

Supporting Information

Selective Angiotensin II AT₂ Receptor Agonists: Arylbenzyl Imidazoles Structure-Activity Relationships

Xiongyu Wu,^a Yiqian Wan,^a Mahalingam A. K.,^a Murugaiah A. M. S.,^a Bianca Plouffe^b, Milad Botros,^c Anders Karlén,^a Mathias Hallberg,^c Nicole Gallo-Payet^b* and Mathias Alterman^{a,*}

Content of Supporting Information

Chemistry

- Experimental section for compounds **6-14, 24, 26-30, 32-41, 43-46, 48, 49, 51-55, 57** including spectroscopic data of the compounds and ¹³C NMR for compounds presented in the experimental part.
- Elemental analysis of the compounds **5-57**.

Biological Assays

- Rat Liver Membrane AT₁ Receptor Binding Assay.
- Porcine (pig) Myometrial Membrane AT₂ Receptor Binding Assay.
- In Vitro Morphological Effects.

Experimental Section

Chemistry. General Considerations. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX 270 spectrometer at 270.2 and 67.8 MHz, respectively. Chemical shifts are given as δ values (ppm) downfield from tetramethylsilane. Elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden or Analytische Laboratorien, Lindlar, Germany. Flash column chromatography was performed on silica gel 60 (0.04-0.063 mm, E. Merck). Thin-layer chromatography was performed on precoated silica gel F-254 plates (0.25 mm, E. Merck) and was visualized with UV light. Analytical RP-LC/MS was performed on a Gilson HPLC system with a Zorbax SB-C8, 5 μm 4.6 \times 50 mm (Agilent Technologies) column, with a Finnigan AQA quadropole mass spectrometer at a flow rate of 1.5 mL/min ($\text{H}_2\text{O}/\text{CH}_3\text{CN}/0.05\% \text{HCOOH}$). All the organic phases were dried over MgSO_4 , unless otherwise is stated. All chemicals were purchased from commercial suppliers and used directly without further purification.

General procedure for compound 5-9. Compound **4**¹⁶ (150 mg, 0.311 mmol) and anisole (150 μL) were dissolved in TFA (5 mL) and stirred overnight. The reaction mixture was evaporated under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in pyridine (1.6 mL) and pyrrolidinopyridine (52.1 mg, 0.35 mmol) was added. The solution was cooled on an ice bath and acyl chloride (20 equiv.) was added under N_2 (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated and purified by column chromatography to give the pure compounds **5-9**.

N-Butylcarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (5). ^{13}C NMR (CDCl_3) δ 172.8, 150.8, 144.2, 137.2, 135.1, 134.9, 132.5, 129.9, 128.9, 127.3, 126.9, 119.5, 50.9, 39.3, 35.9, 30.5, 30.2, 29.6, 26.5, 22.3, 22.2, 13.8.

N-Ethoxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (6). Compound **4** was used according to the general procedure and reacted with ethyl chloroformate (595 μL , 6.22 mmol), which after purification (CH_2Cl_2 : MeOH 7:1) gave compound **6** in 56 % yield (78 mg, 0.174 mmol). ^1H NMR (20% CD_3OD in CDCl_3) δ 7.78 (br s, 1H), 7.55 (d, J = 7.8 Hz, 2H), 7.24 (d, J = 7.8 Hz, 2H), 7.07 (br s, 2H), 6.77 (s, 1H), 5.22 (s, 2H), 4.06 (q, J = 7.1 Hz, 2H), 2.71 (d, J = 7.1 Hz, 2H), 1.95 (m, 1H), 1.17 (t, J = 7.1 Hz, 3H), 0.99 (d, J = 6.4 Hz, 6H); ^{13}C NMR (20% CD_3OD in CDCl_3) δ 153.0, 150.7, 145.1, 137.2, 135.9, 135.0, 132.7, 130.1, 129.5, 127.9, 127.6, 120.2, 62.6, 49.6, 39.5, 30.8, 22.3, 14.3. Anal ($\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_4\text{S}_2$) C, H, N.

N-iso-Butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (7). Compound **4** was used according to the general procedure and reacted with *iso*-butyl chloroformate (807 μL , 6.22 mmol) at 50 °C, which after purification (CHCl_3 : MeOH 20:1) gave compound **7** in 71 % yield (105 mg, 0.221 mmol). ^1H NMR (CD_3OD) δ 8.18 (brs, 1H), 7.58 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.29 (brs, 1H), 7.17 (brs, 1H), 6.82 (s, 1H), 5.30 (s, 2H), 3.70 (d, J = 6.6 Hz, 2H), 2.72 (d, J = 7.1 Hz, 2H), 1.93 (m, 1H), 1.76 (m, 1H), 0.99 (d, J = 6.6 Hz, 6H), 0.81 (d, J = 7.4 Hz, 6H); ^{13}C NMR (CD_3OD) δ 155.7, 150.5, 145.2, 137.0, 136.4, 135.6, 131.0, 130.5, 128.9, 126.6, 121.8, 73.0, 52.2, 40.0, 31.9, 29.1, 22.6, 19.3. Anal ($\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_4\text{S}_2 \times 1/3 \text{H}_2\text{O}$) C, H, N.

N-(Methoxy-ethyloxycarbonyl)-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (8). Compound **4** was used according to the general procedure and reacted with methoxyethyl chloroformate (862 μL , 6.22 mmol), which after purification (CH_2Cl_2 : MeOH 9:1) gave compound **8** in 61 % yield (91 mg, 0.190 mmol). ^1H NMR (20% CD_3OD in CDCl_3) δ 8.00 (br s, 1H), 7.56 (d, J = 7.7 Hz, 2H), 7.19 (d, J = 7.7 Hz, 2H), 7.07 (br s, 2H), 6.75 (s, 1H), 5.20 (s, 2H), 4.14 (br t, J = 4.5 Hz, 2H), 3.52 (br t, J = 6.9 Hz, 2H), 3.32 (s, 3H), 2.70 (d, J = 7.1 Hz, 2H), 1.94 (m, 1H), 0.99 (d, J = 6.4 Hz, 6H); ^{13}C NMR (20% CD_3OD in CDCl_3) δ 153.1, 149.7, 144.0, 136.1, 134.8, 134.6, 132.8, 129.6, 128.8, 127.0, 125.6, 119.8, 70.0, 64.1, 58.2, 50.9, 38.9, 30.2, 21.8. Anal. ($\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_5\text{S}_2 \times 0.5 \text{H}_2\text{O}$) C, H, N.

N-iso-Propyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (9). Compound **4** was used according to the general procedure and reacted with isopropyl chloroformate (1M in toluene, 6.22 mL, 6.22 mmol) at 50 °C, which after purification (CHCl₃: MeOH 20:1) gave compound **9** in 43 % yield (62 mg, 0.134 mmol). ¹H NMR (CD₃OD) δ 8.16 (brs, 1H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.32 (s, 1H), 7.18 (s, 1H), 6.84 (s, 1H), 5.32 (s, 2H), 4.72 (sep, *J* = 6.3 Hz, 1H), 2.73 (d, *J* = 7.1 Hz, 2H), 1.94 (m, 1H), 1.09 (d, *J* = 6.3 Hz, 6H), 1.00 (d, *J* = 6.6 Hz, 6H); ¹³C NMR (CD₃OD) δ 155.5, 151.0, 145.6, 137.2, 136.2, 135.0, 131.0, 130.5, 128.9, 126.8, 122.0, 70.5, 52.1, 40.0, 31.9, 22.6, 22.1. Anal. (C₂₂H₂₇N₃O₄S₂ × H₂O) C, H, N.

N-tert-Butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (10). Compound **4** (44 mg, 0.10 mmol) and anisole (150 μL) were dissolved in TFA (5 mL) and stirred overnight. The reaction mixture was evaporated under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in pyridine (0.7 mL) and pyrrololidinopyridine (19 mg, 0.13 mmol) was added. The solution was cooled on an ice bath and di-tertbutyl carbonate (29.0 mg, 0.133 mmol) was added under N₂ (g) atmosphere. The reaction was stirred at ambient temperature for 1 h. The solvent was removed under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated and purified by column chromatography (CH₂Cl₂: MeOH 20:1) to give compound **10** in 33% yield (16 mg, 0.034 mmol). ¹H NMR (10% CD₃OD in CDCl₃) δ 7.65 (br s, 1H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.94 (br s, 2H), 6.65 (s, 1H), 5.09 (s, 2H), 2.59 (d, *J* = 7.1 Hz, 2H), 1.82 (m, 1H), 1.22 (s, 9H), 0.87 (d, *J* = 6.6 Hz, 6H); ¹³C NMR (10% CD₃OD in CDCl₃) δ 150.5, 149.5, 144.6, 136.6, 135.5, 134.2, 131.7, 129.5, 129.0, 128.0, 127.1, 119.6, 83.0, 50.6, 39.0, 30.3, 27.5, 21.9. Anal. (C₂₃H₂₉N₃O₄S₂) C, H, N.

