Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Stereoselective Synthesis and Structure-Affinity Relationships of Bicyclic κ Receptor Agonists

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Experimental

Chemistry general

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography (tlc): Silica gel 60 F_{254} plates (Merck). Flash chromatography (fc): Silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column, height of SiO_2 column, fraction size, eluent, R_f value. Melting point: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. MS: MAT GCQ (Thermo-Finnigan); EI = electron impact, ESI = electrospray ionization. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Mercury-400BB spectrometer (Varian); δ in ppm related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. HPLC method 1: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher® 60 RP-select B (5 μm), 250-4 mm; flow rate: 1.00 mL/min; injection volume: 5.0 μL; detection at λ = 210 nm; solvents: A: water with 0.05% (v/v) trifluoroacetic acid; B: acetonitrile with 0.05% (v/v) trifluoroacetic acid: gradient elution: (A%): 0 min: 90%, 4 min: 90%, 29 min: 0%, 31 min: 0%, 31.5 min: 90%, 40 min: 90%. HPLC method 2: Equipment: pump: HPLC pump 64 (Knauer); UV-Detector: Variable Wavelenght Monitor (Knauer); data acquisition: D-2500 Chromato-Integrator (Merck Hitachi); injection volume: 20.0 μL; stop time: 2 × t_R; A: column: LiChroCART® 250-4 with Superspher® 100 RP-18; solvent: methanol / water = 75 : 25 + 0.1 % triethylamine; flow rate: 0.6 mL/min; detection: wavelength: 235 nm; B: column: LiChroCART® 250-4 with Superspher® 100 RP-18; solvent: acetonitrile / water = 70 : 30 + 0.1 % triethylamine; flow rate: 1.0 mL/min; detection: wavelength: 254 nm; C: column: phenomenex Gemini 5 μm C18 100A, 250 – 21.2 mm; solvent: methanol / water = 50 : 50 + 0.1 % triethylamine; flow rate: 0.8 mL/min; detection: wavelength: 235 nm.

2-(3,4-Dichlorophenyl)-1-[(*1RS,5SR,6RS*)-6-(pyrrolidin-1-yl)-1,4-diazabicyclo[3.3.1]nonan-4-yl]ethanone (7a)

X-ray crystal structure analysis: Recrystallization from diethyl ether/acetonitrile gave crystals of **7a** which were suitable for X-ray crystal structure analysis.

The crystallographic data of **7a**

Crystal data for $C_{19}H_{25}Cl_2N_3O$, M = 382.32, triclinic, space group $P\bar{1}$ (No. 2), a = 7.118(1), b = 11.118(1), c = 12.171(1) Å, α = 94.46(1), β = 107.28(1), γ = 93.94(1)°, V = 912.7(2) Å^3, D_c = 1.391 g cm^{-3}, μ = 3.293 mm^{-1}, Z = 2, λ = 1.54178 Å, T = 293(2) K, 10437 reflections collected ($\pm h$, $\pm k$, $\pm l$), [($sin\theta$)/λ] = 0.60 Å^{-1}, 3119 independent (R_{int} = 0.062) and 2486 observed reflections [$I \geq 2\sigma(I)$], 226 refined parameters, R = 0.061, wR^2 = 0.204, CCDC. The data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN,[1] absorption correction Denzo,[2] structure solution SHELXS-97,[3] structure refinement SHELXL-97,[4] graphics SCHAKAL (E. Keller, 1997).

Comments on CHECKCIF: PLAT029: Data collection on the Cu-CCD-diffractometer has always problems with the completeness due to geometrical limitations, especially in triclinic space groups. In this case there were additional problems in merging (about 5 % omitted) due to crystal quality.

2-Phenyl-1-[(1*RS*,5*SR*,6*RS*)-6-(pyrrolidin-1-yl)-1,4-diazabicyclo[3.3.1]nonan-4-yl]ethanone (8a)

A solution of **5a** (160 mg, 0.56 mmol) containing 10 % Pd-C (20 mg) in anhydrous methanol (15 mL) was stirred under an atmosphere of hydrogen at room temperature for 2 h. The reaction mixture was filtered through Celite and the filtrate was evaporated. The crude product was dissolved in CH_2Cl_2 (15 mL). Then DCC (173 mg, 0.84 mmol) and phenylacetic acid (115 mg, 0.84 mmol) were added. After 3 h the reaction mixture was washed with 1 M

