

Supporting Information:

Inhalation by Design: Novel Tertiary Amine Muscarinic M₃ Receptor Antagonists with Slow Off-Rate Binding Kinetics for Inhaled Once-Daily Treatment of Chronic Obstructive Pulmonary Disease

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Contents

Biology experimental for the in vitro human bronchus assay, in vivo anaesthetized guinea pig model and in vivo rabbit lung A δ -fibre cough model;

Chemistry experimental details and analytical data for intermediates **1–3**, (*R*)- and (*S*)-**5**, (*S*)-**6**, (*R*)- and (*S*)-**7**, (*S*)-**8**, (*R*)- and (*S*)-**10**, (*R*)- and (*S*)-**12–14**, (*S*)-**17**, (*R*)-**18**, **23**, **24**, **28–31**, **33**, **34**, **41–46**, **54**, **56–63** and test compounds **4**, (*R*)- and (*S*)-**9**, (*R*)- and (*S*)-**11**, (*S*)-**15**, (*S*)-**16**, (*S*)-**19**, (*R*)-**20**, **25**, **26**, **32**, **35**, **48–53**, **55**, **64**.

Experimental Section

Biology. In Vitro Potency in Human Bronchus. Fresh human bronchus tissue was used in accordance with local SOPs and ethical policies and logged on the in-house human tissue inventory system. The tissue was obtained either following surgery at Papworth Hospital, Cambridge or following death, from UK Human Tissue bank (UKHTB) in Leicester and transported on ice in either Krebs buffer,

PBS buffer (Papworth) or kidney perfusion buffer (UKHTB) as soon as possible. Bronchial tissue rings were mounted in 5 mL organ baths, washed continuously with fresh Krebs and placed under an initial tension of 1000–1500 mg. Tissues were re-tensioned every 20–30 min over the course of 1 h, then allowed to equilibrate for a further 30 min prior to stimulation. Tissues were subjected to electrical field stimulation of the following parameters: 10 s train duration every 2 min with 0.3 ms pulse width, 25 Hz frequency and 10 V. The just maximum voltage for each tissue was used throughout the remainder of the experiment with the trains set 10 min apart. Following equilibration to EFS, single concentrations of compound were then added to each tissue as a bolus dose (1 dose per tissue) and left to incubate for 4 h. Following the incubation, compound was washed for a further 16 h and then tissues were challenged with methacholine (30 μ M) and / or histamine (10 μ M) to determine if the tissues remained viable. The % inhibition calculated across tissues was plotted against the antagonist concentration to obtain a four-parameter concentration-response curve from which potency (pK_b) was calculated across tissues from an individual donor. The n reflects the number of individual donors tested.

In Vivo Potency in Anaesthetized Guinea Pigs. The Einthoven anaesthetised guinea pig model was modified to determine anti-muscarinic potency.^{1,2} Briefly, adult male Dunkin-Hartley guinea pigs were anaesthetised with urethane. The trachea and jugular veins were cannulated to allow mechanical ventilation, intratracheal (it.) drug administration and intravenous (iv) infusion of acetylcholine (ACh). Airflow was recorded by a Validyne DP45-14 differential pressure transducer, whilst transpulmonary pressure (P_{TP}) was monitored across a tracheal cannula and oesophageal cannula positioned in the mid-thorax region, using a Validyne DP45-24 differential pressure transducer. A cardiovascular and pulmonary mechanics analyser (Po-Ne-Mah, Linton Instruments, UK) was used to continuously monitor tidal volume, total lung resistance (R_L), systemic arterial blood pressure and heart rate. Following a 30 min stabilisation period, increasing doses of ACh were given to establish a dose which gave an absolute increase in R_L of between 0.060 and 0.300 cm H₂/mL/s. Each animal was then challenged with this dose every 10 min (1 min infusion time) until three consistent responses were obtained, defining the control

bronchoconstrictor response. Test compound in micelle vehicle, or micelle vehicle alone (50 μ L), were dosed via cumulative intratracheal administration at hourly intervals. The bronchoconstrictor challenge was administered hourly, immediately prior to the next escalating dose of compound. The response for each dose was recorded as the maximum increase in resistance (ΔR_L) achieved during the 5 min recording period following the start of bronchoconstrictor challenge. This process was repeated, to produce a 5-point dose-response curve in each animal. Data were expressed as a % of control bronchoconstrictor response.

In Vivo Assessment of A δ -Fiber Firing in the Anaesthetised Rabbit. Animals were anaesthetised with sodium pentobarbitone (20 mg/kg). The trachea was cannulated and connected to a large animal ventilator. The right jugular vein was cannulated and anesthesia maintained with intravenous administration of α -chloralose (40–60 mg/kg). The right carotid artery was cannulated to monitor blood pressure and heart rate. Neuromuscular blockade was achieved using vecuronium bromide. Transpulmonary pressure (PTP) was measured with a differential pressure transducer. A cervical vagus nerve was dissected free from the carotid artery, sympathetic and aortic nerves. The vagus was cleared of its surrounding fascia and cut at the central end. The skin at either side of the incision was sutured to a metal ring to form a well filled with mineral oil. Bipolar plastic coated silver electrodes (exposed at the tips) were used for recording purposes. The vagus nerve was placed on a small black perspex plate for dissection. Thin filaments were teased from the vagus nerve under a binocular microscope and placed on the electrode until a single A δ -fibre / rapidly adapting receptor (RAR) was obtained allowing recording of action potentials. The effects on A δ -fibre firing were measured for test compound (50–1000 μ g) or micelle vehicle (400 μ L) administered intratracheally.

Chemistry. *tert*-Butyl 4-cyano-4,4-diphenylbutanoate (1). A suspension of diphenylacetonitrile (38.6 g, 200 mmol) in *tert*-butanol (200 mL) was warmed to 60 $^{\circ}$ C for 30 min. The resulting solution was cooled to 50 $^{\circ}$ C and treated with a solution of potassium hydroxide (600 mg, 10.7 mmol) in methanol (2 mL). *tert*-Butyl acrylate (30 mL, 200 mmol) was then added dropwise and the mixture stirred at 50 $^{\circ}$ C for

2 h, then at room temperature for 18 h. Additional potassium hydroxide (600 mg, 10.7 mmol) was added and the mixture heated at 50 °C for 3 h. The mixture was cooled, concentrated in vacuo and the residue partitioned between diethyl ether (300 mL) and water (200 mL). The organic layer was dried (sodium sulfate) and concentrated in vacuo to give **1** as a white solid, 58.0 g, 90% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.41 (s, 9H), 2.29 (t, 2H), 2.72 (t, 2H), 7.29–7.33 (m, 1H), 7.36–7.42 (m, 9H) ppm. LRMS: *m/z* 322 [M + H]⁺.

4-Cyano-4,4-diphenylbutanoic acid (2). A mixture of ester **1** (57.5 g, 179 mmol) and 4M hydrochloric acid solution in dioxan (500 mL) was stirred at room temperature for 18 h. The mixture was concentrated in vacuo, the residue was treated with warm diisopropyl ether (150 mL) and cooled to room temperature. The resulting solid was collected by filtration and dried under vacuum to give **2** as a white solid, 36.5 g, 77% yield. ¹H NMR (400 MHz, CD₃OD) δ: 2.35 (t, 2H), 2.76 (t, 2H), 7.30–7.44 (m, 10H) ppm. LRMS: *m/z* 266 [M + H]⁺.

5-Oxo-2,2-diphenylpentanenitrile (3). A solution of acid **2** (500 mg, 1.89 mmol) in tetrahydrofuran (10 mL) was treated with 1,1'-carbonyldiimidazole (305 mg, 1.89 mmol), stirred at room temperature for 18 h, then cooled to 0 °C. Water (2.5 mL) and sodium borohydride (356 mg, 9.42 mmol) were added portionwise and the mixture warmed to room temperature over 18 h. The mixture was treated dropwise with 2M aqueous hydrogen chloride solution (3 mL). The organic solvent was removed in vacuo and the aqueous residue partitioned with ethyl acetate (30 mL). The organic layer was separated, washed with 2M aqueous sodium hydroxide solution (2 × 15 mL), dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate/pentane (1:2–1:1, by volume) to give 5-hydroxy-2,2-diphenylpentanenitrile as a colorless gum, 190 mg, 40% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.56–1.65 (m, 2H), 2.48–2.56 (m, 2H), 3.57–3.62 (t, 2H), 7.28–7.32 (m, 2H), 7.34–7.43 (m, 8H) ppm. LRMS: *m/z* 269 [M + NH₄]⁺.

Dess-Martin periodinane (353 mg, 0.833 mmol) was added to a solution of 5-hydroxy-2,2-diphenylpentanenitrile (190 mg, 0.757 mmol) in dichloromethane (4 mL) and the mixture stirred for 1 h at

room temperature. Additional Dess-Martin periodinane (161 mg, 0.379 mmol) was added and stirring continued for 2 h. The mixture was diluted with dichloromethane (5 mL), treated with 1M aqueous sodium hydroxide solution (5 mL) and stirred for 10 min. The organic layer was separated, washed with water (8 mL), dried (sodium sulfate) and concentrated in vacuo to give **3** as a colorless gum, 169 mg, 90% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.62–1.68 (m, 2H), 2.50–2.54 (m, 2H), 4.54–4.56 (t, 1H), 7.28–7.32 (m, 2H), 7.34–7.42 (m, 8H) ppm.