N-(4,4,4-Trifluoro-butyloxycarbonyl)-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (11). Compound **4** (40.0 mg, 0.107 mmol) and anisole (150 μL) were dissolved in TFA (5 mL) and stirred overnight. The reaction mixture was evaporated under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in THF (10 mL) and DBU (7.97 μL, 0.0533 mmol) was added. A solution of CDI (51.8 mg, 0.320 mmol) and 4,4,4-trifluorobutanol (40.9 mg, 0.320 mmol) in THF (10 mL), which had been stirred at 50 °C for 3.5 h, was added to the reaction mixture. The mixture was stirred at 50 °C for 48 h. The reaction mixture was concentrated and purified on column chromatography (CH₂Cl₂: MeOH 20:1) to give compound **11** in 64% yield (36 mg, 0.068 mmol). ¹H NMR (15% CD₃OD in CDCl₃) δ 7.97 (br s, 1H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.05 (br s, 2H), 6.71 (s, 1H), 5.17 (s, 2H), 4.00 (t, *J* = 5.6 Hz, 2H), 2.65 (d, *J* = 6.9 Hz, 2H), 1.99 (m, 2H), 1.88 (m, 1H), 1.74 (m, 2H), 0.94 (d, *J* = 6.4 Hz); ¹³C NMR (15% CD₃OD in CDCl₃) δ 153.1, 150.5, 144.6, 136.6, 135.3, 135.1, 133.1, 130.1, 129.4, 127.7, 127.1 (q, *J* = 275.7 Hz, CF₃), 126.6, 120.4, 64.5, 51.5, 39.4, 30.7, 30.5 (q, *J* = 29.3 Hz, CCF₃) 22.9, 21.7. Anal. (C₂₃H₂₆F₃N₃O₄S₂) C, H, N.

N-(1-Butyloxy-methylcarbonyl)-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (12). To a solution of **4** (100 mg, 0.232 mmol) in CH₂Cl₂ (5 ml) was added BCl₃ (1.5 mL, 1M in CH₂Cl₂, 1.5 mmol). The mixture was stirred at ambient temperature for 40 min under N₂ atmosphere. The reaction mixture was diluted with EtOAc (100 mL) and washed with water and brine. The organic phase was dried and evaporated. The residue was dissolved in dry THF (4 mL) and DBU (20 μL, 0.13 mmol) was added to the reaction mixture. This mixture was added to a solution of CDI (130 mg, 0.80 mmol) and butoxyacetic acid (104 μL, 0.80 mmol) in dry THF (4 mL) that had been stirred at 50 °C for 2.5 h. The reaction mixture was stirred over night at 50 °C. The reaction was quenched with MeOH (20 mL) and the reaction mixture was concentrated under vacuum. The residue was dissolved in EtOAc (100 mL) and then washed with water. The organic phase was dried and concentrated. The crude product was purified on column chromatography (CHCl₃: MeOH 10:1) to obtain the desired product **12** (27 mg, 0.057 mmol) in 71% yield. ¹H NMR (CD₃OD) δ 7.96 (brs, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz,

2H), 7.21 (brs, 1H), 7.07 (brs, 1H), 6.79 (s, 1H), 5.26 (s, 2H), 3.67 (s, 2H), 3.40 (t, J = 6.8 Hz, 2H), 2.66 (d, J = 6.9 Hz, 2H), 1.88 (m, 1H), 1.48 (m, 2H), 1.29 (m, 4H), 0.96 (d, J = 6.6 Hz, 6H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (CD₃OD) δ 178.3, 148.3, 143.4, 138.0, 137.3, 136.6, 131.1, 130.3, 128.5, 128.2, 127.6, 121.4, 72.4, 72.3, 51.7, 39.9, 32.2, 31.8, 30.7, 22.6, 20.1, 14.3. Anal. (C₂₄H₃₁N₃O₄S₂) C, H, N.

N-Butylaminocarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (13).

To a solution of **4** (42 mg, 0.097 mmol) in CH₂Cl₂ (5 ml) was added BCl₃ (1.5 mL, 1M in CH₂Cl₂, 1.5 mmol). The mixture was stirred at ambient temperature for 40 min under N₂ atmosphere. The reaction mixture was diluted with EtOAc (100 mL) and washed with water and brine. The organic phase was dried and evaporated. The residue was dissolved in acetone (5 mL) and NaOH (0.2 mL, 1M aq, 0.20 mmol) was added. The reaction mixture was stirred for 10 min. To the solution butyl isocyanate (14 μ L, 2.0 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (150 mL) and washed with water and brine. The organic phase was dried and evaporated. The residue was purified on column chromatography (CHCl₃: MeOH 10:1) to afford compound **13** as a white solid in 33% yield (15 mg, 0.032 mmol). ^1H NMR (CDCl₃) δ 7.64 (s, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 6.98 (d, J = 17.8 Hz, 2H), 6.72 (s, 1H), 6.24 (brs, 1H), 5.10 (s, 2H), 3.08 (m, 2H), 2.62 (d, J = 7.1 Hz, 2H), 1.92 (m, 1H), 1.20 (m, 4H), 0.99 (d, J = 6.6 Hz, 6H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CDCl₃) δ 152.2, 150.0, 144.5, 137.0, 135.9, 134.4, 133.0, 129.7, 129.5, 128.1, 127.1, 119.5, 50.7, 39.9, 39.2, 31.6, 30.5, 22.2, 19.8, 13.7. Anal. (C₂₃H₃₀N₄O₃S₂) C, H, N.

N-Butylsulfonyl-3-(4-imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide (14).

To a solution **4** (50 mg, 0.12 mmol) in CH₂Cl₂ (3 mL) was added with 1.0 mL of solution of BCl₃ in dichloromethane. BCl₃ (1.5 mL, 1M in CH₂Cl₂, 1.5 mmol). The mixture was stirred at ambient temperature for 40 min under N₂ atmosphere. The reaction mixture was diluted with EtOAc (100 mL) and washed with water and brine. The organic phase was dried and evaporated. The residue was dissolved in THF (3 mL) and NaOH (1 mL, 1M) was added and the reaction mixture was stirred for 5 min. Butanesulfonyl chloride (45 μ L, 0.35) was added and the reaction mixture was stirred at ambient temperature for 24 h. The reaction mixture was diluted with EtOAc (150 mL) and then washed with water and brine. The organic phase was dried and concentrated. The crude product was recrystallized in acetone to obtain the pure product as white solids in 55% yield (32 mg, 0.064 mmol). ^1H NMR (CDCl₃) δ 8.70(1H, s), 7.64(2H, d, J =8.1), 7.08-7.20(5H,m), 6.59(1H, s), 5.06(2H,s), 3.08(2H, m), 2.57(2H, d, J =7.1), 1.67(1H, m), 1.65(2H, m), 1.29(2H, m), 0.89-0.79(9H, m); ^{13}C NMR (CDCl₃) δ 146.8, 140.9, 138.2, 136.8, 135.0, 131.9, 130.4, 128.6, 127.9, 121.2, 119.8, 54.0, 52.5, 38.9, 30.3, 25.6, 21.9, 21.4, 13.4; IR(cm^{-1}): 3133, 2959, 2871, 1576, 1543, 1514, 1155, 1405, 1258. Anal. (C₂₂H₂₉N₃O₄S₃) C, H, N.

N-(N-Butyl-methylaminocarbonyl)-3-(4-imidazol-1-ylmethylphenyl)-5-iso-

butylthiophene-2-sulfonamide (15). ^{13}C NMR (CDCl₃) δ 153.6, 149.8, 143.3, 136.9, 135.5, 135.1, 134.2, 129.6, 128.7, 127.2, 126.8, 119.8, 51.0, 48.5, 39.3, 34.3, 30.4, 29.7, 22.3, 19.8, 13.8; IR (cm^{-1}): 3119, 3051, 2956, 2931, 2870, 1673, 1575, 1541, 1466, 1391, 1308, 1239.

