A Scalable Synthesis of the Thromboxane Receptor Antagonist 3-{3-[2-(4-Chlorobenzenesulfonamido)ethyl]-5-(4-fluorobenzyl)phenyl}propionic Acid via a Regioselective Heck Cross-Coupling Strategy

D. C. Waite* and C. P. Mason

Department of Process Research and Development, Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK

Abstract:

A regioselective Heck cross-coupling strategy is presented for the large-scale preparation of the thromboxane receptor antagonist 3-{3-[2-(4-chlorobenzenesulfonamido)ethyl]-5-(4fluorobenzyl)phenyl {propionic acid (1). Commercially available 3-bromo-5-iodobenzoic acid was first converted to the corresponding acid chloride, and this was then condensed with 4-fluorobenzene via a Friedel-Crafts acylation reaction to give 3-bromo-5-iodophenyl 4-fluorophenyl ketone. Regioselective cross-coupling with ethyl acrylate and then N-vinylphthalimide, each under phosphine-free Heck conditions, led to formation of ethyl 3-[3-(4-fluorobenzoyl)-5-(2-phthalimidovinyl)phenyl]propenoate. Reduction of the benzophenone moiety and saturation of the olefin double bonds, followed by phthalimide ring cleavage, then gave ethyl 3-[3-(2-aminoethyl)-5-(4-fluorobenzyl)phenyl]propionate monocitrate salt. This was converted to the sulfonamido-substituted arylpropionic acid 1 via a two-step one-pot procedure in which sulfonamide formation was achieved via condensation with 4-chlorobenzenesulfonyl chloride, followed by ethyl ester saponification. The route described avoids hazards identified with the original medicinal chemistry based synthesis and allows bulk quantities of drug substance to be produced for toxicological and clinical trials.

Introduction

Considerable effort has been devoted over the last 15 years to the development of thromboxane receptor antagonists with the aim of providing therapies for diseases such as asthma, unstable angina, deep vein thrombosis, and coronary atherosclerosis.¹ The latter is characterised by the partial blockade of coronary arteries due to build-up of fibrous plaque on the inner surface of the artery wall (stenosis) resulting in restriction of blood flow. Current invasive treatments for the disease include balloon angioplasty, which compresses the plaque build-up in the occluded artery, and coronary artery bypass grafting. The drawback associated with both techniques is that restenosis occurs in approximately 30% of patients 3–6 months after treatment, necessitating repeat angioplasty.

3-{3-[2-(4-Chlorobenzenesulfonamido)ethyl]-5-(4fluorobenzyl)phenyl}propionic acid (1), a potent thromboxane receptor antagonist discovered by chemists at Pfizer,² was progressed into development as a candidate designed to prevent restenosis after balloon angioplasty or artery bypass grafts. Initial bulk synthesis of **1** utilised a medicinal



chemistry based route³ outlined in Scheme 1. Bromine– lithium exchange of 1,3,5-tribromobenzene at -78 °C in diethyl ether followed by quenching of the resulting anion with 4-fluorobenzaldehyde led to isolation of **2** in 78% yield. Double Heck cross-coupling of the dibromide **2** with ethyl acrylate gave **3** in 78% yield, which was then activated as the corresponding acetate and hydrogenated to provide **4** in 85% yield for the two steps. Treatment of diester **4** with 1 equiv of sodium hydroxide in aqueous ethanol resulted in a mixture of monoester **5** (44%), dicarboxylic acid **6** (12%), and unreacted diester **4** (44%), which were separated by column chromatography.

The desired monoacid **5** was then converted via its acid chloride to the corresponding primary amide **7** in 93% yield. Hofmann rearrangement of **7** with concomitant ester hydrolysis gave the corresponding primary amino acid, which was condensed without purification with 4-chlorobenzenesulfonyl chloride to yield **1** in 85% yield.

