

## Supporting Information:

### Molecular Recognition of Noradrenaline by Rigid Biomimetic Tweezers

O. Molt, D. Rübeling, T. Schrader\*

## 1 General Methods

All solvents were freshly distilled. The following anhydrous reaction solvents were distilled from the indicated drying agents: dimethylformamide (calcium hydride or magnesium sulfate), dichloromethane (calcium hydride), chloroform (phosphorus pentoxide), tetrahydrofuran (sodium or lithium aluminium hydride), pyridine (potassium hydroxide). All reagents were purchased at highest commercial grade and used as supplied. 4-Ethynylbenzoic acid chloride was prepared according to literature.<sup>1</sup> Reactions were monitored by thin layer chromatography (TLC) with Merck silica gel 60 F<sub>254</sub> plates. Silica gel 60 for flash chromatography (particle size 230-400 mesh) was supplied by Merck. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted.

Melting points were determined on a Kofler apparatus Thermophan from Reichert and are uncorrected. <sup>1</sup>H spectra were recorded on a Bruker Avance AMX 300, DRX 400 or DRX 500 spectrometer, <sup>13</sup>C and <sup>31</sup>P spectra were recorded on Bruker Avance AC 200 and ARX 200 spectrometer. Chemical shifts are reported as  $\delta$  values in ppm relative to internal tetramethylsilane; multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). Low- and high-resolution electronic ionisation (EI) mass spectra were measured on a MAT 711 Finnigan spectrometer, low- and high-resolution electron spray ionisation (ESI) mass spectra were recorded on a MAT 95 S Finnigan spectrometer. Elemental analyses were performed with Varian Elementar vario, FT-IR spectra were measured on a Bruker IFS 88 spectrometer, and UV-Vis spectroscopy was carried out with a Hitachi U-3410 spectrometer.

## 2 Syntheses

### 2.1 Receptor 1:

**1,9-Dinitrophenazine 4:** A solution of 7.0 g (39 mmol) of phenazine in 16 mL of concentrated sulfuric acid was treated with 89 mL of fuming sulfuric acid (20%) and 70 mL of fuming nitric acid ( $d=1.52$ ) at 0°C. The temperature was raised to 110°C oil bath temperature over 1 h and kept at this temperature for further 30 min. The reaction mixture was cooled to ambient temperature and poured into ice water. The resulting green precipitate was filtered off, washed with water, and dried in vacuo. The dry solid was washed with hot ethanol until the filtrate was uncoloured, dried in vacuo, and recrystallized from acetone. The precipitated 1,6-dinitrophenazine was filtered off and the filtrate was evaporated under reduced pressure. The resulting solid was recrystallized twice from acetic anhydride yielding the product in 90% purity. Yield: 35%. Mp.: 275°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.02 (dd, 2H,  $J$  = 8.8 Hz, 7.3 Hz), 8.38 (dd, 2H,  $J$  = 7.3 Hz, 1.3 Hz), 8.53 (dd, 2H,  $J$  = 8.8 Hz, 1.3 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 126.5, 126.6, 129.6, 129.7, 134.3, 134.8. MS (EI):  $m/z$  = 270, 224, 182, 166. HRMS (EI): calcd. for C<sub>12</sub>H<sub>6</sub>N<sub>4</sub>O<sub>4</sub>:  $m/z$  = 270.0389, found:  $m/z$  = 270.0382.

**1,9-Diaminophenazine 5:** 2.06 g (7.6 mmol, 1 eq) of dinitrophenazine **4** were suspended in 600 mL of refluxing 90% aqueous acetic acid and 4.98 g (76.0 mmol, 10 eq) of zinc powder were added in portions over 90 min. The reaction mixture was refluxed for 5 min and allowed to cool to ambient temperature. The solution was diluted with 600 mL of water and brought to pH 8 with concentrated ammonia. After

<sup>1</sup> A.P. Melissaris, M.H. Litt, *J. Org. Chem.* **1992**, 57, 6998-6999

cooling overnight at 4°C the resulting precipitate was filtered off and dried in vacuo. The crude product was purified by chromatography over silica eluting with ethyl acetate/*n*-hexane 1:1 ( $R_f$  = 0.22). Yield: 35%. Mp.: 266°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.15 (br, 4H), 6.93 (dd, 2H,  $J$  = 7.1 Hz, 1.5 Hz), 7.57 (dd, 2H,  $J$  = 8.6 Hz, 1.5 Hz), 7.63 (dd, 2H,  $J$  = 8.6 Hz, 7.1 Hz). MS (EI):  $m/z$  = 210, 183. HRMS (EI): calcd. for  $\text{C}_{12}\text{H}_{10}\text{N}_4$ :  $m/z$  = 210.0905, found:  $m/z$  = 210.0911.

**4'-(*tert*-Butyldimethylsilyloxy)biphenyl-4-carboxylic acid 6:** 3.70 g (17 mmol, 1 eq) of 4'-hydroxybiphenyl-4-carboxylic acid were dissolved in 70 mL of dry dimethylformamide under argon atmosphere and treated with 6.20 mL (22 mmol, 1.25 eq) of a 50% solution of *tert*-butyldimethylsilylchloride in dichloromethane and 9.0 mL (52 mmol, 3 eq) of diisopropylethylamine. The solution was stirred overnight at ambient temperature and acidified with 70 mL of 1 M phosphoric acid at 0°C. The resulting precipitate was filtered off, dried in vacuo and recrystallized from methanol. Yield: 88%. Mp.: 246°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.24 (s, 6H), 1.01 (s, 9H), 6.94 (d, 2H,  $J$  = 8.6 Hz), 7.53 (d, 2H,  $J$  = 8.6 Hz), 7.66 (d, 2H,  $J$  = 8.6 Hz), 8.16 (d, 2H,  $J$  = 8.6 Hz).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = -4.48, 18.18, 25.61, 120.50, 126.53, 127.22, 128.31, 130.66, 132.75, 146.13, 156.18, 171.78. MS (EI):  $m/z$  = 328, 271. HRMS (EI): calcd. for  $\text{C}_{19}\text{H}_{24}\text{O}_3\text{Si}$ :  $m/z$  = 328.1495, found:  $m/z$  = 328.1489.

**4'-(*tert*-Butyldimethylsilyloxy)biphenyl-4-carboxylic acid chloride 7:** A suspension of 1.45 g (4.42 mmol, 1 eq) of carboxylic acid **6** in 70 mL of dry dichloromethane was treated with 1.6 mL (22.1 mmol, 5 eq) of thionyl chloride and catalytic amounts of dimethylformamide in dry atmosphere. The mixture was stirred for 4.5 h at ambient temperature. The solvent was evaporated under reduced pressure and the resulting solid was used without further purification. Yield: 99%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.24 (s, 6H), 1.01 (s, 9H), 6.95 (d, 2H,  $J$  = 8.8 Hz), 7.53 (d, 2H,  $J$  = 8.8 Hz), 7.68 (d, 2H,  $J$  = 8.8 Hz), 8.16 (d, 2H,  $J$  = 8.8 Hz).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = -4.45, 18.17, 25.57, 120.64, 126.81, 128.43, 131.06, 131.89, 131.98, 147.70, 156.70, 170.92.

**1,9-Bis[4''-(*tert*-butyldimethylsilyloxy)biphenyl-4'-carboxamide]phenazine 8:** A solution of 1.53 g (4.42 mmol, 3 eq) of carboxylic acid chloride **7** in 70 mL of dry chloroform was treated with 0.31 g (1.47 mmol, 1 eq) of diaminophenazine **5**, 0.61 mL (4.42 mmol, 3 eq) of triethylamine and a catalytic amount of 4-dimethylaminopyridine in dry atmosphere. The mixture was stirred overnight at ambient temperature. The solvent was evaporated under reduced pressure and the resulting solid was purified by chromatography over silica eluting with chloroform/acetone 19:1 ( $R_f$  = 0.38) and, if necessary, recrystallized from acetone/chloroform. Yield: 89%. Mp.: 274°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.22 (s, 12H), 1.01 (s, 18H), 6.76 (d, 4H,  $J$  = 8.6 Hz), 7.31 (d, 4H,  $J$  = 8.6 Hz), 7.55 (d, 4H,  $J$  = 8.3 Hz), 7.96 (dd, 2H,  $J$  = 8.8 Hz, 7.3 Hz), 8.04 (d, 2H,  $J$  = 8.8 Hz), 8.10 (d, 4H,  $J$  = 8.3 Hz), 9.05 (d, 2H,  $J$  = 7.3 Hz), 10.23 (s, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = -4.42, 18.16, 25.62, 117.29, 120.51, 122.79, 123.70, 126.98, 127.57, 128.01, 131.87, 132.47, 132.71, 133.66, 143.64, 144.67, 156.16, 165.09. MS (EI):  $m/z$  = 830, 641, 311. HRMS (EI): calcd. for  $\text{C}_{50}\text{H}_{54}\text{N}_4\text{O}_4\text{Si}_2$ :  $m/z$  = 830.3684, found:  $m/z$  = 830.3672.