2-iso-Butylthiophene (16). ^{13}C NMR (CDCl₃) δ 144.3, 126.5, 124.8, 123.0, 39.1, 30.8, 22.2.

N-tert-Butyl-5-iso-butyl-thiophene-2-carboxamide (17). ^{13}C NMR (CDCl₃) δ 161.4, 149.2, 137.6, 127.5, 125.5, 51.8, 39.5, 30.7, 28.9, 22.1.

3-(4-Imidazol-1-ylmethylphenyl)-5-iso-butyl-N-tert-butylthiophene-2-carboxamide (19).

^{13}C NMR (CDCl₃) δ 161.4, 147.4, 140.2, 137.3, 136.3, 136.1, 133.9, 130.0, 129.8, 128.3, 127.6, 119.0, 51.4, 50.4, 39.3, 30.5, 28.4, 22.2; IR (cm-1): 3417, 3113, 2961, 2930, 2868, 1645, 1512.

3-(4-Imidazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-carboxamide (20). ^{13}C NMR

(CD₃OD) δ 167.1, 148.9, 144.1, 137.9, 136.6, 135.1, 131.2, 130.8, 130.1, 129.8, 123.3, 121.6, 53.4, 40.0, 31.8, 22.5.

N-Butylsulfonyl-3-(4-imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-carboxamide (21). ^{13}C NMR (CDCl_3) δ 166.4, 148.9, 144.3, 137.3, 136.4, 134.8, 132.2, 130.0, 129.4, 127.2, 119.9, 53.2, 51.0, 39.5, 30.5, 25.4, 22.3, 21.5, 13.6.

3-(4-Imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophene-2-carbonitrile (22). ^{13}C NMR (CDCl_3) δ 152.2, 150.4, 137.3, 136.8, 133.4, 129.5, 128.2, 127.7, 126.1, 119.3, 115.0, 101.8, 50.4, 39.3, 30.6, 22.1.

5-[3-(4-Imidazol-1-ylmethylphenyl)-5-*iso*-butylthiophen-2-yl]-1H-tetrazole (23). ^{13}C NMR (CDCl_3) δ 152.8, 146.6, 140.7, 136.3, 135.7, 133.8, 128.9, 128.2, 127.3, 124.5, 120.8, 120.651.0, 39.1, 30.5, 22.2; IR (cm^{-1}): 3387, 3117, 3050, 2957, 2927, 1583, 1515, 1084.

N-*tert*-Butyl-5-butylthiophene-2-sulfonamide (24). To a solution of *N-tert*-butylthiophene-2-sulfonamide (5.00 g, 0.0228 mol) in dry THF (43 mL), at -78 °C, was n-BuLi (38.5 mL, 1.6M in hexane, 61.6 mmol) added slowly, under a N_2 atmosphere. The mixture was stirred at -40 °C for 2 h. The solution was cooled to -78 °C and iodo-butane (5.19 mL, 0.046 mol) was added slowly. The reaction mixture was stirred at rt. overnight. The reaction was quenched with NH_4Cl (aq) (10 mL) and extracted with EtOAc. The organic phase was dried and concentrated. The crude product was purified on column chromatography (Hexane; EtOAc 10:1) to give compound **24** (2.92 g, 0.011 mol) in 46% yield. ^1H NMR (CDCl_3) δ 7.41 (d, J = 3.6 Hz, 1H), 6.69 (d, J = 3.8 Hz, 1H), 4.96 (m, 1H), 2.80 (d, J = 7.6 Hz, 2H), 1.65 (m, 2H), 1.37 (m, 2H), 1.26 (s, 9H), 0.92 (t, J = 7.26 Hz, 3H); ^{13}C NMR (CDCl_3) δ 153.0, 141.7, 131.9, 124.0, 54.9, 33.4, 29.9, 22.0, 13.6; Anal. ($\text{C}_{12}\text{H}_{21}\text{NO}_2\text{S}_2$) C, H, N.

N-*tert*-Butyl-5-propylthiophene-2-sulfonamide (25). ^{13}C NMR (CDCl_3) δ 152.3, 141.3, 131.9, 124.1, 54.9, 32.2, 29.9, 24.6, 13.5; IR (cm^{-1}): 3276, 2968, 2936, 1324, 1148.

N-Tert-butyl-5-(3-methoxy-benzyl)-thiophene-2-sulfonamide (26). To a solution of *N-tert*-butylthiophene-2-sulfonamide (1.163 g, 5.303 mmol) in dry THF (20 mL), at -78 °C, was n-BuLi (6.5 mL, 1.6M in hexane, 10 mmol) added slowly, under a N_2 atmosphere. The mixture was stirred at -40 °C for 2 h. The solution was cooled to -78 °C and 1-bromomethyl-3-methoxybenzene (0.817 mL, 5.83 mmol) was added slowly. The reaction mixture was stirred at rt overnight. The reaction was quenched with NH_4Cl (aq) (10 mL) and extracted with EtOAc. The organic phase was dried and concentrated. The crude product was purified on column chromatography (P-ether; EtOAc 10:1) to give compound **26** (0.810 g, 2.39 mmol) in 45% yield. ^1H NMR (CDCl_3) δ 7.42 (d, J = 3.6 Hz, 1H), 7.24 (dd, J = 7.8, 7.8 Hz, 1H), 6.87-6.69 (m, 4H), 4.69 (br s, 1H), 4.11 (s, 2H), 3.79 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (CDCl_3) δ 159.8, 151.1, 142.5, 140.2, 131.9, 129.7, 125.0, 120.9, 114.4, 112.2, 55.2, 55.0, 36.3, 29.9. Anal. ($\text{C}_{16}\text{H}_{21}\text{NO}_3\text{S}_2$) C, H.

2-(2-Methoxy-ethyl)thiophene (27). To a solution of MeI (8.30 g, 0.0585 mol) and NaH (2.21 g, 55% washed twice with p-ether, 0.0507 mol) in THF (25 mL) was 2-thiophen-2-yl-ethanol (4.34 mL, 3.90 mmol) in THF (15 mL) added dropwise at 50 °C over a period of 30 min. The reaction mixture was stirred for 1 h at 50 °C. Water (10 mL) was added and the reaction mixture was extracted with diethylether. The organic phase was dried and concentrated. The crude product was distilled under reduced pressure (85-87 °C/ 19 mm Hg) to give compound **27** (4.84 g, 3.40 mmol) in 87% yield. ^1H NMR (CDCl_3) δ 7.15 (dd, J = 5.1, 1.2 Hz, 1H), 6.95 (dd, J = 5.1, 3.5 Hz, 1H), 6.86 (dd, J = 3.5, 1.0 Hz, 1H), 3.64 (t, J = 6.8 Hz, 2H), 3.40 (s, 3H), 3.11 (t, J = 6.8 Hz, 2H); ^{13}C NMR (CDCl_3) δ 141.2, 126.6, 125.0, 123.5, 73.2, 58.6, 30.3. Anal. ($\text{C}_7\text{H}_{10}\text{OS}$) C, H.

N-*tert*-Butyl-5-(2-Methoxy-ethyl)thiophene-2-sulfonamide (28). ClSO_3H (1.17 mL, 17.6 mmol) was added slowly, at 0 °C, to PCl_5 (1.46 g, 7.01 mmol). To the reaction mixture **27** (2.00 g, 14.1 mmol) was added dropwise over a period of 20 min. The reaction mixture was stirred at 15-20 °C for 1 h. Ice-water (10 mL) was added and the solution was extracted with diethylether and the organic phase was washed with aqueous NaHCO_3 solution, dried and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and CH_3CN (5 mL) and t-BuNH₂ (2.22 mL, 21.1 mmol) was added and stirred overnight at rt. The crude product was purified on column chromatography (P-ether: EtOAc 4:1) to give compound **28** (1.38 g, 4.97 mmol) in 35% yield. ^1H

NMR (CDCl_3) δ 7.42 (d, J = 3.6 Hz, 1H), 6.76 (d, J = 3.6 Hz, 1H), 4.83 (br s, 1H), 3.61 (t, J = 6.3 Hz, 2H), 3.37 (s, 3H), 3.07 (t, J = 6.3 Hz, 2H), 1.27 (s, 9H). ^{13}C NMR (CDCl_3) δ 148.8, 142.4, 131.6, 125.0, 72.2, 58.7, 54.9, 30.8, 29.9. Anal. ($\text{C}_{11}\text{H}_{19}\text{NO}_3\text{S}_2$) C, H, N.

