Supporting Information

Interconversion of Functional Activity by Minor Structural Alterations in Nonpeptide AT_2 Receptor Ligands

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Experimental part

Chemistry.

General Considerations. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Varian Mercury 400 at ambient temperature, if not otherwise stated. Chemical shifts are given as δ values (ppm) downfield from tetramethylsilane and referenced to δ 7.26 and δ 77.16 for $CDCl_3$ and δ 3.31 and δ 49.00 for CD_3OD. Analytical GC-MS with EI ionization was performed on a Varian 3800 or 3900 equipped with a CP-SIL 5 CB Low Bleed (30 m × 0.25 mm) or CP-SIL 8 CB Low Bleed (30 m × 0.25 mm) operating at ionization energy of 70 eV, using He as carrier gas. The oven temperature was 40–320 ºC. Analytical RP-HPLC-MS was performed on a Gilson HPLC system equipped with a Zorbax SB C8, 5 μm (4.6 × 50 mm) column and a Finnigan AQA quadropole mass spectrometer. The mobile phase consisted of H_2O/MeCN (0.05% HCOOH) and the analyses were run in a gradient mode. Preparative RP-HPLC-MS was performed on a Gilson-Finnigan Thermo Quest AQA system equipped with a Zorbax SB-C8, 5 μm 21.2 × 150 mm (Agilent technologies) column at a flow rate of 15 mL/min. The mobile phase consisted of H_2O/MeCN (0.05% HCOOH). Microwave heating was performed using Emrys Initiator^{TM} single mode cavity, producing controlled irradiation at 2450 MHz. Dedicated microwave vials from Biotage were used for the reactions and the temperature of the reaction mixture was measured using a built-in, on-line infrared temperature sensor. Elemental analyses were performed by Analytische Laboratorien, Lindlar, Germany. Dry CH_2Cl_2 was distilled over calcium hydride and dry THF over sodium. Other chemicals and solvents used were of analytical grade and purchased from commercial suppliers, and used without further purification unless stated (e.g. dry THF). Thin-layer chromatography was performed on aluminium plates precoated with silica gel 60 F_{254} (Merck)

and visualized with UV light. Flash chromatography was performed on silica gel 60 (0.040-0.063 mm, Merck).

General procedure A, compounds 13 and 14. Bromobenzylbromid and imidazole were dissolved in DMF. The reaction mixture was stirred over night at ambient temperature. The reaction was diluted with 250 ml of water and extracted with CH_2Cl_2. The combined organic layer was extracted with 1 M HCl and the combined acidic water phase was washed with CH_2Cl_2. The pH was increased to 8 with saturated Na_2CO_3 and extracted with diethylether. The combined organic layer was washed with brine, dried with K_2CO_3, filtered and concentrated under vacuum to yield the pure compounds **13** and **14**.

1-(4-Bromobenzyl)-1*H*-imidazole (13). According to the general procedure A, 4-bromobenzylbromid (5.28 g, 0.021 mol) and imidazole (5.80 g, 0.85 mol) were dissolved in 50 ml DMF. Compound **13** was isolated in 72% yield (3.58 g, 0.015 mol) as colourless oil that solidified upon freezing. ^{1}H NMR ($CDCl_3$), δ, ppm: 7.70-7.68 (m, 1H), 7.51-7.47 (m, 2H), 7.13-7.12 (m, 1H), 7.05-7.02 (m, 2H), 6.90-6.89 (m, 1H), 5.10 (s, 2H). ^{13}C NMR ($CDCl_3$), δ, ppm: 137.4, 135.1, 132.4, 129.5, 129.1, 122.6, 119.4, 50.5. Anal. Calcd. for $C_{10}H_9BrN_2$: C, 50.66; H, 3.83; N, 11.82. Found: C, 50.63; H, 3.71; N, 11.78.