**1,9-Bis(4''-hydroxybiphenyl-4'-carboxamide)phenazine 9:** 0.45 g (1.02 mmol) of bis(silylether) **8** were suspended in 200 mL of a 5% solution of sodium hydroxide in 95% aqueous methanol and stirred overnight at ambient temperature. The mixture was brought to pH 4 with 10% aqueous hydrochloric acid at 0°C. The resulting precipitate was sucked off, washed with chloroform, and dried in vacuo. Yield: 99%. Mp.: >350°C.  $^1\text{H}$  NMR (300 MHz,  $\text{d}_6$ -DMSO):  $\delta$  = 6.77 (d, 4H,  $J$  = 8.6 Hz), 7.46 (d, 4H,  $J$  = 8.6 Hz), 7.70 (d, 4H,  $J$  = 8.3 Hz), 8.00-8.11 (m, 4H), 8.23 (d, 4H,  $J$  = 8.3 Hz), 8.79-8.80 (m, 2H), 9.76 (br, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{d}_6$ -DMSO):  $\delta$  = 117.34, 120.13, 122.24, 125.04, 127.05, 129.18, 129.96, 130.50, 133.45, 135.00, 136.16, 144.37, 144.82, 159.27, 166.90. MS (ESI pos., MeOH):  $m/z$  = 625, 471, 306, 284. HRMS (ESI pos., MeOH): calcd. for  $\text{C}_{38}\text{H}_{26}\text{N}_4\text{O}_4 + \text{Na}$ :  $m/z$  = 625.1852, found:  $m/z$  = 625.1854.

**1,9-Bis(4''-hydroxymethylphosphinoyloxybiphenyl-4'-carboxamide)phenazine 10:** A solution of 0.60 g (4.48 mmol, 6 eq) of methylphosphonic acid dichloride in 15 mL of dry pyridine was dropped to a suspension of 0.45 g (747  $\mu\text{mol}$ , 1 eq) of bisphenol **9** in 60 mL of dry pyridine under argon atmosphere. The mixture was stirred overnight at ambient temperature and afterwards volatile components were

condensed in vacuo at 40°C oil bath temperature. The resulting solid was treated with 35 mL of 1 N hydrochloric acid and 35 mL of chloroform and vigorously stirred overnight at ambient temperature. The precipitate was sucked off and washed with 1 N hydrochloric acid. After drying in vacuo the product was obtained in 90% purity. Yield: 82%. Mp.: >350°C. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO):  $\delta$  = 1.56 (d, 6H,  $J$  = 17.6 Hz), 7.16 (d, 4H,  $J$  = 8.0 Hz), 7.61 (d, 4H,  $J$  = 8.0 Hz), 7.77 (d, 4H,  $J$  = 8.0 Hz), 8.01-8.13 (m, 4H), 8.26 (d, 4H,  $J$  = 8.0 Hz), 8.80-8.92 (m, 2H), 11.18 (s, 2H). <sup>31</sup>P NMR (81 MHz, d<sub>6</sub>-DMSO):  $\delta$  = 30.00. MS (ESI neg., MeOH):  $m/z$  = 757, 378. HRMS (ESI neg., MeOH): calcd. for C<sub>40</sub>H<sub>30</sub>N<sub>4</sub>O<sub>8</sub>P<sub>2</sub><sup>2-</sup>:  $m/z$  = 378.0770, found:  $m/z$  = 378.0775.

**1,9-Bis(4''-hydroxymethylphosphinoyloxybiphenyl-4'-carboxamide)phenazine-bistetabutylammonium salt 1:** 0.28 g (369  $\mu$ mol, 1 eq) of bisphosphonic acid **10** were suspended in 90 mL of methanol and treated with 0.55 mL (554  $\mu$ mol, 1.5 eq) of a 1 M solution of tetrabutylammonium hydroxide in methanol. The mixture was stirred overnight at ambient temperature. After centrifugation (5000 rpm, 5 min) the clear solution was decanted and the solvent was evaporated under reduced pressure. The resulting solid was used without further purification. Yield: 73%. Mp.: 123°C. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO):  $\delta$  = 0.93 (t, 24H,  $J$  = 7.1 Hz), 1.03 (d, 6H,  $J$  = 15.9 Hz), 1.20-1.40 (m, 16H), 1.47-1.66 (m, 16H), 3.09-3.23 (m, 16H), 7.08 (d, 4H,  $J$  = 7.3 Hz), 7.42 (d, 4H,  $J$  = 7.3 Hz), 7.64 (d, 4H,  $J$  = 7.0 Hz), 7.95-8.13 (m, 4H), 8.33 (d, 4H,  $J$  = 7.0 Hz), 8.71-8.88 (m, 2H), 11.58 (s, 2H). <sup>13</sup>C NMR (75 MHz, d<sub>6</sub>-DMSO):  $\delta$  = 14.84, 15.95 (d,  $J$  = 134.6 Hz), 20.56, 24.41, 58.84, 120.59, 122.02, 122.11, 124.95, 127.17, 128.31, 130.14, 132.37, 133.63, 135.37, 136.55, 144.34, 144.62, 156.58, 166.91. <sup>31</sup>P NMR (81 MHz, d<sub>6</sub>-DMSO):  $\delta$  = 20.21. MS (ESI neg., MeOH):  $m/z$  = 779, 679, 601, 378. HRMS (ESI neg., MeOH): calcd. for C<sub>40</sub>H<sub>30</sub>N<sub>4</sub>O<sub>8</sub>P<sub>2</sub><sup>2-</sup>:  $m/z$  = 378.0770, found:  $m/z$  = 378.0782.

## 2.2 Receptor 2:

**4-Ethynylbenzoic acid *tert*-butylester 11:** 13.6 g (82 mmol, 1 eq) of 4-ethynylbenzoic acid chloride and 11.6 g (103 mmol, 1.25 eq) of potassium *tert*-butoxide were suspended in 120 mL of *tert*-butanol under dry atmosphere and stirred overnight at 40°C oil bath temperature. The mixture was concentrated under reduced pressure, diluted with water and extracted twice with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The resulting solid was used without further purification. Yield: 70%. Mp.: 128°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.59 (s, 9H), 3.22 (s, 1H), 7.53 (d, 2H,  $J$  = 8.5 Hz), 7.94 (d, 2H,  $J$  = 8.5 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 28.54, 80.09, 81.76, 83.36, 126.56, 129.67, 129.80, 132.29, 165.42. MS (EI):  $m/z$  = 202, 147, 146, 129, 101. HRMS (EI): calcd. for C<sub>13</sub>H<sub>14</sub>O<sub>2</sub>:  $m/z$  = 202.0994, found:  $m/z$  = 202.0998.

**4-(4'-Hydroxyphenylethynyl)benzoic acid *tert*-butylester 12:** A solution of 10.0 g (49.0 mmol, 1 eq) of ethyne **11** in 90 mL of freshly distilled triethylamine was treated with 10.9 g (49.0 mmol, 1 eq) of 4-iodophenol, 94 mg (0.5 mmol, 0.01 eq) of copper(I) iodide, 908 mg (3.5 mmol, 0.07 eq) of triphenylphosphine, and 694 mg (1.0 mmol, 0.02 eq) of bis(triphenylphosphino)palladium(II) chloride under argon atmosphere. The solution was stirred at 80°C oil bath temperature for 3 h. After cooling to ambient temperature the resulting precipitate was sucked off and washed with triethylamine. The filtrate was evaporated in vacuo and the resulting oil was redissolved in dichloromethane and washed twice with 3% aqueous hydrochloric acid. After drying over anhydrous magnesium sulfate the solvent was evaporated under reduced pressure affording the crude product which was purified by chromatography over silica eluting with ethyl acetate/*n*-hexane 1:2 ( $R_f$  = 0.32). Yield: 40%. Mp.: 214°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.60 (s, 9H), 4.99 (s, 1H), 6.83 (d, 2H,  $J$  = 8.8 Hz), 7.45 (d, 2H,  $J$  = 8.8 Hz), 7.53 (d, 2H,  $J$  = 8.4 Hz), 7.95 (d, 2H,  $J$  = 8.4 Hz). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + 15% d<sub>4</sub>-MeOH):  $\delta$  = 27.14, 80.60, 86.12, 91.82, 114.65, 116.94, 127.27, 128.35, 130.15, 132.40, 137.25, 156.81, 164.83. MS (EI):  $m/z$  = 294, 238, 221. HRMS (EI): calcd. for C<sub>19</sub>H<sub>18</sub>O<sub>3</sub>:  $m/z$  = 294.1256, found:  $m/z$  = 294.1261.