N-tert-Butyl-4-iso-butylbenzenesulfonamide (29). SO_2Cl_2 (28.6 mL, 0.430 mol) was added drop wise do a stirred and cooled (0°C) solution of iso-butylbenzene (13.1 mL, 0.0830 mol), and the mixture was stirred at 40°C for 30 min. The reaction mixture was poured into a stirred ice-water mixture (150 mL) and extracted with ethyl acetate. The combined organic phase was washed with water and brine. The organic phase was dried and concentrated. The residue was dissolved in CHCl_3 (100 mL) and *t*-butylamine (43.7 mL, 0.416 mol) was added drop wise. The reaction mixture was stirred for 1 h at r.t. Toluene (200 mL) was added and the reaction mixture was washed with brine and water. The organic phase was dried and concentrated. The crude product was purified on column chromatography (hexane: acetone 4:1) to give the pure compound **29** (12.0 g, 0.0445 mol) in 54% yield. ^1H NMR (CDCl_3) δ 7.84 (d, J = 8.4, 2H), 7.27 (d, J = 8.3, 2H), 5.11 (brs, 1H), 2.55 (d, J = 7.3, 2H), 1.90 (m, 1H), 1.65 (m, 2H), 1.21 (s, 9H), 0.92 (d, J = 6.6, 6H); ^{13}C NMR (CDCl_3) δ 146.4, 140.7, 129.9, 129.5, 126.8, 54.5, 45.1, 30.1, 22.3. Anal. ($\text{C}_{14}\text{H}_{23}\text{NO}_2\text{S}$) C, H, N.

N-tert-Butyl-4-butylbenzenesulfonamide (30). To the solution of 4-butylbenzene sulfonyl chloride (23.9 g, 0.103 mol) in CHCl_3 (300 mL) was *t*-butylamine (33.0 mL, 0.308 mol) added. The reaction mixture was stirred at r.t. for 1 h. Water (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 . The combined organic phase was washed with brine and water. The organic phase was dried and concentrated to give the pure compound **30** (25.8 g, 0.096 mol) in 93% yield. ^1H NMR (CDCl_3) δ 7.79 (m, 2H), 7.25 (m, 2H), 5.03 (s, 1H), 2.65 (t, J = 7.6 Hz, 2H), 1.60 (m, 2H), 1.35 (m, 2H), 1.20 (s, 9H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ , 147.8, 140.8, 128.9, 127.1, 54.6, 35.6, 33.3, 30.2, 22.4, 14.0. Anal. ($\text{C}_{14}\text{H}_{23}\text{NO}_2\text{S}$) C, H, N.

N-tert-Butyl-4-butyloxybenzenesulfonamide (31). ^{13}C NMR (CDCl_3) δ 162.1, 134.7, 129.0, 114.4, 68.1, 54.4, 31.1, 30.1, 19.2, 13.8; IR (cm^{-1}): 3274, 2962, 2934, 2874, 1596, 1498, 1319, 1257.

N-tert-Butyl-5-iso-propyloxybenzene-2-sulfonamide (32). To the solution of 4-*iso*-propoxybenzene sulfonyl chloride (268.4 mg, 1.144 mmol) in dry CH_2Cl_2 (12 mL) was *t*-butylamine (1.00 mL, 9.52 mmol) added. The reaction mixture was stirred at r.t. for 1 h. Water (5 mL) was added and the reaction mixture was extracted with CH_2Cl_2 . The combined organic phase was washed with brine and water. The organic phase was dried and concentrated to give the pure compound **32** (305.3 mg, 1.125 mmol) in 98% yield. ^1H NMR (CDCl_3) δ 7.79 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.78 (br s, 1H), 4.61 (m, 1H), 1.35 (d, J = 6.1 Hz, 6H), 1.20 (s, 9H); ^{13}C NMR (CDCl_3) δ 160.9, 134.5, 129.0, 115.3, 70.2, 54.4, 30.1, 21.8. Anal. ($\text{C}_{13}\text{H}_{21}\text{NO}_3\text{S} \times 1/3 \text{H}_2\text{O}$) C, H, N.

N-tert-Butyl-3-(4-imidazol-1-ylmethylphenyl)-5-butylthiophene-2-sulfonamide (41). To a solution of **24** (2.90 g, 10.5 mmol) in dry THF (40 mL), at -78 °C, was n-BuLi (16.2 mL, 1.6M in hexane, 25.9 mmol) added slowly, under a N_2 atmosphere. The mixture was stirred at -20 °C for 4 h. The solution was cooled to -78 °C and triisopropyl borate (13.3 mL, 57.6 mmol) was added slowly. The reaction mixture was stirred at rt overnight. The reaction was quenched with HCl (20 mL, 2M) and extracted with EtOAc. The organic phase was dried and concentrated. The resulting boronic acid **33** was used without further purification. A reaction tube was charged with the boronic acid **33** (606 mg, 1.90 mmol), **3¹⁶** (300.0 mg, 1.265 mmol), $\text{Pd}(\text{PPh}_3)_4$ (44 mg, 0.038 mmol), NaOH (4.0 mL, 1.25M, 5.1 mmol), toluene (15 mL), and ethanol (4 mL). The reaction tube was flushed with $\text{N}_{2(g)}$ and sealed with a screw cap. The reaction mixture was heated at 100 °C for 2 h. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc. The organic phase was dried and concentrated. The crude product was purified on column chromatography (CHCl_3 : MeOH 20:1) to provide compound **41** (447.7 mg, 1.037 mmol) in 82% yield. ^1H NMR (CDCl_3) δ 7.57 (d, J = 8.2 Hz, 2H), 7.54 (s, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.06 (s,

1H), 6.89 (s, 1H), 6.73 (s, 1H), 5.14 (s, 2H), 4.48 (s, 1H), 2.79 (t, $J = 7.5$ Hz, 2H), 1.66 (m, 2H), 1.38 (m, 2H), 0.97 (s, 9H), 0.92 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 149.9, 142.4, 137.4, 136.4, 135.0, 129.9, 129.6, 128.0, 127.3, 119.1, 54.5, 50.4, 33.2, 29.6, 29.5, 22.0, 13.7. Anal. ($\text{C}_{22}\text{H}_{29}\text{N}_3\text{O}_2\text{S}_2$) C, H, N.

***N*-tert-Butyl-3-(4-imidazol-1-ylmethylphenyl)-5-propylthiophene-2-sulfonamide (42).** ^{13}C NMR (CDCl_3) δ 149.6, 142.3, 137.2, 136.4, 136.2, 135.0, 129.6, 128.0, 127.3, 119.2, 54.5, 50.5, 31.9, 29.5, 24.4, 13.

***N*-tert-Butyl-3-(4-imidazol-1-ylmethylphenyl)-5-(3-methoxy-benzyl)thiophene-2-sulfonamide (43).** To a solution of **26** (788 mg, 2.32 mmol) in dry THF (20 mL), at -78 °C, was n-BuLi (3.63 mL, 1.6M in hexane, 5.80 mmol) added slowly, under a N_2 atmosphere. The mixture was stirred at -20 °C for 4 h. The solution was cooled to -78 °C and triisopropyl borate (0.81 mL, 3.5 mmol) was added slowly. The reaction mixture was stirred at rt overnight. The reaction was quenched with HCl (8 mL, 2M) and extracted with EtOAc. The organic phase was dried and concentrated. The resulting boronic acid **35** was flushed trough a silica column (CH_2Cl_2 : MeOH 40:1) before further use. A reaction tube was charged with the boronic acid **35** (243 mg, 0.633 mmol), **3¹⁶** (150 mg, 0.633 mmol), $\text{Pd}(\text{PPh}_3)_4$ (36.6 mg, 0.0317 mmol), NaOH (2.46 mL, 1.54M, 3.80 mmol), toluene (15 mL), and ethanol (2 mL). The reaction tube was flushed with $\text{N}_{2(g)}$ and sealed with a screw cap. The reaction mixture was heated at 100 °C for 3 h. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc. The organic phase was dried and concentrated. The crude product was purified on column chromatography (CH_2Cl_2 : MeOH 40:1) to provide compound **43** (188.2 mg, 0.3797 mmol) in 60% yield. ^1H NMR (CDCl_3) δ 7.60 (br s, 1H), 7.55 (d, $J = 8.1$ Hz, 2H), 7.21 (d, $J = 7.4$ Hz, 1H), 7.20 (d, $J = 8.1$ Hz, 2H), 7.06 (br s, 1H), 6.89 (br s, 1H), 6.86-6.78 (m, 2H), 6.77 (s, 1H), 6.74 (s, 1H), 5.13 (s, 2H), 4.69 (br s, 1H), 4.08 (s, 2H), 3.77 (s, 3H), 0.98 (s, 9H); ^{13}C NMR (CDCl_3) δ 159.7, 148.0, 142.3, 140.0, 137.5, 137.3, 136.3, 134.7, 129.7, 129.6, 129.4, 128.7, 127.3, 120.9, 119.2, 114.4, 112.2, 55.1, 54.5, 50.4, 36.0, 29.4. Anal. ($\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_3\text{S}_2 \times 7/4 \text{ H}_2\text{O}$) C, H, N.