5-[(3*S*)-3-Phenoxyprolidin-1-yl]-2,2-diphenylpentanamide (4). A solution of aldehyde **3** (165 mg, 0.663 mmol) in dichloromethane (5 mL) was treated with (*S*)-3-phenoxyprolidine hydrochloride (145 mg, 0.729 mmol) and triethylamine (101 μL, 0.729 mmol). The mixture was stirred for 10 min at room temperature then treated with acetic acid (1 drop) and stirred for 20 min. Sodium triacetoxyborohydride (183 mg, 0.862 mmol) was added and the mixture stirred for 5 h. The mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium hydrogen carbonate solution (10 mL). The organic layer was separated, dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with dichloromethane/methanol/0.88 specific gravity ammonia (97:3:0.3–95:5:0.5, by volume) to give 5-[(3*S*)-3-phenoxyprolidin-1-yl]-2,2-diphenylpentanenitrile as a pale brown gum, 123 mg, 47% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.56–1.65 (m, 2H), 1.88–1.95 (m, 1H), 2.23–2.32 (m, 1H), 2.43–2.63 (m, 5H), 2.70–2.79 (m, 3H), 4.82–4.86 (m, 1H), 6.82–6.84 (d, 2H), 6.87–6.91 (t, 1H), 7.22–7.42 (m, 12H) ppm. LRMS: *m/z* 397 [M + H]⁺.

5-[(3*S*)-3-Phenoxyprolidin-1-yl]-2,2-diphenylpentanenitrile (120 mg, 0.304 mmol) and potassium hydroxide (340 mg, 6.06 mmol) in 3-methyl-3-pentanol (5 mL) were stirred at reflux for 18 h. The solvent was removed in vacuo and the residue partitioned between ethyl acetate (20 mL) and water (10 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with dichloromethane/methanol/0.88 specific gravity ammonia

(95:5:0.5–92:8:0.8, by volume) to give **4** as a colorless gum, 77 mg, 62% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.32–1.41 (m, 2H), 1.85–1.93 (m, 1H), 2.20–2.29 (m, 1H), 2.38–2.54 (m, 5H), 2.68–2.79 (m, 3H), 4.80–4.84 (m, 1H), 6.81–6.83 (d, 2H), 6.88–6.91 (t, 1H), 7.21–7.36 (m, 12H) ppm. LRMS: *m/z* 415 [M + H]⁺. Anal. (C₂₇H₃₀N₂O₂·0.05CH₂Cl₂) C, H, N.

5-Oxo-5-[(3*S*)-3-phenoxyprolidin-1-yl]-2,2-diphenylpentanenitrile ((*S*)-5). A mixture of acid **2** (2.40 g, 9.0 mmol), (*S*)-3-phenoxyprolidine (1.99 g, 9.96 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.55 g, 9.96 mmol), 1-hydroxybenzotriazole hydrate (1.35 g, 9.96 mmol) and triethylamine (1.38 mL, 9.96 mmol) in dichloromethane (40 mL) was stirred at room temperature for 18 h. The mixture was diluted with dichloromethane (100 mL) and washed sequentially with 1M aqueous hydrochloric acid solution (70 mL), 1M aqueous sodium hydroxide solution (30 mL) and brine (30 mL). The organic layer was dried (sodium sulfate) and concentrated in vacuo. The residue was recrystallized from ethanol to give (*S*)-**5** as a solid, 2.83 g, 76% yield. ¹H NMR (400 MHz, CD₃OD) δ: 2.07–2.21 (m, 2H), 2.33–2.38 (m, 1H), 2.43–2.47 (m, 1H), 2.69–2.84 (m, 2H), 3.44–3.55 (m, 2H), 3.58–3.67 (m, 2H), 4.96–5.04 (m, 1H), 6.89 (d, 2H), 6.93–6.96 (m, 1H), 7.24–7.46 (m, 12H) ppm. LRMS: *m/z* 412 [M + H]⁺.

5-Oxo-5-[(3*R*)-3-phenoxyprolidin-1-yl]-2,2-diphenylpentanenitrile ((*R*)-5). The title compound was prepared from acid **2** and (*R*)-3-phenoxyprolidine, using the same method as that described for (*S*)-**5**, to afford (*R*)-**5**, 41% yield. ¹H NMR (400 MHz, CD₃OD) δ: 2.07–2.21 (m, 2H), 2.33–2.38 (m, 1H), 2.43–2.47 (m, 1H), 2.69–2.84 (m, 2H), 3.44–3.55 (m, 2H), 3.58–3.67 (m, 2H), 4.96–5.04 (m, 1H), 6.89 (d, 2H), 6.93–6.96 (m, 1H), 7.24–7.46 (m, 12H) ppm. LRMS: *m/z* 412 [M + H]⁺.

5-[(3*S*)-3-(3-Methoxyphenoxy)prolidin-1-yl]-5-oxo-2,2-diphenylpentanenitrile ((*S*)-6). The title compound was prepared from acid **2** and (*S*)-3-(3-methoxyphenoxy)prolidine, using the same method as that described for (*S*)-**5**. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 specific gravity ammonia (98:2:0.2–95:5:0.5, by volume) to give (*S*)-**6** as a colorless oil, 100% yield. ¹H NMR (400 MHz, CD₃OD) δ: 2.03–2.20 (m, 2H), 2.32–2.37

(m, 1H), 2.43–2.47 (m, 1H), 2.66–2.84 (m, 2H), 3.44–3.67 (m, 4H), 3.74 (s, 3H), 4.94–5.00 (m, 1H), 6.44–6.55 (m, 3H), 7.13–7.19 (m, 1H), 7.28–7.46 (m, 10H) ppm. LRMS: m/z 412 $[M + H]^+$.

5-Methyl-5-[(3*S*)-3-phenoxyprolidin-1-yl]-2,2-diphenylhexanenitrile ((*S*)-7). A solution of amide (*S*)-5 (3.31 g, 8.07 mmol) in tetrahydrofuran (90 mL) was cooled to -20 °C. Zirconium chloride (3.76 g, 16.15 mmol) was added and the mixture stirred at -20 °C for 1 h. Methyl magnesium chloride (3M in tetrahydrofuran, 24 mL, 72.0 mmol) was then added dropwise and the mixture stirred for 2 h below -10 °C. The reaction was quenched with 1M aqueous sodium hydroxide solution (25 mL), filtered through Celite, and the filter cake washed with ethyl acetate (2 × 50 mL). The filtrate was washed with brine (70 mL), concentrated in vacuo and the residue recrystallized from hexane/ethyl acetate to afford (*S*)-7 as a pale orange solid, 2 g, 59% yield. ¹H NMR (400 MHz, CD₃OD) δ : 0.99 (s, 3H), 1.04 (s, 3H), 1.23–1.27 (m, 2H), 1.85–1.93 (m, 1H), 2.07–2.16 (m, 1H), 2.40–2.45 (m, 2H), 2.58–2.67 (m, 2H), 2.72–2.78 (m, 1H), 2.87–2.91 (m, 1H), 4.75–4.79 (m, 1H), 6.80 (d, 2H), 6.88–6.92 (m, 1H), 7.21–7.36 (m, 12H) ppm. LRMS: m/z 425 $[M + H]^+$.

5-Methyl-5-[(3*R*)-3-phenoxyprolidin-1-yl]-2,2-diphenylhexanenitrile ((*R*)-7). A solution of amide (*R*)-5 (0.84 g, 2.05 mmol) in tetrahydrofuran (15 mL) was cooled to -10 °C. Titanium (IV) chloride (0.23 mL, 2.05 mmol) was added and the mixture stirred at -10 °C for 15 min. Methyl magnesium bromide (3M in diethyl ether, 4.1 mL, 12.3 mmol) was then added dropwise and the mixture stirred for 10 min below -5 °C and then 18 h at room temperature. The mixture was quenched with water (4 mL), diluted with ethyl acetate (20 mL) and decanted. The residual solid was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate:hexane (60:40, by volume) to give (*R*)-7, 0.47 g, 54% yield. LRMS: m/z 425 $[M + H]^+$.

5-[(3*S*)-3-(3-Methoxyphenoxy)prolidin-1-yl]-5-methyl-2,2-diphenylhexanenitrile ((*S*)-8).

The title compound was prepared from amide (*S*)-6, using the same Grignard method as that described for

(*S*)-7. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 specific gravity ammonia (97.5:2.5:0.25–95:5:0.5, by volume) to give (*S*)-8 as a brown oil, 78% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.01 (s, 3H), 1.07 (s, 3H), 1.43–1.47 (m, 2H), 1.86–1.93 (m, 1H), 2.08–2.19 (m, 1H), 2.47–2.59 (m, 3H), 2.65–2.69 (m, 1H), 2.73–2.86 (m, 2H), 3.73 (s, 3H), 4.74–4.79 (m, 1H), 6.38–6.43 (m, 2H), 6.47–6.50 (m, 1H), 7.11–7.15 (m, 1H), 7.24–7.42 (m, 10H) ppm. LRMS: *m/z* 456 [M + H]⁺.

5-Methyl-5-[(3*S*)-3-phenoxyprolidin-1-yl]-2,2-diphenylhexanamide ((*S*)-9). The title compound was prepared from nitrile (*S*)-7, using the same nitrile hydrolysis method as that described for 4, to give (*S*)-9 as a white solid, 1.66 g, 82% yield. ¹H NMR (400 MHz, CD₃OD) δ: 0.97 (s, 3H), 1.02 (s, 3H), 1.19–1.33 (m, 2H), 1.82–1.91 (m, 1H), 2.02–2.17 (m, 1H), 2.37–2.47 (m, 2H), 2.48–2.64 (m, 2H), 2.65–2.75 (m, 1H), 2.81–2.89 (m, 1H), 4.75 (m, 1H), 6.76–6.83 (m, 2H), 6.86–6.92 (m, 1H), 7.17–7.38 (m, 12H) ppm. LRMS: *m/z* 443 [M + H]⁺. Anal. (C₂₉H₃₄N₂O₂·0.5H₂O) C, H, N. HPLC analysis: ≥99.89% purity.