**4-(4'-Hydroxyphenylethynyl)-benzoic acid 13:** A mixture of 0.2 g (680  $\mu$ mol) of ester **12** in 15 mL of formic acid was stirred overnight at ambient temperature under dry atmosphere. The solvent was

evaporated under reduced pressure and the resulting solid was recrystallized from ethanol/water 1:1. Yield: 93%. Mp.: 244°C. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO):  $\delta$  = 4.38 (br, 1H), 6.82 (d, 2H, *J* = 8.5 Hz), 7.42 (d, 2H, *J* = 8.5 Hz), 7.61 (d, 2H, *J* = 8.3 Hz), 7.95 (d, 2H, *J* = 8.3 Hz). <sup>13</sup>C NMR (75 MHz, d<sub>6</sub>-DMSO):  $\delta$  = 88.23, 94.27, 113.27, 117.20, 128.61, 130.89, 131.48, 132.50, 134.65, 159.86, 168.15. MS (EI): *m/z* = 238, 221, 121. HRMS (EI): calcd. for C<sub>15</sub>H<sub>10</sub>O<sub>3</sub>: *m/z* = 238.0630, found: *m/z* = 238.0637.

**1,3-Bis[4'-(4''-hydroxyphenylethynyl)benzoylaminomethyl]benzene 14:** A mixture of 0.67 g (2.8 mmol, 2 eq) of benzoic acid **13**, 0.61 g (3.0 mmol, 2.1 eq) of dicyclohexylcarbodiimide, 0.65 g (4.2 mmol, 3 eq) of N-hydroxybenzotriazole, and catalytic amounts of 4-dimethylaminopyridine in 50 mL of dry tetrahydrofuran was treated with 0.19 mL (1.4 mmol, 1 eq) of *m*-xylylenediamine under argon atmosphere and stirred overnight at ambient temperature. The resulting precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by chromatography over silica eluting with chloroform/acetone 2:1 (*R<sub>f</sub>* = 0.32). Yield: 57%. Mp.: 256°C. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO):  $\delta$  = 4.47 (d, 4H, *J* = 6.0 Hz), 6.79 (d, 4H, *J* = 8.6 Hz), 7.13-7.21 (m, 2H), 7.22-7.30 (m, 2H), 7.38 (d, 4H, *J* = 8.6 Hz), 7.56 (d, 4H, *J* = 8.3 Hz), 7.87 (d, 4H, *J* = 8.3 Hz), 9.11 (t, 2H, *J* = 6.0 Hz). <sup>13</sup>C NMR (75 MHz, d<sub>6</sub>-acetone/d<sub>4</sub>-methanol 1:1):  $\delta$  = 43.85, 87.40, 92.76, 114.09, 116.35, 126.96, 127.15, 127.66, 128.15, 129.23, 131.84, 133.99, 134.46, 140.35, 159.21, 167.62. MS (ESI pos., MeOH): *m/z* = 599. HRMS (ESI pos., MeOH): calcd. for C<sub>38</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>+Na: *m/z* = 599.1947, found: *m/z* = 599.1943.

**1,3-Bis[4'-(4''-hydroxymethylphosphinoyloxyphenylethynyl)benzoylaminomethyl]benzene 15:** A solution of 0.13 g (225  $\mu$ mol, 1 eq) of bisphenol **14** and 0.09 g (676  $\mu$ mol, 3 eq) of methylphosphonic acid dichloride in 10 mL of dry tetrahydrofuran was treated with 0.09 mL (676  $\mu$ mol, 3 eq) of triethylamine at 0°C under argon atmosphere. The mixture was stirred at 0°C for 70 min and subsequent at ambient temperature for 3 h. The resulting precipitate was filtered off and the filtrate was poured into 10 mL of 3% aqueous hydrochloric acid. 10 mL of *n*-hexane were added and the mixture was vigorously stirred overnight at ambient temperature. The precipitating product was filtered off and washed with 1 N hydrochloric acid. The combined filtrates were evaporated under reduced pressure and the resulting solid was washed with 1 N hydrochloric acid to yield further product. Yield: 35%. Mp.: 241°C. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO):  $\delta$  = 1.50 (d, 6H, *J* = 17.6 Hz), 4.48 (d, 4H, *J* = 5.6 Hz), 7.17-7.34 (m, 8H), 7.54 (d, 4H, *J* = 8.3 Hz), 7.59 (d, 4H, *J* = 8.3 Hz), 7.87 (d, 4H, *J* = 8.3 Hz), 9.16 (t, 2H, *J* = 5.6 Hz). <sup>13</sup>C NMR (75 MHz, d<sub>6</sub>-DMSO):  $\delta$  = 14.43 (d, *J* = 140.3 Hz), 43.95, 89.75, 92.16, 118.97, 122.32, 122.40, 126.40, 127.07, 128.94, 129.40, 132.56, 134.40, 135.39, 141.05, 156.41, 166.84. <sup>31</sup>P NMR (81 MHz, d<sub>6</sub>-DMSO):  $\delta$  = 29.33. Elemental analysis: calcd. for C<sub>40</sub>H<sub>34</sub>N<sub>2</sub>O<sub>8</sub>P<sub>2</sub>: C 65.57, H 4.68, N 3.82, found: C 65.49, H 4.69, N 4.35.

**1,3-Bis[4'-(4''-hydroxymethylphosphinoyloxyphenylethynyl)benzoylaminomethyl]benzene-bistetra-butylammonium salt 2:** 13.3 mg (18  $\mu$ mol, 1 eq) of bisphosphonic acid **15** were suspended in 2 mL of methanol and treated with 36.0  $\mu$ L (36  $\mu$ mol, 2 eq) of a 1 M solution of tetrabutylammonium hydroxide in methanol. The mixture was stirred overnight at ambient temperature. The solvent was evaporated under reduced pressure and the resulting solid was used without further purification. Yield: 99%. Mp.: 135°C. <sup>1</sup>H NMR (300 MHz, d<sub>4</sub>-MeOH):  $\delta$  = 1.01 (t, 24H, *J* = 7.3 Hz), 1.30-1.47 (m, 22H), 1.57-1.72 (m, 16H), 3.12-3.27 (m, 16H), 4.58 (s, 4H), 7.22 (d, 4H, *J* = 8.0 Hz), 7.25-7.40 (m, 4H), 7.46 (d, 4H, *J* = 8.3 Hz), 7.56 (d, 4H, *J* = 8.0 Hz), 7.83 (d, 4H, *J* = 8.3 Hz), 9.04 (t, 2H, *J* = 5.8 Hz). <sup>13</sup>C NMR (75 MHz, d<sub>4</sub>-MeOH):  $\delta$  = 13.29 (d, *J* = 140.2 Hz), 13.97, 20.70, 24.79, 44.47, 59.50, 88.66, 92.50, 118.69, 122.09, 122.18, 127.36, 128.20, 128.56, 129.80, 132.50, 133.93, 134.89, 140.55, 154.90, 169.30. <sup>31</sup>P NMR (81 MHz, d<sub>4</sub>-MeOH):  $\delta$  = 25.82. MS (ESI neg., MeOH): *m/z* = 753, 653, 575. HRMS (ESI neg., MeOH): calcd. for C<sub>40</sub>H<sub>32</sub>N<sub>2</sub>O<sub>8</sub>P<sub>2</sub><sup>2-</sup>: *m/z* = 365.0817, found: *m/z* = 365.0704.

### 2.3 Receptor 3:

**4'-Acetoxybiphenyl-4-carboxylic acid 16:** A mixture of 3.0 g (14 mmol) of 4'-hydroxybiphenyl-4-carboxylic acid in 50 mL of acetic anhydride was treated with catalytic amounts of concentrated sulfuric acid and stirred at 75°C oil bath temperature for 6 h in dry atmosphere. The solution was cooled overnight at 4°C and the precipitating product was filtered off and washed with water. The filtrate was treated with water at 0°C and further precipitating product was filtered off and washed with water. Yield: 95%. Mp.: >350°C. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO): δ = 2.30 (s, 3H), 7.26 (d, 2H, *J* = 8.8 Hz), 7.78 (d, 2H, *J* = 8.8 Hz), 7.80 (d, 2H, *J* = 8.3 Hz), 8.02 (d, 2H, *J* = 8.3 Hz). <sup>13</sup>C NMR (75 MHz, d<sub>6</sub>-DMSO): δ = 22.26, 123.85, 128.16, 129.47, 131.03, 131.33, 137.96, 144.82, 152.01, 168.47, 170.45. MS (EI): *m/z* = 256, 214, 197. HRMS (EI): calcd. for C<sub>15</sub>H<sub>12</sub>O<sub>4</sub>: *m/z* = 256.0736, found: *m/z* = 256.0743.

**4'-Acetoxybiphenyl-4-carboxylic acid chloride 17:** A suspension of 1.0 g (3.9 mmol, 1 eq) of carboxylic acid **16** in 20 mL of dichloromethane was treated with 2.8 mL (39.0 mmol, 10 eq) of thionyl chloride and catalytic amounts of dimethylformamide in dry atmosphere. The mixture was stirred overnight at ambient temperature. The solvent was evaporated under reduced pressure and the resulting solid was used without further purification. Yield: 99%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.35 (s, 3H), 7.23 (d, 2H, *J* = 8.6 Hz), 7.65 (d, 2H, *J* = 8.6 Hz), 7.70 (d, 2H, *J* = 8.6 Hz), 8.19 (d, 2H, *J* = 8.6 Hz). MS (EI): *m/z* = 274, 232, 197.