***N*-tert-Butyl-3-(4-imidazol-1-ylmethylphenyl)-5-(2-Methoxy-ethyl)thiophene-2-sulfonamide (44).** To a solution of **28** (600.0 mg, 2.163 mmol) in dry THF (30 mL), at -78 °C, was n-BuLi (3.38 mL, 1.6M in hexane, 5.41 mmol) added slowly, under a N_2 atmosphere. The mixture was stirred at -20 °C for 4 h. The solution was cooled to -78 °C and triisopropyl borate (0.75 mL, 3.2 mmol) was added slowly. The reaction mixture was stirred at rt overnight. The reaction was quenched with HCl (5 mL, 2M) and extracted with EtOAc. The organic phase was dried and concentrated. The resulting boronic acid **36** was flushed trough a silica column (CH_2Cl_2 : MeOH 20:1) before further use. A reaction tube was charged with the boronic acid **36** (564 mg, 1.76 mmol), **3¹⁶** (96.8 mg, 0.408 mmol), $\text{Pd}(\text{PPh}_3)_4$ (27.1 mg, 0.02343 mmol), Na_2CO_3 (0.42 mL, 2.0M, 0.82 mmol), DME (8 mL), ethanol (1 mL), and water (1.5 mL). The reaction tube was flushed with $\text{N}_{2(g)}$ and sealed with a screw cap. The reaction mixture was heated at 100 °C overnight. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc. The organic phase was dried and concentrated. The crude product was purified on column chromatography (CH_2Cl_2 : MeOH 20:1) to provide compound **44** (34.6 mg, 0.0780 mmol) in 20% yield. ^1H NMR (CDCl_3) δ 7.74 (br s, 1H), 7.60 (d, $J = 8.1$ Hz, 2H), 7.25 (d, $J = 8.1$ Hz, 2H), 7.13 (br s, 1H), 6.95 (br s, 1H), 6.83 (s, 1H), 5.19 (s, 2H), 4.35 (br s, 1H), 3.64 (t, $J = 6.4$ Hz, 2H), 3.39 (s, 3H), 3.08 (t, $J = 6.3$ Hz, 2H), 1.01 (s, 9H); ^{13}C NMR (CDCl_3) δ 145.9, 142.1, 137.5, 137.1, 135.9, 135.1, 129.8, 129.0, 128.7, 127.5, 119.4, 72.1, 58.8, 54.6, 50.8, 30.6, 29.6. Anal. ($\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}_3\text{S}_2$) C, H, N.

***N*-tert-Butyl-2-(4-imidazol-1-ylmethylphenyl)-4-*iso*-butylbenzenesulfonamide (45).** To a solution of *N*-tert-butyl-4-*iso*-butylbenzenesulfonamide (**29**) (2.69 g, 9.99 mmol) in dry THF (50 mL), at -78 °C, was n-BuLi (15.6 mL, 1.6M in hexane, 25.0 mmol) added slowly, under a N_2 atmosphere. The mixture was stirred at -20 °C for 4 h. The solution was cooled to -78 °C and triisopropyl borate (4.6 mL, 20 mmol) was added slowly. The reaction mixture was stirred at rt overnight. The reaction was quenched with HCl (15 mL, 2M) and extracted with EtOAc. The

organic phase was dried and concentrated. The resulting boronic acid **37** was used without further purification. A reaction tube was charged with the boronic acid **37** (1.2 g, 0.38 mol), **3**¹⁶ (98.8 mg, 0.417 mmol), Pd(PPh₃)₄ (29 mg, 0.025 mmol), NaOH (3.0 mL, 1.0M, 3.0 mmol), toluene (15 mL), and etanol (2.5 mL). The reaction tube was flushed with N_{2(g)} and sealed with a screw cap. The reaction mixture was heated at 100 °C for 2 h. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc. The organic phase was dried and concentrated. The crude product was purified on column chromatography (CHCl₃: MeOH 20:1) to provide compound **45** (93.7 mg, 0.220 mmol) in 53% yield. ¹H NMR (CDCl₃) δ 8.05 (d, *J* = 8.1 Hz, 1H), 7.80 (s, 1H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.30 (m, 3H), 7.07 (m, 3H), 5.24 (s, 2H), 2.56 (d, *J* = 7.1 Hz, 2H), 1.90 (m, 1H), 1.01 (s, 9H), 0.93 (d, *J* = 6.6 Hz, 6H); ¹³C NMR (CDCl₃) δ 146.2, 139.9, 138.9, 138.8, 136.7, 135.5, 132.8, 130.3, 128.4, 128.2, 127.9, 126.6, 119.5, 54.0, 50.6, 44.7, 29.8, 29.4, 22.0. Anal. (C₂₄H₃₁N₃O₂S × ½ H₂O) C, H, N.

N-tert-Butyl-2-(4-imidazol-1-ylmethylphenyl)-4-butylbenzenesulfonamide (46). To a solution of *N*-*tert*-butyl-4-butylbenzenesulfonamide (**30**) (1.90 g, 7.05 mmol) in dry THF (50 mL), at -78 °C, was n-BuLi (13.22 mL, 1.6M in hexane, 21.15 mmol) added slowly, under a N₂ atmosphere. The mixture was stirred at -20 °C for 4 h. The solution was cooled to -78 °C and triisopropyl borate (3.25 mL, 14.0 mmol) was added slowly. The reaction mixture was stirred at rt overnight. The reaction was quenched with HCl (15 mL, 2M) and extracted with EtOAc. The organic phase was dried and concentrated. The resulting boronic acid **38** was used without further purification. A reaction tube was charged with the boronic acid **38** (294.3 mg, 0.9396 mmol), **3**¹⁶ (97.3 mg, 0.410 mmol), Pd(PPh₃)₄ (20.2 mg, 0.0175 mmol), NaOH (1.10 mL, 1.54M, 1.69 mmol), toluene (10 mL), and ethanol (2.0 mL). The reaction tube was flushed with N_{2(g)} and sealed with a screw cap. The reaction mixture was heated at 100 °C for overnight. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc. The organic phase was dried and concentrated. The crude product was purified on column chromatography (CH₂Cl₂: MeOH 40:1) to provide compound **46** (168.6 mg, 0.3962 mmol) in 96% yield. ¹H NMR (CDCl₃) δ 8.03 (d, *J* = 8.1 Hz, 1H), 7.98 (br s, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.31-7.23 (m, 3H), 7.16 (br s, 1H), 7.07 (d, *J* = 1.6 Hz, 1H), 7.00 (br s, 1H), 5.25 (s, 2H), 3.64 (s, 1H), 2.66 (t, *J* = 7.7 Hz, 2H), 1.61 (m, 2H), 1.34 (m, 2H), 0.98 (s, 9H), 0.91 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 147.4, 140.1, 139.2, 139.0, 137.0, 135.5, 132.2, 130.5, 128.4, 128.1, 127.9, 127.0, 119.5, 54.3, 50.9, 35.2, 33.1, 29.7, 22.3, 13.9. Anal. (C₂₄H₃₁N₃O₂S × ½ H₂O) C, H, N.

N-Tert-butyl-2-(4-imidazol-1-ylmethylphenyl)-4-butoxybenzenesulfonamide (47). ¹³C NMR (CDCl₃) δ 161.3, 141.1, 139.7, 137.2, 135.9, 133.6, 130.6, 130.3, 128.8, 126.8, 119.4, 118.2, 112.8, 68.1, 54.2, 50.6, 31.0, 29.7, 19.1, 13.7.

