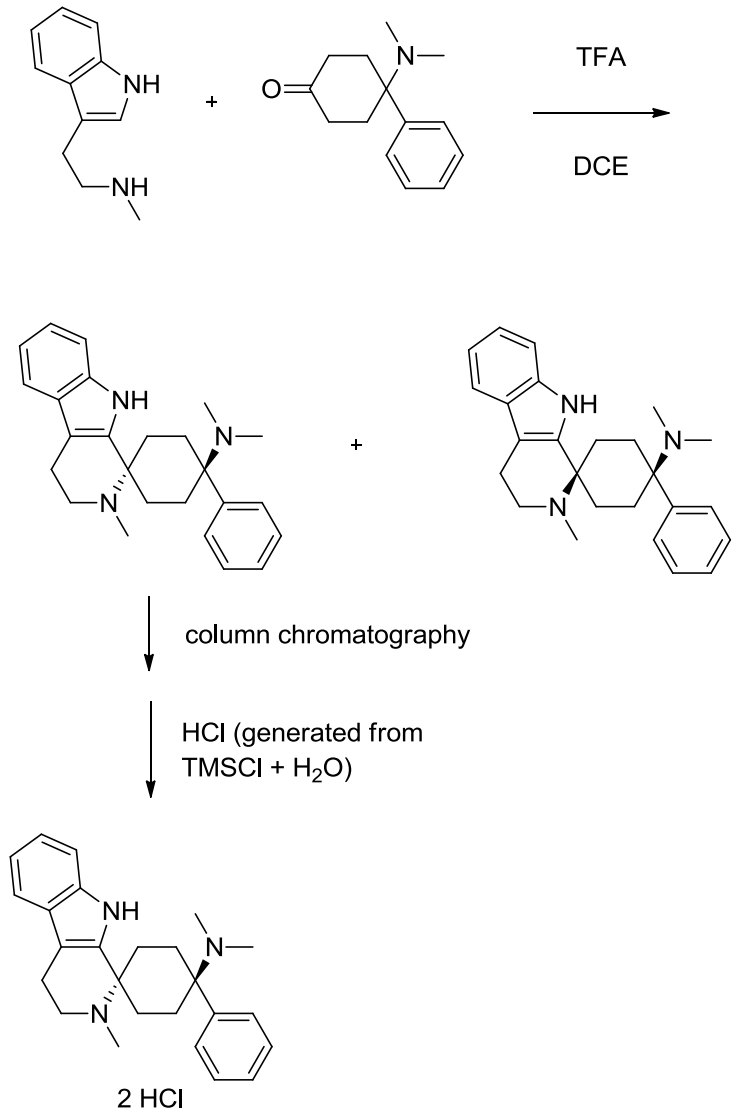
For preparation of the dihydrochloride, 557 mg of the free base were suspended in 2-butanone (7 ml), and chlorotrimethylsilane (500 µl, 3.75 mmol) was added. The

solid formed was filtered off with suction and dried. The dihydrochloride of the trans diastereoisomer of the spiroamine was obtained in a yield of 670 mg as a white solid with an mp of 243-247 °C.

2D NOESY:
The 2D NOESY shows a cis-relationship of the azole NH and the dimethylamino group in the head position. Thereby, **5a** was shown to be the trans-spiroamine.

2.6 Synthesis of Compound 6a

2',3',4',9'-Tetrahydro- *N,N,*2'-trimethyl-4-phenyl-spiro[cyclohexane-1,1'-pyrido[3,4-b]-indol]-4-amine, trans-, dihydrochloride



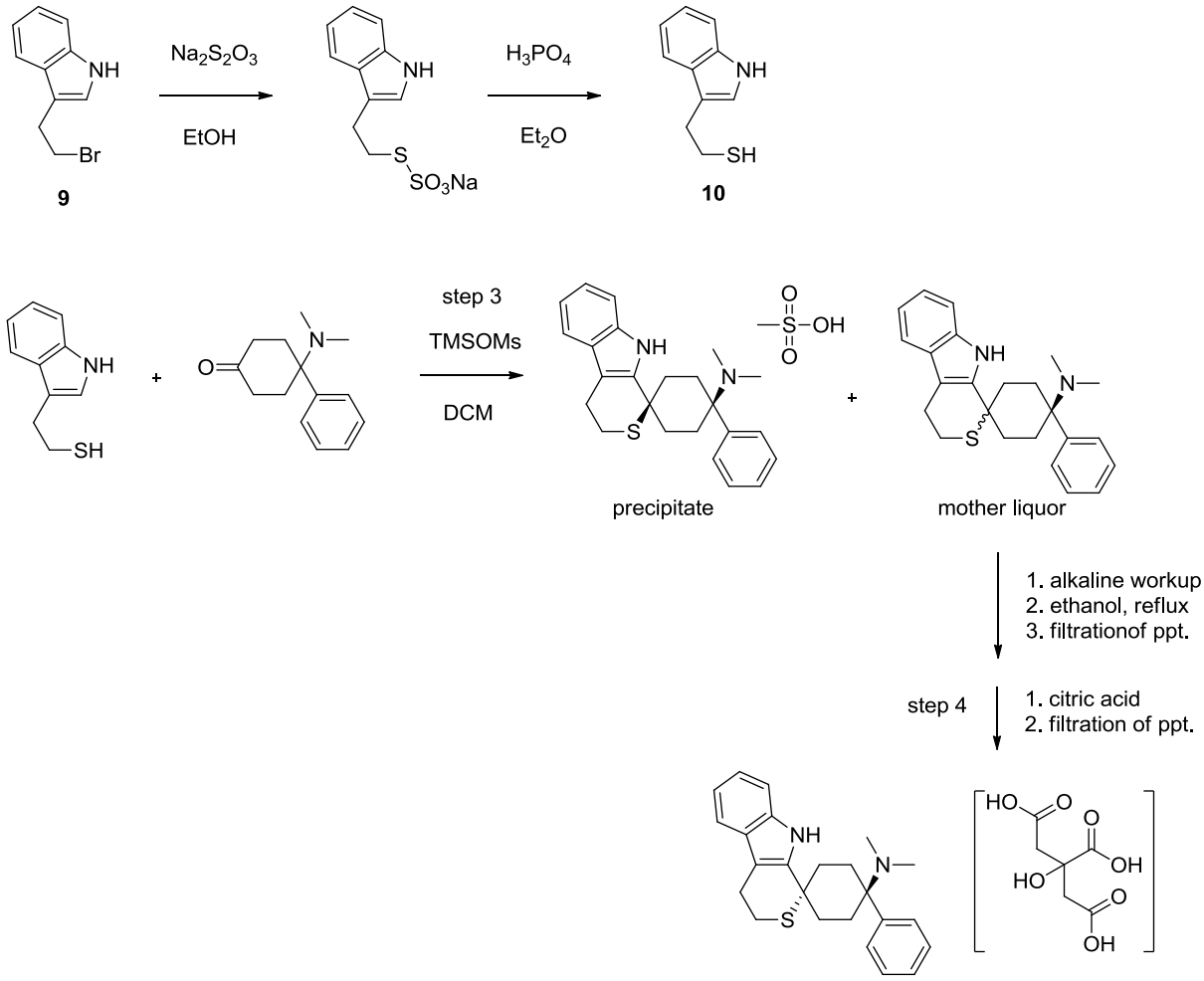
6a was synthesized in analogy to **5a**. Workup under basic conditions and evaporation led to a brown solid (1,56 g), which was suspended in methanol (15 ml) and stirred for 1 hr. The white solid (509 mg) was filtered and purified by column chromatogram-phy [silica gel 60 (20 g); Methanol/Dichloromethane/30-w/w ammonia 150 : 50 : 4 (1400 ml)]. The trans diastereoisomer **6a** (white solid, melting point: 252–256 °C) was obtained in a yield of 3 % (42 mg).