**1,9-Bis(4''-acetoxybiphenyl-4'-carboxamidomethyl)benzene 18:** A solution of 1.07 g (3.90 mmol, 2 eq) of carboxylic acid chloride **17** in 20 mL of dichloromethane was treated with 0.26 mL (1.95 mmol, 1 eq) of *m*-xylylenediamine and 0.81 mL (5.85 mmol, 3 eq) of triethylamine in dry atmosphere. The mixture was stirred overnight at ambient temperature. The resulting precipitate was sucked off and washed thoroughly with water and dichloromethane. The remaining solid was dried in vacuo and used without further purification. Yield: 93%. Mp.: 265°C. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO): δ = 2.50 (s, 6H), 4.50 (d, 4H, *J* = 5.8 Hz), 7.22 (d, 4H, *J* = 8.3 Hz), 7.25-7.39 (m, 4H), 7.74 (d, 8H, *J* = 8.8 Hz), 7.96 (d, 4H, *J* = 8.3 Hz), 9.16 (t, 2H, *J* = 5.8 Hz). <sup>13</sup>C NMR (75 MHz, d<sub>6</sub>-DMSO): δ = 22.25, 43.90, 123.78, 126.93, 126.99, 127.83, 129.29, 129.32, 129.59, 134.60, 138.06, 141.20, 143.20, 151.84, 167.22, 170.58. MS (EI): *m/z* = 612, 570, 416, 197. HRMS (EI): calcd. for C<sub>38</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>: *m/z* = 612.2260, found: *m/z* = 612.2266.

**1,9-Bis(4''-hydroxybiphenyl-4'-carboxamidomethyl)benzene 19:** A mixture of 1.35 g (2.2 mmol, 1 eq) of protected bisphenol **18** and 0.91 g (6.6 mmol, 3 eq) of potassium carbonate in 25 mL of methanol was stirred overnight at ambient temperature. The solution was brought to pH 1 with 1 N hydrochloric acid. The resulting precipitate was sucked off, washed with 1 N hydrochloric acid and used without further purification. Yield: 99%. Mp.: 279°C. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO): δ = 4.48 (d, 4H, *J* = 5.6 Hz), 6.86 (d, 4H, *J* = 8.5 Hz), 7.15-7.33 (m, 4H), 7.54 (d, 4H, *J* = 8.5 Hz), 7.65 (d, 4H, *J* = 8.1 Hz), 7.90 (d, 4H, *J* = 8.1 Hz), 9.07 (t, 2H, *J* = 5.6 Hz). <sup>13</sup>C NMR (75 MHz, d<sub>6</sub>-DMSO): δ = 43.88, 117.19, 126.91, 126.95, 127.05, 129.22, 129.31, 129.56, 131.13, 133.46, 141.26, 144.09, 159.06, 167.32. MS (ESI neg., MeOH): *m/z* = 563, 527. HRMS (ESI neg., MeOH): calcd. for C<sub>34</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub><sup>-</sup>: *m/z* = 527.1971, found: *m/z* = 527.1992.

**1,9-Bis(4''-hydroxymethylphosphinoyloxybiphenyl-4'-carboxamidomethyl)benzene 20:** A solution of 2.01 g (15.1 mmol, 6 eq) of methylphosphonic acid dichloride in 5 mL of dry pyridine was dropped to a solution of 1.33 g (2.52 mmol, 1 eq) of bisphenol **19** in 30 mL of dry pyridine over 30 min under argon atmosphere. The mixture was stirred for 5 h at ambient temperature and afterwards volatile components were condensed in vacuo at 40°C oil bath temperature. The resulting solid was treated with 25 mL of 1 N hydrochloric acid and 25 mL of chloroform and vigorously stirred overnight at ambient temperature. The insoluble product was sucked off and washed with 1 N hydrochloric acid. Yield: 64%. Mp.: 234°C. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO): δ = 1.52 (d, 6H, *J* = 17.3 Hz), 4.49 (d, 4H, *J* = 5.5 Hz), 7.13-7.39 (m, 8H), 7.71 (d, 4H, *J* = 8.8 Hz), 7.72 (d, 4H, *J* = 8.3 Hz), 7.94 (d, 4H, *J* = 8.3 Hz), 9.13 (t, 2H, *J* = 5.5 Hz). <sup>13</sup>C NMR (75 MHz, d<sub>6</sub>-DMSO): δ = 13.67 (d, *J* = 141.0 Hz), 43.88, 117.18, 122.52, 126.99, 127.65, 127.76, 129.30, 129.49, 134.36, 136.54, 141.18, 143.24, 159.02, 167.23. <sup>31</sup>P NMR (81 MHz, d<sub>6</sub>-DMSO):

$\delta$  = 29.99. MS (ESI neg., MeOH):  $m/z$  = 683, 605, 302. HRMS (ESI neg., MeOH): calcd. for  $C_{36}H_{33}N_2O_8P_2$ :  $m/z$  = 683.1712, found:  $m/z$  = 683.1711.

**1,9-Bis(4''-hydroxymethylphosphinoyloxybiphenyl-4'-carboxamidomethyl)benzene-bistetabutyl-ammonium salt **3**:** 0.10 g (146  $\mu$ mol, 1 eq) of bisphosphonic acid **20** were suspended in 10 mL of methanol and treated with 290  $\mu$ L (292  $\mu$ mol, 2.0 eq) of a 1 M solution of tetrabutylammonium hydroxide in methanol. The mixture was stirred overnight at ambient temperature. The solvent was evaporated under reduced pressure and the resulting solid was used without further purification. Yield: 99%. Mp.: 135°C.  $^1H$  NMR (300 MHz,  $d_6$ -DMSO):  $\delta$  = 0.93 (t, 24H,  $J$  = 7.2 Hz), 1.18-1.38 (m, 22H), 1.42-1.63 (m, 16H), 3.05-3.18 (m, 16H), 4.49 (d, 4H,  $J$  = 5.3 Hz), 7.12-7.27 (m, 8H), 7.57 (d, 4H,  $J$  = 8.6 Hz), 7.70 (d, 4H,  $J$  = 8.0 Hz), 7.95 (d, 4H,  $J$  = 8.0 Hz), 9.16 (t, 2H,  $J$  = 5.3 Hz).  $^{13}C$  NMR (75 MHz,  $d_4$ -MeOH):  $\delta$  = 13.29 (d,  $J$  = 139.4 Hz), 13.90, 20.73, 24.79, 46.44, 59.50, 117.23, 122.37, 127.11, 127.36, 127.73, 129.00, 129.80, 133.87, 136.03, 140.66, 145.25, 156.32, 169.84.  $^{31}P$  NMR (81 MHz,  $d_4$ -MeOH):  $\delta$  = 25.51. MS (ESI neg., MeOH):  $m/z$  = 605, 341. HRMS (ESI neg., MeOH): calcd. for  $C_{36}H_{32}N_2O_8P_2^{2-}$ :  $m/z$  = 341.0817, found:  $m/z$  = 341.0844.

### 3 Job-Plots

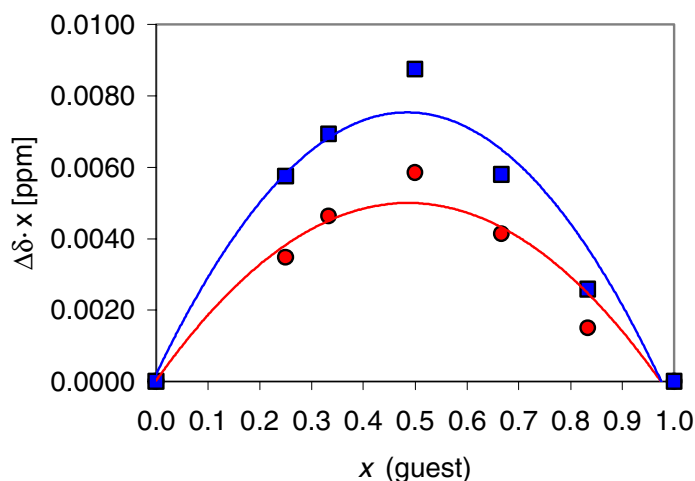
Two equimolar solutions ( $c \approx 5$  mM) of host and guest compound in  $d_4$ -methanol were prepared and combined in varying ratios in NMR tubes. Thus, the sum of the concentration was the same in each sample. The samples were measured on 400 or 500 MHz spectrometer and the guest signals were analyzed.