N-tert-Butyl-2-(4-imidazol-1-ylmethylphenyl)-4-iso-propoxybenzenesulfonamide (48). To a solution of **32** (290.6 mg, 1.064 mmol) in dry THF (20 mL), at -78 °C, was n-BuLi (1.67 mL, 1.6M in hexane, 2.66 mmol) added slowly, under a N₂ atmosphere. The mixture was stirred at -20 °C for 4 h. The solution was cooled to -78 °C and triisopropyl borate (0.37 mL, 1.6 mmol) was added slowly. The reaction mixture was stirred at rt. overnight. The reaction was quenched with HCl (2 mL, 2M) and extracted with EtOAc. The organic phase was dried and concentrated. The resulting boronic acid **40** was flushed trough a silica column (CH₂Cl₂: MeOH 40:1) before further use. A reaction tube was charged with the boronic acid **40** (188 mg, 0.596 mol), **3**¹⁶ (98.3 mg, 0.415 mmol), Pd(PPh₃)₄ (29.6 mg, 0.0256 mmol), NaOH (1.54 mL, 1.54M, 2.38 mmol), toluene (12 mL), and etanol (3.0 mL). The reaction tube was flushed with N_{2(g)} and sealed with a screw cap. The reaction mixture was heated at 100 °C for 4 h. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc. The organic phase was dried and concentrated. The crude product was purified on column chromatography (CH₂Cl₂: MeOH 40:1) to provide compound **48** (166.6 mg, 0.3897 mmol) in 94% yield. ¹H NMR (CDCl₃) δ 8.03 (d, *J* = 8.9 Hz, 1H), 7.75 (br s, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.11 (br s, 1H), 6.95 (br s, 1H), 6.89 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.72 (d, *J* = 2.5 Hz, 1H), 5.20 (s, 2H), 4.61 (m, 1H), 3.60 (br s, 1H), 1.34 (d, *J* = 6.1 Hz, 6H), 0.98 (s, 9H); ¹³C NMR (CDCl₃) δ 160.2, 141.2, 139.7, 137.2,

135.9, 133.4, 130.6, 130.3, 129.0, 126.8, 119.3, 119.2, 113.6, 70.3, 54.2, 50.6, 29.7, 21.8. Anal. (C₂₃H₂₉N₃O₃S) C, H, N.

N-Butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-butylthiophene-2-sulfonamide

(49). Compound **41** (263 mg, 0.610 mmol) and anisole (150 μ L) were dissolved in TFA (10 mL) and stirred overnight. The reaction mixture was evaporated under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in pyridine (3.0 mL) and pyrrolidinopyridine (91.6 mg, 0.618 mmol) was added. The solution was cooled on an ice bath and butyl chloroformate (786 μ L, 0.618 mmol) was added under N₂ (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated and purified by column chromatography (CHCl₃: MeOH 10:1) to give the entitled compound in 10% yield (29 mg, 0.061 mmol). ¹H NMR (CD₃OD) δ 7.94 (s, 1H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.20 (s, 1H), 7.06 (s, 1H), 6.8 (s, 1H), 5.25 (s, 2H), 3.88 (t, *J* = 6.3 Hz, 2H), 2.84 (t, *J* = 7.4 Hz, 2H), 1.68 (m, 1H), 1.44 (m, 4H), 1.26 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (CD₃OD) δ 159.5, 150.2, 143.9, 138.4, 137.2, 136.6, 131.0, 129.5, 128.5, 128.0, 121.4, 66.5, 51.7, 49.0, 34.7, 32.1, 30.5, 23.2, 20.1, 14.1. Anal. (C₂₃H₂₉N₃O₄S₂) C, H, N.

N-Butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-propylthiophene-2-sulfonamide

(50). ¹³C NMR (30%CD₃OD in CDCl₃) δ 153.7, 151.5, 144.8, 137.0, 135.7, 135.2, 133.0, 130.118, 128.7, 127.6, 127.3, 120.3, 66.3, 51.3, 32.3, 30.9, 24.7, 19.1, 13.8.

N-Butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-(3-methoxy-benzyl)thiophene-2-sulfonamide (51). Compound **43** (56.2 mg, 0.113 mmol) and anisole (75 μ L) were dissolved in TFA (2.0 mL) and stirred overnight. The reaction mixture was evaporated under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in pyridine (2.0 mL) and pyrrolidinopyridine (106 mg, 0.714 mmol) was added. The solution was cooled on an ice bath and butyl chloroformate (90.8 μ L, 0.714 mmol) was added under N₂ (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated and purified by column chromatography (CH₂Cl₂: MeOH 15:1) to give the entitled compound in 50% yield (30.6 mg, 0.0567 mmol). ¹H NMR (CDCl₃) δ 9.91 (br s, 1H), 7.90 (br s, 1H), 7.50 (d, *J* = 7.4 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.15-6.65 (m, 8H), 5.08 (s, 2H), 4.09 (s, 2H), 3.98 (t, *J* = 6.5 Hz, 2H), 3.78 (s, 3H), 1.47 (m, 2H), 1.22 (m, 2H), 0.84 (t, 7.3 Hz, 3H); ¹³C NMR (CDCl₃) δ 159.8, 153.5, 149.3, 149.3, 143.4, 139.9, 136.3, 135.0, 134.8, 134.5, 129.8, 128.6, 127.2, 125.5, 121.1, 119.7, 114.6, 112.2, 65.5, 55.2, 51.1, 36.2, 30.6, 18.8, 13.6. Anal. (C₂₇H₂₉N₃O₅S₂) C, H, N.

N-Butyloxycarbonyl-3-(4-imidazol-1-ylmethylphenyl)-5-(2-Methoxy-ethyl)thiophene-2-sulfonamide (52). Compound **44** (27.8 mg, 0.0641 mmol) was dissolved in CH₂Cl₂ (2 mL) under N₂ (g) atmosphere and BCl₃ (1.0 mL, 1M CH₂Cl₂) was added and the reaction mixture was stirred for 40 min. To the reaction mixture Na₂CO₃ (10% aq, 50mL) was added and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine and water then dried and evaporated. The residue was dissolved in pyridine (1.2 mL) and pyrrolidinopyridine (19 mg, 0.13 mmol) was added. The solution was cooled on an ice bath and ethyl chloroformate (16.3 μ L, 0.128 mmol) was added under N₂ (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated and purified by column chromatography (CH₂Cl₂:MeOH 15:1) to give the entitled compound in 49% yield (15.0 mg, 0.0314 mmol). ¹H NMR (5%CD₃OD in CDCl₃) δ 7.86 (br s, 1H), 7.51 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.05 (br s, 1H), 6.99 (br s, 1H), 6.83 (s, 1H), 5.18 (s, 2H), 4.03 (t, *J* = 6.5 Hz, 2H), 3.67 (t, *J* = 6.2 Hz, 2H), 3.10 (t, *J* = 6.2 Hz, 2H), 1.52 (m, 2H), 1.26 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (5%CD₃OD in CDCl₃) δ 151.7, 148.1, 144.7, 136.9, 135.2, 134.8, 133.0,

129.9, 129.4, 127.4, 127.2, 119.8, 72.0, 66.3, 58.8, 51.1, 30.7, 30.5, 18.8, 13.6. Anal. ($C_{22}H_{27}N_3O_5S_2 \times \frac{1}{2} H_2O$) C, H, N.

***N*-Butyloxycarbonyl-2-(4-imidazol-1-ylmethylphenyl)-4-*iso*-butylbenzenesulfonamide**

(53). Compound **45** (90.0 mg, 0.211 mmol) was dissolved in CH_2Cl_2 (5 mL) under N_2 (g) atmosphere and BCl_3 (1.5 mL, 1M CH_2Cl_2) was added and the reaction mixture was stirred for 40 min. To the reaction mixture Na_2CO_3 (10% aq, 50mL) was added and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine and water then dried and evaporated. The residue was dissolved in pyridine (2 mL) and pyrrolidinopyridine (36 mg, 0.24 mmol) was added. The solution was cooled on an ice bath and butyl chloroformate (276 μ L, 2.23 mmol) was added under N_2 (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated and purified by column chromatography ($CHCl_3$:MeOH 10:1) to give the entitled compound in 67% yield (66.7 mg, 0.142 mmol). 1H NMR ($CDCl_3$) δ 8.14(1H, d, $J=8.1$), 7.72(1H, s), 7.36~7.19(6H, m), 7.04(3H, m), 5.19(2H, s), 3.98(2H, t, $J=6.5$), 2.56(2H, d, $J=7.1$), 1.93(1H, m), 1.41 (2H, m), 1.21(2H, m), 0.93(6H, d, $J=6.6$), 0.85(3H, t, $J=7.1$); ^{13}C NMR ($CDCl_3$) δ 151.8, 147.7, 140.4, 139.6, 137.1, 135.3, 134.9, 133.2, 130.5, 129.9, 128.6, 128.0, 127.0, 119.9, 66.3, 45.1, 30.6, 30.1, 22.4, 18.9, 13.6. Anal. ($C_{25}H_{31}N_3O_4S$) C, H, N.