^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm: 16.6, 28.7, 30.2, 35.6, 38.2, 46.5, 56.0, 58.8, 106.6, 110.8, 118.0, 119.1, 121.2, 126.5, 127.0, 127.3, 127.5, 135.6, 139,0, 139.1.

Furthermore, the cis diastereoisomer (white solid, melting point: 218–222 °C) was obtained in a yield of 19 % (288 mg).

2.7 Synthesis of Compound 7a [6]

4',9'-Dihydro-*N,N*-dimethyl-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-thiopyrano[3,4-b]-indol]-4-amine, trans-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1)



Step 3: 4',9'-Dihydro-*N,N*-dimethyl-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-thiopyrano-[3,4-b]indol]-4-amine, trans-

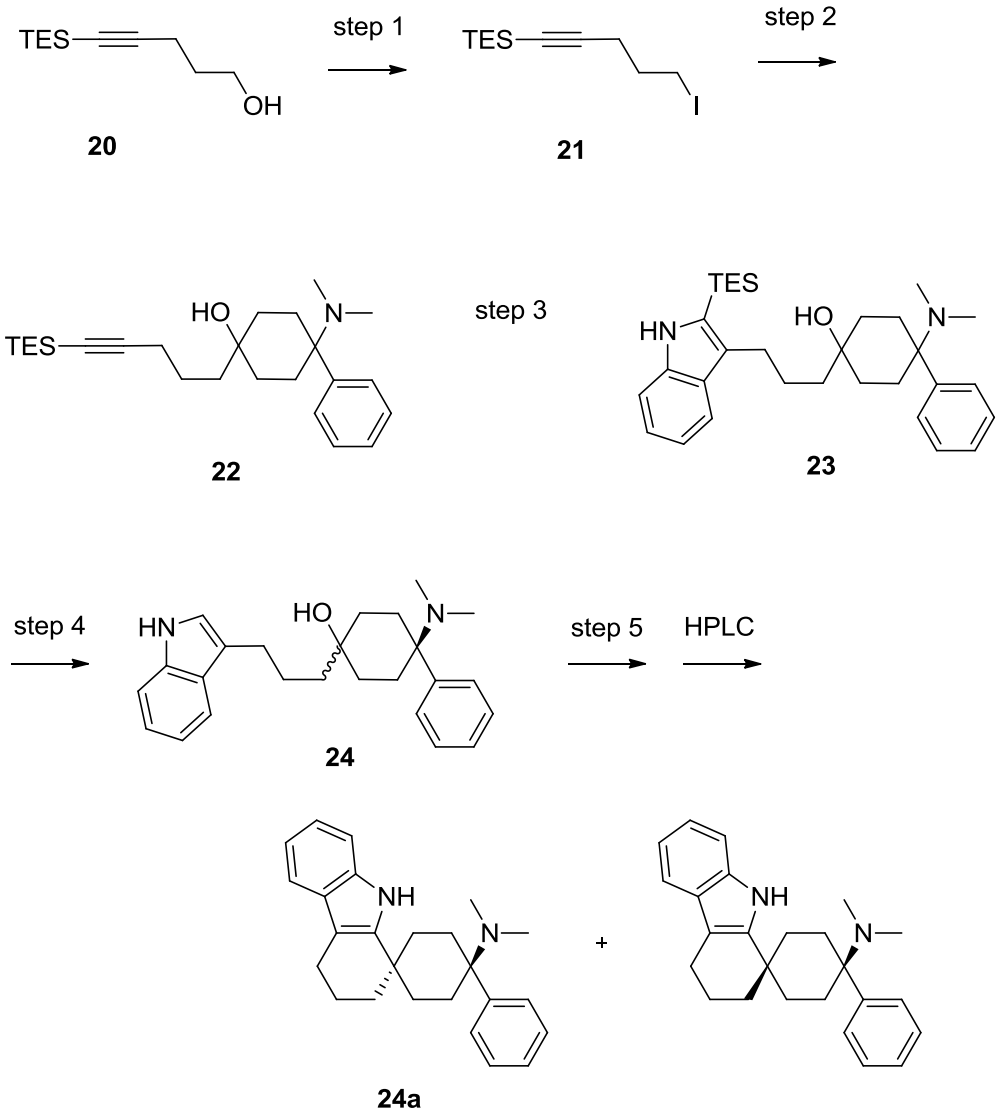
4-*N,N*-Dimethylamino-4-phenylcyclohexanone (326 mg, 1.5 mmol) and 2-(1*H*-indol-3-yl)ethanethiol (266 mg, 1.5 mmol) were initially introduced into abs. DCM (10 ml)

under argon. The methanesulfonic acid trimethylsilyl ester (254 µl, 1.65 mmol) was then added. The mixture was stirred at rt for 4 d. The methanesulfonate which had precipitated out was filtered off with suction and washed with DCM (3 x 0.5 ml). The methanesulfonate of the cis diastereoisomer was obtained in a yield of 306 mg as a white solid with an mp of 243-245 °C.
The DCM phase was worked up under alkaline conditions (1N NaOH, 30 ml, vigorous stirring for 1 h), the phases were separated and the MC phase was concentrated. The residue was covered with a layer of anhydrous ethanol (10 ml) and the mixture was stirred under reflux for 30 min. After standing at rt for several hours, the precipitate was filtered off with suction, washed with ethanol (4 x 1 ml) and then dried. A mixture of the cis and trans diastereoisomer of the free base of 4',9'-dihydro-*N,N*-dimethyl-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-thiopyrano[3,4-b]indol]-4-amine was obtained in a yield of 182 mg.