#### Job-plot of noradrenaline\*HCl and receptor **1**:

1.73 mg (8.42  $\mu$ mol) guest in 1.75 mL, 9.96 mg (8.02  $\mu$ mol) host in 1.65 mL

$c_G$ [M]	$c_H$ [M]	$x_G$	$\delta 1$ [ppm]	$\Delta\delta 1 \cdot x$ [ppm]	$\delta 2$ [ppm]	$\Delta\delta 2 \cdot x$ [ppm]
1.20E-03	3.65E-03	0.25	6.8522	0.0035	4.7136	0.0057
1.60E-03	3.24E-03	0.33	6.8522	0.0046	4.7114	0.0069
2.41E-03	2.43E-03	0.50	6.8500	0.0058	4.7081	0.0088
3.21E-03	1.62E-03	0.67	6.8445	0.0041	4.6993	0.0058
4.01E-03	8.10E-04	0.83	6.8401	0.0015	4.6937	0.0026
4.81E-03	0.00E+00	1.00	6.8383	0.0000	4.6906	0.0000

Graphical representation of the curves:

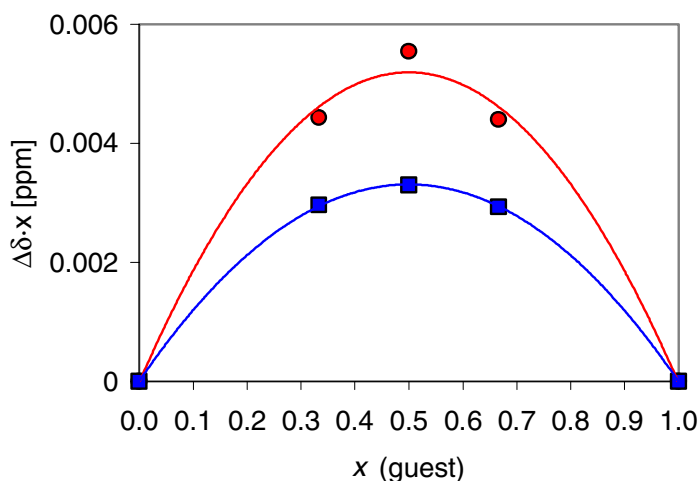


### Job-plot of noradrenaline\*HCl and receptor 3:

1.98 mg (9.63  $\mu$ mol) guest in 1.6 mL, 11.17 mg (9.57  $\mu$ mol) host in 1.6 mL

$c_G$ [M]	$c_H$ [M]	$x_G$	$\delta 1$ [ppm]	$\Delta\delta 1 \cdot x$ [ppm]	$\delta 2$ [ppm]	$\Delta\delta 2 \cdot x$ [ppm]
2.01E-03	3.99E-03	0.33	3.0226	0.0044	6.6986	0.0030
3.01E-03	2.99E-03	0.50	3.0248	0.0055	6.7009	0.0033
4.01E-03	1.99E-03	0.67	3.0293	0.0044	6.7031	0.0029
6.02E-03	0.00E+00	1.00	3.0359	0.0000	6.7075	0.0000

Graphical representation of the curves:



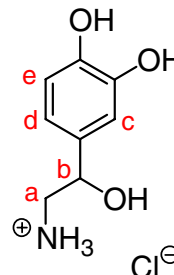
## 4 $^1\text{H}$ NMR Experiments

**$^1\text{H}$  NMR Titrations:** Ten NMR tubes were filled each with 0.7 mL of a solution of the guest compound ( $c_{\text{guest}} \approx 1$  mM) in  $\text{d}_4$ -methanol. The host compound (1.5 equiv corresponding to the guest) was dissolved in 0.63 mL of the same solvent, and the resulting solution was added with increasing volumes from 0.25 to 5 equiv to the guest solution in ten NMR tubes. The samples were measured on 400 or 500 MHz spectrometer at 300 K. Volume and concentration changes were taken into account during analysis. The association constants were calculated by non-linear regression methods. The relatively high errors are mainly due to the intensive signals of the tetrabutylammonium counterions which hamper or prevent the analysis of the samples with excess host compound. Another reason can be found in the high hygroscopicity of the host compounds and the relatively small complexation induced shifts.

#### 4.1 NMR titration 1 of noradrenaline\*HCl with receptor 1:

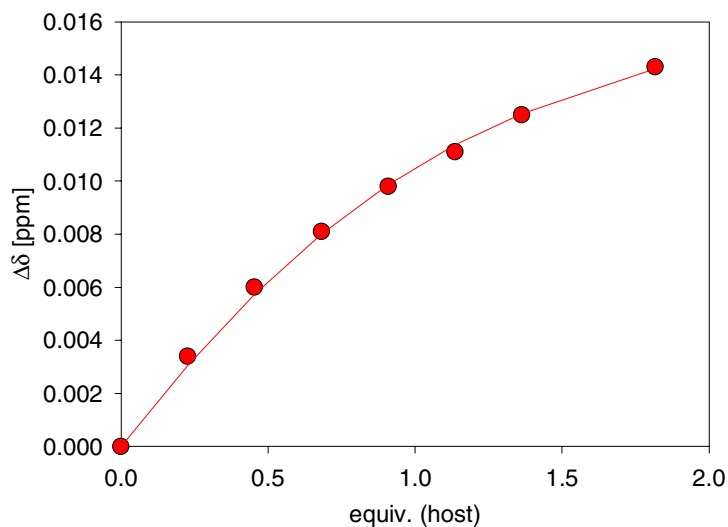
2.27 mg (11.01  $\mu\text{mol}$ ) guest in 8 mL, 19.57 mg (15.76  $\mu\text{mol}$ ) host in 0.63 mL

$c_G [\text{M}]$	$c_H [\text{M}]$	$eq_H$	$\delta_1 [\text{ppm}]$	$\Delta\delta_1 [\text{ppm}]$	$\delta_2 [\text{ppm}]$	$\Delta\delta_2 [\text{ppm}]$
1.38E-03	0,00E+00	0,00.	4.7069	0.0000	6.8409	0.0000
1.36E-03	3,09E-04	0,23	4.7103	0.0034	6.8432	0.0023
1.34E-03	6,10E-04	0,45	4.7129	0.0060	6.8451	0.0043
1.33E-03	9,04E-04	0,68	4.7150	0.0081	6.8471	0.0063
1.31E-03	1.19E-03	0.91	4.7167	0.0098	6.8474	0.0066
1.30E-03	1.47E-03	1.14	4.7180	0.0111	6.8494	0.0085
1.28E-03	1.75E-03	1.36	4.7194	0.0125	6.8505	0.0097
1.25E-03	2.27E-03	1.82	4.7212	0.0143	6.8519	0.0111
1.20E-03	3.26E-03	2.73	-	-	6.8519	0.0111



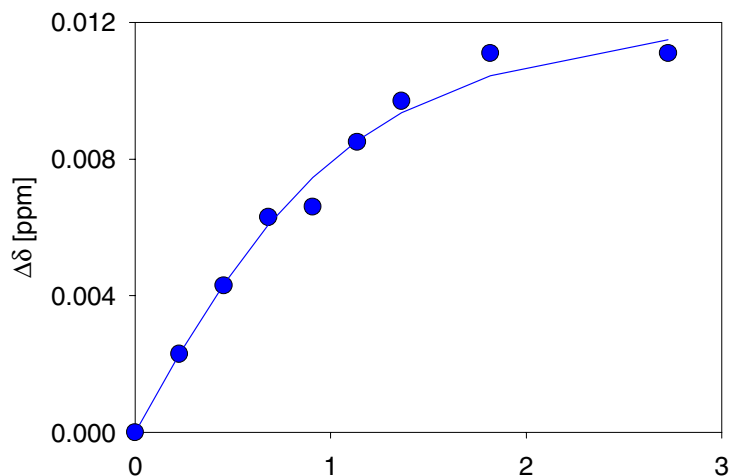
Proton 1 ( $H_b$ ):  $K_a = 1797 \text{ M}^{-1}$  ( $\pm 27\%$ ),  $\Delta\delta_{\text{sat}} = 0.0200 \text{ ppm}$  ( $\pm 8\%$ ), saturation: 72%.

Graphical representation of the titration curve:



Proton 2 ( $H_c$ ):  $K_a = 2745 \text{ M}^{-1}$  ( $\pm 42\%$ ),  $\Delta\delta_{\text{sat}} = 0.0134 \text{ ppm}$  ( $\pm 9\%$ ), saturation: 83%.

