Supporting Information for *J. Org. Chem.*

**A Facile One-Pot Preparation of Alkyl Aminoaryl
Sulfides for the Synthesis of GW7647 as an
Agonist of Peroxisome Proliferator-Activated
Receptor α**

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General Considerations: ^1H and ^{13}C NMR spectra were recorded on 300 MHz and 500 MHz instruments in CDCl_3 or $\text{DMSO}-d_6$, using TMS as the internal standard. Mass spectra were recorded by the electron impact method (70 eV) or chemical ionization method. Commercially obtained anhydrous THF and reagents were used without further purification.

General Procedure for the Formation of Alkyl Aminoaryl Sulfides (Table 2)

To a solution of halo anilines (2.0 mmol) in anhydrous THF (30 mL), a solution of $i\text{-PrMgCl}$ (2.0 M solution in diethyl ether, 4.0 mmol) was added at 0 °C under N_2 atmosphere and a solution of $t\text{-BuLi}$ (1.7 M solution in pentane, 4.0 mmol) was slowly added for 15 min at -78 °C. After 30 min, sulfur powder (2.0 mmol) was then added and the reaction mixture was slowly warmed up to room temperature for 30 min. Finally, alkyl halide (2.0 mmol) was added at 0 °C. The reaction was monitored by thin layer chromatography. After the reaction was complete, it was quenched with aqueous NH_4Cl (35 mL). The organic layer was separated and then the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layer was washed with water, dried (MgSO_4), filtrated, and evaporated under reduced pressure to give the crude product. The crude compound was purified by chromatography on silica gel to obtain the desired product.

2-Benzylsulfanyl-phenylamine (Table 2, entry 1): The title compound was prepared from 2-haloaniline (2.0 mmol) and benzyl bromide (2.0 mmol). Flash chromatography (eluent: hexane/EtOAc = 3/1) gave the pure product as a light brown solid (for 2-iodoaniline, 319 mg, 74% and for 2-bromoaniline, 284 mg, 66%). mp 37-38 °C. ^1H NMR (300 MHz, CDCl_3): δ 7.24-7.19 (m, 3H), 7.17-7.07 (m, 4H), 6.68 (dd, 1H, J = 8.0,

1.2 Hz), 6.61 (td, 1H, $J = 7.6, 1.2$), 4.23 (br s, 2H), 3.89 (s, 2H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 148.8, 138.5, 136.7, 130.2, 129.1, 128.5, 127.2, 118.6, 115.1, 39.8. HRMS (EI): calcd. for $\text{C}_{13}\text{H}_{13}\text{NS}$ (M^+), 215.0769; found, 215.0769.

3-Benzylsulfanyl-phenylamine (Table 2, entry 2): The title compound was prepared from 3-haloaniline (2.0 mmol) and benzyl bromide (2.0 mmol). Flash chromatography (eluent: hexane/EtOAc = 3/1) gave the pure product as a brown solid (for 3-iodoaniline, 357 mg, 83% and for 3-bromoaniline, 349 mg, 81%) mp 45-47 °C. ^1H NMR (300 MHz, CDCl_3): δ 7.30-7.22 (m, 5H), 7.03 (t, 1H), 6.70 (dt, 1H), 6.62 (t, 1H), 6.48 (dt, 1H), 4.09 (s, 2H), 3.60 (bs, 2H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 147.0, 137.8, 137.6, 129.8, 129.0, 128.7, 127.3, 119.7, 116.0, 113.4, 38.9. HRMS (EI): calcd. for $\text{C}_{13}\text{H}_{13}\text{NS}$ (M^+), 215.0769; found, 215.0770.

4-Benzylsulfanyl-phenylamine (Table 2, entry 3): The title compound was prepared from 4-haloaniline (2.0 mmol) and benzyl bromide (2.0 mmol). Flash chromatography (eluent: hexane/EtOAc = 3/1) gave the pure product as a brown oil (for 4-iodoaniline, 405 mg, 94% and for 4-bromoaniline, 379 mg, 88%). ^1H NMR (300 MHz, CDCl_3): δ 7.27-7.08 (m, 7H), 6.54 (dt, 2H), 3.92 (s, 2H), 3.66 (br s, 2H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 146.4, 138.6, 134.9, 129.1, 128.5, 127.0, 123.1, 115.6, 41.9. HRMS (EI): calcd. for $\text{C}_{13}\text{H}_{13}\text{NS}$ (M^+), 215.0769; found, 215.0769.