Step 4: *N,N*-Dimethyl-4-phenyl-4',9'-dihydro-3'*H*-spiro[cyclohexane-1,1'-thiopyrano[3,4-b]indol]-4-amine, trans-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1)

The diastereoisomer mixture of the free base obtained (172 mg, 0.457 mmol) was dissolved in hot ethanol (130 ml), citric acid (88.6 mg, 0.461 mmol) was added and the mixture was stirred at 65 °C for 10 min. After cooling to RT, the mixture was stirred for 20 h. The solid formed was filtered off with suction, washed with cold ethanol (2 x 0.5 ml) and then dried. 85 mg of the hemicitrate of the trans spirothioether **7a** were obtained were obtained (mp 241-243 °C).

2.8 Synthesis of Compound 8a [7]



20 **21** **22** **23** **24** **24a**

Step 5: 2,3,4,9-Tetrahydro-*N,N*-dimethyl-4'-phenyl-spiro[carbazole-1,1'-cyclohexane]-4'-amine (**8**)

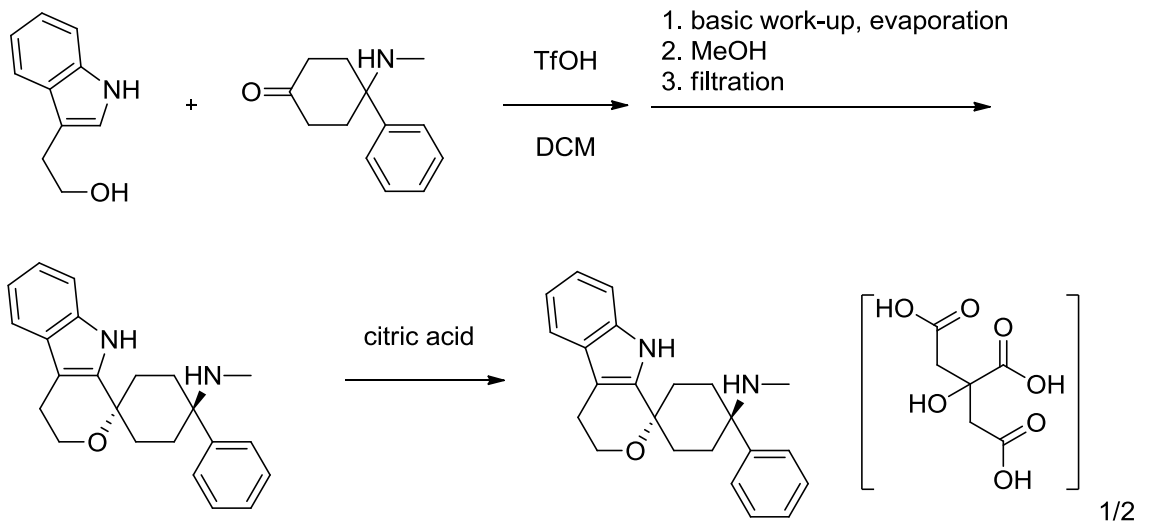
Yield: 102 mg (33%), light-coloured solid, mixture of diastereomers.
The proton NMR indicates a diastereomeric mixture ~ 1.2° : 1*.

The diastereomer mixture obtained was separated by means of preparative HPLC [column: Gemini 5µ C18, 250 x 4.6 mm, elutant: CH_3CN: H2O: DEA = 750: 250: 1; 1 ml/min].
(**8a**, trans diastereomer): retention time: 18.05 min, MH+: 359.3
Yield: 56 mg (18%)
1H-NMR (600 MHz; DMSO-d_6): 1.43 (d, 2 H); 1.62 (t, 2 H); 1.78 (m, 4 H); 2.05 (s, 6 H); 2.33 (t, 2 H); 2.56-2.59 (m, 4 H); 6.91 (t, 1 H); 6.98 (t, 1 H); 7.25 (m, 1 H); 7.31 (d,

1 H); 7.34-7.37 (m, 5 H); 10.53 (br s, 1 H).
HPLC-MS: rt = 3.7 min, m/z 359.3 [M + H]+

2.9 Synthesis of Compound 28a [8]

4',9'-Dihydro-*N*-methyl-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine, trans-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1):



Step 1: 4',9'-Dihydro-*N*-methyl-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine, trans-

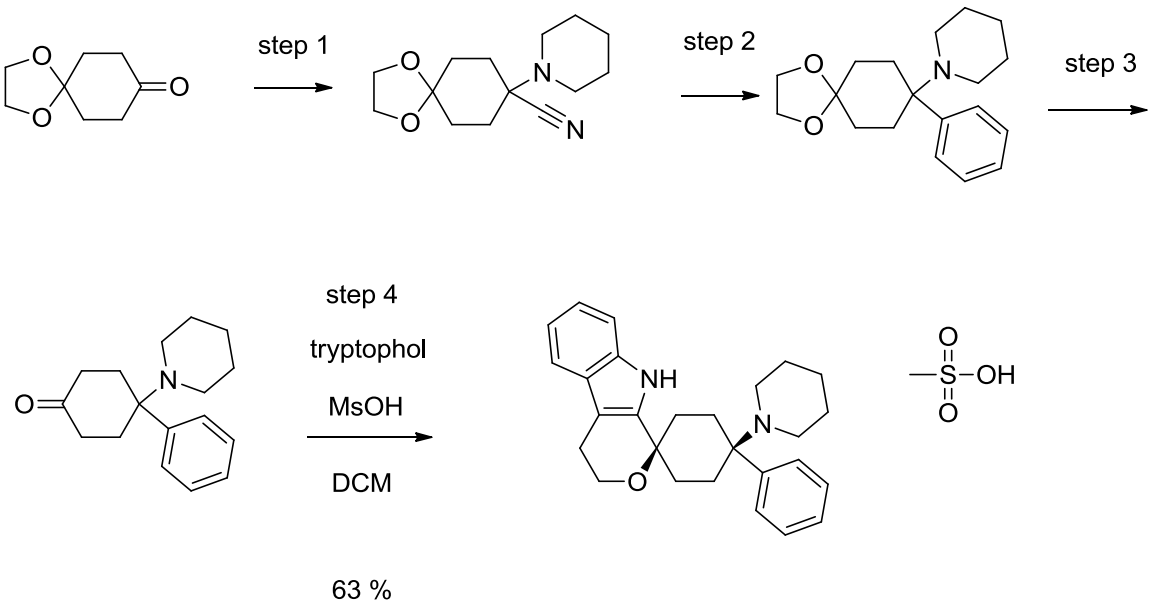
The trans diastereoisomer of the spiroether was obtained in a yield of 630 mg (mp 260-262 °C).

step 2: 4',9'-dihydro-*N*-methyl-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine, trans-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1):

600 mg of the free base were dissolved in hot ethanol (150 ml), and a hot solution of citric acid (600 mg, 3.12 mmol) in ethanol (10 ml) was added. After cooling to approx. 5 °C, the mixture was left to stand for 12 h. The solid formed was filtered off

with suction. 663 mg of the hemicitrate of the trans spiroether were obtained (white solid, mp 252-254 °C).