Graphical representation of the titration curve:





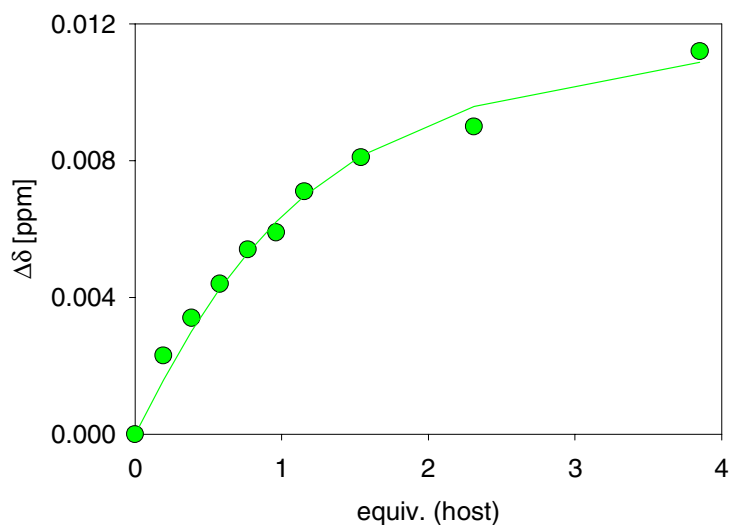
## 4.2 NMR titration 2 of noradrenaline\*HCl with receptor 1:

2.09 mg (10.16  $\mu\text{mol}$ ) guest in 7 mL, 15.30 mg (12.32  $\mu\text{mol}$ ) host in 0.63 mL

$c_G[M]$	$c_H[M]$	$eq_H$	$\delta I [ppm]$	$\Delta\delta I [ppm]$
1.45E-03	0.00E+00	0.00	4.6909	0.0000
1.43E-03	2.75E-04	0.19	4.6932	0.0023
1.41E-03	5.43E-04	0.39	4.6942	0.0034
1.39E-03	8.04E-04	0.58	4.6953	0.0044
1.37E-03	1.06E-03	0.77	4.6963	0.0054
1.35E-03	1.30E-03	0.96	4.6967	0.0059
1.34E-03	1.54E-03	1.16	4.6980	0.0071
1.30E-03	2.01E-03	1.54	4.6990	0.0081
1.24E-03	2.86E-03	2.31	4.6998	0.0090
1.13E-03	4.35E-03	3.85	4.7020	0.0112

Proton 1 ( $H_b$ ):  $K_a = 1298 \text{ M}^{-1}$  ( $\pm 26\%$ ),  $\Delta\delta_{\text{sat}} = 0.0133 \text{ ppm}$  ( $\pm 7\%$ ), saturation: 84%.

Graphical representation of the titration curve:



## 4.3 NMR titration of adrenaline\*HCl with receptor 1:

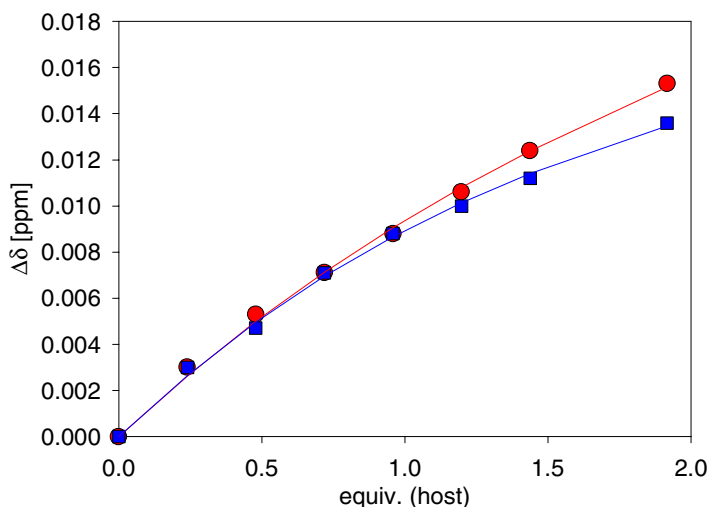
2.46 mg (11.21  $\mu\text{mol}$ ) guest in 8 mL, 21.02 mg (16.93  $\mu\text{mol}$ ) host in 0.63 mL

$c_G[M]$	$c_H[M]$	$eq_H$	$\delta I [ppm]$	$\Delta\delta I [ppm]$	$\delta 2 [ppm]$	$\Delta\delta 2 [ppm]$
1.60E-03	0.00E+00	0.00	6.7757	0.0000	6.8463	0.0000
1.58E-03	3.78E-04	0.24	6.7727	0.0030	6.8493	0.0030
1.56E-03	7.46E-04	0.48	6.7710	0.0047	6.8516	0.0053
1.54E-03	1.10E-03	0.72	6.7686	0.0071	6.8534	0.0071
1.51E-03	1.45E-03	0.96	6.7669	0.0088	6.8551	0.0088
1.49E-03	1.79E-03	1.20	6.7657	0.0100	6.8569	0.0106
1.48E-03	2.12E-03	1.44	6.7645	0.0112	6.8587	0.0124

1.44E-03	2.76E-03	1.92	6.7621	0.0136	6.8616	0.0153
$\Delta\delta_{\text{sat}}$				0.0277 ( $\pm 14\%$ )		0.0495 ( $\pm 18\%$ )
saturation				49%		31%

The calculated association constant  $K_a$  has a value of  $255 \text{ M}^{-1}$  ( $\pm 29\%$ ).

Graphical representation of the titration curves:



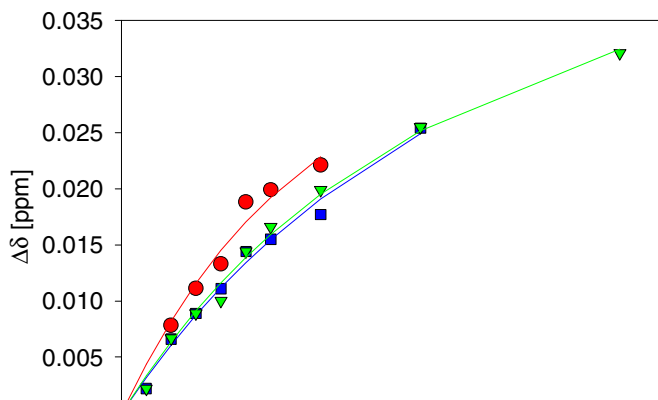
#### 4.4 NMR titration of dopamine\*HCl with receptor 1:

2.35 mg (12.38  $\mu\text{mol}$ ) guest in 8 mL, 22.25 mg (17.92  $\mu\text{mol}$ ) host in 0.63 mL

$c_G [M]$	$c_H [M]$	$eq_H$	$\delta 1 [ppm]$	$\Delta\delta 1 [ppm]$	$\delta 2 [ppm]$	$\Delta\delta 2 [ppm]$	$\delta 3 [ppm]$	$\Delta\delta 3 [ppm]$
1.55E-03	0.00E+00	0.00	3.0812	0.0000	6.7406	0.0000	6.7141	0.0000
1.53E-03	3.51E-04	0.23	3.0812	0.0000	6.7384	0.0022	6.7119	0.0022
1.51E-03	6.94E-04	0.46	3.0734	0.0078	6.7340	0.0066	6.7074	0.0067
1.49E-03	1.03E-03	0.69	3.0701	0.0111	6.7317	0.0089	6.7052	0.0089
1.47E-03	1.35E-03	0.92	3.0679	0.0133	6.7295	0.0111	6.7041	0.0100
1.46E-03	1.67E-03	1.15	3.0624	0.0188	6.7262	0.0144	6.6997	0.0144
1.44E-03	1.98E-03	1.38	3.0613	0.0199	6.7251	0.0155	6.6975	0.0166
1.41E-03	2.59E-03	1.84	3.0591	0.0221	6.7229	0.0177	6.6942	0.0199
1.35E-03	3.71E-03	2.76	3.0635	0.0177	6.7152	0.0254	6.6886	0.0255
1.24E-03	5.69E-03	4.60	-	-	-	-	6.6820	0.0321
$\Delta\delta_{\text{sat}}$				0.0476 ( $\pm 37\%$ )		0.0719 ( $\pm 25\%$ )		0.0635 ( $\pm 10\%$ )
saturation				37%		35%		51%

The calculated association constant  $K_a$  has a value of  $335 \text{ M}^{-1}$  ( $\pm 53\%$ ).