1-(3-Bromobenzyl)-1*H*-imidazole (14). According to the general procedure A, 3-bromobenzylbromid (4.02 g, 0.016 mol) and imidazole (4.56 g, 0.67 mol) were dissolved in 50 ml DMF. Compound **14** was isolated in 73% yield (2.75 g, 0.012 mol) as colourless oil. ^{1}H NMR ($CDCl_3$), δ, ppm: 7.54-7.53 (m, 1H), 7.46-7.43 (m, 1H), 7.29 (dd, J = 1.9, 1.9 Hz, 1H),

7.22 (dd, J = 8.0, 8.0 Hz, 1H), 7.11-7.10 (m, 1H), 7.07-7.04 (m, 1H), 6.89-6.88 (m, 1H), 5.08 (s, 2H). ^{13}C NMR ($CDCl_3$), δ, ppm: 138.6, 137.6, 131.6, 130.7, 130.3, 130.3, 125.9, 123.2, 119.4, 50.2. Anal. Calcd. for $C_{10}H_9BrN_2$: C, 50.66; H, 3.83; N, 11.82. Found: C, 50.76; H, 3.86; N, 11.97.

General procedure B, compounds 15–17. To a cooled (-78 ºC) solution of compounds **9** and **10**, in dry THF, was *n*-BuLi (1.6 M in hexane) added under nitrogen atmosphere and stirred for 1 hour. The temperature was raised to -30 ºC and kept for 3 hours and subsequently decreased to -40 ºC. Triisopropyl borate was then added. The reaction was stirred over night at room temperature. The reaction was cooled (0 ºC) and treated with an excess of 2 M HCl solution. The mixture was extracted with EtOAc and the combined organic phase was washed with water and brine. The organic layer was dried with $MgSO_4$, filtered and evaporated. The crude products **11** and **12** were then used in the next step without further purification. A microwave vial (2-5 mL) was charged with the crude boronic acid, compound **13** or **14**, toluene, ethanol, 2 M Na_2CO_3 and $Pd(PPh_3)_4$. The reaction mixture was flushed with nitrogen, sealed and heated by microwave irradiation to 150 ºC for 5 min. The reaction mixture was diluted with EtOAc and water. The water phase was extracted with EtOAc and the combined organic phase was washed with water and brine, dried with K_2CO_3 or $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography to isolate the pure compounds **15–17**.

***N-tert*-Butyl-2-(3-imidazol-1-ylmethylphenyl)-4-isobutyl-benzenesulfonamide (15)**

According to the general procedure B compound **9** (3.04 g, 11.27 mmol) was dissolved in dry THF (50 mL) and reacted with n-BuLi (18 mL, 1.6 M in hexane, 28.8 mmol) and triisopropyl

borate (3.9 mL, 16.9 mmol). A microwave vial (2-5 mL) was charged with the crude boronic acid **11** (214 mg, <0.68 mmol), compound **14** (95 mg, 0.40 mmol), 3.5 mL of toluene, 0.5 mL of ethanol, Na_2CO_3 (2 M, 0.80 mL, 1.6 mmol) and $Pd(PPh_3)_4$ (25 mg, 0.022 mmol). The crude product was purified twice by column chromatography ($CHCl_3$:MeOH 20:1) to isolate compound **15** as a colour less oil in 75% yield (127.5 mg, 0.30 mmol). ^{1}H NMR ($CDCl_3$), δ, ppm: 8.05 (d, *J* = 8.1 Hz, 1H), 7.58-7.57 (m, 1H), 7.45-7.39 (m, 3H), 7.25 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.21-7.16 (m, 1H), 7.09-7.08 (m, 1H), 7.04 (d, *J* = 1.9 Hz, 1H), 6.98-6.97 (m, 1H), 5.16 (s, 2H), 3.47 (s, 1H), 2.54 (d, *J* = 7.2 Hz, 2H), 1.97-1.83 (m, 1H), 0.97 (s, 9H), 0.91 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$), δ, ppm: 146.4, 140.6, 139.5, 139.2, 137.5, 136.3, 133.0, 130.2, 129.7, 129.4, 128.81, 128.76, 128.6, 127.1, 119.4, 54.5, 50.8, 45.1, 30.2, 29.9, 22.4.