Three issues were identified that severely limited the scalability of the route described above:

(1) Low-temperature lithiation of tribromobenzene was performed as a slurry in the hazardous solvent diethyl ether. Substitution with THF, an inherently safer solvent, resulted in polylithiation and a mixture of products upon quenching. In addition, the stability of *m*-bromophenyllithium slurries is questionable, with Bretherick⁴ reporting the explosive decomposition of such a slurry. It was suggested that a runaway exothermic intermolecular condensation reaction of the solid haloorganolithium reagent was the causative factor.

(2) Nonselective hydrolysis of the symmetrical diester **4** was inefficient, with **5** requiring laborious chromatographic

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purification in order to separate it from the dicarboxylic acid **6** and unreacted **4**.

(3) Conversion of the amide **7** to the corresponding amine utilised a Hofmann rearrangement, a problematic transformation with potential hazards associated with the exothermic nature of the reaction and the instability of the *N*-chloroamide intermediate generated in situ.

Production of bulk quantities of drug substance clearly required an efficient synthesis that was more amenable to scale-up.

Results and Discussion

Route Strategy. Our aim in devising an alternative route that avoided the problems highlighted above was to utilise a simple unsymmetrical 1,3,5-trisubstituted aromatic precursor on which regioselective transformations could be carried out to introduce the appropriate side chains of **1**.

Heck cross-coupling methodology remained an attractive option to introduce the carboxyethyl and aminoethyl side chains, while Friedel–Crafts acylation of fluorobenzene, followed by reduction of the resultant benzophenone, would allow introduction of the 4-fluorobenzyl substituent without recourse to low-temperature lithiation chemistry. This analysis led back to a 3,5-dihalogenated benzoic acid as a suitable precursor.

To avoid the low-yielding half ester hydrolysis and the potentially hazardous Hofmann rearrangement, selectivity

Scheme 2. Retrosynthetic analysis



was required in the two proposed Heck arylation reactions, enabling differentiated carboxyethyl and sulfonamidoethyl synthons to be introduced.

A literature review revealed reports of the selective crosscoupling of bromoiodoaromatics with acrylates, control being dependent on the catalyst used in the reaction.⁵ Aryl iodides were reported to readily undergo cross-coupling using palladium acetate as catalyst whilst aryl bromides reacted only in the presence of both palladium acetate and a triarylphosphine ligand.

Further literature searches found no precedent for Heck cross-coupling of *N*-vinylsulfonamides with aryl halides. However, formation of primary phenethylamine side chains had been achieved via Heck cross-coupling of aryl halides with *N*-vinylphthalimide^{6,7} or *N*-vinyloxazolone⁸ followed by suitable reduction and deprotection.

These precedents led us to believe that by adopting 3-bromo-5-iodobenzoic acid (8) as our starting material we could synthesise 1 without encountering any of the problems identified in the original route.

Alternative Route Synthesis. 3-Bromo-5-iodobenzoic acid (8) was first converted to the corresponding acid chloride using thionyl chloride/DMF in refluxing dichloromethane.⁹ This was used without isolation in a Friedel–Crafts acylation reaction with fluorobenzene to give the benzophenone **9** (Scheme 2) as a cream solid, in 78% yield.

Our attention then turned to implementing the regioselective Heck cross-coupling strategy. Treatment of **9** with ethyl acrylate in the presence of palladium acetate and triethylamine in refluxing acetonitrile gave the desired cinnamate **10** (Scheme 3) in 79% crystallised yield. GC/ MS studies of the crude reaction mixture indicated formation of only 0.4% of the corresponding bis(cinnamate), confirming the excellent selectivity of non-phosphine Heck conditions for cross-coupling of aryl iodides compared with aryl bromides.

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Heck cross-coupling of **10** with *N*-vinylphthalimide was initially accomplished on a small scale in the presence of diisopropylamine, tri-o-tolylphosphine, and palladium acetate in toluene at 100 °C in a sealed tube to give **11**, isolated as a yellow solid in 67% yield. Process development then demonstrated that the reaction could also be achieved at atmospheric pressure in refluxing xylene, the higher temperature presumably compensating for the reduction in reaction pressure. Performing the reaction at lower temperatures in refluxing acetonitrile or toluene at atmospheric pressure resulted in an unacceptably slow conversion rate.