NaOH. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9.5/0.5 with 0.5 % NH_3, R_f = 0.39) to afford 136 mg (78 %) of **8a** as a colourless oil. $C_{19}H_{27}N_3O$ (M_r = 313.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.67 – 1.84 (m, 6H, 2x 7-H and 4x N(CH_2CH_2)$_2$), 2.28 – 2.37 (m, 0.80H, 6-H), 2.38 – 2.49 (m, 2H, N(CH_2CH_2)$_2$), 2.53 – 2.60 (m, 0.20H, 6-H), 2.70 – 2.76 (m, 2H, N(CH_2CH_2)$_2$), 2.77 – 3.00 (m, 4H, NCH_2), 3.02 – 3.18 (m, 2H, NCH_2), 3.25 (td, J = 13.3/5.5 Hz, 0.20H. NCH_2), 3.39 (dd, J = 13.3/6.3 Hz, 0.80H, NCH_2), 3.56 (td, J = 13.3/5.5 Hz, 0.80H, NCH_2), 3.74 (d, J = 15.7 Hz, 0.80H, $COCH_2$Ar), 3.81 (d, J = 15.7 Hz, 0.80H, $COCH_2$Ar), 3.78 – 3.82 (m, 0.40H, 0.20x 5-H and 0.20x $COCH_2$Ar), 3.89 (d, J = 15.7 Hz, 0.20H, $COCH_2$Ar), 4.18 (dd, J = 13.3/6.3 Hz, 0.20H, NCH_2), 4.75 (s broad, 0.80H, 5-H), 7.18 – 7.31 (m, 5H, arom. H). Ratio of rotational isomers 80:20. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1629 (s, C=O), 695 (m, arom. out of plane). MS (EI): *m/z* [%] = 313 (M, 27). HPLC (Method 2C): t_R = 13.5 min, purity 96.4 %.

Phenyl-[(*1RS,5SR,6RS*)-6-(pyrrolidin-1-yl)-1,4-diazabicyclo[3.3.1]nonan-4-yl]methanone (9a)

A solution of **5a** (188 mg, 0.66 mmol) containing 10 % Pd-C (20 mg) in anhydrous methanol (15 mL) was stirred under an atmosphere of hydrogen at room temperature for 2 h. The reaction mixture was filtered through Celite and the filtrate was evaporated. The crude product was dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. Then triethylamine (140 µL, 1.00 mmol) and benzoyl chloride (115 µL, 1.00 mmol) were added. After 1.5 h the reaction mixture was washed with 1 M NaOH. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1 with 1 % NH_3, R_f = 0.45) to afford 95 mg (48 %) of

9a as a colourless oil. $C_{18}H_{25}N_3O$ (M_r = 299.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.61 – 1.79 (m, 4H, N(CH_2CH_2)$_2$), 1.81 – 2.04 (m, 2H, 7-H), 2.10 – 2.18 (m, 2x 0.32H, N(CH_2CH_2)$_2$), 2.21 – 2.30 (m, 0.68H, 6H), 2.40 – 2.44 (m, 3x 0.32H, N(CH_2CH_2)$_2$ and 6-H), 2.48 – 2.58 (m, 2x 0.68H, N(CH_2CH_2)$_2$), 2.62 – 2.72 (m, 2x 0.68H, N(CH_2CH_2)$_2$), 2.79 – 2.97 (m, 2H, NCH_2), 3.02 – 3.19 (m, 3.68H, NCH_2), 3.26 (dd, J = 13.3/5.5 Hz, 0.68H, NCH_2), 3.29 – 3.40 (m, 0.32H, NCH_2), 3.53 (td, J = 13.3/5.5 Hz, 0.32H. NCH_2), 3.72 (td, J = 13.3/4.7 Hz, 0.68H, NCH_2), 3.90 (s broad, 0.32H, 5-H), 4.02 (dd, J = 13.3/5.5 Hz, 0.32H, NCH_2), 4.81 (s broad, 0.68H, 5-H), 7.38 – 7.49 (m, 5H, arom. H). Ratio of rotational isomers 68:32. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1618 (s, C=O), 727 and 690 (m, arom. out of plane). MS (EI): *m/z* [%] = 299 (M, 27), 77 (C_6H_5, 82). HPLC (Method 2C): t_R = 10.7 min, purity 99.1 %.