***N*-Butyloxycarbonyl-2-(4-imidazol-1-ylmethylphenyl)-4-butylbenzenesulfonamide (54).**

Compound **46** (57.6 mg, 0.135 mmol) was dissolved in CH_2Cl_2 (5 mL) under N_2 (g) atmosphere and BCl_3 (1.5 mL, 1M CH_2Cl_2) was added and the reaction mixture was stirred for 30 min. To the reaction mixture Na_2CO_3 (10% aq, 50mL) was added and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine and water then dried and evaporated. The residue was dissolved in pyridine (1.2 mL) and pyrrolidinopyridine (40 mg, 0.27 mmol) was added. The solution was cooled on an ice bath and butyl chloroformate (34.5 μ L, 0.271 mmol) was added under N_2 (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated and purified by column chromatography (CH_2Cl_2 :MeOH 10:1) followed by purification with prep-HPLC (AcNC in water 20-80%) to give the entitled compound in 43% yield (27.5 mg, 0.0582 mmol). 1H NMR ($CDCl_3$) δ 8.95 (br s, 1H), 8.20 (d, $J=8.3$ Hz, 1H), 7.66 (br s, 1H), 7.38 (d, $J=8.0$ Hz, 2H), 7.34 (dd, $J=8.3, 1.6$ Hz, 1H), 7.11 (d, $J=8.0$ Hz, 2H), 7.05 (d, $J=1.6$ Hz, 1H), 6.83 (br s, 2H), 5.10 (s, 2H), 4.00 (t, $J=6.5$ Hz, 2H), 2.67 (t, $J=7.5$ Hz, 2H), 1.62 (m, 2H), 1.48 (m, 2H), 1.36 (m, 2H), 1.22 (m, 2H), 0.92 (t, $J=7.2$ Hz, 3H), 0.86 (t, $J=7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 151.9, 148.5, 140.2, 139.9, 136.7, 135.1, 134.7, 132.3, 130.8, 129.9, 127.7, 127.2, 126.9, 119.2, 65.9, 50.9, 35.4, 33.0, 30.5, 22.4, 18.8, 13.8, 13.6. Anal. ($C_{25}H_{31}N_3O_4S$) C, H, N.

***N*-Ethyloxycarbonyl-2-(4-imidazol-1-ylmethylphenyl)-4-butylbenzenesulfonamide (55).**

Compound **46** (81.1 mg, 0.191 mmol) was dissolved in CH_2Cl_2 (5 mL) under N_2 (g) atmosphere and BCl_3 (0.8 mL, 1M CH_2Cl_2) was added and the reaction mixture was stirred for 40 min. To the reaction mixture Na_2CO_3 (10% aq, 50mL) was added and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine and water then dried and evaporated. The residue was dissolved in pyridine (2 mL) and pyrrolidinopyridine (57 mg, 0.38 mmol) was added. The solution was cooled on an ice bath and ethyl chloroformate (38.5 μ L, 0.381 mmol) was added under N_2 (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated and purified by column chromatography (CH_2Cl_2 :MeOH 10:1) to give the entitled compound in 60% yield (50.5 mg, 0.114 mmol). 1H NMR ($CDCl_3$) δ 9.07 (br s, 1H), 8.18 (d, $J=8.3$ Hz, 1H), 7.95 (br s, 1H), 7.37 (d, $J=8.1$ Hz, 2H), 7.33 (dd, $J=$

8.3, 1.5 Hz, 1H), 7.15 (d, J = 8.1 Hz, 2H), 7.04 (d, J = 1.5 Hz), 6.94 (br s, 1H), 6.91 (br s, 1H), 5.16 (s, 2H), 4.04 (q, J = 7.1 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H), 1.61 (m, 2H), 1.35 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3) δ 152.1, 148.4, 140.1, 140.0, 136.4, 135.1, 134.3, 132.2, 130.8, 130.3, 130.0, 127.7, 127.1, 125.7, 119.7, 62.0, 51.2, 35.4, 33.0, 22.3, 14.2, 13.8. Anal. ($\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_4\text{S} \times \frac{1}{2}\text{H}_2\text{O}$) C, H, N.

N-Butyloxycarbonyl-2-(4-imidazol-1-ylmethylphenyl)-4-butoxybenzenesulfonamide (56). ^{13}C NMR (CDCl_3) δ 162.5, 151.0, 142.5, 139.6, 136.2, 134.0, 133.3, 129.8, 128.6, 127.5, 123.8, 120.3, 118.1, 113.0, 68.3, 66.4, 51.9, 31.0, 30.5, 19.1, 18.8, 13.8, 13.6.

N-Butyloxycarbonyl-2-(4-imidazol-1-ylmethylphenyl)-4-iso-propoxybenzenesulfonamide (57). Compound **48** (79.0 mg, 0.185 mmol) and anisole (75 μL) were dissolved in TFA (3.5 mL) and stirred overnight. The reaction mixture was evaporated under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in pyridine (3.0 mL) and pyrrolidinopyridine (68 mg, 0.46 mmol) was added. The solution was cooled on an ice bath and butyl chloroformate (58.7 μL , 0.462 mmol) was added under N_2 (g) atmosphere. The reaction was stirred at ambient temperature overnight. The solvent was removed under vacuum and co-evaporated with acetonitrile twice. The residue was dissolved in ethyl acetate (50 mL) and washed with citric acid (10% aq) and water. The organic phase was dried, evaporated and purified by column chromatography (CH_2Cl_2 : MeOH 8:1) to give the entitled compound in 49% yield (42.7 mg, 0.0905 mmol). ^1H NMR (15% CD_3OD in CDCl_3) δ 8.08 (d, J = 9.1 Hz, 1H), 7.83 (br s, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.05 (br s, 2H), 6.92 (dd, J = 9.1, 2.5 Hz, 1H), 6.66 (d, J = 2.5 Hz, 1H), 5.19 (s, 2H), 4.60 (m, 1H), 3.95 (t, J = 6.5 Hz, 2H), 1.44 (m, 2H), 1.31 (d, J = 5.9 Hz, 6H), 1.17 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (15% CD_3OD in CDCl_3) δ 161.4, 151.5, 142.8, 139.4, 135.2, 133.2, 129.8, 128.5, 127.1, 120.1, 119.3, 113.8, 70.7, 66.3, 50.7, 30.6, 21.8, 18.9, 13.6. Anal. ($\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_5\text{S} \cdot 0.5\text{H}_2\text{O}$) C, H, N.

Elemental Analysis

Compound	Formula	Calculated			Found		
		%C	%H	%N	%C	%H	%N
5 ($\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_3\text{S}_2$)		60.1	6.4	9.1	60.2	6.1	9.0
6 ($\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_4\text{S}_2$)		56.4	5.6	9.4	56.4	5.6	9.4
7 ($\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_4\text{S}_2 \times \frac{1}{3}\text{H}_2\text{O}$)		57.4	6.2	8.7	57.6	6.3	8.4
8 ($\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_5\text{S}_2 \times \frac{1}{2}\text{H}_2\text{O}$)		54.3	5.8	8.6	54.3	5.8	8.5
9 ($\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_4\text{S}_2 \times \text{H}_2\text{O}$)		55.1	6.1	8.8	55.5	5.9	8.5
10 ($\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_4\text{S}_2$)		58.1	6.2	8.7	58.1	6.2	8.7
11 ($\text{C}_{23}\text{H}_{26}\text{F}_3\text{N}_3\text{O}_4\text{S}_2$)		52.2	5.0	7.9	52.1	5.0	7.8
12 ($\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_4\text{S}_2$)		58.9	6.4	8.6	58.8	6.5	8.4
13 ($\text{C}_{23}\text{H}_{30}\text{N}_4\text{O}_3\text{S}_2$)		58.2	6.4	11.8	57.8	6.3	11.4
14 ($\text{C}_{22}\text{H}_{29}\text{N}_3\text{O}_4\text{S}_3$)		53.3	5.9	8.5	53.2	5.7	8.7
15 ($\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_3\text{S}_2 \times \frac{1}{2}\text{H}_2\text{O}$)		57.9	6.7	11.3	57.6	6.6	11.0
16 ($\text{C}_8\text{H}_{12}\text{S}$)		68.5	8.6		68.8	8.8	
17 ($\text{C}_{13}\text{H}_{21}\text{NOS}$)		65.2	8.8	5.9	65.5	9.0	5.9
19 ($\text{C}_{23}\text{H}_{29}\text{N}_3\text{OS} \times \text{H}_2\text{O}$)		66.8	7.6	10.2	66.9	7.3	9.9
20 ($\text{C}_{19}\text{H}_{21}\text{N}_3\text{OS}$)		67.2	6.2	12.4	67.4	6.4	12.3
21 ($\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_3\text{S}_2 \cdot \frac{1}{2}\text{HCOOH}$)		58.5	6.3	8.7	58.1	6.4	8.3
22 ($\text{C}_{19}\text{H}_{19}\text{N}_3\text{S}$)		71.0	6.0	13.1	71.1	6.2	13.1
23 ($\text{C}_{19}\text{H}_{20}\text{N}_6\text{S} \cdot \frac{1}{2}\text{HCOOH}$)		60.6	5.5	21.7	60.6	5.4	21.5