Upon scaling the reaction, we were disappointed to observe complete failure of the cross-coupling using the refluxing xylene conditions detailed above. Careful investigation implicated the batch of phosphine ligand used in scale-up as the causative factor. Although the species responsible for suppressing the cross-coupling was not identified, replacement with a fresh source of tri-*o*-tolylphosphine allowed smooth cross-coupling again in 65% yield. To our surprise, the complete omission of the phosphine ligand source also allowed the reaction to proceed with only a modest decrease in the isolated yield (58%) of **11**. This result contradicted previous reports that claim a phosphine ligand is necessary for efficient cross-coupling of aryl bromides with olefins.⁵ The reliability of the phosphine-

free conditions led us to prepare **11** on multikilogram scale via this procedure.

Attention next turned to reduction of the benzophenone and saturation of the olefin side chains. Simultaneous reduction could not be achieved cleanly via hydrogenation over a variety of palladium catalysts in a selection of solvents. Instead, a two-step process was demonstrated whereby an ionic hydrogenation using triethylsilane in trifluoroacetic acid¹⁰ reduced the benzophenone moiety of **11** to give **12** (83% isolated yield) and then standard palladium-catalysed hydrogenation gave **13** as a colourless crystalline solid isolated in 92% yield.

Deprotection of the phthalimide moiety in **13** using aqueous methylamine in refluxing THF lacked selectivity, with 10% aminolysis of the ethyl ester accompanying ring cleavage. Thus, alternative conditions were employed utilising aqueous hydrazine in refluxing industrial methylated spirits (IMS).^{6,7} These conditions were found to give selective deprotection, with the desired amine **14** isolated initially as a crude yellow oil and then purified by crystallisation as the corresponding citrate salt, isolated in 87% yield from **13**. Conversion of **14** to **1** was accomplished in a two-step, one-pot procedure. Sulfonylation was performed with 4-chlorobenzenesulfonyl chloride and triethylamine in tetrahydrofuran, and the crude reaction mixture was then treated with aqueous sodium hydroxide at reflux to hydrolyse the ethyl ester. Acidification led to isolation of **1** in 87% yield.

In summary, a safe, scalable synthesis of **1** has been demonstrated in 21% overall yield and has been used to prepare bulk quantities of drug substance for use in toxicological and clinical trials.

Experimental Section

3-Bromo-5-iodophenyl 4-Fluorophenyl Ketone (9). To a stirred suspension of 3-bromo-5-iodobenzoic acid (11.6 kg, 35.5 mol) in dichloromethane (58 L) under a nitrogen atmosphere was added DMF (134 mL, 1.72 mol), and the suspension was brought to gentle reflux. Thionyl chloride (8.45 kg, 71 mol) was added over a period of 20 min, and the reaction mixture was stirred at reflux for 7 h. The dark brown solution was concentrated to approximately 20 L volume by atmospheric distillation, and cyclohexane (60 L) was then added. The mixture was further distilled to give a final solution of the intermediate acid chloride in cyclohexane (25 L).

The acid chloride solution was diluted with dichloromethane (46 L), and aluminium chloride (5.2 kg, 39 mol) was added in one portion. The dark brown suspension was brought to gentle reflux, and fluorobenzene (23.85 kg, 39 mol) was added over a 30-min period. Reflux was maintained for a further 6 h, and then the mixture was cooled to ambient temperature. Demineralised water (11.6 kg) was added to the reaction mixture whilst the temperature was maintained below 15 °C. Upon completion of this addition, a further 46.4 kg of demineralised water was added and the phases were separated. The organic extract was washed with