***N-tert*-Butyl-2-(4-imidazol-1-ylmethylphenyl)-5-isobutyl-benzenesulfonamide (16)**

According to the general procedure B compound **10** (2.13 g, 7.92 mmol) was dissolved in dry THF (30 mL) and reacted with n-BuLi (13 mL, 1.6 M in hexane, 20.8 mmol) and triisopropyl borate (3.9 mL, 16.9 mmol). A microwave vial (2-5 mL) was charged with the crude boronic acid **12** (200 mg, <0.64 mmol), compound **13** (86 mg, 0.36 mmol), 3.5 mL of toluene, 0.5 mL of ethanol, Na_2CO_3 (2 M, 0.72 mL, 1.5 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.020 mmol). The crude product was purified by column chromatography first (CH_2Cl_2:MeOH 20:1) and secondly ($CHCl_3$:MeOH 20:1) to isolate compound **16** as a white solid in 87% yield (134 mg, 0.32 mmol). ^{1}H NMR ($CDCl_3$), δ, ppm: 7.94 (d, *J* = 1.8 Hz, 1H), 7.69-7.68 (m, 1H), 7.52-7.49 (m, 2H), 7.32 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.25-7.22 (m, 2H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.12 (m, 1H), 6.95 (m, 1H), 5.20 (s, 2H), 3.55 (s, 1H), 2.57 (d, *J* = 7.2 Hz, 2H), 1.99-1.86 (m, 1H), 0.98 (s, 9H), 0.92 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$), δ, ppm: 142.2, 141.7, 139.9, 137.5, 136.6,

136.1, 132.7, 132.2, 130.8, 129.6, 129.0, 127.0, 119.4, 54.5, 20.7, 45.0, 30.3, 29.9, 22.4. Anal. Calcd. for $C_{25}H_{36}N_2O_3S$: C: 67.73, H: 7.34, N: 9.87. Found: C, 67.57; H, 7.27; N, 9.72.

***N-tert*-Butyl-2-(3-imidazol-1-ylmethylphenyl)-5-isobutyl-benzenesulfonamide (17)**

According to the general procedure B compound **10** (2.13 g, 7.92 mmol) was dissolved in dry THF (30 mL) and reacted with n-BuLi (13 mL, 1.6 M in hexane, 20.8 mmol) and triisopropyl borate (3.9 mL, 16.9 mmol). A microwave vial (2-5 mL) was charged with the crude boronic acid **12** (200 mg, <0.64 mmol), compound **14** (91 mg, 0.38 mmol), 3.5 mL of toluene, 0.5 mL of ethanol, Na_2CO_3 (2 M, 0.80 mL, 1.5 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.021 mmol). The crude product was purified by column chromatography first ($CHCl_3$:MeOH 20:1) and secondly ($CHCl_3$:MeOH 30:1) to isolate compound **17** as a white solid in 83% yield (134 mg, 0.32 mmol). ^{1}H NMR ($CDCl_3$), δ, ppm: 7.94 (d, *J* = 1.8 Hz, 1H), 7.73-7.72 (m, 1H), 7.44-7.42 (m, 3H), 7.33 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.23-7.20 (m, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.10 (m, 1H), 7.00 (m, 1H), 5.18 (s, 2H), 3.51 (s, 1H), 2.57 (d, *J* = 7.2 Hz, 2H), 1.99-1.86 (m, 1H), 0.96 (s, 9H), 0.92 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$), δ, ppm: 142.3, 141.65, 140.5, 137.3, 136.7, 136.0, 132.7, 132.1, 129.9, 129.7, 129.4, 129.1, 128.9, 127.2, 119.5, 54.5, 51.0, 45.0, 30.3, 29.9, 22.4. Anal. Calcd. for $C_{25}H_{36}N_2O_3S \times 1/3\ H_2O$: C, 66.82; H, 7.33; N, 9.74. Found: C, 66.69; H, 7.32; N, 9.70.