4-Benzylsulfanyl-2-bromo-phenylamine (Table 2, entry 4): The title compound was prepared from 2,4-dibromoaniline (2.0 mmol) and benzyl bromide (2.0 mmol). Flash chromatography (eluent: hexane/EtOAc = 3/1) gave the pure product as a yellow

oil (435 mg, 74%). ^1H NMR (300 MHz, CDCl_3): δ 7.39 (d, 1H), 7.29-7.12 (m, 5H), 7.04 (dd, 1H), 6.61 (d, 1H), 4.11 (br s, 2H), 3.93 (s, 2H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 144.2, 138.4, 137.6, 134.0, 129.4, 128.8, 127.5, 124.5, 116.0, 109.3, 42.1. HRMS (EI): calcd. for $\text{C}_{13}\text{H}_{12}\text{NS}^{81}\text{Br}$ (M^+), 294.9853; found, 294.9853.

4-Benzylsulfanyl-2-methyl-phenylamine (Table 2, entry 5): The title compound was prepared from 4-iodo-2-methylaniline (2.0 mmol) and benzyl bromide (2.0 mmol). Flash chromatography (eluent: hexane/EtOAc = 3/1) gave the pure product as a clear oil (394 mg, 86%). ^1H NMR (300 MHz, CDCl_3): δ 7.32-7.24 (m, 5H), 7.16 (t, 1H), 6.86 (d, 1H), 6.82 (t, 1H), 6.65 (dd, 1H), 4.11 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 160.1, 138.1, 137.8, 130.0, 129.2, 128.9, 127.6, 122.1, 115.2, 112.6, 55.6, 39.2. HRMS (EI): calcd. for $\text{C}_{14}\text{H}_{15}\text{NS}$ (M^+), 229.0925; found, 229.0921.

4-(4-Aminophenylsulfanyl)-benzonitrile (Table 2, entry 6): The title compound was prepared from 4-iodoaniline (2.0 mmol) and 4-(bromomethyl)benzonitrile (2.0 mmol). Flash chromatography (eluent: hexane/EtOAc = 3/1) gave the pure product as a yellow solid, mp 130-132 °C (428 mg, 89%). ^1H NMR (300 MHz, CDCl_3): δ 7.50 (dt, 2H), 7.19 (d, 2H), 7.05 (dt, 2H), 6.54 (dt, 2H), 3.89 (s, 2H), 3.75 (br s, 2H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 147.0, 144.5, 135.6, 132.2, 129.8, 121.3, 119.1, 115.6, 110.7, 41.8. HRMS (EI): calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{S}$ (M^+), 240.0721; found, 240.0721.

4-(2-Methyl-allylsulfanyl)-phenylamine (Table 2, entry 7): The title compound was prepared from 4-iodoaniline (2.0 mmol) and 3-bromo-2-methylprop-1-ene (2.0 mmol). Flash chromatography (eluent: hexane/EtOAc = 3/1) gave the pure product as a

dark brown oil (333 mg, 93%). ^1H NMR (300 MHz, CDCl_3): δ 7.21 (dt, 2H), 6.59 (dt, 2H), 4.67 (m, 2H), 3.65 (br s, 2H), 3.35 (s, 2H), 1.83 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 146.2, 141.6, 134.7, 123.5, 115.6, 113.8, 44.8, 21.1. HRMS (EI): calcd. for $\text{C}_{10}\text{H}_{13}\text{NS}$ (M^+) 179.0769; found 179.0768.