5-Methyl-5-[(3*R*)-3-phenoxyprolidin-1-yl]-2,2-diphenylhexanamide ((*R*)-9). The title compound was prepared from nitrile (*R*)-7 using the same nitrile hydrolysis method as that described for 4, to give (*R*)-9, 62% yield. ¹H NMR (400 MHz, CD₃OD) δ: 0.97 (s, 3H), 1.02 (s, 3H), 1.19–1.33 (m, 2H), 1.82–1.91 (m, 1H), 2.02–2.17 (m, 1H), 2.37–2.47 (m, 2H), 2.48–2.64 (m, 2H), 2.65–2.75 (m, 1H), 2.81–2.89 (m, 1H), 4.75 (m, 1H), 6.76–6.83 (m, 2H), 6.86–6.92 (m, 1H), 7.17–7.38 (m, 12H) ppm. LRMS: *m/z* 443 [M + H]⁺. Anal. (C₂₉H₃₄N₂O₂·0.3CH₂Cl₂) C, H, N.

5-[(3*S*)-3-(3-Methoxyphenoxy)prolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((*S*)-10). The title compound was prepared from nitrile (*S*)-8, using the same nitrile hydrolysis method as that described for 4 to give (*S*)-10 as a pale yellow gum, 96% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.03 (s, 3H), 1.08 (s, 3H), 1.24–1.30 (m, 2H), 1.89–1.98 (m, 1H), 2.08–2.16 (m, 1H), 2.40–2.46 (m, 2H), 2.65–2.76 (m, 2H), 2.79–2.88 (m, 1H), 2.91–2.98 (m, 1H), 3.74 (s, 3H), 4.77–4.82 (m, 1H), 6.37–6.42 (m, 2H), 6.51 (dd, 1H), 7.12–7.16 (m, 1H), 7.22–7.36 (m, 10H) ppm. LRMS: *m/z* 474 [M + H]⁺.

5-[(3*S*)-3-(3-Hydroxyphenoxy)pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((*S*)-11).

Boron tribromide (1M in dichloromethane, 20.7 mL, 20.7 mmol) was added to a solution of amide (*S*)-10 (2.45 g, 5.18 mmol) in dichloromethane (25 mL) at 0 °C and the mixture stirred for 20 min. The reaction was quenched with 0.88 specific gravity ammonia solution and stirred at room temperature for 20 min. The mixture was extracted with dichloromethane (3 × 25 mL) and the combined organic layers dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with pentane:(ethyl acetate:methanol:0.88 specific gravity ammonia (90:10:1, by volume)) (1:1–1:2, by volume) to give (*S*)-11 as a white foam, 1.42 g, 60% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.06 (s, 3H), 1.11 (s, 3H), 1.30–1.34 (m, 2H), 1.94–2.01 (m, 1H), 2.08–2.17 (m, 1H), 2.42–2.46 (m, 2H), 2.77–2.93 (m, 3H), 2.99–3.05 (m, 1H), 4.79 (m, 1H), 6.30 (d, 2H), 6.37–6.40 (d, 1H), 7.02–7.06 (m, 1H), 7.23–7.36 (m, 10H) ppm. LRMS: *m/z* 459 [M + H]⁺. Anal. (C₂₉H₃₄N₂O₃·0.7H₂O) C, H, N. HPLC analysis: ≥99.5% purity.

5-[(3*S*)-3-(Benzyloxy)pyrrolidin-1-yl]-5-oxo-2,2-diphenylpentanenitrile ((*S*)-12). The title compound was prepared from acid **2** and (*S*)-3-(benzyloxy)pyrrolidine, using the same method as that described for (*S*)-5, to give (*S*)-12 as a pale orange solid, 70% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.86–2.15 (m, 2H), 2.32–2.43 (m, 2H), 2.75–2.82 (m, 2H), 3.35–3.62 (m, 4H), 4.14–4.21 (m, 1H), 4.45–4.56 (m, 2H), 7.22–7.44 (m, 15H) ppm. LRMS: *m/z* 425 [M + H]⁺.

5-[(3*R*)-3-(Benzyloxy)pyrrolidin-1-yl]-5-oxo-2,2-diphenylpentanenitrile ((*R*)-12). N,N'-Carbonyldiimidazole (27 g, 162 mmol) was added to a solution of acid **2** (36 g, 135 mmol) in tetrahydrofuran (600 mL) and the mixture stirred for 3 h at room temperature. A solution of (*R*)-3-(benzyloxy)pyrrolidine (31 g, 142 mmol) in tetrahydrofuran (300 mL) was added and the mixture stirred at room temperature for 18 h. The mixture was filtered, concentrated in vacuo and the residue partitioned between water (200 mL) and ethyl acetate (600 mL). The organic layer was separated, washed sequentially with water (100 mL), 2M aqueous hydrochloric acid solution (2 × 100mL) and brine (100

mL), dried (sodium sulfate) and concentrated in vacuo. The residue was triturated with diethyl ether to give (*R*)-**12**, 48.2g, 83% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.87–2.15 (m, 2H), 2.32–2.44 (m, 2H), 2.74–2.82 (m, 2H), 3.35–3.61 (m, 4H), 4.14–4.22 (m, 1H), 4.46–4.57 (m, 2H), 7.23–7.44 (m, 15H) ppm. LRMS: *m/z* 425 [M + H]⁺.

5-[(3*S*)-3-(Benzyloxy)pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((*S*)-13**).** Amide (*S*)-**12** was subjected to the same Grignard method as that described for (*S*)-**7**. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 specific gravity ammonia (99:1:0.1–92:8:0.8, by volume) to give 5-[(3*S*)-3-(benzyloxy)pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexane nitrile as a brown oil, 76% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.02 (s, 3H), 1.04 (s, 3H), 1.41–1.55 (m, 2H), 1.77–1.85 (m, 1H), 1.93–2.01 (m, 1H), 2.50–2.55 (m, 3H), 2.63–2.77 (m, 3H), 4.03–4.08 (m, 1H), 4.45 (s, 2H), 7.22–7.42 (m, 15H) ppm. LRMS: *m/z* 439 [M + H]⁺.

5-[(3*S*)-3-(Benzyloxy)pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexane nitrile was subjected to the same nitrile hydrolysis method as that described for **4**. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate:methanol:0.88 specific gravity ammonia (98:2:0.2, by volume) to give (*S*)-**13** as a colorless gum, 78% yield. ¹H NMR (400 MHz, CD₃OD) δ: 0.98 (s, 3H), 1.00 (s, 3H), 1.23–1.27 (m, 2H), 1.73–1.80 (m, 1H), 1.87–1.96 (m, 1H), 2.40–2.65 (m, 5H), 2.69–2.73 (m, 1H), 3.98–4.03 (m, 1H), 4.42 (m, 2H), 7.22–7.32 (m, 11H), 7.35–7.38 (m, 4H) ppm. LRMS: *m/z* 458 [M + H]⁺.

5-[(3*R*)-3-(Benzyloxy)pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((*R*)-13**).** Amide (*R*)-**12** was subjected to the same Grignard method as that described for (*S*)-**7**. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol (97.5:2.5, by volume). The purified residue was azeotroped sequentially with pentane (2 × 250 mL), diethyl ether (2 × 250 mL) and pentane (2 × 250 mL) to give 5-[(3*R*)-3-(benzyloxy)pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexane nitrile as a solid. ¹H NMR (400 MHz, CD₃OD) δ: 1.02 (s, 3H), 1.04 (s, 3H), 1.42–1.54 (m, 2H), 1.78–1.86 (m,

1H), 1.93–2.02 (m, 1H), 2.47–2.60 (m, 3H), 2.63–2.77 (m, 3H), 4.04–4.08 (m, 1H), 4.43–4.49 (s, 2H), 7.23–7.43 (m, 15H) ppm. LRMS: m/z 439 $[M + H]^+$.

5-[(3*R*)-3-(Benzyloxy)pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexane nitrile was subjected to the same nitrile hydrolysis method as that described for **4**, to give (*R*)-**13** as a solid, 89% yield. ¹H NMR (400 MHz, CD₃OD) δ : 0.99–1.01 (m, 6H), 1.24–1.28 (m, 2H), 1.75–1.82 (m, 1H), 1.88–1.97 (m, 1H), 2.40–2.44 (m, 3H), 2.49–2.68 (m, 2H), 2.71–2.76 (m, 1H), 4.00–4.05 (m, 1H), 4.39–4.46 (m, 2H), 7.22–7.38 (m, 15H) ppm. LRMS: m/z 458 $[M + H]^+$.