[(*1RS,5SR,6RS*)-6-(Pyrrolidin-1-yl)-4-(4-methylphenylsulfonyl)-1,4-diazabicyclo[3.3.1]nonane (10a)

A mixture of **5a** (234 mg, 0.82 mmol), 10 % Pd-C (25 mg) and anhydrous methanol (10 mL) was stirred under an atmosphere of hydrogen at room temperature for 2 h. The reaction mixture was filtered through Celite and the filtrate was evaporated. The crude product was dissolved in CH_2Cl_2 (15 mL). Then triethylamine (140 µL, 1.00 mmol) and tosyl chloride (190 mg, 1.00 mmol) were added. After 3 h the reaction mixture was washed with 1 M NaOH. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography [∅ = 3 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9.5/0.5 + 0.5 % NH_3, R_f = 0.14 (CH_2Cl_2/MeOH 9/1)] to afford 99 mg (35 %) of **10a** as a colourless oil. $C_{18}H_{27}N_3O_2S$ (M_r = 349.5). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.67 – 1.83 (m, 5H, 1x 7-H and 4x N(CH_2CH_2)$_2$), 1.85 – 1.98 (m, 1H, 7-H), 2.30 (ddd, J = 12.5/7.0/3.9 Hz, 1H, 6-H), 2.39 (s, 3H, $ArCH_3$), 2.42 – 2.51 (m, 2H, NCH_2), 2.72 – 2.81 (m, 4H, N(CH_2CH_2)$_2$), 2.90 – 2.97 (m, 1H, NCH_2), 2.99 – 3.11 (m, 3H, NCH_2), 3.37 – 3.52 (m,

2H, NC*H*$_2$), 4.07 (s broad, 1H, 5-H), 7.24 (d, J = 7.8 Hz, 2H, 3'-H$_{tosylate}$, 5'-H$_{tosylate}$), 7.88 (d, J = 7.8 Hz, 2H, 2'-H$_{tosylate}$, 6'-H$_{tosylate}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1152 (s, S=O), 815 (m, arom. out of plane). MS (EI): *m/z* [%] = 349 (M, 3), 194 (M – $SO_2C_6H_4CH_3$, 14). HPLC (Method 1): t_R = 12.0 min, purity 96.2 %.

[(*1RS,5SR,6RS*)-N,N-Dimethyl-4-(4-methylphenylsulfonyl)-1,4-diazabicyclo[3.3.1]nonan-6-amine (10b)

A mixture of **5b** (50 mg, 0.17 mmol), 10 % Pd-C (5 mg) and anhydrous methanol (10 mL) was stirred under an atmosphere of hydrogen at room temperature for 2 h. The reaction mixture was filtered through Celite and the filtrate was evaporated. The crude product was dissolved in CH_2Cl_2 (15 mL). Then triethylamine (100 µL, 0.72 mmol) and tosyl chloride (67 mg, 0.35 mmol) were added. After 3 h the reaction mixture was washed with 1 M NaOH. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1, R_f = 0.15) to afford 38 mg (80 %) of **10b** as a pale yellow oil. $C_{18}H_{29}N_3O_2S$ (M_r = 351.2). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.00 (t, J = 7.0 Hz, 6H, N(CH_2CH_3)$_2$, 1.63 – 1.74 (m, 1H, 7-H), 1.97 – 2.11 (m, 1H, 7-H), 2.39 (s, 3H, Ar*CH*$_3$), 2.60 – 2.82 (m, 5H, 6-H, 2x 9-H and 2x 2-H or 3-H), 2.83 – 2.94 (m, 4H, N(*CH*$_2$CH$_3$)$_2$, 3.00 – 3.14 (m, 2H, 8-H), 3.43 – 3.59 (m, 2H, 2x 2-H or 3-H), 4.08 (s broad, 1H, 5-H), 7.26 (d, J = 7.8 Hz, 2H, 3'-H$_{tosylate}$, 5'-H$_{tosylate}$), 7.78 (d, J = 7.8 Hz, 2H, 2'-H$_{tosylate}$, 6'-H$_{tosylate}$). ^{13}C NMR ($CDCl_3$): δ [ppm] = 13.4 (2C, NCH$_2$*C*H$_3$), 21.7 (1C, Ar*C*H$_3$), 28.6 (1C, C-7), 42.6 (2C, N*C*H$_2$CH$_3$), 42.9 (1C, C-2 or C-3), 46.8 (1C, C-6), 50.2 (1C, C-2 or C-3), 51.5 (1C, C-8), 53.3 (1C, C-9), 60.1 (1C, C-5), 127.3 (2C, C-2$_{tosylate}$, C-6$_{tosylate}$), 130.0 (2C, C-3$_{tosylate}$, C-5$_{tosylate}$), 138.9 (1C, C-1$_{tosylate}$), 143.3 (1C, C-4$_{tosylate}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1157 (s, S=O), 814 (m,

arom. out of plane). MS (ESI): *m/z* [%] = 352 (MH, 100). HPLC (Method 1): t_R = 10.5 min, purity 98.2 %.