2-(4-Amino-phenylsulfanyl)-1-phenyl-ethanone (Table 2, entry 8): The title compound was prepared from 4-iodoaniline (2.0 mmol) and 2-bromo-1-phenylethanone (2.0 mmol). Flash chromatography (eluent: hexane/EtOAc = 3/1) gave the pure product as a brown solid, mp 103-106 °C (448 mg, 92%). ^1H NMR (300 MHz, CDCl_3): δ 7.91 (m, 2H), 7.56 (m, 1H), 7.44 (m, 2H), 7.22 (dt, 2H), 6.57 (dt, 2H), 4.07 (s, 2H), 3.76 (br s, 2H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 194.7, 147.1, 135.8, 135.5, 133.4, 129.0, 128.8, 121.5, 115.8, 43.5. HRMS (EI): calcd. for $\text{C}_{14}\text{H}_{13}\text{NOS}$ (M^+), 243.0718; found, 243.0719.

(4-Amino-phenylsulfanyl)-acetic acid *tert*-butyl ester (Table 2, entry 9): The title compound was prepared from 4-iodoaniline (2.0 mmol) and *tert*-butyl 2-bromoacetate (2.0 mmol). Flash chromatography (eluent: hexane/EtOAc = 3/1) gave the pure product as a yellow oil (454 mg, 95%). ^1H NMR (300 MHz, CDCl_3): δ 7.29 (dt, 2H), 6.60 (dt, 2H), 3.74 (br s, 2H), 3.37 (s, 2H), 1.40 (s, 9H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 169.7, 147.0, 135.0, 122.5, 115.8, 81.8, 40.6, 28.3. HRMS (EI): calcd., for $\text{C}_{12}\text{H}_{17}\text{NO}_2\text{S}$ (M^+), 239.0980; found, 239.0980.

4-(5-Phenyl-pentylsulfanyl)-phenylamine (Table 2, entry 10): The title compound was prepared from 4-iodoaniline (2.0 mmol) and 1-(5-bromopentyl)benzene (2.0 mmol). Flash chromatography (eluent: hexane/EtOAc = 3/1) gave the pure product as a clear oil

(456 mg, 84%). ^1H NMR (300 MHz, CDCl_3): δ 7.29-7.11 (m, 7H), 6.60 (dt, 2H), 3.50 (br s, 2H), 2.75 (t, 2H), 2.58 (t, 2H), 1.62-1.53 (m, 4H), 1.47-1.39 (m, 2H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 145.9, 142.8, 134.0, 129.5, 128.6, 128.4, 125.8, 115.8, 36.5, 36.0, 31.2, 29.5, 28.5. HRMS (EI): calcd. for $\text{C}_{17}\text{H}_{21}\text{NS}$ (M^+), 271.1395; found, 271.1393.

4-Cyclohexylmethylsulfanyl-phenylamine (Table 2, entry 11): The title compound was prepared from 4-iodoaniline (2.0 mmol) and (bromomethyl)cyclohexane (2.0 mmol). Flash chromatography (eluent: hexane/EtOAc = 3/1) gave the pure product as a clear oil (359 mg, 81%). ^1H NMR (300 MHz, CDCl_3): δ 7.42 (d, 2H, J = 8.8 Hz), 7.21 (dt, 2H), 6.60 (dt, 2H), 3.66 (br s, 2H), 2.67 (d, 2H), 1.86 (d, 2H), 1.76-1.57 (m, 3H), 1.54-1.36 (m, 1H), 1.30-1.08 (m, 3H), 1.02-0.85 (m, 2H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 145.7, 139.0, 133.5, 115.8, 115.1, 44.1, 37.7, 32.9, 26.6, 26.3. HRMS (EI): calcd. for $\text{C}_{13}\text{H}_{19}\text{NS}$ (M^+), 221.1238; found, 221.1242.