5-[(3*S*)-3-Hydroxypyrrolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((*S*)-14). Iron (III) chloride (1.57 g, 9.70 mmol) was added to a solution of amide (*S*)-**13** (385 mg, 0.84 mmol) in dichloromethane (10 mL) and the mixture stirred at room temperature for 3 h. The reaction was quenched by the addition of 2M aqueous hydrochloric acid solution (6 mL), filtered through Arbocel and the filtrate basified with 0.88 specific gravity ammonia solution (20 mL). The filtrate was extracted with dichloromethane (2 \times 25 mL), and the combined organic layers dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate:methanol:0.88 specific gravity ammonia (95:5:0.5–85:15:1.5, by volume) to give (*S*)-**14** as a brown gum, 415 mg, 60% yield. ¹H NMR (400 MHz, CD₃OD) δ : 0.99 (s, 6H), 1.23–1.27 (m, 2H), 1.56–1.64 (m, 1H), 1.89–1.98 (m, 1H), 2.40–2.44 (m, 3H), 2.47–2.52 (m, 1H), 2.61–2.67 (m, 1H), 2.74–2.78 (m, 1H), 4.17–4.22 (m, 1H), 7.22–7.26 (m, 2H), 7.29–7.33 (m, 4H), 7.37 (d, 4H) ppm. LRMS: m/z 368 $[M + H]^+$.

5-[(3*R*)-3-Hydroxypyrrolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((*R*)-14). 1M aqueous hydrochloric acid solution (10.95 mL, 10.95 mmol) and 20% palladium hydroxide on carbon (1 g) were added to a solution of amide (*R*)-**13** (5.0 g, 10.95 mmol) in ethanol (250 mL) and the mixture was stirred at 50 °C, under 50 psi of hydrogen gas, for 28 h. The mixture was filtered through Arbocel and concentrated in vacuo. The residue was treated with 0.88 specific gravity ammonia solution (10 mL) and extracted with ethyl acetate (3 \times 50 mL). The combined organic layers were washed with brine (50 mL),

dried (sodium sulfate) and concentrated in vacuo to give (*R*)-**14** as a white foam, 3.63 g, 90% yield. ¹H NMR (400 MHz, CD₃OD) δ: 0.99 (s, 6H), 1.23–1.27 (m, 2H), 1.56–1.63 (m, 1H), 1.89–1.96 (m, 1H), 2.39–2.44 (m, 3H), 2.46–2.52 (m, 1H), 2.61–2.67 (m, 1H), 2.74–2.78 (m, 1H), 4.17–4.22 (m, 1H), 7.22–7.26 (m, 2H), 7.29–7.33 (m, 4H), 7.36–7.39 (m, 4H) ppm. LRMS: *m/z* 367 [M + H]⁺.

5-[(3*S*)-3-(2-Hydroxyphenoxy)pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((*S*)-15**).**

Diisopropylazodicarboxylate (0.22 mL, 1.12 mmol) was added to a solution of alcohol (*R*)-**14** (205 mg, 0.56 mmol), triphenyl phosphine (293 mg, 1.12 mmol) and 2-hydroxyphenol (616 mg, 5.59 mmol) in tetrahydrofuran (4 mL) at 0 °C and the solution stirred for 2 h. Triphenyl phosphine (293 mg, 1.12 mmol) and diisopropylazodicarboxylate (0.22 mL, 1.12 mmol) were added and the solution stirred at room temperature for 16 h. Diisopropylazodicarboxylate (0.22 mL, 1.12 mmol) was added and the solution stirred at room temperature for 4 h. The mixture was concentrated in vacuo and the residue purified using an Isolute SCX-2 cartridge, eluting with methanol, followed by a solution of 1M ammonia in methanol. The basic fractions were concentrated in vacuo and the residue purified by column chromatography on silica gel, eluting with pentane:(ethyl acetate:methanol:0.88 specific gravity ammonia (90:10:1, by volume)) (1:0–1:1, by volume) to give (*S*)-**15** as a brown gum, 98 mg, 38% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.02 (s, 3H), 1.06 (s, 3H), 1.25–1.29 (m, 2H), 1.87–1.94 (m, 1H), 2.03–2.11 (m, 1H), 2.41–2.45 (m, 2H), 2.51–2.57 (m, 1H), 2.66–2.70 (dd, 1H), 2.75–2.84 (m, 2H), 4.80–4.85 (m, 1H), 6.71–6.84 (m, 4H), 7.21–7.37 (m, 10H) ppm. LRMS: *m/z* 459 [M + H]⁺. Anal. (C₂₉H₃₄N₂O₃·0.9H₂O) C, H, N.

5-[(3*S*)-3-(4-Chloro-3-hydroxy-phenoxy)-pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((*S*)-16**).** The title compound was prepared from alcohol (*R*)-**14** and 2-chlororesorcinol, using a similar method to that described for (*S*)-**15**. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate:methanol:0.88 specific gravity ammonia (98:2:0.2–94:6:0.6, by volume) to give a mixture of regioisomers that were separated by HPLC on a Luna C8(2) acidic column, eluting with acetonitrile:water:diethylamine (1:1:0.05, by volume) to give (*S*)-**16** as a white solid, 12% yield. ¹H NMR (400 MHz, CD₃OD) δ: 0.98 (s, 3H), 1.04 (s, 3H), 1.23–1.27 (q, 2H), 1.87–1.95 (m, 1H), 2.05–2.13 (m,

1H), 2.41–2.47 (m, 2H), 2.54–2.60 (m, 1H), 2.62–2.66 (dd, 1H), 2.71–2.77 (q, 1H), 2.86–2.90 (q, 1H), 4.69–4.74 (m, 1H), 6.32–6.36 (m, 2H), 7.07–7.09 (d, 1H), 7.20–7.24 (m 2H), 7.27–7.30 (t, 4H), 7.35–7.37 (m, 4H) ppm. LRMS: m/z 493 [M + H]⁺.

5-[(3S)-3-(4-Methoxyphenoxy)pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((S)-17).

The title compound was prepared from alcohol (*R*)-**14** and 4-methoxyphenol, using a similar method to that described for (*S*)-**15**. The residue was purified by column chromatography on silica gel, eluting with pentane:ethyl acetate (100:0–50:50, by volume), then further purified by column chromatography on silica gel, eluting with ethyl acetate:methanol:0.88 specific gravity ammonia (100:0:0–95:5:0.5, by volume) to give (*S*)-**17** as a white foam, 36 mg, 14% yield. ¹H NMR (400 MHz, CD₃OD) δ: 0.96 (s, 3H), 1.02 (s, 3H), 1.19–1.25 (m, 2H), 1.81–1.91 (m, 1H), 2.00–2.11 (m, 1H), 2.35–2.60 (m, 4H), 2.66–2.72 (m, 1H), 2.77–2.81 (m, 1H), 3.73 (s, 3H), 4.64–4.69 (m, 1H), 6.72–6.81 (m, 4H), 7.20–7.39 (m, 10H) ppm. LRMS: m/z 473 [M + H]⁺.

5-[(3R)-3-(3-Methoxyphenoxy)pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((R)-10).

The title compound was prepared from alcohol (*S*)-**14** and 3-methoxyphenol, using a similar method to that described for (*S*)-**15**. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol (95:5–90:10, by volume) to give (*R*)-**10** as a colorless oil, 20 mg, 7% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.05 (s, 3H), 1.10 (s, 3H), 1.18–1.37 (m, 2H), 1.92–2.00 (m, 1H), 2.10–2.16 (m, 1H), 2.40–2.45 (m, 2H), 2.72–2.95 (m, 3H), 2.97–3.05 (m, 1H), 3.74 (s, 3H), 4.80–4.14 (m, 1H), 6.38–6.40 (m, 2H), 6.51 (d, 1H), 7.12–7.16 (m, 2H), 7.22–7.37 (m, 9H) ppm. LRMS: m/z 472 [M + H]⁺.

5-[(3R)-3-(3-Fluoro-5-methoxy-phenoxy)pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((R)-18). The title compound was prepared from alcohol (*S*)-**14** and 3-fluoro-5-methoxyphenol, using a similar method to that described for (*S*)-**15**. The residue was purified using an Isolute SCX-2 cartridge, eluting with methanol, followed by a solution of 2M ammonia in methanol. The basic fractions were concentrated in vacuo to give (*R*)-**18** as a pale brown foam, 150 mg, 75% yield. ¹H NMR (400 MHz, CD₃OD) δ: 0.98 (s, 3H), 1.03 (s, 3H), 1.21–1.26 (m, 2H), 1.81–1.89 (m, 1H), 2.06–2.15 (m, 1H), 2.38–

2.46 (m, 2H), 2.50–2.61 (m, 2H), 2.67–2.72 (m, 1H), 2.78–2.85 (m, 1H), 3.74 (s, 3H), 4.69–4.74 (m, 1H), 6.14–6.19 (m, 2H), 6.24–6.28 (m, 1H), 7.21–7.36 (m, 10H) ppm. LRMS: m/z 491 [M + H]⁺.

5-[(3*S*)-3-(4-Hydroxyphenoxy)pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((*S*)-19).

The title compound was prepared from amide (*S*)-17 using a similar method to that described for (*S*)-11. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate, then ethyl acetate:methanol:0.88 specific gravity ammonia (95:5:0.5, by volume) to give (*S*)-19 as a white foam, 16 mg, 46% yield. ¹H NMR (400 MHz, CD₃OD) δ: 0.97 (s, 3H), 1.03 (s, 3H), 1.20–1.25 (m, 2H), 1.81–1.89 (m, 1H), 2.01–2.09 (m, 1H), 2.39–2.44 (m, 2H), 2.51–2.61 (m, 2H), 2.67–2.73 (m, 1H), 2.77–2.81 (m, 1H), 4.62–4.66 (m, 1H), 6.63–6.69 (m, 4H), 7.21–7.37 (m, 10H) ppm. LRMS: m/z 458 [M – H][–].