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demineralised water (2 \times 40 L) and concentrated by distillation in vacuo to approximately 25 L volume. Residual dichloromethane and fluorobenzene were replaced with methanol via distillation at atmospheric pressure and constant volume. The methanolic solution was cooled to ambient temperature over 12 h, resulting in crystallisation. The solid was filtered and dried in vacuo to yield 9 (11.38 kg, 79.2%) as a tan solid: mp 88-91 °C; ¹H NMR (300 MHz, CDCl₃) $\delta = 7.16 - 7.22$ (2H, m), 7.79 - 7.84 (3H, m), 7.93 (1H, s), 8.07 (1H, s) ppm; ¹³C NMR (75.4 MHz, CDCl₃) δ = 94.36, 115.90 ($J_{CF} = 21$ Hz), 123.15, 131.86, 132.68 ($J_{CF} = 8$ Hz), 132.79, 137.03, 140.63, 143.13, 165.78 ($J_{CF} = 245$ Hz), 191.89 ppm. Anal. Calcd for C13H7BrFIO: C, 38.55; H, 1.74. Found: C, 38.46; H, 1.63. MS (Thermospray): m/z 423 (M + NH₄)⁺. IR (KBr): 3060 (aryl C-H), 1657 (C=O), 1592 (aryl C=C) cm⁻¹.

Ethyl 3-[3-Bromo-5-(4-fluorobenzoyl)phenyl]propenoate (10). To a stirred suspension of 9 (2.0 kg, 4.93 mol) in acetonitrile (40 L) at ambient temperature under an atmosphere of nitrogen were added, sequentially, palladium acetate (55.4 g, 0.25 mol), ethyl acrylate (0.544 kg, 5.43 mol), and triethylamine (0.55 kg, 5.43 mol). The brown solution was heated to gentle reflux (78 °C), maintained at this temperature for 2 h, then cooled to ambient temperature, and filtered through Hyflo filter aid. The filter cake was washed with ethyl acetate (40 L), and the filtrate was washed with water (40 L). The organic phase was separated and concentrated in vacuo to 5 L volume. Residual acetonitrile and ethyl acetate were replaced by methanol via distillation at atmospheric pressure and constant volume. The methanolic solution was allowed to cool to ambient temperature, resulting in crystallisation. The solid was granulated for 8 h, filtered off, and dried in vacuo to give the desired product **10** as a tan solid (1.47 kg, 79.1%): mp 75–77 °C; ¹H NMR $(300 \text{ MHz}, \text{CDCl}_3) \delta = 1.33 (3\text{H}, \text{t}, J = 7.1 \text{ Hz}), 4.27 (2\text{H},$ q, J = 7.1 Hz), 6.47 (1H, d, J = 16.1 Hz), 7.17-7.26 (2H, m), 7.62 (1H, d, J = 16.1 Hz), 7.78–7.87 (5H, m) ppm; ¹³C NMR (75.4 MHz, CDCl₃) δ = 14.26, 60.82, 115.83 (J_{CF} = 21 Hz), 121.23, 123.15, 127.62, 132.63 ($J_{CF} = 8$ Hz), 132.78, 133.58, 133.94, 136.75, 139.82, 141.58, 165.70 ($J_{CF} = 245$ Hz), 166.01, 192.81 (s) ppm. Anal. Calcd for C₁₈H₁₄-BrFO₃: C, 57.32; H, 3.74. Found: C, 57.21; H, 3.61. MS (Thermospray): m/z 377 (M⁺). IR (KBr): 3080 (aryl C–H), 2983 (alkyl C-H), 1717 (C=O), 1653 (C=O), 1597 (aryl C=C) cm⁻¹.

Ethyl 3-[3-(4-Fluorobenzoyl)-5-(2-phthalimidovinyl)phenyl]propenoate (11). To a stirred suspension of 10 (2.5kg, 6.63 mol), *N*-vinylphthalimide (1.205 kg, 6.96 mol), and palladium acetate (74.4 g, 0.33 mol) in xylene (12 L) at ambient temperature under an atmosphere of nitrogen was added a solution of diisopropylamine (1.16 L, 8.27 mol) in xylene (0.5 L). The dark brown slurry was heated to reflux and maintained at 137 °C for 3 h. The reaction mixture was then cooled to ambient temperature and diluted with dichloromethane (46 L). The fine suspension was filtered through Hyflo filter aid, and the filtrate was washed sequentially with 1 M HCl (12.6 L) and demineralised water (25.2 L). The separated organic phase was distilled at ambient temperature