4-Benzyl-1,4-diazabicyclo[3.3.1]nonan-6-one Dimethyl Acetal (12)

Under N_2 atmosphere trimethyl orthoformate (4.4 mL, 40 mmol) was added to a solution of **4** (920 mg, 4.0 mmol) and p-toluenesulfonic acid (1520 mg, 8.0 mmol) in methanol (50 mL). The mixture was heated to reflux for 16 h. Then a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography [∅ = 3 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9.5/0.5 → 9/1, R_f = 0.27 (CH_2Cl_2/MeOH 9/1)] to afford 871 mg (79 %) of **12** as a colourless oil. $C_{16}H_{24}N_2O_2$ (M_r = 276.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.89 (dd, J = 14.1/4.7 Hz, 1H, 7-H), 2.00 – 2.11 (m, 1H, 7-H), 2.46 – 2.54 (m, 1H, NC*H*$_2$), 2.76 – 2.88 (m, 3H, 5-H and 2x NC*H*$_2$), 2.93 (dd, J = 14.1/6.3 Hz, 1H, NC*H*$_2$), 3.04 – 3.17 (m, 3H, NC*H*$_2$), 3.15 (s, 3H, OC*H*$_3$), 3.24 (s, 3H, OC*H*$_3$), 3.26 – 3.33 (m, 1H, NC*H*$_2$), 3.79 (d, J = 14.1 Hz, 1H, PhC*H*$_2$N), 3.90 (d, J = 14.1 Hz, 1H, PhC*H*$_2$N), 7.18 – 7.34 (m, 5H, arom. H). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1108 (s, C-O), 732 and 697 (m, arom. out of plane). MS (EI): *m/z* [%] = 276 (M, 100), 245 (M – OCH_3, 15), 91 ($PhCH_2$, 16).

4-Tosyl-1,4-diazabicyclo[3.3.1]nonan-6-one Dimethyl Acetal (13)

A mixture of **12** (857 mg, 3.1 mmol), 10 % Pd-C (85 mg) and anhydrous methanol (20 mL) was stirred under an atmosphere of hydrogen at room temperature for 2 h. The reaction mixture was filtered through Celite and the filtrate was evaporated. The crude product was dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. Then triethylamine (650 µL, 4.7 mmol) and tosyl chloride (896 mg, 4.7 mmol) were added. After 1 h the reaction was terminated by addition of 1 M NaOH. The organic layer was separated and the aqueous layer was extracted

with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography [∅ = 3 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9.5/0.5 → 9/1, R_f = 0.56 (CH_2Cl_2/MeOH 9/1)] to afford 932 mg (80 %) of **13** as a colourless oil. $C_{16}H_{24}N_2O_4S$ (M_r = 340.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.66 – 1.78 (m, 1H, 7-H), 1.87 (dd, J = 14.9/5.5 Hz, 1H, 7-H), 2.40 (s, 3H, ArC*H*$_3$), 2.74 – 2.82 (m, 2H, NC*H*$_2$), 2.91 (dd, J = 14.1/7.0 Hz, 1H, NC*H*$_2$), 2.97 – 3.11 (m, 3H, NC*H*$_2$), 3.09 (s, 3H, OC*H*$_3$), 3.20 (s, 3H, OC*H*$_3$), 3.29 – 3.38 (m, 1H, NC*H*$_2$), 3.42 – 3.49 (m, 1H, NC*H*$_2$), 4.01 (s, 1H, 5-H), 7.26 (d, J = 8.6 Hz, 2H, 3'-$H_{tosylate}$, 5'-$H_{tosylate}$), 7.70 (d, J = 8.6 Hz, 2H, 2'-$H_{tosylate}$, 6'-$H_{tosylate}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1156 (s, S=O), 1102 (s, C-O), 815 (m, arom. out of plane). MS (EI): *m/z* [%] = 340 (M, 6), 309 (M – OCH_3, 7), 185 (M – $SO_2C_6H_4CH_3$, 28). HPLC (Method 1): t_R = 14.5 min, purity 98.0 %.