2.10 Synthesis of Compound 38b [9, 10]

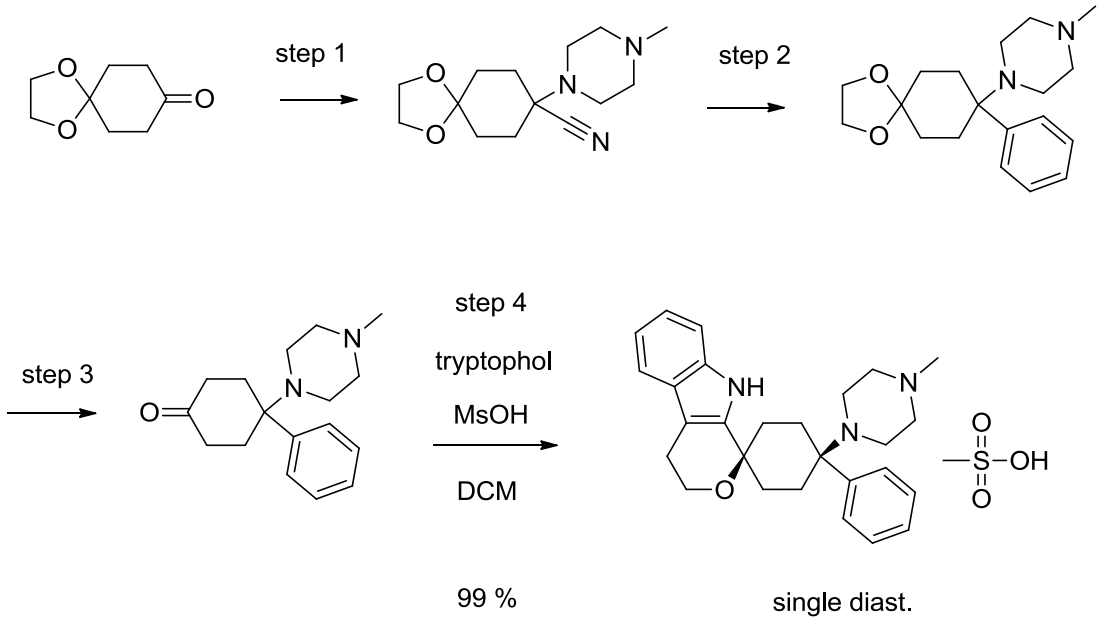


Step 4: 4',9'-Dihydro-4-phenyl-4-(piperidin-1-yl)- 3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indole] methanesulfonate, cis-

The ketone (257 mg, 1 mmol) was placed together with tryptophol (161 mg, 1 mmol) in absolute dichloromethane (50 ml). Methanesulfonic acid (0.13 ml, 2 mmol) was then added. The preparation was stirred for 24 h at RT and the methanesulfonate **38b** gradually precipitated out. The lilac-coloured solid was drawn off by suction, washed with dichloromethane (2 × 5 ml) and the cis diastereomer was obtained in a yield of 63 % (311 mg) with a melting point of 157 °C.

1H-NMR (600 MHz; DMSO-d_6): 1.14 (m, 1 H); 1.57-1.65 (m, 3 H); 1.75 (m, 4 H); 1.94 (d, 2 H); 2.11 (m, 2 H); 2.30-2.36, 2.37 (m, s, 2 H, 6 H); 2.70 (t, 2 H); 2.96 (d, 2 H); 3.72 (d, 2 H); 3.98 (m, 2 H); 6.93 (t, 1 H); 6.98 (t, 1 H); 7.18 (d, 1 H); 7.37 (d, 1 H); 7.639 (m, 3 H); 7.76 (d, 2 H); 8.89 (m, 1 H); 10.59 (br s; 1 H).

2.11 Synthesis of Compound 39b

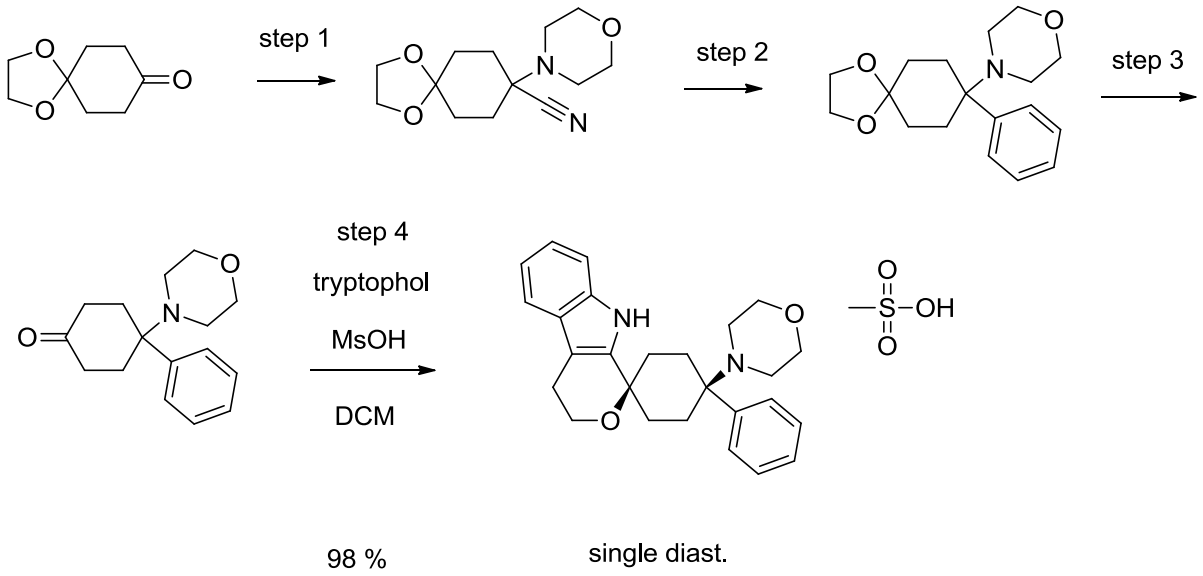


Step 4: 4',9'-Dihydro-4-(4-methylpiperazin-1-yl)-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indole], cis-, methanesulfonate

The ketone (272 mg, 1 mmol) was placed together with tryptophol (161 mg, 1 mmol) in absolute dichloromethane (50 ml). Methanesulfonic acid (0.13 ml, 2 mmol) was then added. The reaction mixture was stirred for 4 h at RT and the methanesulfonate of the cis spiroether gradually precipitated out. The orange-coloured solid was drawn off by suction, washed with dichloromethane (2 × 10 ml) and obtained in a yield of 99 % (600 mg) with a melting point of 96–102 °C.