General procedure C, compounds 4–6. Compounds **15**–**17** were dissolved in dry CH_2Cl_2 and cooled to 0 °C and reacted with an excess of 1.0 M BCl_3 in hexane fractions under nitrogen. The reaction was left at room temperature for 1 hour. The reaction mixture was then evaporated and co-evaporated several times with $CHCl_3$. The residue was dissolved in CH_2Cl_2

and water (3:1). Na_2CO_3 was added and the reaction mixture was cooled to 0 °C and *n*-butyl chloroformate was added and the reaction was left to reach room temperature over night. The reaction mixture was diluted with $CHCl_3$ organic and the phases were separated. The organic phase was washed with water and brine, dried over $MgSO_4$ and evaporated. The residue was purified on preparative RP-HPLC (H_2O/MeCN with 0.05% HCOOH) to give the pure products **15–17**.

***N*-(Butoxycarbonyl)-2-(3-imidazol-1-ylmethylphenyl)-4-isobutyl-benzenesulfonamide (4)**

According to the general procedure C compound **15** (135 mg, 0.32 mmol) was reacted with BCl_3 (1.3 mL, 1.0 M in hexane, 1.3 mmol) and afterwards with Na_2CO_3 (94 mg, 0.89 mmol) and n- butyl chloroformate (33 μL, 0.26 mmol). The crude product was first purified by column chromatography ($CHCl_3$:MeOH 10:1) and then preparative HPLC (H_2O/MeCN with 0.05% HCOOH) to isolate compound **4** as a white solid in 27% yield (40 mg, 0.085 mmol). ^{1}H NMR (CD_3OD), δ, ppm: 8.06 (d, *J* = 8.2 Hz, 1H), 7.72-7.70 (m, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.29 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.26-7.20 (m, 2H), 7.15-7.12 (m, 1H), 7.06-7.04 (m, 1H), 7.03 (d, *J* = 1.9 Hz, 1H), 7.02-6.99 (m, 1H), 5.17 (s, 2H), 3.95 (t, *J* = 6.6 Hz, 2H), 2.52 (d, *J* = 7.2 Hz, 2H), 1.95-1.82 (m, 1H), 1.46-1.39 (m, 2H), 1.22-1.13 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.82 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (CD_3OD), δ, ppm: 152.1, 147.9, 140.7, 140.2, 137.4, 135.4, 135.3, 133.3, 130.6, 129.4, 129.1, 128.79, 128.77, 127.9, 127.1, 120.3, 66.5, 51.3, 45.3, 30.8, 30.3, 22.4, 19.0, 13.7. Anal. Calcd. for $C_{25}H_{31}N_3O_4S \times 1.5\ H_2O \times 1$ HCOOH: C, 57.54; H, 6.69; N, 7.75 **Found:** C, 57.66; H, 6.21; N, 7.85.

***N*-(Butoxycarbonyl)-2-(4-imidazol-1-ylmethylphenyl)-5-isobutyl-benzenesulfonamide (5)**

According to the general procedure C compound **16** (131 mg, 0.31 mmol) was reacted with

BCl_3 (1.2 mL, 1.0 M in hexane, 1.2 mmol) and afterwards with Na_2CO_3 (146 mg, 1.4 mmol) and *n*-butyl chloroformate (51 μL, 0.40 mmol). The crude product was first purified by column chromatography ($CHCl_3$:MeOH 10:1) and then preparative HPLC (H_2O/MeCN with 0.05% HCOOH) to isolate compound **5** as a white solid in 46% yield (66 mg, 0.14 mmol). ^1H NMR ($CDCl_3$), δ, ppm: 8.08 (d, *J* = 1.8 Hz, 1H), 7.74-7.73 (m, 1H), 7.41-7.37 (m, 3H), 7.18-7.13 (m, 3H), 6.90-6.89 (m, 1H), 6.86-6.85 (m, 1H), 5.13 (s, 2H), 4.00 (t, *J* = 6.6 Hz, 2H), 2.61 (d, *J* = 7.1 Hz, 2H), 2.01-1.91 (m, 1H), 1.51-1.44 (m, 2H), 1.27-1.17 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 6H), 0.86 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$), δ, ppm: 151.6, 142.2, 139.8, 137.7, 137.5, 136.9, 134.9, 133.7, 132.2, 131.1, 130.2, 127.5, 127.2, 119.5, 66.3, 51.1, 45.0, 30.7, 30.3, 22.5, 19.0, 13.8. Anal. Calcd. for $C_{25}H_{31}N_3O_4S$: C, 63.94; H, 6.65; N, 8.95. Found: C, 63.72; H, 6.80; N, 8.90.