(*1RS,5SR,6RS*)-4-Tosyl-1,4-diazabicyclo[3.3.1]nonan-6-yl Methanesulfonate (16)

Under N_2 atmosphere mesyl chloride (25 µL, 0.32 mmol) was added to a solution of **15** (45 mg, 0.15 mmol) and NEt_3 (70 µL, 0.50 mmol) in CH_2Cl_2 (10 mL). After 2 h at rt the reaction was terminated by addition of 0.1 M NaOH. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (∅ = 2 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1, R_f = 0.53) to afford 42 mg (83 %) of **16** as a pale yellow oil. $C_{15}H_{22}N_2O_5S_2$ (M_r = 374.5). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.05 – 2.14 (m, 2H, 7-H), 2.41 (s, 3H, ArC*H*$_3$), 2.77 – 2.91 (m, 3H, NC*H*$_2$), 2.93 – 3.08 (m, 3H, NC*H*$_2$), 3.10 (s, 3H, O_2SC*H*$_3$), 3.31 (dd, J = 14.1/6.3Hz, 1H, NC*H*$_2$), 3.44 – 3.54 (m, 1H, NC*H*$_2$), 4.15 – 4.19 (m, 1H, 5-H), 4.91 (ddd, J = 11.0/7.8/3.9 Hz, 1H, 6-H), 7.29 (d, J = 7.8 Hz, 2H, 3'-$H_{tosylate}$, 5'-$H_{tosylate}$), 7.70 (d, J = 7.8 Hz, 2H, 2'-$H_{tosylate}$, 6'-$H_{tosylate}$). IR (neat): $\tilde{\nu}$

[cm^{-1}] = 1155 (s, S=O), 815 (m, arom. out of plane). MS (EI): *m/z* [%] = 374 (M, 14), 279 (M – $S0_2CH_3$, 11), 219 (M – $SO_2C_6H_4CH_3$, 89).

(*1RS,5SR,6RS*)-4-Tosyl-1,4-diazabicyclo[3.3.1]nonan-6-yl Toluene-4-sulfonate (17)

Under N_2 atmosphere tosyl chloride (954 mg, 5.0 mmol) was added to a solution of **15** (750 mg, 2.5 mmol), 4-dimethylaminopyridine (340 mg, 2.8 mmol) and NEt_3 (1050 µL, 7.5 mmol) in CH_2Cl_2 (50 mL). After 16 h at rt the reaction was terminated by addition of 0.1 M NaOH. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (K_2CO_3), filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (∅ = 4 cm, V = 20 mL, CH_2Cl_2/MeOH 9.5/0.5, R_f = 0.26) to afford 790 mg (70 %) of **17** as a colourless oil. $C_{21}H_{26}N_2O_5S_2$ (M_r = 450.6). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.92 – 2.02 (m, 2H, 7-H), 2.40 (s, 3H, ArC*H*$_3$), 2.43 (s, 3H, ArC*H*$_3$), 2.74 (d, J = 14.1 Hz, 1H, 9-H), 2.84 (dd, J = 14.1/4.7 Hz, 1H, NC*H*$_2$), 2.93 – 3.13 (m, 4H, NC*H*$_2$), 3.33 (td, J = 13.3/4.7 Hz, 1H, NC*H*$_2$), 3.42 (dd, J = 13.3/7.0Hz, 1H, NC*H*$_2$), 4.03 – 4.06 (m, 1H, 5-H), 4.57 (td, J = 9.4/3.9 Hz, 1H, 6-H), 7.24 (d, J = 7.8 Hz, 2H, 3'-$H_{tosylate}$, 5'-$H_{tosylate}$), 7.32 (d, J = 7.8 Hz, 2H, 3'-$H_{tosylate}$, 5'-$H_{tosylate}$), 7.72 (d, J = 7.8 Hz, 2H, 2'-$H_{tosylate}$, 6'-$H_{tosylate}$), 7.78 (d, J = 7.8 Hz, 2H, 2'-$H_{tosylate}$, 6'-$H_{tosylate}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1157 (s, S=O), 814 (m, arom. out of plane). MS (EI): *m/z* [%] = 450 (M, 7), 295 (M – $SO_2C_6H_4CH_3$, 21), 125 (M – $SO_2C_6H_4CH_3$ – $OSO_2C_6H_4CH_3$, 100). HPLC (Method 1): t_R = 19.0 min, purity 98.0 %.