2.12 Synthesis of Compound 40b

4',9'-Dihydro-4-morpholino-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indole], cis-, methanesulfonate



Step 1: 8-Morpholino-1,4-dioxaspiro[4.5]decane-8-carbonitrile

Morpholine (80.2 g, 0.92 mol), 1,4-dioxaspiro[4.5]decan-8-one (30.0 g, 0.192 mol) and potassium cyanide (30.0 g, 0.46 mol) were added to a mixture of 4 N hydrochloric acid (50 ml) and methanol (30 ml) under ice cooling. The mixture was stirred for 74 h at room temperature and then, after addition of water (80 ml), extracted with diethyl ether (4 × 100 ml). After volume reduction, the residue was dissolved in dichloromethane (200 ml) and dried overnight with magnesium sulfate. The organic phase was concentrated and the ketal was obtained as a yellow solid with a melting point of 95–97 °C in a yield of 95 % (47.8 g).

Step 2: 4-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)morpholine hydrochloride

Bromobenzene (3.0 , 0.019 mol) and a small amount of iodine was added under argon to a mixture of magnesium (2.9 g, 0.119 mol) and anhydrous THF (15 ml). After 30 min the preparation was heated to 50 °C and the Grignard reaction started with boiling. Within 20 min further bromobenzene (15.7 g, 0.1 mol), dissolved in THF (50 ml), was added and the mixture was boiled for 1.5 h under reflux. Under ice cooling, the aminonitrile (10.0 g, 0.0396 mol), dissolved in THF (60 ml), was added to the preparation within 20 min. The reaction mixture was then heated for 4 h to 70 °C. The reaction was terminated after a further reaction time of 16 h at room temperature by adding NH_4Cl solution (60 ml) under ice cooling. The aqueous phase

was extracted with diethyl ether (2 × 70 ml), the organic phase was extracted with water (50 ml) and saturated NaCl solution (50 ml) and concentrated. A yellow crystal mush (11 g) remained which apart from the desired phenyl compound **4** also contained the unreacted aminonitrile **2**. The resulting crude product was dissolved in methyl ethyl ketone (140 ml) and trimethylchlorosilane (7.5 ml, 0.059 mol) was added under ice cooling. After 15 min a white precipitate began to form, which was drawn off by suction after 6 h. 6.5 g (49 %) of the hydrochloride with a melting point of 250–252 °C was obtained.

Step 3: 4-Morpholino-4-phenylcyclohexanone

The hydrochloride (6.5 g, 19.1mmol) was dissolved in 7.5 N hydrochloric acid (22 ml) and stirred for 24 h at room temperature. After completion of the hydrolysis the reaction mixture was extracted with Et_2O (2 × 50 ml). The aqueous phase was made alkaline with 5 N sodium hydroxide solution under ice cooling, extracted with dichloromethane (3 × 50 ml) and concentrated. The ketone was isolated as a beige-coloured solid with a melting point of 116–119 °C and a yield of 84 % (4.1 g).

Step 4: 4',9'-Dihydro-4-morpholino-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indole], cis-, methanesulfonate

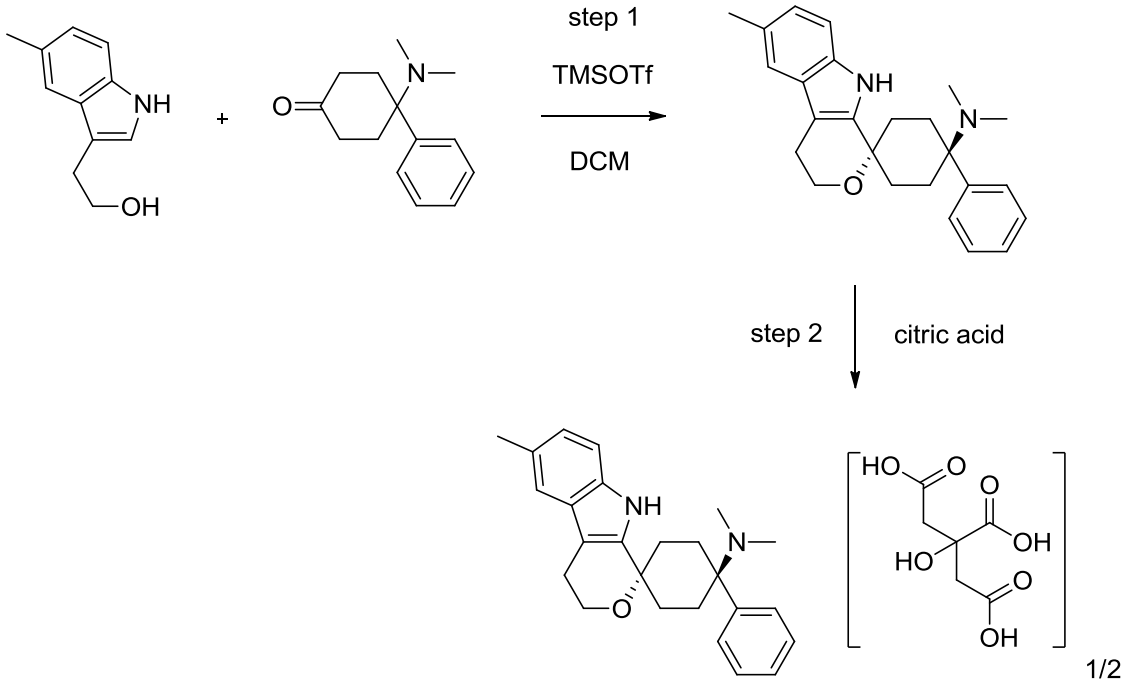
The ketone (259 mg, 1 mmol) was placed together with tryptophol (161 mg, 1 mmol) in absolute dichloromethane (50 ml). Methanesulfonic acid (0.13 ml, 2 mmol) was then added. The preparation was stirred for 16 h at RT and the methanesulfonate of the cis spiroether gradually precipitated. The colourless solid was filtered with suction, washed with dichloromethane (2 × 20 ml) and obtained in a yield of 98 % (492 mg) with a melting point of 175 °C.

1H-NMR (600 MHz; DMSO-d_6): 1.63 (t, 3 H); 1.96 (d, 2 H); 2.36 (t, 4 H); 2.45, 2.46 (app d, 6 H); 2.70 (t, 2 H); 2.90 (d, 2 H); 3.58 (d, 2 H); 3.76 (d, 2 H); 3.91 (d, 2 H); 3.98 (m, 2 H); 6.93 (t, 1 H); 6.98 (t, 1 H); 7.19 (d, 1 H); 7.38 (d, 1 H); 7.64 (m, 3 H); 7.76 (d, 2 H); 9.75 (br, 1 H); 10.62 (br s; 1 H).