until all dichloromethane had been removed, and the resulting solution was diluted with xylene (5.0 L) and allowed to cool to ambient temperature over 8 h, which resulted in precipitation. The precipitate was filtered and dried in vacuo for 24 h to yield the desired product 11 (1.811 kg, 58.2%) as a yellow solid: mp 172-175 °C; ¹H NMR (300 MHz, CDCl₃) $\delta = 1.35$ (3H, t, J = 7.13 Hz), 4.28 (2H, q, J = 7.13 Hz), 6.52 (1H, d, J = 16.1 Hz), 7.17–7.23 (2H, m), 7.43 (1H, d, J = 15.4 Hz), 7.70 (1H, s), 7.75–7.94 (10H, m) ppm; ¹³C NMR (75.4 MHz, CDCl₃) $\delta = 14.31, 60.72, 115.74$ ($J_{CF} =$ 21 Hz), 118.16, 119.44, 120.23, 123.85, 127.91, 128.61, 128.88, 131.57, 132.67 ($J_{CF} = 8$ Hz), 133.33, 134.74, 135.30, 137.31, 138.83, 143.0, 165.70 ($J_{CF} = 245$ Hz), 166.17, 166.45, 194.36 ppm. Anal. Calcd for C₂₈H₂₀FNO₅: C, 71.64; H, 4.29; N, 2.98. Found: C, 71.42; H, 4.21; N, 2.93. MS (Thermospray): *m*/*z* 470 (MH⁺). IR (KBr): 3060 (aryl C-H), 2983-2939 (alkyl C-H), 1720 (C=O), 1708 (C=O), 1652 (C=O), 1595 (aryl C=C) cm⁻¹.

Ethyl 3-[3-(4-Fluorobenzyl)-5-(2-phthalimidovinyl)phenyl]propenoate (12). To a stirred solution of 11 (1.694 kg, 3.61 mol) in trifluoroacetic acid (11.8 L) at 10-15 °C under an atmosphere of nitrogen was added triethylsilane (2.88 L, 18 mol) over a 1.45-h period, the reaction temperature being maintained below 20 °C. The dark green solution was warmed to ambient temperature over a 12-h period, which resulted in crystallisation. The solid was filtered off, washed with hexane (6.0 L), and dried in vacuo to give the desired product 12 (1.38 kg, 83.2%) as a yellow crystalline solid: mp 127–130 °C; ¹H NMR (300 MHz, CDCl₃) $\delta =$ 1.34 (3H, t, J = 6.9 Hz), 3.97 (2H, s), 4.27 (2H, q, J = 6.9 Hz), 6.44 (1H, d, J = 16.1 Hz), 6.97–7.02 (2H, m), 7.14– 7.29 (4H, m) 7.35 (1H, d, J = 15.0 Hz), 7.47 (1H, s), 7.62 (1H, d, J = 15.0 Hz) 7.65 (1H, d, J = 16.1 Hz) 7.76–7.80 (2H, m), 7.90-7.93 (2H, m) ppm; ¹³C NMR (75.4 MHz, CDCl₃) $\delta = 14.32, 40.84, 60.49, 115.41 (J_{CF} = 21 Hz),$ 118.34, 118.82, 118.83, 119.10, 123.68, 127.59, 128.46, $130.29 (J_{CF} = 8 \text{ Hz}), 131.59, 134.56, 135.22, 135.98, 136.02,$ 142.11, 144.11, 161.55 ($J_{CF} = 245$ Hz), 166.21, 166.78 ppm. Anal. Calcd for C₂₈H₂₂FNO₄: C, 73.84; H, 4.87; N, 3.08. Found: C, 73.69; H, 4.81; N, 3.04. MS (Thermospray): *m/z* 456 (MH⁺). IR (KBr): 3060 (aryl C-H), 2983-2939 (alkyl C-H), 1720 (C=O), 1702 (C=O), 1506 (aryl C=C) cm⁻¹.