5-[(3*R*)-3-(3-Hydroxyphenoxy)pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((*R*)-11).

The title compound was prepared from amide (*R*)-10, using a similar method to that described for (*S*)-11. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 specific gravity ammonia (95:5:0.5–92:8:0.8, by volume) to give (*R*)-11 as a colorless gum, 68% yield. ¹H NMR (400 MHz, CD₃OD) δ: 0.99 (s, 3H), 1.05 (s, 3H), 1.23–1.28 (m, 2H), 1.85–1.90 (m, 1H), 2.06–2.12 (m, 1H), 2.40–2.45 (m, 2H), 2.57–2.69 (m, 2H), 2.72–2.79 (m, 1H), 2.85–2.90 (m, 1H), 4.70–4.73 (m, 1H), 6.26–6.30 (m, 2H), 6.36 (d, 1H), 7.00–7.04 (m, 1H), 7.21–7.25 (m, 2H), 7.27–7.31 (m, 4H), 7.33–7.36 (m, 4H) ppm. LRMS: m/z 459 [M + H]⁺. Anal. (C₂₉H₃₄N₂O₃·0.6H₂O) C, H, N. HPLC analysis: ≥98.3% purity.

5-[(3*R*)-3-(3-Fluoro-5-hydroxy-phenoxy)-pyrrolidin-1-yl]-5-methyl-2,2-diphenylhexanamide ((*R*)-20). The title compound was prepared from amide (*R*)-18 using a similar method to that described for (*S*)-11. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 specific gravity ammonia (95:5:0.5, by volume) to give (*R*)-20 as a pale brown foam, 71 mg, 49% yield. ¹H NMR (400 MHz, CD₃OD) δ: 1.01 (s, 3H), 1.05 (s, 3H), 1.24–1.28 (m, 2H), 1.85–1.92 (m, 1H), 2.07–2.15 (m, 1H), 2.40–2.45 (m, 2H), 2.59–2.67 (m, 2H), 2.73–2.79 (q, 1H),

2.87–2.91 (m, 1H), 4.68–4.72 (m, 1H), 6.03–6.12 (m, 3H), 7.21–7.26 (m, 2H), 7.28–7.32 (m, 4H), 7.33–7.37 (m, 4H) ppm. LRMS: m/z 477 $[M + H]^+$, 475 $[M - H]^-$. Anal. ($C_{29}H_{33}FN_2O_3 \cdot 0.3CH_2Cl_2$) C, H, N.

5-Oxo-5-(3-phenoxyazetid-1-yl)-2,2-diphenylpentanenitrile (23). The title compound was prepared from acid **2** and 3-phenoxyazetid-1-yl using a similar method to that described for (*S*)-**5**. The residue was purified by column chromatography on silica gel, eluting with pentane:ethyl acetate (100:0–0:100, by volume) to give **23** as a colorless oil, 2.28 g, 75% yield. 1H NMR (400 MHz, $CDCl_3$) δ : 2.20–2.25 (m, 2H), 2.75–2.82 (m, 2H), 3.97–4.08 (m, 2H), 4.28–4.40 (m, 2H), 4.85–4.90 (m, 1H), 6.65–6.74 (m, 2H), 6.98–7.04 (m, 1H), 7.24–7.43 (m, 12H) ppm. LRMS: m/z 397 $[M + H]^+$.

5-Oxo-5-(4-phenoxy-piperidin-1-yl)-2,2-diphenylpentanenitrile (24). The title compound was prepared from acid **2** and 4-phenoxy-piperidine using a similar method to that described for (*S*)-**5**. The residue was triturated with diethyl ether and purified by column chromatography on silica gel, eluting with pentane:ethyl acetate (75:25–50:50, by volume) to give **24** as a white solid, 14.4 g, 95% yield. 1H NMR (400 MHz, $CDCl_3$) δ : 1.74–1.90 (m, 4H), 2.45–2.49 (m, 2H), 2.79–2.83 (m, 2H), 3.27–3.33 (m, 1H), 3.54–3.61 (m, 1H), 3.62–3.74 (m, 2H), 4.49–4.53 (m, 1H), 6.87–6.91 (m, 2H), 6.93–6.98 (m, 1H), 7.26–7.43 (m, 12H) ppm. LRMS: m/z 426 $[M + H]^+$.

5-Methyl-5-(3-phenoxyazetid-1-yl)-2,2-diphenylhexanamide (25). Amide **23** was subjected to the same Grignard method as that described for (*S*)-**7**, to give 5-methyl-5-(3-phenoxyazetid-1-yl)-2,2-diphenylhexanenitrile as a colorless oil, 38% yield. 1H NMR (400 MHz, $CDCl_3$) δ : 0.95 (s, 6H), 1.34–1.41 (m, 2H), 2.43–2.54 (m, 2H), 3.15–3.22 (m, 2H), 3.45–3.55 (m, 2H), 4.65–4.75 (m, 1H), 6.73–6.78 (m, 2H), 6.90–6.98 (m, 1H), 7.22–7.45 (m, 12H) ppm. LRMS: m/z 411 $[M + H]^+$.

5-Methyl-5-(3-phenoxyazetid-1-yl)-2,2-diphenylhexanenitrile was subjected to the same nitrile hydrolysis method as that described for **4**, to give **25** as a white solid, 88% yield. 1H NMR (400 MHz, $CDCl_3$) δ : 0.91 (s, 6H), 1.12–1.20 (m, 2H), 2.42–2.48 (m, 2H), 3.12–3.18 (m, 2H), 3.45–3.55 (m, 2H), 4.62–4.73 (m, 1H), 5.55 (bs, 2H), 6.75–6.78 (m, 2H), 6.92–6.96 (m, 1H), 7.20–7.41 (m, 12H) ppm. LRMS: m/z 429 $[M + H]^+$. Anal. ($C_{28}H_{32}N_2O_2 \cdot 0.2H_2O$) C, H, N.

5-Methyl-5-(4-phenoxy piperidin-1-yl)-2,2-diphenylhexanamide (26). Amide **24** was subjected to the same Grignard method as that described for (*S*)-**7**. The residue was purified by column chromatography on silica gel, eluting with pentane:ethyl acetate (3:1–2:1, by volume) and then further purified using an Isolute SCX-2 cartridge, eluting with methanol, followed by a solution of 1M ammonia in methanol, to give 5-methyl-5-(4-phenoxy piperidin-1-yl)-2,2-diphenylhexanenitrile as a yellow gum, 3.83 g, 41% yield. ¹H NMR (400 MHz, CDCl₃) δ: 1.04 (s, 6H), 1.54–1.58 (m, 2H), 1.71–1.80 (m, 2H), 1.99–2.02 (m, 2H), 2.25 (m, 2H), 2.53–2.57 (m, 2H), 2.70–2.75 (m, 2H), 4.22–4.28 (m, 1H), 6.92–6.96 (m, 3H), 7.28–7.32 (m, 4H), 7.35–7.39 (m, 4H), 7.45–7.47 (m, 4H) ppm. LRMS: *m/z* 439 [M + H]⁺.

5-Methyl-5-(4-phenoxy piperidin-1-yl)-2,2-diphenylhexanenitrile was subjected to the same nitrile hydrolysis method as that described for **4**. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 specific gravity ammonia (100:0:0–90:10:1, by volume) to give **26** as a colorless glass, 193 mg, 93% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.99 (s, 6H), 1.25–1.29 (m, 2H), 1.60–1.68 (m, 2H), 1.89–1.93 (m, 2H), 2.20–2.25 (m, 2H), 2.42–2.46 (m, 2H), 2.64–2.68 (m, 2H), 4.20–4.27 (m, 1H), 6.85–6.89 (m, 3H), 7.20–7.26 (m, 4H), 7.30–7.34 (m, 4H), 7.37–7.40 (m, 4H) ppm. LRMS: *m/z* 457 [M + H]⁺. Anal. (C₃₀H₃₆N₂O₂·0.15H₂O) C, H, N.

tert-Butyl 4-[(3-bromobenzyl)oxy]piperidine-1-carboxylate (28). Sodium hydride (60% dispersion in mineral oil, 3.31 g, 83.0 mmol) was added to a solution of 1-*tert*-butoxycarbonyl-4-hydroxy piperidine (16.64 g, 83.0 mmol) in tetrahydrofuran (200 mL) at 0 °C and the mixture stirred for 30 min. 3-Bromobenzyl bromide (20.66 g, 83.0 mmol) was added and the mixture stirred at room temperature for 18 h. The reaction was quenched with water (50 mL) and concentrated in vacuo. The aqueous residue was extracted with ethyl acetate (2 × 100 mL) and the combined organic layers washed with brine (100 mL), dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with pentane:ethyl acetate (90:10–80:20, by volume) to give **28** as a colorless oil, 18.64 g, 61% yield. ¹H NMR (400 MHz, CDCl₃) δ: 1.45 (s, 9H), 1.54–1.62 (m, 2H), 1.81–1.88 (m, 2H), 3.08–

3.14 (m, 2H), 3.52–3.58 (m, 1H), 3.73–3.79 (m, 2H), 4.51 (s, 2H), 7.18–7.26 (m, 2H), 7.38–7.41 (m, 1H), 7.49 (m, 1H) ppm. LRMS: m/z 372 [M + H]⁺.