***N*-(Butoxycarbonyl)-2-(3-imidazol-1-ylmethylphenyl)-5-isobutyl-benzenesulfonamide (6)**

According to the general procedure C compound **17** (97 mg, 0.23 mmol) was reacted with BCl_3 (0.9 mL, 1.0 M in hexane, 0.92 mmol) and afterwards with Na_2CO_3 (109 mg, 1.0 mmol) and *n*-butyl chloroformate (38 μL, 0.30 mmol). The crude product was first purified by column chromatography ($CHCl_3$:MeOH 10:1) and then preparative HPLC (H_2O/MeCN with 0.05% HCOOH) to isolate compound **6** as a white solid in 51% yield (55 mg, 0.12 mmol). ^1H NMR ($CDCl_3$), δ, ppm: 8.12 (d, *J* = 1.8 Hz, 1H), 7.43-7.41 (m, 1H), 7.38 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.31-7.24 (m, 3H), 7.16 (d, *J* = 7.7 Hz, 1H), 6.97-6.95 (m, 2H), 6.86-6.83 (m, 1H), 4.97 (s, 2H), 4.02 (t, *J* = 6.6 Hz, 2H), 2.62 (d, *J* = 7.1 Hz, 2H), 2.05-1.90 (m, 1H), 1.53-1.46 (m, 2H), 1.29-1.20 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 6H), 0.87 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$), δ, ppm: 152.2, 142.1, 140.2, 137.85, 137.78, 136.8, 134.9, 133.5, 131.9, 131.4, 129.45, 129.42, 128.4, 127.0, 125.9, 119.6, 66.1, 51.2, 45.0, 30.8, 30.3, 22.5, 19.0, 13.8. Anal. Calcd. for $C_{25}H_{31}N_3O_4S$: C, 63.94; H, 6.65; N, 8.95. Found: C, 63.73; H, 6.57; N, 8.78.

Biology.

Porcine (pig) Myometrial Membrane AT_2 Receptor Binding Assay. Myometrial membranes were prepared from porcine uteri according to the method by Nielsen *et al.*[1] A presumable interference by binding to AT_1 receptors was blocked by addition of 1 μM losartan. Binding of [^{125}I]Ang II to membranes was conducted in a final volume of 0.5 mL containing 50 mM Tris–HCl (pH 7.4), 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA, homogenate corresponding to 10 mg of the original tissue weight, [^{125}I]Ang II (80,000-85,000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25 °C for 1.5 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets, which had been presoaked overnight with 0.3% polyethylamine, using a Brandel cell harvester. The filters were washed with 3 × 3 mL of Tris–HCl (pH 7.4) and transferred to tubes. The radioactivity was measured in a γ-counter. The characteristics of the Ang II binding AT_2 receptor was determined by using six different concentrations (0.03-5 nmol/L) of the labeled [^{125}I]-AngII. Nonspecific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by subtracting the nonspecific binding from the total bound [^{125}I]AngII. The apparent dissociation constant K_i values were calculated from IC_{50} values using the Cheng-Prusoff equation (K_d = 0.73 ± 0.06 nM, [L] = 0.057 nM). The binding data were best fitted with a one-site fit. All determinations were performed in triplicate.

General Considerations for In Vitro Morphological Effects. The chemicals used in the present study were obtained from the following sources: Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), HAT supplement (Hypoxanthine, Aminopterin, Thymidine), gentamycin from Gibco BRL (Burlington, Ont, Canada); [Val^5]-angiotensin II

from Bachem (Marina Delphen, CA, USA). PD123,319 was obtained from RBI (Natick, MA, USA). All other chemicals were of grade A purity.