Ethyl 3-[3-(4-Fluorobenzyl)-5-(2-phthalimidoethyl)phenyl]propionate (13). A stirred solution of 12 (2.577 kg, 5.66 mol) in ethyl acetate (38.6 L) was hydrogenated over 5% Pd/C (258 g, 50% wet) at ambient temperature and at 345 kPa (50 psi) of pressure for 5 h. The solution was filtered through a pad of Celite, which was subsequently washed with ethyl acetate (20 L). The filtrate was concentrated by atmospheric distillation with residual ethyl acetate being replaced with absolute ethanol to give a final volume of 19.1 L. The ethanolic solution was cooled over 12 h, which resulted in crystallisation. The solid was filtered off and dried in vacuo to give the desired product 13 (2.38 kg, 91.5%) as a colourless crystalline solid: mp 70-72 °C; ¹H NMR (300 MHz, CDCl₃) $\delta = 1.21$ (3H, t, J = 7.1 Hz), 2.51 (2H, t, J = 7.8 Hz), 2.85 (2H, t, J = 7.8 Hz), 2.92 (2H, t, J = 7.7 Hz), 3.85-3.91 (4H, m), 4.10 (2H, q, J = 7.1

Hz), 6.83–6.95 (5H, m), 7.02–7.08 (2H, m), 7.67–7.73 (2H, m), 7.78–7.83 (2H, m) ppm; ¹³C NMR (75.4 MHz, CDCl₃) $\delta = 14.2$, 30.83, 34.39, 35.92, 39.23, 40.93, 60.36, 115.14, ($J_{CF} = 21$ Hz), 123.16, 126.77, 127.24, 127.38, 130.15 ($J_{CF} = 8$ Hz), 132.07, 133.88, 136.70, 138.49, 141.20, 141.34, 161.33 ($J_{CF} = 245$ Hz), 168.06, 172.75 ppm. Anal. Calcd for C₂₈H₂₆FNO₄: C, 73.19; H, 5.70; N, 3.05. Found: C, 73.18; H, 5.67; N, 3.04. MS (Thermospray): m/z 477 (M + NH₄⁺). IR (KBr): 3040 (aryl C–H), 2939–2983 (alkyl C–H), 1726 (C=O), 1712 (C=O), 1510 (aryl C=C) cm⁻¹.

Ethyl 3-[3-(2-Aminoethyl)-5-(4-fluorobenzyl)phenyl]propionate Monocitrate Salt 14). To a stirred suspension of 13 (500 g, 1.09 mol) in industrial methylated spirits (2.5 L) and water (500 mL) was added hydrazine hydrate (61 mL, 1.26 mol), and the mixture was brought to reflux. Reflux was maintained for 2 h, after which time the reaction mixture was cooled to ambient temperature and 1 N K₂CO₃-(aq) (10 L) and dichloromethane (7.5 L) were added sequentially. The phases were separated, and the organic extract was concentrated in vacuo to a golden oil. The crude oil was diluted with a 1:1 mixture of ethyl acetate/hexane (5 L), and the golden solution was stirred with 1 M aqueous citric acid (5 L) for 1 h, which resulted in crystallisation. The solid was filtered off and dried in vacuo to give the desired citrate salt 14 (491.7 g, 86.7%) as a colourless crystalline solid: mp 104-107 °C; ¹H NMR (300 MHz, DMSO) $\delta = 1.11$ (3H, t, J = 7.1 Hz), 2.42–2.58 (12H, m), 2.72-2.80 (4H, m), 2.98 (2H, t, J = 7.86 Hz), 3.86 (2H, s), 3.99 (2H, q, J = 7.13 Hz), 6.92–6.96 (3H, m), 7.05–7.12 (2H, m), 7.20-7.25 (2H, m) ppm; ¹³C NMR (75.4 MHz, DMSO) $\delta = 14.55, 30.64, 33.46, 35.47, 40.29, 40.35, 44.97,$ $60.28, 71.84, 115.50 (J_{CF} = 21 \text{ Hz}), 126.80, 127.27, 127.49,$ 130.87 ($J_{CF} = 8$ Hz), 137.78, 137.99, 141.53, 141.93, 161.17 $(J_{\rm CF} = 245 \text{ Hz})$, 171.98, 172.59, 177.68 ppm. Anal. Calcd for C₂₆H₃₂FNO₉: C, 59.88; H, 6.18; N, 2.69. Found: C, 59.96; H, 6.16; N, 2.68. MS (Thermospray): m/z 330.7 (M $-C_6H_8O_7^+$). IR (KBr): 3500 (NH), 3140–2900 (OH), 1731 (C=O), 1724 (C=O), 1508 $(aryl C=C) cm^{-1}$.