Graphical representation of the titration curves:



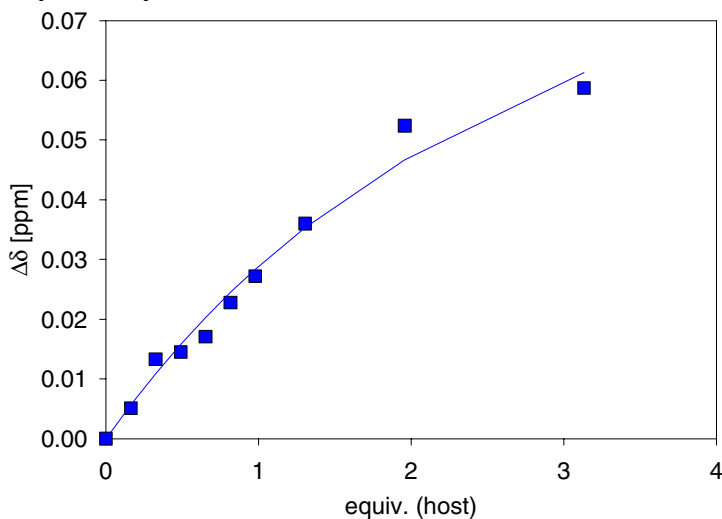
#### 4.5 NMR titration of (R)-propranolol\*HCl with receptor 1:

3.56 mg (12.03  $\mu\text{mol}$ ) guest in 7 mL, 15.35 mg (12.37  $\mu\text{mol}$ ) host in 0.63 mL

$c_G [M]$	$c_H [M]$	$eq_H$	$\delta I [ppm]$	$\Delta\delta I [ppm]$
1.72E-03	0.00E+00	0.00	1.3355	0.0000
1.69E-03	2.76E-04	0.16	1.3304	0.0051
1.67E-03	5.45E-04	0.33	1.3222	0.0133
1.65E-03	8.07E-04	0.49	1.3210	0.0145
1.63E-03	1.06E-03	0.65	1.3184	0.0171
1.60E-03	1.31E-03	0.82	1.3127	0.0228
1.58E-03	1.55E-03	0.98	1.3083	0.0272
1.54E-03	2.01E-03	1.31	1.2995	0.0360
1.47E-03	2.87E-03	1.96	1.2831	0.0524
1.35E-03	4.23E-03	3.13	1.2768	0.0587
$\Delta\delta_{\text{sat}}$ saturation				0.2472 ( $\pm 33\%$ ) 24%

The calculated association constant  $K_a$  has a value of  $127 \text{ M}^{-1}$  ( $\pm 46\%$ ).

Graphical representation of the titration curve:



#### 4.6 NMR titration of L-tyrosine methylester\*HCl with receptor 1:

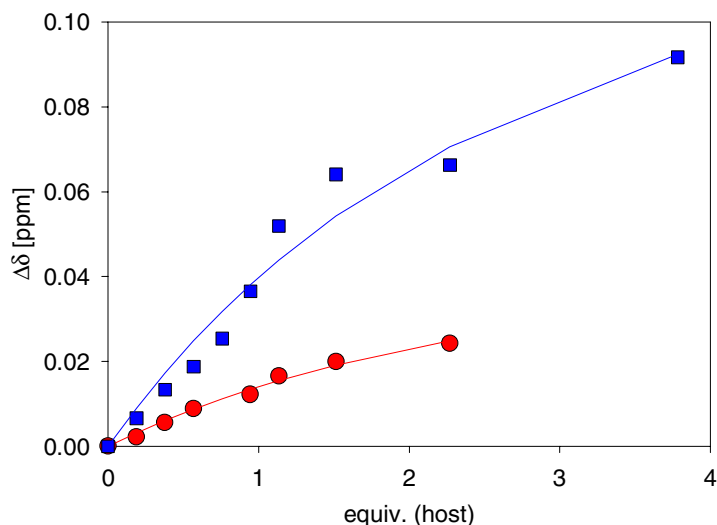
3.29 mg (14.18  $\mu\text{mol}$ ) guest in 7 mL, 20.99 mg (16.91  $\mu\text{mol}$ ) host in 0.63 mL

$c_G [M]$	$c_H [M]$	$eq_H$	$\delta I [ppm]$	$\Delta\delta I [ppm]$	$\delta 2 [ppm]$	$\Delta\delta 2 [ppm]$
2.03E-03	0.00E+00	0.00	6.7583	0.0000	3.8062	0.0000
2.00E-03	3.78E-04	0.19	6.7561	0.0022	3.7996	0.0066
1.97E-03	7.45E-04	0.38	6.7527	0.0056	3.7929	0.0133
1.94E-03	1.10E-03	0.57	6.7494	0.0089	3.7874	0.0188
1.92E-03	1.45E-03	0.76	-	-	3.7808	0.0254
1.89E-03	1.79E-03	0.95	6.7461	0.0122	3.7697	0.0365
1.87E-03	2.12E-03	1.14	6.7417	0.0166	3.7543	0.0519
1.82E-03	2.75E-03	1.51	6.7384	0.0199	3.7421	0.0641

1.73E-03	3.93E-03	2.27	6.7340	0.0243	3.7399	0.0663
1.58E-03	5.96E-03	3.78	-	-	3.7145	0.0917
$\Delta\delta_{\text{sat}}$ saturation				0.0721 ( $\pm 33\%$ ) 34%		0.1984 ( $\pm 33\%$ ) 46%

The calculated association constant  $K_a$  has a value of  $166 \text{ M}^{-1}$  ( $\pm 54\%$ ).

Graphical representation of the titration curves:



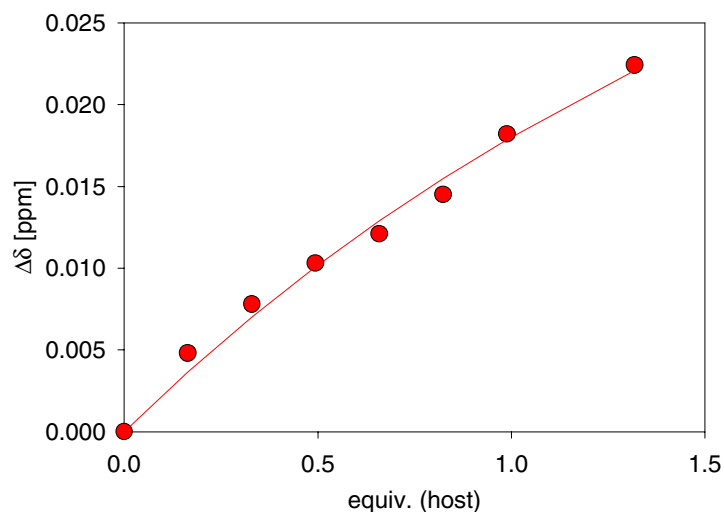
#### 4.7 NMR titration of L-tryptophan methylester\*HCl with receptor 1:

3.05 mg (11.97  $\mu\text{mol}$ ) guest in 7 mL, 15.43 mg (12.43  $\mu\text{mol}$ ) host in 0.63 mL

$c_G [M]$	$c_H [M]$	$eq_H$	$\delta I [ppm]$	$\Delta\delta I [ppm]$
1.71E-03	0.00E+00	0.00	7.3722	0.0000
1.69E-03	2.78E-04	0.16	7.3674	0.0048
1.66E-03	5.48E-04	0.33	7.3644	0.0078
1.64E-03	8.11E-04	0.49	7.3619	0.0103
1.62E-03	1.07E-03	0.66	7.3601	0.0121
1.60E-03	1.32E-03	0.82	7.3577	0.0145
1.58E-03	1.56E-03	0.99	7.3540	0.0182
1.53E-03	2.02E-03	1.32	7.3498	0.0224
$\Delta\delta_{\text{sat}}$ saturation				0.0795 ( $\pm 55\%$ ) 28%

The calculated association constant  $K_a$  has a value of  $241 \text{ M}^{-1}$ .

Graphical representation of the titration curve:



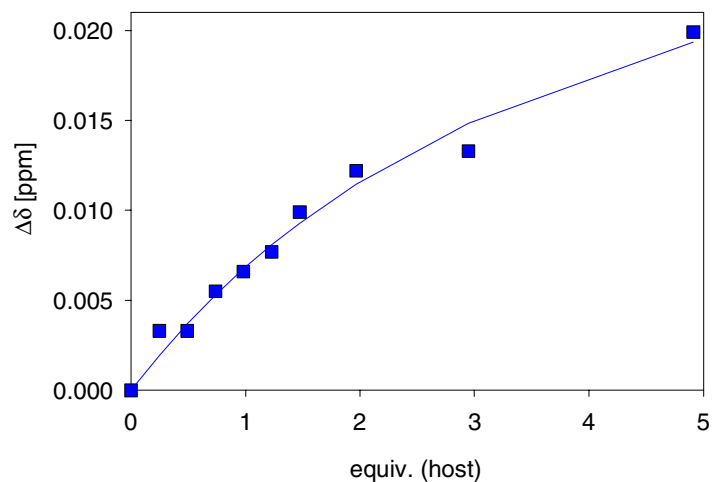
#### 4.8 NMR titration of noradrenaline\*HCl with receptor 3:

2.47 mg (12.00  $\mu\text{mol}$ ) guest in 8 mL, 21.68 mg (18.57  $\mu\text{mol}$ ) host in 0.63 mL

$c_G$ [M]	$c_H$ [M]	$eq_H$	$\delta I$ [ppm]	$\Delta\delta I$ [ppm]
1.50E-03	0.00E+00	0.00	3.0481	0.0000
1.48E-03	3.64E-04	0.25	3.0458	0.0023
1.46E-03	7.19E-04	0.49	3.0447	0.0034
1.45E-03	1.07E-03	0.74	3.0414	0.0067
1.43E-03	1.40E-03	0.98	3.0414	0.0067
1.41E-03	1.73E-03	1.23	3.0381	0.0100
1.40E-03	2.06E-03	1.47	3.0370	0.0111
1.36E-03	2.68E-03	1.96	3.0315	0.0166
1.30E-03	3.84E-03	2.95	3.0293	0.0188
1.20E-03	5.89E-03	4.91	3.0204	0.0277
$\Delta\delta_{\text{sat}}$ saturation				0.0722 ( $\pm 26\%$ ) 38%

The calculated association constant  $K_a$  has a value of  $119 \text{ M}^{-1}$  ( $\pm 38\%$ ).