5-Azido-4-tosyl-1,4-diazabicyclo[4.2.1]nonane (18a,b)

Under N_2-atmosphere a mixture of **16** (100 mg, 0.27 mmol) and sodium azide (130 mg, 2.0 mmol) in dry DMF (5 mL) was heated to 80 °C. After 14 h the reaction mixture was diluted with 2 M NaOH and extracted with small portions of ethyl acetate (6x). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The

residue was purified by flash column chromatography [∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 50/1 → 9.5/0.5, R_f= 0.23 (**18a**) and 0.20 (**18b**) with CH_2Cl_2/MeOH 9.5/0.5].

18a: $C_{14}H_{19}N_3O_2S$ (M_r = 321.4), pale yellow oil, 19.2 mg (22 %). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.78 – 1.89 (m, 1H, 7-H), 1.97 – 2.08 (m, 1H, 7-H), 2.37 (s, 3H, ArC*H*$_3$), 2.54 (d broad, J = 14.1 Hz, 1H, 2-H or 3-H), 2.63 – 2.79 (m, 3H, 1x 2-H or 3-H, 1x 8-H and 1x 9-H), 2.80 – 2.97 (m, 4H, 6-H, 1x 2-H or 3-H, 1x 8-H and 1x 9-H), 3.49 (d broad, J = 14.1 Hz, 1H, 1x 2-H or 3-H), 5.73 (d, J = 7.0 Hz, 1H, 5-H), 7.27 (d, J = 8.6 Hz, 2H, 3'-$H_{tosylate}$, 5'-$H_{tosylate}$), 7.70 (d, J = 8.6 Hz, 2H, 2'-$H_{tosylate}$, 6'-$H_{tosylate}$). ^{13}C NMR ($CDCl_3$): δ [ppm] = 21.8 (1C, Ar*C*H$_3$), 28.1 (1C, C-7), 43.4 (1C, C-2 or C-3), 43.9 (1C, C-6), 52.5 (1C, C-8 or C-9), 55.3 (1C, C-8 or C-9), 55.6 (1C, C-2 or C-3), 74.4 (1C, C-5), 127.6 (2C, C-$2_{tosylate}$, C-$6_{tosylate}$), 130.1 (2C, C-$3_{tosylate}$, C-$5_{tosylate}$), 137.5 (1C, C-$1_{tosylate}$), 143.5 (1C, C-$4_{tosylate}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2097 (s, N=N=N), 1149 (s, S=O), 814 (m, arom. out of plane). MS (EI): *m/z* [%] = 321 (M, 5), 279 (M – N_3, 61).

18b: $C_{14}H_{19}N_3O_2S$ (M_r = 321.4), colourless oil, 27.8 mg (32 %). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.66 – 1.75 (m, 1H, 7-H), 1.78 – 1.89 (m, 1H, 7-H), 2.37 (s, 3H, ArC*H*$_3$), 2.45 – 2.52 (m, 1H, 6-H), 2.58 (dd, J = 13.4/5.7 Hz, 1H, 9-H), 2.61 – 2.71 (m, 1H, 2-H), 2.77 – 2.87 (m, 1H, 8-H), 2.98 – 3.22 (m, 4H, 1x 2-H, 1x 3-H, 1x 8-H and 1x 9-H), 3.41 (dd, J = 15.3/5.7 Hz, 1H, 1x 3-H), 5.47 (d, J = 3.8 Hz, 1H, 5-H), 7.26 (d, J = 8.6 Hz, 2H, 3'-$H_{tosylate}$, 5'-$H_{tosylate}$), 7.66 (d, J = 8.6 Hz, 2H, 2'-$H_{tosylate}$, 6'-$H_{tosylate}$). ^{13}C NMR ($CDCl_3$): δ [ppm] = 21.8 (1C, Ar*C*H$_3$), 28.5 (1C, C-7), 41.7 (1C, C-3), 44.2 (1C, C-6), 49.5 (1C, C-9), 57.1 (1C, C-2), 57.2 (1C, C-8), 75.0 (1C, C-5), 127.5 (2C, C-$2_{tosylate}$, C-$6_{tosylate}$), 130.1 (2C, C-$3_{tosylate}$, C-$5_{tosylate}$), 136.8 (1C, C-$1_{tosylate}$), 144.3 (1C, C-$4_{tosylate}$). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2098 (s, N=N=N), 1158 (s, S=O), 814 (m, arom. out of plane). MS (EI): *m/z* [%] = 321 (M, 4), 279 (M – N_3, 31).