24	(C ₁₂ H ₂₁ NO ₂ S ₂)	52.3	7.7	5.4	52.5	7.7	5.2
25	(C ₁₁ H ₁₉ NO ₂ S ₂)	50.4	7.3	5.4	50.7	7.2	5.3
26	(C ₁₆ H ₂₁ NO ₃ S ₂)	56.6	6.2	4.1	56.5	6.3	4.3
27	C ₇ H ₁₀ OS	59.1	7.1		58.9	7.2	
28	(C ₁₁ H ₁₉ NO ₃ S ₂)	47.6	6.9	5.1	47.8	6.9	5.0
29	(C ₁₄ H ₂₃ NO ₂ S)	62.4	8.6	5.2	62.6	8.5	5.3
30	(C ₁₄ H ₂₃ NO ₂ S)	62.4	8.6	5.2	62.3	8.6	5.2
31	(C ₁₄ H ₂₃ NO ₃ S)	58.9	8.1	4.9	59.0	8.4	5.0
32	(C ₁₃ H ₂₁ NO ₃ S × 1/3 H ₂ O)	56.3	7.9	5.1	56.6	8.2	5.3
41	(C ₂₂ H ₂₉ N ₃ O ₂ S ₂)	61.2	6.8	9.7	61.0	6.8	9.4
42	(C ₂₁ H ₂₇ N ₃ O ₂ S ₂)	60.4	6.5	10.1	60.1	6.6	9.9
43	(C ₂₆ H ₂₉ N ₃ O ₃ S ₂ × 7/4 H ₂ O)	59.2	6.2	8.0	58.9	6.0	8.4
44	(C ₂₁ H ₂₇ N ₃ O ₃ S ₂)	58.2	6.3	9.7	57.8	6.3	9.3
45	(C ₂₄ H ₃₁ N ₃ O ₂ S × 1/2 H ₂ O)	66.3	7.4	9.6	66.5	7.1	9.2
46	(C ₂₄ H ₃₁ N ₃ O ₂ S × 1/2 H ₂ O)	66.3	7.4	9.6	66.0	7.5	9.7
47	(C ₂₄ H ₃₁ N ₃ O ₃ S × 1/2 H ₂ O)	64.0	7.2	9.3	63.9	7.1	9.2
48	(C ₂₃ H ₂₉ N ₃ O ₃ S)	64.6	6.8	9.8	64.3	6.9	9.6
49	(C ₂₃ H ₂₉ N ₃ O ₄ S ₂)	58.1	6.2	8.8	58.2	6.1	8.7
50	(C ₂₂ H ₂₇ N ₃ O ₄ S ₂ × 1/2 H ₂ O)	56.2	6.0	8.9	55.9	5.8	8.8
51	(C ₂₇ H ₂₉ N ₃ O ₅ S ₂)	60.1	5.4	7.8	60.4	5.8	7.9
52	(C ₂₂ H ₂₇ N ₃ O ₅ S ₂ × 1/2 H ₂ O)	54.3	5.8	8.6	54.7	6.0	8.2
53	(C ₂₅ H ₃₁ N ₃ O ₄ S)	63.9	6.7	9.0	63.5	6.5	8.8
54	(C ₂₅ H ₃₁ N ₃ O ₄ S)	63.9	6.7	9.0	64.0	6.7	8.9
55	(C ₂₃ H ₂₇ N ₃ O ₄ S × 1/2 H ₂ O)	61.3	6.3	9.3	61.3	6.5	9.3
56	(C ₂₅ H ₃₁ N ₃ O ₅ S)	61.8	6.4	8.7	61.7	6.4	8.7
57	(C ₂₄ H ₂₉ N ₃ O ₅ S × 1/2 H ₂ O)	60.0	6.3	8.7	60.3	6.6	8.9

Rat Liver Membrane AT₁ Receptor Binding Assay. Rat liver membranes were prepared according to the method of Dudley et al.²⁵ Binding of [¹²⁵I]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 MgCl₂, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA (bovine serum albumin), liver homogenate corresponding to 5 mg of the original tissue weight, [¹²⁵I]Ang II (80000-85000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25 °C for 2 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets, which had been pre-soaked 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 AT1 receptor was determined by using six different concentrations (0.03-5 nmol/L) of the labeled [125I]-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 [125I]AngII. The apparent dissociation constant *K_i* values were calculated from IC₅₀ values using the Cheng-Prusoff equation (*K_d* = 1.7 (0.1 nM, [L] = 0.057 nM). The binding data were best fitted with a one-site fit. All determinations were performed in triplicate.

Porcine (pig) Myometrial Membrane AT₂ Receptor Binding Assay. Myometrial membranes were prepared from porcine uteri according to the method by Nielsen et al.²⁶ A presumable interference by binding to AT₁ receptors was blocked by addition of 1 μ M losartan.²⁷ Binding of [¹²⁵I]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 MgCl₂, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA, homogenate corresponding to 10 mg of the original tissue weight, [¹²⁵I]Ang II (80000-85000 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 pre-soaked overnight with 0.3% polyethylamine, using a Brandel cell harvester. The filters were washed with 3 \times 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 AT1 receptor was determined by using six different concentrations (0.03-5 nmol/L) of the labeled [¹²⁵I]-AngII. Nonspecific binding was determined in the presence of 1 μ M Ang II. The specific binding was determined by subtracting the nonspecific binding from the total bound [¹²⁵I]AngII. The apparent dissociation constant K_i values were calculated from IC₅₀ values using the Cheng-Prusoff equation ($K_d = 1.7$ (0.1 nM, [L] = 0.057 nM). The binding data were best fitted with a one-site fit. All determinations were performed in triplicate.

In Vitro Morphological Effects. General. 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); [Val5]-angiotensin II from Bachem (Marina Delphen, CA, USA). **61** was 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 cultured (passage 7 to 30) in DMEM with 10% fetal bovine serum (FBS, Gibco BRL, Burlington, ONT, Canada), HAT supplement and 50 mg/L gentamycin at 37°C in 75 cm² Nunclon Delta flasks in a humidified atmosphere of 93% air and 7% CO₂, as previously described.²⁸ Subcultures were performed at subconfluence. Under these conditions, cells express only the AT₂ receptor subtype.^{28,29} Cells were stimulated once a day for three days (first stimulation 24 hours after plating). Cells were cultured for three subsequent days under these conditions. For all experiments, cells were plated at the same initial density of 4 \times 10⁴ cells /35 mm Perti dish. Cells were treated without (control cells), with [Val5]Ang II (0.1 μ M) or **50**, **56** (0.1 μ M), in the absence or in the presence of the inhibitor, **61** (1 μ M), an AT₂ receptor antagonist (each introduced daily with inhibitors applied 30 min prior to Ang II or **50**, **56**).

Determination of Cells with Neurites. Cells were examined daily under a phase contrast microscope and micrographs were taken after three days under the various experimental conditions. Cells with at least one neurite longer than a cell body were counted as positive for neurite outgrowth. At least 140 cells were counted in three independent experiments.³⁰

Data Analysis. The data were presented as mean \pm S.E.M. of the number of experiments indicated in the text, each performed in duplicate or triplicate. Statistical analyses of the data were performed using the one-way analysis of variance (ANOVA) test. Homogeneity of variance was assessed by Bartlett's test and p values were obtained from Dunnett's tables.