The NOESY shows a cis-relationship of the azole NH and the phenyl group in the head position. Thereby, **40b** was shown to be the cis-spiroether.

2.13 Synthesis of Compound 47a [11]

4',9'-Dihydro-*N,N,*6'-trimethyl-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine, trans-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1)



Step 1: 4',9'-Dihydro-*N,N,*6'-trimethyl-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine, trans-

Methanol (30 ml) was added to the solid residue obtained after the solvent had been distilled off, and the mixture was heated, and stirred for 15 h. The suspended solid was filtered off with suction. The trans diastereoisomer of the spiroether was obtained (430 mg, mp 259-270 °C).

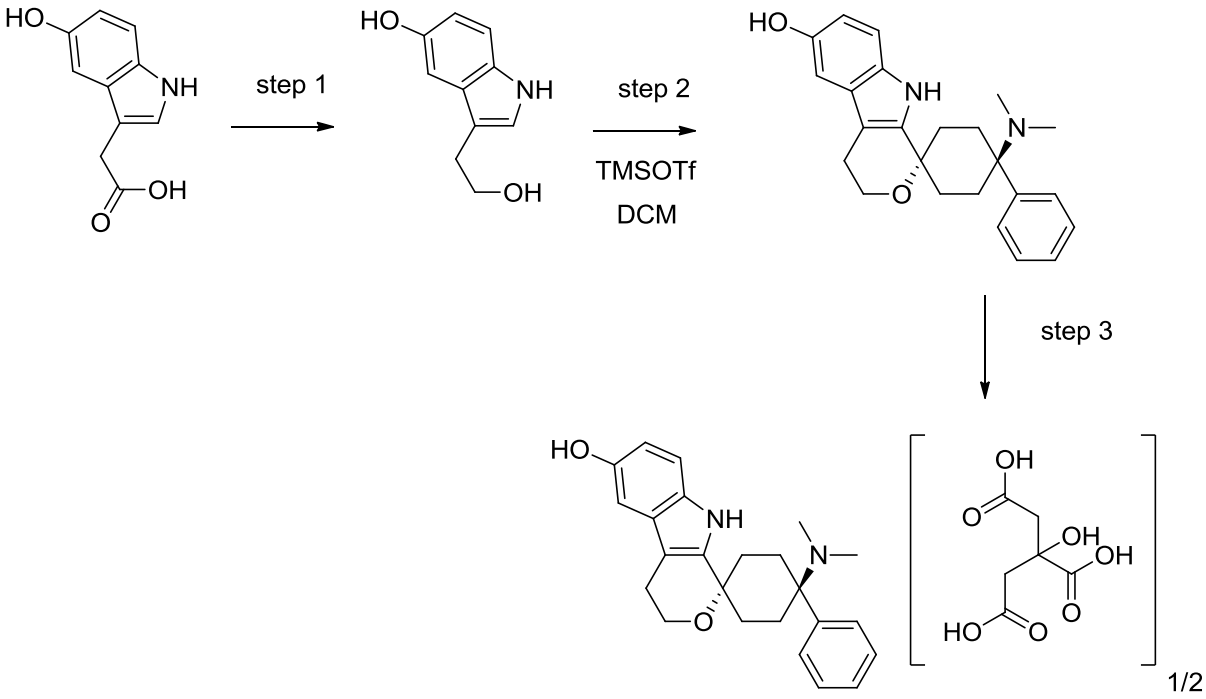
Step 2: 4',9'-Dihydro-*N,N,*6'-trimethyl-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine, trans-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1)

350 mg of the free base were dissolved in hot ethanol (300 ml), and a hot solution of citric acid (300 mg, 1.56 mmol) in ethanol (10 ml) was added. After approx. 15 minutes, crystals precipitated while refluxing. After cooling to approx. 5 °C, the mixture was left to stand for 2 h. The solid formed was filtered with suction. 380 mg (white solid, mp 243-265 °C) of the hemicitrate of the trans spiroether was obtained. 1H-NMR (600 MHz; DMSO-d_6): 1.73-1.58 (m, 4 H); 2.13 (s, 6 H); 2.26 (m,2 H); 2.36 (s, 3 H); 2.55-2.64 (m, 6 H); 3.87 (m, 2 H); 6.86 (d, 1 H); 7.16 (s, 1 H); 7.22 (d, 1 H); 7.29 (t, 1 H); 7.36-7.42 (m, 4 H); 10.59 (br s; 1 H).

The NOESY shows a cis-relationship of the azole NH and the dimethylamino group in the head position. Thereby, **47a** was shown to be the trans-spiroether.

2.14 Synthesis of Compound 48a [12]

4',9'-Dihydro-4-(dimethylamino)-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-6'-ol, trans-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1)



Step 2: 4',9'-Dihydro-4-(dimethylamino)-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-6'-ol, trans-

Methanol (50 ml) was added to the solid residue obtained after the solvent had been distilled off. The clear solution formed was concentrated to approx. 10 ml and left to stand at 5 °C for 2 h. The solid which had precipitated out from methanol was filtered off with suction. The trans diastereomer was obtained (180 mg, mp 252-257 °C).

1H-NMR (400 MHz; DMSO-d6): 1.72-1.84 (m, 4 H); 2.12 (s, 6 H); 2.23 (t; 7 H); 2.54-2.69 (m; 6 H); 3.86 (t, 2 H); 6.55 (dd, 1 H); 6.69 (d; 1 H); 7.12 (d, 1 H); 7.29 (t, 1 H); 7.36-7.42 (m, 4 H); 8.50 (bs, 1 H); 10.40 (bs, 1 H).