5-Benzyl-12-methyl-1,2,3,4,5,6-hexahydro-2,6-methano-[1,4]diazocino[6,7-b]quinoline (26)

A solution of **4** (1000 mg, 4.3 mmol) and o-aminoacetophenone (1040 µL, 8.6 mmol) in glacial acetic acid (30 mL) was heated to reflux under N_2 for 16 h. Then the reaction mixture was cooled to room temperature, made alkaline with KOH solution and extracted with CH_2Cl_2 (3x). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography [∅ = 4 cm, l = 15 cm, V = 20 mL, CH_2Cl_2/MeOH 50/1 → 9.5/0.5, R_f = 0.28 (CH_2Cl_2/MeOH 9/1)] to give 1034 mg (73 %) of **26** as a colourless solid, mp 68 °C. $C_{22}H_{23}N_3$ (M_r = 329.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.06 – 2.15 (m, 4-H), 2.37 (dd, J = 11.7/3.1 Hz, 1H, 4-H), 2.57 (s, 3H, C*H*$_3$), 3.00 (d broad, J = 13.3 Hz, 1H, 3-H), 3.15 (d, J = 13.3 Hz, 1H, PhC*H*$_2$N), 3.28 (d, J = 13.3 Hz, 1H, 13-H), 3.42 (td, J = 13.3/4.7 Hz, 1H, 3-H), 3.64 (d, J = 13.3 Hz, 1H, 13-H), 3.88 (s broad, 1H, 6-H), 4.06 (d, J = 18.0 Hz, 1H, 1-H), 4.07 (d, J = 13.3 Hz, 1H, PhC*H*$_2$N), 4.41 (d, J = 18.0 Hz, 1H, 1-H), 7.22 – 7.27 (m, 1H, 4'-H_{phenyl}), 7.32 (t, J = 7.0 Hz, 2H, 3'-H_{phenyl} and 5'-H_{phenyl}), 7.44 (d, J = 7.0 Hz, 2H, 2'-H_{phenyl} and 6'-H_{phenyl}), 7.56 (t, J = 7.8 Hz, 1H, 10-H), 7.70 (t, J = 7.8 Hz, 1H, 9-H), 8.05 (d, J = 7.8 Hz, 1H, 11-H), 8.13 (d, J = 7.8 Hz, 1H, 8-H). ^{13}C NMR ($CDCl_3$): δ [ppm] = 13.2 (1C, *C*H$_3$), 45.0 (1C, C-4), 52.2 (1C, C-13), 53.0 (1C, C-1), 54.9 (1C, C-3), 56.1 (1C, C-6), 59.9 (1C, Ph*C*H$_2$N), 123.5 (1C, C-11), 126.4 (1C, C-10), 126.5 (1C, C-12a), 127.1 (1C, C-4'$_{phenyl}$), 127.7 (1C, C-11a), 128.4 (2C, C-3'$_{phenyl}$ and C-5'$_{phenyl}$), 128.7 (1C, C-9), 129.6 (2C, C-2'$_{phenyl}$ and C-6'$_{phenyl}$), 130.3 (1C, C-8), 138.0 (1C, C-1'$_{phenyl}$), 140.2 (1C, C-12), 168.2 (1C, C-7a), 185.0 (1C, C-6a). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 1495 (m, C=C), 1445 (m, C-H), 756, 731, 697 (s, arom. out of plane). MS (EI): *m/z* [%] = 329 (M, 84), 238 (M - $PhCH_2$, 4), 91 ($PhCH_2$, 10). HPLC (Method 2A): t_R = 15.6 min, purity 99.1 %. HPLC (Method 2B): t_R = 14.0 min, purity 98.7 %.

12-Methyl-1,2,3,4,5,6-hexahydro-2,6-methano-[1,4]diazocino[6,7-b]quinoline (27)

Dry ammonium formate (794 mg, 12.6 mmol) was added to a solution of **26** (832 mg, 2.52 mmol) containing 10 % Pd-C (85 mg) in anhydrous methanol (50 mL) under an atmosphere