4-[(3-Bromobenzyl)oxy]piperidine (29). Hydrochloric acid solution (4M in dioxan, 340 mL) was added to a solution of **28** (18.64 g, 50.0 mmol) in dioxan (50 mL) and the mixture stirred at room temperature for 2.5 h. The mixture was concentrated in vacuo, the residue dissolved in 2M aqueous hydrochloric acid solution (200 mL) and washed with diethyl ether (2 × 100 mL). The aqueous layer was adjusted to pH 10 with 2M aqueous sodium hydroxide solution, then extracted with diethyl ether (3 × 200 mL). The combined organic layers were dried (sodium sulfate) and concentrated in vacuo to give **29** as a colorless oil, 13.39 g, 98% yield. ¹H NMR (400 MHz, CDCl₃) δ: 1.45–1.55 (m, 2H), 1.92–1.97 (m, 2H), 2.58–2.64 (m, 2H), 3.07–3.13 (m, 2H), 3.42–3.49 (m, 1H), 4.51 (s, 2H), 7.17–7.27 (m, 2H), 7.37–7.40 (m, 1H), 7.50 (m, 1H) ppm. LRMS: m/z 270 [M + H]⁺.

5-{4-[(3-Bromobenzyl)oxy]piperidin-1-yl}-5-methyl-2,2-diphenylhexanamide (30). Acid **2** and piperidine **29** were subjected to the same amide coupling method as that described for (*S*)-**5**, to give 5-{4-[(3-bromobenzyl)oxy]piperidin-1-yl}-5-oxo-2,2-diphenylpentanenitrile, 95% yield. ¹H NMR (400 MHz, CDCl₃) δ: 1.63 (m, 2H), 1.82 (m, 2H), 2.46 (m, 2H), 2.80 (m, 2H), 3.17 (m, 1H), 3.35 (m, 1H), 3.51–3.64 (m, 2H), 3.88 (m, 1H), 4.44–4.53 (m, 2H), 7.17–7.42 (m, 14H) ppm. LRMS: m/z 519 [M + H]⁺.

5-{4-[(3-Bromobenzyl)oxy]piperidin-1-yl}-5-oxo-2,2-diphenylpentanenitrile was subjected to the same Grignard method as that described for (*S*)-**7**, to give 5-{4-[(3-bromobenzyl)oxy]piperidin-1-yl}-5-methyl-2,2-diphenylhexanenitrile as a yellow gum, 33% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.98 (s, 6H), 1.46–1.60 (m, 4H), 1.88–1.91 (m, 2H), 2.04–2.09 (m, 2H), 2.46–2.50 (m, 2H), 2.65–2.68 (m, 2H), 3.28–3.34 (m, 1H), 4.50 (s, 2H), 7.18–7.42 (m, 13H), 7.51 (s, 1H) ppm. LRMS: m/z 533 [M + H]⁺.

5-{4-[(3-Bromobenzyl)oxy]piperidin-1-yl}-5-methyl-2,2-diphenylhexanenitrile was subjected to the same nitrile hydrolysis method as that described for **4**, to give **30** as a colorless gum, 99% yield. ¹H NMR (400 MHz, CD₃OD) δ: 0.97 (s, 6H), 1.23–1.27 (m, 2H), 1.48–1.57 (m, 2H), 1.82–1.87 (m, 2H),

2.07–2.12 (m, 2H), 2.40–2.44 (m, 2H), 2.62–2.66 (m, 2H), 3.29–3.37 (m, 1H), 4.48 (s, 2H), 7.21–7.42 (m, 13H), 7.49 (s, 1H) ppm. LRMS: m/z 551 $[M + H]^+$.

5-(4-Hydroxy-piperidin-1-yl)-5-methyl-2,2-diphenylhexanamide (31). Amide **30** was subjected to the same hydrogenation method as that described for (*R*)-**14**, to give **31** as a white foam, 3.39 g, 95% yield. ^1H NMR (400 MHz, CD_3OD) δ : 0.97 (s, 6H), 1.23–1.27 (m, 2H), 1.39–1.48 (m, 2H), 1.74–1.78 (m, 2H), 2.06–2.11 (m, 2H), 2.40–2.44 (m, 2H), 2.65–2.68 (m, 2H), 3.47 (m, 1H), 7.23–7.39 (m, 10H) ppm. LRMS: m/z 381 $[M + H]^+$.

5-[4-(3-Hydroxyphenoxy)piperidin-1-yl]-5-methyl-2,2-diphenylhexanamide (32). The title compound was prepared from **31** and resorcinol, using a similar method to that described for (*S*)-**15**. The residue was purified using an Isolute SCX-2 cartridge, eluting with methanol, then with a solution of 1M ammonia in methanol. Basic fractions were concentrated in vacuo and further purified by chromatography on silica gel, eluting with dichloromethane:methanol:0.88 specific gravity ammonia (98:2:0.2–95:5:0.5, by volume). The resulting residue was further purified by preparative thin layer chromatography using a silica coated plate, eluting with dichloromethane:methanol:0.88 specific gravity ammonia (80:20:2, by volume) to give **32** as a gum, 14% yield. ^1H NMR (400 MHz, CD_3OD) δ : 1.05 (s, 6H), 1.30–1.34 (m, 2H), 1.66–1.74 (m, 2H), 1.91–1.96 (m, 2H), 2.34–2.47 (m, 4H), 2.70–2.79 (m, 2H), 4.21–4.27 (m, 1H), 6.32–6.38 (m, 3H), 7.00–7.05 (m, 1H), 7.23–7.40 (m, 10H) ppm. LRMS: m/z 473 $[M + H]^+$. Anal. ($\text{C}_{30}\text{H}_{36}\text{N}_2\text{O}_3 \cdot 0.5\text{CH}_2\text{Cl}_2$) C, H, N.

1-(4-Cyano-4,4-diphenylbutanoyl)azetidin-3-yl-methanesulfonate (33). N,N-Dimethylformamide (1 drop) was added to a suspension of acid **2** (7.8 g, 29 mmol) and oxalyl chloride (5.2 mL, 60.0 mmol) in dichloromethane (40 mL) and the mixture stirred at room temperature for 2 h. The mixture was concentrated in vacuo and the residue azeotroped with toluene (3×50 mL) to give 4-cyano-4,4-diphenylbutanoyl chloride, which was dissolved in dichloromethane (40 mL) and triethylamine (12.3 mL, 87.0 mmol), and added dropwise to a solution of azetidin-3-yl-methanesulfonate hydrochloride (5.53 g, 29.0 mmol) in dichloromethane (50 mL) at -78 °C, and the mixture stirred for 1 h. The reaction was

quenched with 2M aqueous hydrochloric acid solution (50 mL). The organic layer was separated, dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate:pentane (50:50–100:0, by volume) to give **33** as a yellow oil, 11.4 g, 97% yield. ¹H NMR (400 MHz, CDCl₃) δ: 2.17–2.29 (m, 2H), 2.71–2.80 (m, 2H), 3.05 (s, 3H), 4.03–4.20 (m, 2H), 4.26–4.38 (m, 2H), 5.18–5.22 (m, 1H), 7.24–7.45 (m, 10H) ppm. LRMS: *m/z* 399 [M + H]⁺.

5-{3-[2-(Benzyloxy)phenoxy]azetidin-1-yl}-5-methyl-2,2-diphenylhexanenitrile (34). Mesylate **33** and 2-(benzyloxy)phenol were subjected to a similar method as that described for **40**, to give 5-{3-[2-(benzyloxy)phenoxy]azetidin-1-yl}-5-oxo-2,2-diphenylpentanenitrile as a yellow oil, 77% yield. ¹H NMR (400 MHz, CDCl₃) δ: 2.18–2.24 (m, 2H), 2.75–2.80 (m, 2H), 4.02–4.10 (m, 2H), 4.23–4.33 (m, 2H), 4.82–4.91 (m, 1H), 5.08 (s, 2H), 6.62–6.65 (m, 1H), 6.84–6.99 (m, 3H), 7.24–7.43 (m, 15H) ppm. LRMS: *m/z* 503 [M + H]⁺.

5-{3-[2-(Benzyloxy)phenoxy]azetidin-1-yl}-5-oxo-2,2-diphenylpentanenitrile was subjected to a similar Grignard method as that described for (*S*)-**7**. The residue was purified by column chromatography on silica gel, eluting with pentane:ethyl acetate (85:15–50:50, by volume) to give **34** as a yellow oil, 10% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.98 (s, 6H), 1.35–1.42 (m, 2H), 2.45–2.58 (m, 2H), 3.20–3.32 (m, 2H), 3.40–3.55 (m, 2H), 4.68–4.78 (m, 1H), 5.13 (s, 2H), 6.64–6.72 (d, 1H), 6.85–6.99 (m, 3H), 7.24–7.48 (m, 15H) ppm. LRMS: *m/z* 517 [M + H]⁺.

5-[3-(2-Hydroxyphenoxy)azetidin-1-yl]-5-methyl-2,2-diphenylhexanamide (35). Nitrile **34** was subjected to the same nitrile hydrolysis method as that described for **4**, to give 5-{3-[2-(benzyloxy)phenoxy]azetidin-1-yl}-5-methyl-2,2-diphenylhexanamide as a colorless gum, 55% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.90 (s, 6H), 1.15–1.22 (m, 2H), 2.42–2.52 (m, 2H), 3.18–3.32 (m, 2H), 3.40–3.58 (m, 2H), 4.65–4.78 (m, 1H), 5.13 (s, 2H), 5.40–5.60 (m, 2H), 6.62–6.70 (m, 1H), 6.82–6.97 (m, 3H), 7.23–7.44 (m, 15H) ppm. LRMS: *m/z* 535 [M + H]⁺.