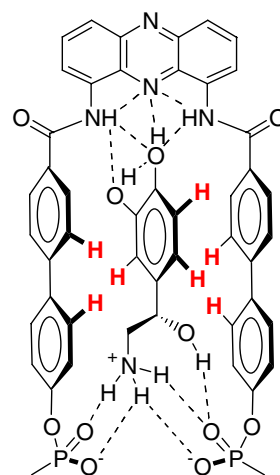
Graphical representation of the titration curve:



#### 4.9 VT <sup>1</sup>H NMR of the complex between receptor 1 and noradrenaline\*HCl

1.05 mg (5.11 μmol) guest and 0.73 mg (0.63 μmol) host in 0.70 mL d<sub>4</sub>-methanol

T [°C]	δ (guest) [ppm]	δ (host) [ppm]
25	6.8291 (d), 6.7451 (d), 6.6957 (dd)	7.5988 (d), 7.4193 (d)
-3	6.7685 (br)	7.6307 (d), 7.4497 (d)
-13	6.7382 (br)	7.6434 (d), 7.4603 (d)
-23	6.7321 (br)	7.6556 (d), 7.4707 (d)
-33	6.7200 (br)	7.6690 (d), 7.4810 (d)
-53	6.7740 (br), 6.6762 (br)	7.6957 (d), 7.5013 (d)
-73	6.7704 (br), 6.6598 (br)	7.7133 (d), 7.5174 (d)
-93	6.7898 (s), 6.6550 (s)	7.7336 (br), 7.5323 (d)



#### 4.10 Self association of receptor 1 in d<sub>4</sub>-methanol

4.69 mg (3.78 μmol) guest in 0.7 mL

c [M]	δ1 [ppm]	δ2 [ppm]	δ3 [ppm]
5.4E-03	8.7610	8.1520	7.6264
3.6E-03	8.7731	8.1608	7.6326
2.5E-03	8.7820	8.1652	7.6364
1.9E-03	8.7842	8.1686	7.6381
1.6E-03	8.7853	8.1686	7.6386
6.8E-04	8.7963	-	-
3.4E-04	8.8041	8.1774	7.6452

The calculated self association constant K<sub>sa</sub> has a value of 54 M<sup>-1</sup> (+/- 63%).

#### 4.11 Self association of receptor 1 in D<sub>2</sub>O/ d<sub>4</sub>-methanol 1:1

6.17 mg (4.97 μmol) guest in 0.7 mL

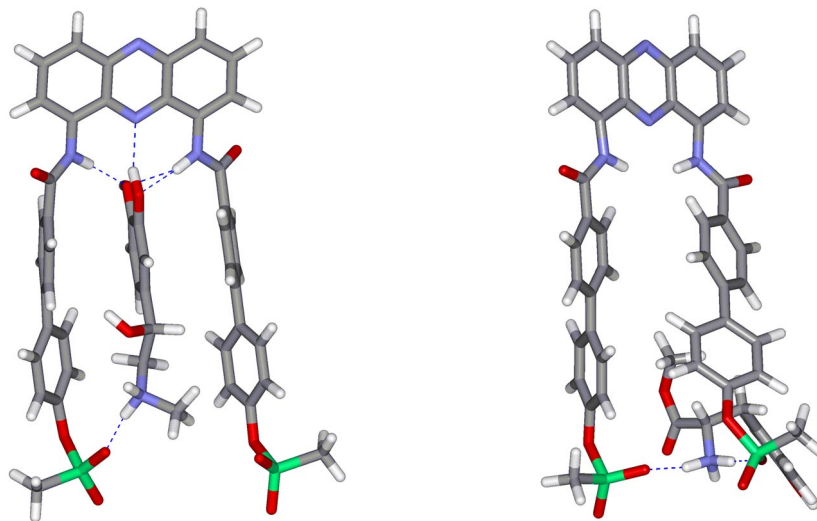
c [M]	δ1 [ppm]	δ2 [ppm]
7.1E-03	8.2415	7.6226
4.3E-03	8.2968	7.6933
2.8E-03	8.3432	7.7486
2.1E-03	8.3741	7.7883
1.8E-03	8.3918	7.8149
1.4E-03	8.4150	7.8491
1.1E-03	8.4515	7.8911
7.1E-04	8.4869	7.9387
3.6E-04	8.5255	8.0116

The calculated self association constant K<sub>sa</sub> has a value of 437 M<sup>-1</sup> (+/- 8%).

## 5 Miscellaneous

**Molecular Modeling Experiments:** Force-field calculations were performed on a Silicon Graphics O2 workstation with MacroModel 7.0 from Schrödinger Inc. using the AMBER\* force-field. The simulations were conducted in water applying the GB/SA solvation model. Monte-Carlo conformational searches were performed over 3000 steps, followed by a molecular dynamics calculation for 10 ps at 300 K. Snapshots were taken every ps and superimposed afterwards.

Molecular modelling studies support our receptor design and partly explain the observed binding selectivities. Compared to noradrenaline the N-methyl-substituent of adrenaline disturbs the essential bisphosphonate-ammonium interaction by shielding the ammonium group from one phosphonate moiety. In the case of the amino acid methyl esters and propranolol presumably a different binding geometry exists because the  $\alpha$ -substituent respectively the increased chain length with a greater aromatic residue inhibit the inclusion of the guests



*Figure 1.* Complexes between receptor **1** and adrenaline (left) and tyrosine methyl ester (right) according to Monte-Carlo simulations in water.

**FT-IR Experiments:** FT-IR spectra were recorded of noradrenaline hydrochloride, free host **1** as well as the respective 1:1 complex. For this purpose methanolic solutions of the analytes were treated with KBr and evaporated under reduced pressure. The IR spectrum of the complex was identical to the addition of host and guest spectra, with the following exception: the strong band for the host's anionic P-O bond (symmetrical and asymmetrical vibrational stretch) shifted from 1109.2 to 1072.2  $\text{cm}^{-1}$  and from 1169.4 to 1173.1  $\text{cm}^{-1}$  ( $\Delta = 37.0$  and 3.7  $\text{cm}^{-1}$ ).

**ESI-MS experiments:** ESI mass spectra were recorded on a Finnigan MAT 95. Samples (20  $\mu\text{L}$ ) were introduced as  $10^{-7}$  M solutions in HPLC-grade methanol at flow rates of 20  $\mu\text{L min}^{-1}$ . Heated capillary temperature: 150  $^{\circ}\text{C}$ . Ion spray potential: 3.5 kV (positive ESI), 3.0 kV (negative ESI). About 20–30 scans were averaged to improve the signal-to-noise ratio.

**UV/VIS experiments:** UV-Vis spectra were recorded on a Hitachi U-3410 spectrometer. Samples were measured in quartz cuvettes ( $d=1$  cm) as  $5 \cdot 10^{-5}$  or  $5 \cdot 10^{-6}$  M solutions in HPLC-grade methanol in the range of 200 to 700 nm at ambient temperature. The absorption bands of receptor **1** showed no or small shifts in  $\lambda$  or  $\epsilon$  at addition of noradrenaline hydrochloride (NA).

	$\lambda_{\max}$ [nm] ( $\lg \varepsilon$ [ $\text{l}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ ])		
host <b>1</b>	269.6 (5.367)	371.0 (4.158)	438.2 (3.981)
host <b>1</b> + 1 eq NA	269.6 (5.381)	371.0 (4.164)	437.9 (3.985)
host <b>1</b> + 10 eq NA	270.2 (5.401)	-	-

**Film balance experiments:** A NIMA 601BAM film balance (trough size 700 x 100 mm<sup>2</sup>) equipped with a Wilhelmy plate was used for measuring surface pressure as a function of molecular area at ambient temperature. Pure water (purified by ELGA Purelab UHQ, >18 M $\Omega$ ) and aqueous 100  $\mu\text{M}$  guest solutions were used as subphases, all of which did not give any appreciable values of surface pressure under compression in the examined area ranges. Lipid monolayers were obtained by spreading 50  $\mu\text{L}$  of a 3.5 mM stearic acid solution in chloroform onto the subphases. The recorded  $\pi$ -A-isotherm cycles (barrier speed: 50 cm<sup>2</sup>/min) revealed no or only small isotherm changes of the stearic acid monolayer caused by dissolved guests. Receptor **1** was incorporated into the lipid monolayers by dropping 24  $\mu\text{L}$  of a 3mM receptor solution in methanol onto the subphases at a surface pressure of 15 mN/m. Time-dependent  $\pi$ -A-isotherm cycles were recorded until no further effects could be observed.