of nitrogen. The reaction mixture was heated to reflux for 3 h, then additional ammonium formate (794 mg, 12.6 mmol) was added. After heating the mixture to reflux for 16 h, it was cooled and filtered through Celite. The filtrate was evaporated in vacuo. The residue was purified by flash column chromatography [∅ = 4 cm, l = 15 cm, V = 20 mL, CH_2Cl_2/MeOH 9/1, R_f = 0.35 (CH_2Cl_2/MeOH 9/1 + 1 % NH_3)] to give 535 mg (89 %) of **27** as a pale yellow solid, mp 131 °C. $C_{15}H_{17}N_3$ (M_r = 239.3). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.09 (s broad, 1H, N*H*), 2.49 (dd, J = 12.5/3.9 Hz, 1H, 4-H), 2.57 (s, 3H, C*H*$_3$), 2.63 (td, J = 12.5/3.9 Hz, 1H, 4-H), 2.99 (d broad, J = 13.3 Hz, 1H, 3-H), 3.19 (d broad, J = 13.3 Hz, 1H, 13-H), 3.45 (td, J = 13.3/4.7 Hz, 1H, 3-H), 3.66 (d broad, J = 13.3 Hz, 1H, 13-H), 3.95 (s broad, 1H, 6-H), 4.07 (d, J = 18.0 Hz, 1H, 1-H), 4.40 (d, J = 18.0 Hz, 1H, 1-H), 7.51 – 7.56 (m, 1H, 10-H), 7.64 – 7.69 (m, 1H, 9-H), 8.00 – 8.04 (m, 2H, 8-H and 11-H). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3197 (m, NH), 1499 (m, C=C), 1448 (m, C-H), 755 and 732 (m, arom. out of plane). MS (EI): *m/z* [%] = 239 (M, 100).

5-Benzyl-10-methoxy-2,3,4,5,6,7-hexahydro-2,6-methano-1H-[1,4]diazocino[6,7-b]indole (29)

A solution of **4** (200 mg, 0.87 mmol) and p-methoxyphenylhydrazine hydrochloride (303 mg, 1.74 mmol) in HCl(g)-saturated ethanol (70 mL) was heated to reflux under N_2 for 14 h. Then the reaction mixture was cooled to room temperature, made alkaline with KOH solution and extracted with diethyl ether (3x). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (∅ = 2 cm, l = 15 cm, V = 10 mL, CH_2Cl_2/MeOH 9/1, R_f = 0.12). After evaporation a solid (159 mg) was obtained, which was recrystallized from ethanol/water to give 80 mg (28 %) of **29** as a colourless solid, mp 215 °C (under decomposition). $C_{21}H_{23}N_3O$ (M_r = 333.4). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.22 (td, J = 11.7/3.9 Hz, 1H, 4-H), 2.33 (dd, J = 11.7/3.9 Hz, 1H, 4-H), 2.95 (d broad, J = 14.1 Hz, 1H, 3-H), 3.12 (d broad, J = 12.5 Hz, 1H,

12-H), 3.34 (dd, J = 13.3/4.7 Hz, 1H, 3-H), 3.40 (d, J = 13.3 Hz, 1H, PhC*H*$_2$N), 3.52 (dd, J = 12.5/1.6 Hz, 1H, 12-H), 3.59 (d, J = 13.3 Hz, 1H, 1-H), 3.66 (s broad, 1H, 6-H), 3.87 (s, 3H, OC*H*$_3$), 3.91 (d, J = 16.4 Hz, 1H, 1-H), 4.37 (d, J = 16.4 Hz, 1H, 1-H), 6.87 (dd, J = 8.6/2.3 Hz, 1H, 9-H), 6.94 (d, J = 2.3 Hz, 1H, 11-H), 7.25 – 7.31 (m, 2H, 8-H and 4'-H$_{phenyl}$), 7.34 – 7.42 (m, 4H, 2'-H$_{phenyl}$, 3'-H$_{phenyl}$, 5'-H$_{phenyl}$ and 6'-H$_{phenyl}$), 7.67 (s broad, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ [ppm] = 46.1 (1C, C-4), 49.6 (1C, C-6), 49.9 (1C, C-1), 53.6 (1C, C-12), 55.0 (1C, C-3), 56.2 (1C, O*C*H$_3$), 61.0 (1C, Ph*C*H$_2$N), 100.5 (1C, C-11), 112.0 (1C, C-8), 112.1 (1C, C-9), 112.5 (1C, C-11b), 125.5 (1C, C-11a), 127.5 (1C, C-4'$_{phenyl}$), 128.8 (2C, C-2'$_{phenyl}$ and C-6'$_{phenyl}$), 129.0 (2C, C-3'$_{phenyl}$ and C-5'$_{phenyl}$), 130.1 (1C, C-7a), 130.6 (1C, C-1'$_{phenyl}$), 138.6 (1C, C-6a), 154.4 (1C, C-10). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3025 (w, N-H), 1453 (m, C-H), 794, 787, 743 and 702 (m, arom. out of plane). MS (EI): *m/z* [%] = 333 (M, 43), 242 (M - PhCH$_2$, 18), 91 (PhCH$_2$, 15). HPLC (Method 1): t_R = 16.6 min, purity 97.9 %.

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