Cell Culture. NG108-15 cells (provided by Drs M. Emerit and M. Hamon; INSERM, U. 238, Paris, France) were used to study the *in vitro* morphological effects. In their undifferented state, neuroblastoma x glioma hybrid NG108-15 cells have a rounded shape and divide actively. The cells were cultured form passage 18 to 25 in Dulbecco's modified Eagle's medium (DMEM, Gibco BRL, Burlington, Ont., Canada) with 10% fetal bovine serum (FBS, Gibco), HAT supplement and 50 mg/L gentamycin at 37 °C in 75 cm^2 Nunclon Delta flasks in a humidified atmosphere of 93% air and 7% CO_2, as previously described.[2,3] Subcultures were performed at subconfluency. Under these conditions, cells express only the AT_2 receptor subtype.[2,3] Cells were treated during three days, once a day (first treatment 24 hours after plating), and micrographs were taken the fourth day. For all experiments, cells were plated at the same initial density of 3.6×10^4 cells/35 mm Petri dish. To determine a good test concentration, all compounds were tested at various concentrations ranging from 0.1 nM to 100 nM. No tendency of cell death was observed. Cells were treated without (control cells), or with [Val^5]-angiotensin II (100 nM) or with compound **3** (10 nM), **4** (10 and 100 nM), **5** (10 nM) or **6** (10 nM) in the absence or in the presence of PD 123,319 (10 μM), an AT_2 receptor antagonist. The antagonist was introduced daily 30 min prior to Ang II, compound **3**, **4**, **5** or **6**. Compound **3** (10 nM), **4** (10 and 100 nM), **5** (10 nM) or **6** (10 nM) were also tested in the presence of Ang II (100 nM) where the compounds were introduced daily 30 min prior to Ang II, to evaluate antagonistic properties.

Determination of Cells with Neurites. Cells were examined under a phase contrast microscope and pictures were taken at the end of the experimental period (on the fourth day).

Cells with at least one neurite longer than a cell body were counted as positive for neurite outgrowth. The number of cells with neurites was reported as the percentage of the total amount of cells in the micrographs and at least 400 cells were counted in three independent experiments and each condition was performed in duplicate.[4] The data are represented as mean ± SEM of the average number of cells on a micrograph.

Data Analysis.

The data are presented as mean ± SEM of the average number of cells on a micrograph. Statistical analyses of the data were performed using the two-way ANOVA test. Homogeneity of variance was assessed by Bartlett's test, and *p* values were obtained from Dunnett's tables.

General Protocol for Conformational Analysis. Simplified model structures were built of the compounds by replacing the n-butyl chain connected to the sulfoncarbamate with a methyl group. Conformational analysis was performed in MacroModel[5] using the OPLS 2005 force field and the Generalized Born Solvent Accessible (GB/SA) surface area method for water developed by Still *et al*.[6] The conformational search was conducted using the Systematic Unbound Multiple Minimum[7] search method, using 1,000 search steps per investigated torsion angle. The number of torsion angles allowed to vary simultaneously during each Monte Carlo step ranged from 1 to n-1, where n is the total number of investigated torsion angles. Truncated Newton Conjugate Gradient minimization with a maximum of 500 iterations was used for the minimization with the derivative convergence criterion set to 0.05 kJ mol^{-1} $Å^{-1}$. A subsequent minimization was performed on the found conformations with the derivative convergence set to 0.001 kJ mol^{-1} $Å^{-1}$. Conformations within 5 kcal mol^{-1} (21 kJ mol^{-1}) of the lowest energy minimum were saved in the conformational search.

DISCOtech Analysis. The DISCOtech[8] module in SYBYL[9] was used to search for an alignment of interesting features among the conformations identified for the model structures of **1** and **2**, and in a second analysis also including **5** and **6**. The DISCOtech setting "Features by Class" was used to only search for models containing a negative center, the interactions from the imidazole ring (both the nitrogen and the projected interaction point at the receptor), at least three hydrogen bond acceptors, and at least two hydrophobic features. The tolerance for a feature match between two molecules was set to start at 0.25 Å and increased, if necessary, in increments of 0.25 Å up to 2.5 Å. **1** was used as the reference molecule in the analysis.

References

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