3-{3-[2-(4-Chlorobenzenesulfonamido)ethyl]-5-(4-fluorobenzyl)phenyl}propionic acid (1). To a stirred suspension of **14** (769 g, 1.47 mol) in ethyl acetate (3.9 L)

and demineralised water (3.9 L) was added 10 N NaOH (530 mL). The resulting biphasic solution was stirred for 30 min before being separated. The organic phase was then washed with brine (200 mL) and evaporated in vacuo to a golden oil.

To a stirred solution of the oil in tetrahydrofuran (973 mL) under a nitrogen atmosphere at 0-5 °C were added sequentially triethylamine (226 mL, 1.62 mol) and a solution of 4-chlorobenzenesulfonyl chloride (315 g, 1.49 mol) in tetrahydrofuran (973 mL), the reaction temperature being maintained below 10 °C. The reaction mixture was then warmed to ambient temperature before demineralised water (2.0 L) and 1 N NaOH (3.7 L, 3.7 mol) were added sequentially. The reaction mixture was then heated to reflux and maintained at 65 °C for 2 h before being cooled to ambient temperature over 12 h. The yellow solution was then partitioned between ethyl acetate (4.9 L) and 1 M HCl (5.8 L), and the separated organic extract was washed with demineralised water (2 \times 2.4 L). The organic extract was concentrated by distillation (1.7 L residual volume) before hexane (1.41 L) was added and the mixture cooled to ambient temperature, resulting in crystallisation. The solid was granulated for 8 h, then filtered off, and dried in vacuo to yield 1 (607.9 g, 86.5%) as a white crystalline solid: mp 97–100 °C; ¹H NMR (300 MHz, CDCl₃) δ = 2.60 (2H, t, J = 7.3 Hz), 2.71 (2H, t, J = 6.4 Hz), 2.90 (2H, t, J = 7.3Hz), 3.17 (2H, m), 3.87 (2H, s), 4.68 (1H, bt, J = 6.4 Hz), 6.71 (1H, s), 6.84-6.99 (4H, m), 7.07-7.12 (2H, m), 7.43 (2H, d, J = 8.0 Hz), 7.72 (2H, d, J = 8.0 Hz) ppm; ¹³C NMR (75.4 MHz, CDCl₃) δ = 30.61, 35.65, 35.74, 40.90, 44.17, 115.30 ($J_{CF} = 21$ Hz), 126.87, 127.29, 127.39, 128.44, 129.36, 130.22 ($J_{CF} = 8$ Hz), 136.37, 138.08, 138.57, 139.11, 140.89, 141.96, 161.55 ($J_{CF} = 245$ Hz), 177.67 ppm. Anal. Calcd for $C_{24}H_{23}ClFNO_4S$: C, 60.56; H, 4.87; N, 2.94. Found: C, 60.53; H, 4.80; N, 2.88. MS (Thermospray): m/z 494 (M + NH₄⁺). IR (KBr): 3253 (NH), 3085 (aryl C-H), 3040-2893 (OH), 1706 (C=O), 1604 (aryl C=C), 1509 (aryl C=C) cm⁻¹.

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