Ammonium formate (50 mg, 0.8 mmol) was added to a mixture of 5-{3-[2-(benzyloxy)phenoxy]azetidin-1-yl}-5-methyl-2,2-diphenylhexanamide (35 mg, 65.0 μmol) and 20%

palladium hydroxide on carbon (20 mg) in ethanol (10 mL) and the mixture heated at reflux for 4 h. The reaction was filtered through Arbocel and concentrated in vacuo. The residue was partitioned between saturated aqueous sodium hydrogen carbonate solution (20 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with additional ethyl acetate (20 mL) and the combined organic layers dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate:methanol (95:5, by volume) to give **35** as a colorless oil, 100% yield. ¹H NMR (400 MHz, CDCl₃) δ: 1.02 (s, 6H), 1.22–1.32 (m, 2H), 2.31–2.49 (m, 2H), 2.57–2.72 (m, 2H), 3.98–4.04 (m, 1H), 4.15–4.24 (m, 2H), 5.40–5.70 (bm, 2H), 6.77–6.86 (m, 4H), 7.22–7.38 (m, 10H) ppm. LRMS: *m/z* 445 [M + H]⁺.

5-[3-(4-Chloro-3-methoxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenyl-hexanenitrile (41).

The title compound was prepared from mesylate **39** and 4-chloro-3-methoxyphenol, using a similar method to that described for **40**, to give **41** as colorless oil, 85% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.95 (s, 6H), 1.35–1.40 (m, 2H), 2.45–2.53 (m, 2H), 3.16–3.20 (m, 2H), 3.45–3.52 (m, 2H), 3.86 (s, 3H), 4.62–4.70 (m, 1H), 6.20–6.25 (m, 1H), 6.40–6.43 (m, 1H), 7.18–7.45 (m, 11H) ppm. LRMS: *m/z* 475 [M + H]⁺.

5-[3-(3-Chloro-5-methoxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenyl-hexanenitrile (42).

The title compound was prepared from mesylate **39** and 3-chloro-5-methoxyphenol, using a similar method to that described for **40**, to give **42** as a colorless oil, 75% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.95 (s, 6H), 1.35–1.40 (m, 2H), 2.45–2.53 (m, 2H), 3.06–3.15 (m, 2H), 3.40–3.48 (m, 2H), 3.78 (s, 3H), 4.58–4.66 (m, 1H), 6.20 (s, 1H), 6.35 (s, 1H), 6.50 (s, 1H), 7.22–7.45 (m, 10H) ppm. LRMS: *m/z* 475 [M + H]⁺.

5-[3-(3-Fluoro-5-methoxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenyl-hexanenitrile (43).

The title compound was prepared from mesylate **39** and 3-fluoro-5-methoxyphenol, using a similar method to that described for **40**, to give **43** as a colorless oil, 90% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.95 (s, 6H), 1.35–1.40 (m, 2H), 2.45–2.53 (m, 2H), 3.06–3.15 (m, 2H), 3.40–3.48 (m, 2H), 3.75 (s, 3H),

4.58–4.64 (m, 1H), 6.05–6.12 (m, 2H), 6.20–6.26 (m, 1H), 7.22–7.45 (m, 10H) ppm. LRMS: m/z 459 [M + H]⁺.

5-[3-(5-Allyloxy-2,4-dichloro-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenyl-hexanenitrile

(44). The title compound was prepared from mesylate **39** and 5-allyloxy-2,4-dichlorophenol³, using a similar method to that described for **40**, to give **44** as a colorless gum, 93% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.98 (s, 6H), 1.31–1.40 (m, 2H), 2.41–2.55 (m, 2H), 3.20–3.25 (m, 2H), 3.48–3.58 (m, 2H), 4.55–4.58 (m, 2H), 4.62–4.75 (m, 1H), 5.32–5.38 (m, 1H), 5.40–5.48 (m, 1H), 5.95–6.10 (m, 1H), 6.28 (s, 1H), 7.25–7.45 (m, 11H) ppm. LRMS: m/z 535 [M + H]⁺.

5-[3-(2-Fluoro-3-methoxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenyl-hexanenitrile (45).

The title compound was prepared from mesylate **39** and 2-fluoro-3-methoxyphenol, using a similar method to that described for **40**, to give **45**, 73% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.95 (s, 6H), 1.34–1.40 (m, 2H), 2.44–2.53 (m, 2H), 3.20–3.27 (m, 2H), 3.43–3.52 (m, 2H), 3.88 (s, 3H), 4.65–4.74 (m, 1H), 6.34–6.39 (m, 1H), 6.58–6.64 (m, 1H), 6.88–6.95 (m, 1H), 7.25–7.47 (m, 10H) ppm. LRMS: m/z 459 [M + H]⁺.

5-[3-(2-Fluoro-5-methoxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenyl-hexanenitrile (46).

The title compound was prepared from mesylate **39** and 2-fluoro-5-methoxyphenol, using the same method as that described for **40**, to give **46**, 68% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.95 (s, 6H), 1.36–1.42 (m, 2H), 2.44–2.53 (m, 2H), 3.20–3.27 (m, 2H), 3.43–3.52 (m, 2H), 3.77 (s, 3H), 4.65–4.74 (m, 1H), 6.27–6.34 (m, 1H), 6.38–6.42 (m, 1H), 6.95–7.02 (m, 1H), 7.25–7.47 (m, 10H) ppm. LRMS: m/z 459 [M + H]⁺.

5-{3-(4-Chloro-3-hydroxy-phenoxy)-azetidin-1-yl}-5-methyl-2,2-diphenylhexanamide (48).

The title compound was prepared from nitrile **41**, using the same two-step method as that described for **47**. Nitrile hydrolysis of **41** gave 5-{3-(4-chloro-3-methoxy-phenoxy)-azetidin-1-yl}-5-methyl-2,2-diphenylhexanamide as a colorless oil, 91% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.85 (s, 6H), 1.08–1.22 (m, 2H), 2.38–2.50 (m, 2H), 3.15–3.20 (m, 2H), 3.40–3.55 (m, 2H), 3.85 (s, 3H), 4.60–4.72 (m, 1H),

5.30–5.55 (m, 2H), 6.20–6.23 (m, 1H), 6.38–6.41 (m, 1H), 7.18–7.40 (m, 11H) ppm. LRMS: m/z 493 [M + H]⁺.

Demethylation of 5-{3-(4-chloro-3-methoxy-phenoxy)-azetidin-1-yl}-5-methyl-2,2-diphenylhexanamide gave **48** as a colorless foam, 270 mg, 93% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.85 (s, 6H), 1.08–1.22 (m, 2H), 2.40–2.50 (m, 2H), 3.10–3.20 (m, 2H), 3.50–3.58 (m, 2H), 4.58–4.66 (m, 1H), 5.45–5.55 (m, 1H), 5.75–5.90 (m, 1H), 6.25–6.32 (m, 1H), 6.38–6.40 (m, 1H), 7.15–7.40 (m, 11H) ppm. LRMS: m/z 479 [M + H]⁺. Anal. (C₂₈H₃₁ClN₂O₃·0.3CH₂Cl₂) C, H, N. HPLC analysis: ≥98.5% purity.

5-{3-(3-Chloro-5-hydroxy-phenoxy)-azetidin-1-yl}-5-methyl-2,2-diphenylhexanamide (49).

The title compound was prepared from nitrile **42**, using the same two-step method as that described for **47**. Nitrile hydrolysis of **42** gave 5-[3-(3-chloro-5-methoxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenylhexanamide as a colorless oil, 90% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.95 (s, 6H), 1.15–1.20 (m, 2H), 2.38–2.45 (m, 2H), 3.02–3.10 (m, 2H), 3.37–3.43 (m, 2H), 3.75 (s, 3H), 4.55–4.63 (m, 1H), 5.40–5.65 (m, 2H), 6.18 (s, 1H), 6.30 (s, 1H), 6.48 (s, 1H), 7.20–7.40 (m, 10H) ppm. LRMS m/z 493 [M + H]⁺.

Demethylation of 5-[3-(3-chloro-5-methoxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenylhexanamide gave **49** a colorless oil, 92% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.90 (s, 6H), 1.08–1.18 (m, 2H), 2.35–2.45 (m, 2H), 3.06–3.15 (m, 2H), 3.40–3.46 (m, 2H), 4.55–4.60 (m, 1H), 5.45 (bs, 2H), 6.15 (s, 1H), 6.25 (s, 1H), 6.40 (s, 1H), 7.20–7.40 (m, 10H) ppm. Anal. (C₂₈H₃₁ClN₂O₃·0.6H₂O) C, H, N.

5-{3-(3-Fluoro-5-hydroxy-phenoxy)-azetidin-1-yl}-5-methyl-2,2-diphenylhexanamide (50).

The title compound was prepared from nitrile **43**, using the same two-step method as that described for **47**. Nitrile hydrolysis of **43** gave 5-[3-(3-fluoro-5-methoxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenylhexanamide as a colorless oil, 90% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.95 (s, 6H), 1.42–1.55

(m, 2H), 2.40–2.48 (m, 2H), 3.06–3.15 (m, 2H), 3.40–3.45 (m, 2H), 3.78 (s, 3H), 4.58–4.66 (m, 1H), 5.40–5.55 (m, 2H), 6.03–6.12 (m, 2H), 6.20–6.25 (m, 1H), 7.22–7.45 (m, 10H) ppm.