Step 3: 4',9'-Dihydro-4-(dimethylamino)-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-6'-ol, trans-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1)

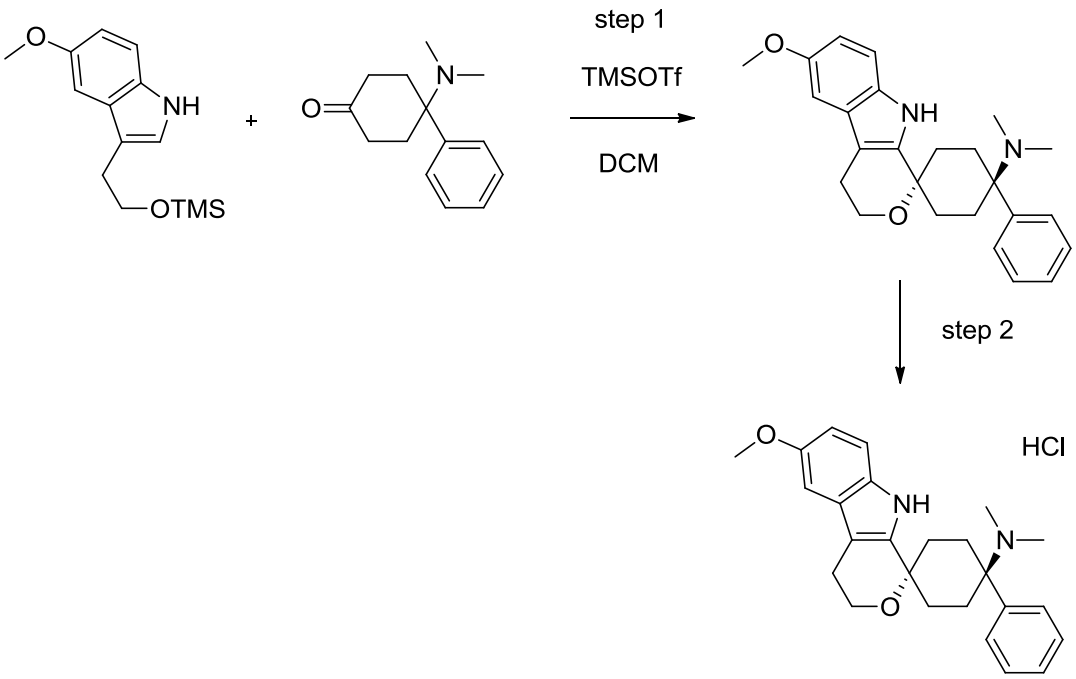
160 mg of the free base were dissolved in hot ethanol (20 ml), and a hot ethanolic citric acid solution (150 mg, 0.78 mmol in 10 ml) was added. A crystalline solid already precipitated out at the boiling point. To bring the crystallization to completion, the mixture was left at 5 °C for 20 h. The solid formed was filtered with suction. The

hemicitrate of the trans spiroether was obtained in a yield of 125 mg (white solid, mp 248-254 °C).

HRMS (ESI) m/z calcd. for $C_{24}H_{28}N_2O_2 + H^+$: calcd.: 377.2224; found: 377.2221.

2.15 Synthesis of Compound 49a [13]

4',9'-Dihydro-6'-methoxy-*N,N*-dimethyl-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine hydrochloride



Step 1: 4',9'-Dihydro-6'-methoxy-*N,N*-dimethyl-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine

Methanol (70 ml) was added to the largely solid residue obtained after the solvent had been distilled off, the mixture was stirred for 2 h and the suspension obtained was filtered. 478 mg of one of the two possible diastereoisomers of the spiroether were obtained with an mp of 244-246 °C.

step 2: 4',9'-Dihydro-6'-methoxy-*N,N*-dimethyl-4-phenyl-3'*H*-spiro[cyclohexane-1,1'-pyrano[3,4-b]indol]-4-amine hydrochloride

430 mg of the free base were dissolved in 2-butanone (25 ml), chlorotrimethylsilane (250 µl, 1.98 mmol) was added and the mixture was stirred at RT for 30 minutes. The solid formed was filtered off with suction. The hydrochloride of the spiroether was obtained in a yield of 396 mg as a white solid with a mp of 279-280 °C.

3 ASSAY DESCRIPTION

3.1 Receptor Binding Assay

The human MOP and NOP binding assays were run in microtiter plates (Costar 3632; Corning Life Sciences, Tewksbury, MA) with wheat germ agglutinin-coated scintillation proximity assay beads (GE Health-care, Chalfont St. Giles, Buckinghamshire, UK). Cell membrane preparations of CHO-K1 cells transfected with the human μ-opioid receptor (MOP receptor; Art.-No. RBHOMM, lot-No. #307-065-A) or with the human nociceptin/orphanin FQ receptor (NOP; Art.-No. RBHORLM, Lot-No.#1956) were purchased from PerkinElmer Life Sciences Inc. (Boston, MA, USA). [^{3}H]Naloxone or [^{3}H]Nociceptin (both purchased from PerkinElmer Life and Analytical Sciences, Boston, MA) were used as a ligands for the MOP or NOP binding studies, respectively. As assay buffer for the MOPand NOP binding studies, 50 mM Tris-HCl, pH 7.4, supplemented with 0.05% sodium azide or 50 mM HEPES, 10 mM $MgCl_2$, 1 mM EDTA (pH 7.4) was used, respectively. The final assay volume of 250 µl per well included 1 nM [^{3}H]naloxone or 0.5 nM [^{3}H]Nociceptin as a ligand and either test compound in dilution series. The test compounds were diluted with 25% dimethyl sulfoxide in H2O to yield a final 0.5% dimethyl sulfoxide concentration, which served as a respective vehicle control. The assays were started by the addition of the beads (1 mg beads per well), which had been preloaded for 15 min at room temperature with 23.4 µg human MOP membranes or 25.4 µg human NOP membranes per 250 µl of final assay volume. After short mixing, the assays were run for 90 min at room temperature. The microtiter plates were then centrifuged for 20 min at 500 rpm, and the signal rate was measured by means of a 1450 Microbeta Trilux (PerkinElmer/Wallac, Freiburg, Germany). Half-maximal inhibitory concentration (IC_{50}) values reflecting 50% displacement of [^{3}H]naloxone- or [^{3}H]Nociceptin-specific receptor binding were calculated by nonlinear regression analysis. Individual experiments were run in duplicate and were repeated three times in independent experiments. The Ki values

for the test substances were calculated from IC_{50} values by transformation according to the Cheng-Prusoff equation (Cheng and Prusoff 1973).

The human KOP and DOP binding assays were run according to Linz et al. 2014[14]

3.2 Agonist-stimulated [^{35}S]GTPγS Binding

The [^{35}S]GTPγS assay was carried out as a homogeneous scintillation proximity assay as described by Gillen et al. (2000), with the following modifications. It was run in microtiter plates (Costar 3632; Corning Life Sciences), in which each well contained 1.5 mg of wheat germ agglutinin-coated scintillation proximity assay beads (GE Healthcare) in a final volume of 200 µl. To test the agonistic activity of test compounds on human recombinant MOP- or NOP-expressing cell membranes from Chinese hamster ovary-K1 cells, 10 µg of membrane proteins per assay were incubated with 0.4 nM [^{35}S]GTPγS (GE Healthcare) and different concentration of agonists in buffer containing 20 mM HEPES, pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 1 mM dithiothreitol, 1.28 mM NaN_3, and 10 µM GDP for 45 min at 25°C. The microtiter plates were thereafter centrifuged for 10 min at 830 g in an Omnifuge 2.ORS microtiter plate centrifuge (Kendro Laboratory Products, Langenselbold, Germany) to sediment the SPA beads. The microtiter plates were sealed with top seals® and the bound radioactivity [cpm] was determined after a delay of 15 min by means of a 1450 Microbeta Trilux (PerkinElmer/Wallac, Freiburg, Germany).