1-(4-Aminophenylsulfanyl)-hex-5-en-2-ol (Table 2, entry 12): The title compound was prepared from 4-iodoaniline (2.0 mmol) and 2-(but-3-enyl)oxirane (2.0 mmol). Flash chromatography (eluent: hexane/EtOAc = 3/1) gave the pure product as a yellow oil (389 mg, 87%). ^1H NMR (300 MHz, CDCl_3): δ 7.26 (dt, 2H), 6.61 (dt, 2H), 5.79 (m, 1H), 4.98 (m, 2H), 3.73 (br s, 2H), 3.59 (m, 1H), 2.97 (dd, 1H), 2.68 (dd, 1H), 2.59 (bs, 1H), 2.24-2.05 (m, 2H), 1.66-1.50 (m, 3H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 146.6, 138.4, 134.6, 122.1, 115.9, 115.0, 68.7, 44.9, 35.2, 30.2. HRMS (EI): calcd. for $\text{C}_{12}\text{H}_{17}\text{NOS}$ (M^+), 223.1031; found, 223.1032.

General Procedure for the Formation of Alkyl (Alkylamino)aryl Sulfides (Table 3)

To a solution of 4-bromobenzylamine hydrochloride or 4-bromophenethylamine (2.0 mmol) in anhydrous THF (30 mL), a solution of *i*PrMgCl (2.0 M solution in diethyl ether, 4.0 mmol) was added at 0 °C under N₂ atmosphere and then a solution of *t*-BuLi (1.7 N solution in pentane, 4.0 mmol) was slowly added for 15 min at -78 °C. After 30 min, sulfur powder (2.0 mmol) was added and the reaction mixture was slowly warmed up to room temperature for 30 min. Finally, alkyl halide (2.0 mmol) was slowly added. The reaction was monitored by thin layer chromatography. After the reaction was completed, the reaction mixture was quenched with aqueous NH₄Cl (35 mL). The organic layer was separated and then the aqueous layer was extracted with EtOAc (3×30 mL). The combined extract was washed with water, dried (MgSO₄), filtrated, and evaporated under reduced pressure to give the crude product. The crude compound was purified by chromatography on silica gel to obtain the desired compound.

4-Benzylsulfanyl-benzylamine (Table 3, entry 1): The title compound was prepared from 4-bromobenzylamine hydrochloride (2.0 mmol) and benzyl bromide (2.0 mmol). Flash chromatography (eluent: 5% MeOH in CH₂Cl₂) gave the pure product as a white solid, mp 95-98 °C (440 mg, 96%). ¹H NMR (300 MHz, CDCl₃): δ 7.29-7.18 (m, 9H), 4.09 (s, 2H), 3.81 (s, 2H). ¹³C NMR (75.5 MHz, CDCl₃): δ 141.9, 137.8, 134.6, 130.6, 129.0, 128.7, 127.8, 127.3, 46.2, 39.6. HRMS (EI): calcd. for C₁₄H₁₅NS (M⁺), 229.0925; found, 229.0928.

2-(4-Benzylsulfanyl-phenyl)-ethylamine (Table 3, entry 2): The title compound was prepared from 4-bromophenethylamine (2.0 mmol) and benzyl bromide (2.0 mmol). Flash chromatography (eluent: 5% MeOH in CH₂Cl₂) gave the pure product as a brown

solid, mp 98-101 °C (477 mg, 98%). ¹H NMR (300 MHz, CDCl₃): δ 7.28-7.21 (m, 7H), 7.09 (d, 2H), 4.09 (s, 2H), 2.94 (t, 2H), 2.70 (t, 2H), 1.75 (br s, 2H). ¹³C NMR (75.5 MHz, CDCl₃): δ 138.4, 137.8, 134.0, 130.7, 129.6, 129.0, 128.7, 127.3, 43.5, 39.7, 29.9. HRMS (EI): calcd. for C₁₅H₁₇NS (M⁺), 243.1082; found, 243.1083.

***tert*-Butyl [4-(2-aminoethyl)-phenylsulfanyl]-acetate (Table 3, entry 3):** The title compound was prepared from 4-bromophenethylamine (2.0 mmol) and *tert*-butyl 2-bromoacetate (2.0 mmol). Flash chromatography (eluent: 5% MeOH in CH₂Cl₂) gave the pure product as a yellow oil (503 mg, 94%). ¹H NMR (300 MHz, CDCl₃): δ 7.32 (d, 2H), 7.17 (d, 2H), 4.98 (br s, 2H), 3.51 (s, 2H), 3.18 (t, 2H), 3.02 (t, 2H), 1.40 (s, 9H). ¹³C NMR (75.5 MHz, CDCl₃): δ 169.1, 135.7, 134.2, 130.5, 129.7, 82.3, 41.6, 38.0, 34.2, 28.1. HRMS (EI): calcd. for C₁₄H₂₁NO₂S (M⁺), 267.1293; found, 267.1294.