4 In vivo procedures

Animal testing was performed in accordance with the recommendations and policies of the International Association for the Study of Pain[15] and the German Animal Welfare Law. All study protocols were approved by the local government committee for animal research, which is advised by an independent Ethics Committee. Animals were assigned randomly to treatment groups. Different doses and vehicles were tested in a randomized fashion. Although the operators performing the behavioral

tests were not formally ‘blinded’ with respect to the treatment, they were not aware of the study hypothesis or the nature of differences between drugs.
Data were analyzed by means of one- or two-factor analysis of variance (ANOVA), with or without repeated measures, depending on the experimental design. Significance of treatment, time, or treatment by time interaction effects was analyzed by means of Wilks’ Lambda. In case of a significant treatment effect, pair-wise comparisons were performed by post hoc analysis using the Bonferroni test. Results were considered statistically significant if $p < 0.05$. ED10 or ED50 values and 95% confidence intervals (CIs) were determined at the time of the peak effect by semi-logarithmic regression analysis or according to Litchfield and Wilcoxon[16] based on % MPE data.

4.1 Tail-flick Model of Acute Nociceptive Pain

The tail-flick test was carried out in NMRI mice using a modification of the method described by D’Amour and Smith [17]. The tail-flick latency in seconds, the time to withdraw the tail from a radiant heat source (bulb 8V/50W), was measured using a semi-automated device (tail-flick analgesiemeter Typ 55/12/10.fl; Labtec, Dr Hess, Aachen, Germany). The heat source was adjusted to produce a baseline (BL) tail-flick latency of 3−5 s prior to all experiments, and the setting remained constant thereafter. A cut-off time of 12 s was used to prevent tissue damage in animals showing no response. The increase in tail-flick latency was taken as a measure of antinociception and calculated as a percentage of the maximum possible effect (% maximum possible effect [MPE]). The maximum possible antinociceptive effect was defined as the lack of a tail-flick reaction up to the cut-off time of 12 s. The % MPE was calculated according to the formula:

$$[(T1 - T0) / (T2 - T0)] \times 100$$

where T0 and T1 were latencies before and after intravenous or oral drug administration, respectively, and T2 was the cut-off time.

4.2 Model of streptozotocin induced diabetic polyneuropathy

A model of polyneuropathic pain was established in male CD-1 mice according to the method described by Christoph et. al..[18]

Induction of diabetes

Mice were intravenously injected with streptozotocin (200 mg/kg) (Sigma Aldrich Chemie, Munich, Germany) dissolved in citrate solution (citric acid: 0.1 mol/L – $Na_2PO_4x2H_2O$: 0.2 mol/L with final vol. V/V = 53.7/46.3 and final pH 4.6). Diabetes was confirmed one week later by measurement of tail vein blood glucose level with Haemoglukotest 20R–800R (Boehringer Mannheim GmbH, Mannheim, Germany) and a Reflectance colorimeter (Hestia Pharma GmbH, Mannheim, Germany). Mice with a final blood glucose level of at least 25 mM were considered diabetic and were included in the study. Control animals were treated with vehicle solution.

Pain behavior testing

One and two weeks after streptozotocin or vehicle treatment, diabetic and non-diabetic control animals were randomly allocated to the different treatment groups (n = 10). Vehicle controls were tested with each dosing group. Animals were used for a maximum of 2 tests, with a wash-out period of at least 7 days. For nociceptive and hyperalgesic testing, animals were placed on a 50°C hot metal plate under a transparent Plexiglas box (13 x 13 x 10 cm, l x w x h) for periods of 2 min and the number of nocifensive reactions (licking/shaking of the hind paws, licking of the genitals, jumping) was counted 15 min (baseline) before and 15, 30, 45, and 60 min after drug or vehicle treatment. Anti-hyperalgesic effects were expressed as % maximum possible effects (MPE), using baseline values of diabetic and of non-diabetic controls as 0% and 100% MPE, respectively. Statistical data analysis was done by means of ANOVA with post hoc Bonferroni test.

5 References

(1) Example 1 from: Hinze, C.; Aulenbacher, O.; Sundermann, B.; Oberboersch, S.; Friderichs, E.; Englberger, W.; Koegel, B.-Y.; Linz, K.; Schick, H.; Sonnenschein, H.; Henkel, B.; Rose, V. S.; Lipkin, M. J. Preparation of spirocyclic indoles as ORL-1 receptor ligands for the treatment of pain. U.S. Patent 805,357,6, Nov 8, 2011.
(2) Example 24 from Hinze, C.; Aulenbacher, O.; Sundermann, B.; Oberboersch, S.; Friderichs, E.; Englberger, W.; Koegel, B.-Y.; Linz, K.; Schick, H.; Sonnenschein, H.; Henkel, B.; Rose, V. S.; Lipkin, M. J. Preparation of spirocyclic indoles as ORL-1 receptor ligands for the treatment of pain. U.S. Patent 805,357,6, Nov 8, 2011.
(3) Example 25 from Hinze, C.; Aulenbacher, O.; Sundermann, B.; Oberboersch, S.; Friderichs, E.; Englberger, W.; Koegel, B.-Y.; Linz, K.; Schick, H.; Sonnenschein, H.; Henkel, B.; Rose, V. S.; Lipkin, M. J. Preparation of spirocyclic indoles as ORL-1 receptor ligands for the treatment of pain. U.S. Patent 805,357,6, Nov 8, 2011.
(4) Example 49 from Hinze, C.; Aulenbacher, O.; Sundermann, B.; Oberboersch, S.; Friderichs, E.; Englberger, W.; Koegel, B.-Y.; Linz, K.; Schick, H.; Sonnenschein, H.; Henkel, B.; Rose, V. S.; Lipkin, M. J. Preparation of spirocyclic indoles as ORL-1 receptor ligands for the treatment of pain. U.S. Patent 805,357,6, Nov 8, 2011.
(5) Example 9 from Hinze, C.; Aulenbacher, O.; Sundermann, B.; Oberboersch, S.; Friderichs, E.; Englberger, W.; Koegel, B.-Y.; Linz, K.; Schick, H.; Sonnenschein, H.; Henkel, B.; Rose, V. S.; Lipkin, M. J. Preparation of spirocyclic indoles as ORL-1 receptor ligands for the treatment of pain. U.S. Patent 805,357,6, Nov 8, 2011.
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