***tert*-Butyl 2-[4-(2-aminoethyl)-phenylsulfanyl]-2-methylpropanoate (Table 3, entry 4):** To a solution of 4-bromophenethylamine (400.2 mg, 2.0 mmol) in anhydrous THF (30 mL) was slowly added ⁱPrMgCl (2.0 M solution in diethyl ether, 2.0 mL, 4.0 mmol) at 0 °C for 10 min under N₂. After 30 min, *t*-BuLi (1.7 M solution in pentane, 2.4 mL, 4.0 mmol) was slowly added at -78 °C for 20 min and the reaction mixture was stirred for an additional 30 min. Sulfur powder (64 mg, 2.0 mmol) was added at once and the reaction mixture was slowly warmed up to room temperature for 30 min. After the reaction was complete, the solvent was completely removed by an evaporator under the atmosphere. To a solution of the residual product in MeOH (30 mL) was added KOH (117.8 mg, 2.1 mmol). The reaction mixture was heated at 60 °C for additional 1 h. After that time, the reaction mixture was poured into NH₄Cl solution (35 mL) and

extracted with EtOAc (3×30 mL). The combined organic layer was washed with H₂O, dried (MgSO₄), filtered off, and then concentrated on a rotary evaporator. The crude compound was purified by chromatography (eluent: 5% MeOH in CH₂Cl₂) on silica gel to obtain the pure product as a white oil (544 mg, 92%). ¹H NMR (300 MHz, CDCl₃): δ 7.44 (d, 7H, *J* = 8.0 Hz), 7.16 (d, 7H, *J* = 8.0), 2.97 (t, 2H), 2.76 (t, 2H), 1.44 (s, 6H), 1.43 (s, 9H). ¹³C NMR (75.5 MHz, CDCl₃): δ 173.5, 141.5, 137.4, 129.4, 81.3, 51.7, 43.8, 40.2, 28.3, 26.5. HRMS (EI): calcd. for C₁₆H₂₅NO₂S (M⁺), 295.1606; found, 295.1605.

^1H and ^{13}C -NMR Spectra of Compounds

2-Benzylsulfanyl-phenylamine (Table 2, entry 1, ref 1)

3-Benzylsulfanyl-phenylamine (Table 2, entry 2, ref 2)

4-Benzylsulfanyl-phenylamine (Table 2, entry 3, ref 3)

4-Benzylsulfanyl-2-bromo-phenylamine (Table 2, entry 4)

4-Benzylsulfanyl-2-methyl-phenylamine (Table 2, entry 5)

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4-(4-Aminophenylsulfanyl)-benzonitrile (Table 2, entry 6)

4-(2-Methyl-allylsulfanyl)-phenylamine (Table 2, entry 7)

2-(4-Amino-phenylsulfanyl)-1-phenyl-ethanone (Table 2, entry 8, ref 4)

(4-Amino-phenylsulfanyl)-acetic acid *tert*-butyl ester (Table 2, entry 9)

4-(5-Phenyl-pentylsulfanyl)-phenylamine (Table 2, entry 10)

4-Cyclohexylmethylsulfanyl-phenylamine (Table 2, entry 11)

1-(4-Aminophenylsulfanyl)-hex-5-en-2-ol (Table 2, entry 12)

4-Benzylsulfanyl-benzylamine (Table 3, entry 1, ref 5)

2-(4-Benzylsulfanyl-phenyl)-ethylamine (Table 3, entry 2)

tert-Butyl [4-(2-aminoethyl)-phenylsulfany] acetate (Table 3, entry 3)

tert-Butyl 2-[4-(2-aminoethyl)-phenylsulfanyl]-2-methylpropanoate (Table 3, entry 4, ref 6)

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