Demethylation of 5-[3-(3-fluoro-5-methoxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenylhexanamide gave **50** as a colorless oil, 25% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.95 (s, 6H), 1.20–1.26 (m, 2H), 2.40–2.46 (m, 2H), 3.20–3.28 (m, 2H), 3.60–3.65 (m, 2H), 4.64–4.70 (m, 1H), 5.50–5.60 (m, 1H), 6.00 (s, 1H), 6.02–6.06 (m, 1H), 6.18–6.23 (m, 1H), 6.25–6.35 (m, 1H), 7.20–7.35 (m, 10H) ppm. LRMS: *m/z* 463 [M + H]⁺. Anal. (C₂₈H₃₁FN₂O₃·0.5H₂O) C, H, N.

5-{3-(2,4-Dichloro-5-hydroxy-phenoxy)-azetidin-1-yl}-5-methyl-2,2-diphenylhexanamide

(51). Potassium hydroxide (523 mg, 9.33 mmol) was added to a solution of nitrile **44** (250 mg, 0.46 mmol) in 3-methyl-3-pentanol (5 mL) and the mixture heated under reflux for 18 h. The mixture was concentrated in vacuo and the residue partitioned between ethyl acetate (20 mL) and water (20 mL). The aqueous layer was separated and extracted with ethyl acetate (20 mL), and the combined organic layers dried (sodium sulfate) and concentrated in vacuo. The residue was treated with 4M hydrochloric acid solution in dioxane (10 mL, 40 mmol) and the solution stirred at 60 °C for 30 min. The solvent was removed in vacuo and the residue basified with 0.88 specific gravity ammonia. The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organic layers dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol (100:1–10:1, by volume) to give **51** as a colorless oil, 147 mg, 61% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.98 (s, 6H), 1.18–1.25 (m, 2H), 2.41–2.55 (m, 2H), 3.32–3.38 (m, 2H), 3.75–3.82 (m, 2H), 4.68–4.75 (m, 1H), 5.65–5.75 (m, 1H), 5.95–6.05 (m, 1H), 6.43 (s, 1H), 7.20–7.40 (m, 11H) ppm. LRMS: *m/z* 513 [M + H]⁺. Anal. (C₂₈H₃₀Cl₂N₂O₃·0.3CH₂Cl₂) C, H, N.

5-[3-(2-Fluoro-3-hydroxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenyl-hexanamide (52).

The title compound was prepared from nitrile **45**, using the same two-step method as that described for **47**. Nitrile hydrolysis of **45** gave 5-[3-(2-fluoro-3-methoxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenyl-hexanamide as a colorless oil, 72% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.95 (s, 6H), 1.17–

1.25 (m, 2H), 2.40–2.48 (m, 2H), 3.20–3.28 (m, 2H), 3.50–3.60 (m, 2H), 3.90 (s, 3H), 4.65–4.74 (m, 1H), 5.46–5.75 (bm, 2H), 6.20–6.27 (m, 1H), 6.56–6.63 (m, 1H), 6.80–6.86 (m, 1H), 7.25–7.40 (m, 10H) ppm. LRMS: m/z 477 [M + H]⁺.

Demethylation of 5-[3-(2-fluoro-3-methoxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenyl-hexanamide gave **52** as a colorless foam, 390 mg, 100% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.95 (s, 6H), 1.17–1.26 (m, 2H), 2.43–2.49 (m, 2H), 3.20–3.28 (m, 2H), 3.45–3.60 (m, 2H), 4.65–4.74 (m, 1H), 5.49–5.76 (bm, 2H), 6.20–6.27 (m, 1H), 6.57–6.62 (m, 1H), 6.80–6.85 (m, 1H), 7.23–7.38 (m, 10H) ppm. LRMS: m/z 463 [M + H]⁺. Phenol **52** (390 mg) was dissolved in methanol (5 mL) and treated with a solution of 2M hydrogen chloride in diethyl ether (5 mL). The mixture was concentrated in vacuo and azeotroped with diethyl ether (10 mL). The residue was recrystallized from ethanol to give the hydrochloride salt of **52** as a colorless solid, 300 mg. Anal. (C₂₈H₃₁FN₂O₃·1.0HCl) C, H, N. HPLC analysis: ≥97.4% purity.

5-[3-(2-Fluoro-5-hydroxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenyl-hexanamide (53).

The title compound was prepared from nitrile **46**, using the same two-step method as that described for **47**. Nitrile hydrolysis of **46** gave 5-[3-(2-fluoro-5-methoxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenyl-hexanamide as a colorless oil, 96% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.92 (s, 6H), 1.12–1.20 (m, 2H), 2.40–2.48 (m, 2H), 3.16–3.21 (m, 2H), 3.43–3.50 (m, 2H), 3.76 (s, 3H), 4.60–4.72 (m, 1H), 5.46–5.60 (bm, 1H), 5.65–5.75 (bm, 1H), 6.25–6.33 (m, 1H), 6.34–6.40 (m, 1H), 6.91–6.99 (m, 1H), 7.22–7.40 (m, 10H) ppm. LRMS: m/z 477 [M+H]⁺.

Demethylation of 5-[3-(2-fluoro-5-methoxy-phenoxy)-azetidin-1-yl]-5-methyl-2,2-diphenyl-hexanamide gave **53** as a colorless oil, 51% yield. ¹H NMR (400 MHz, CDCl₃) δ: 1.04 (s, 6H), 1.22–1.33 (m, 2H), 2.46–2.57 (m, 2H), 3.43–3.55 (m, 2H), 3.92–4.00 (m, 2H), 4.75–4.86 (m, 1H), 5.72–5.82 (bm, 2H), 6.35–6.48 (m, 2H), 6.83–6.92 (m, 1H), 7.20–7.38 (m, 10H) ppm. LRMS: m/z 463 [M + H]⁺. Anal. (C₂₈H₃₁FN₂O₃·0.4CH₂Cl₂) C, H, N.

5-Methyl-2,2-diphenyl-5-[3-(3-propenyloxy-benzyloxy)-azetid-1-yl]-hexanamide (54).

Sodium hydride (60% dispersion in mineral oil, 24 mg, 0.596 mmol) was added portionwise to a solution of alcohol **38** (166 mg, 0.496 mmol) in N,N-dimethylformamide (2 mL) at 0 °C and the mixture stirred for 15 min. 1-Allyloxy-3-bromomethyl-benzene³ (169 mg, 0.746 mmol) was added and the mixture stirred for 0.5 h at 0 °C. The mixture was quenched with 2M aqueous hydrochloric acid solution (2 mL), then basified with saturated aqueous sodium hydrogen carbonate solution. The mixture was partitioned between ethyl acetate (50 mL) and water (10 mL). The aqueous layer was separated and extracted with ethyl acetate (50 mL). The combined organic layers were dried (sodium sulfate), concentrated in vacuo and the residue purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 specific gravity ammonia (100:0:0–98:2:0.2, by volume) to give 5-methyl-2,2-diphenyl-5-[3-(3-allyloxy-benzyloxy)-azetid-1-yl]-hexanenitrile as a colorless gum, 130 mg, 54% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.93 (s, 6H), 1.26–1.38 (m, 2H), 2.38–2.50 (m, 2H), 2.96–3.10 (m, 2H), 3.18–3.36 (m, 2H), 4.06–4.18 (m, 1H), 4.39 (s, 2H), 4.52–4.58 (m, 2H), 5.25–5.33 (m, 1H), 5.37–5.47 (m, 1H), 6.00–6.11 (m, 1H), 6.81–6.93 (m, 3H), 7.20–7.45 (m, 11H) ppm. LRMS: *m/z* 481 [M + H]⁺.

5-Methyl-2,2-diphenyl-5-[3-(3-allyloxy-benzyloxy)-azetid-1-yl]-hexanenitrile was subjected to the same nitrile hydrolysis method as that described for **4**, to give **54** as a colorless gum, 130 mg, 96% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.87 (s, 6H), 1.07–1.19 (m, 2H), 1.64–1.76 (m, 3H), 2.37–2.47 (m, 2H), 2.94–3.10 (m, 2H), 3.20–3.40 (m, 2H), 4.08–4.20 (m, 1H), 4.35 (s, 2H), 4.83–4.93 (m, 1H), 5.35–5.65 (d, 2H), 6.34–6.40 (d, 1H), 6.88–6.98 (m, 3H), 7.20–7.40 (m, 11H) ppm. LRMS: *m/z* 499 [M + H]⁺.

5-[3-(3-Hydroxy-benzyloxy)-azetid-1-yl]-5-methyl-2,2-diphenyl-hexanamide (55). Amide **54** (65 mg, 0.131 mmol) was treated with a solution of 4M hydrochloric acid in dioxane (2 mL, 8 mmol) and water (0.2 mL) and the solution stirred at 85 °C for 30 min. The solvent was removed in vacuo and the residue partitioned between ethyl acetate (25 mL) and saturated aqueous sodium hydrogen carbonate solution (20 mL). The aqueous layer was separated and extracted with ethyl acetate (20 mL). The

combined organic layers were dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with pentane:(ethyl acetate:methanol:0.88 specific gravity ammonia (90:10:1, by volume)) (75:25–50:50, by volume) to give **55** as a colorless foam, 42 mg, 70% yield. ¹H NMR (400 MHz, CDCl₃) δ: 0.90 (s, 6H), 1.16–1.25 (m, 2H), 2.38–2.48 (m, 2H), 3.02–3.12 (m, 2H), 3.28–3.40 (m, 2H), 4.06–4.17 (m, 1H), 4.31 (s, 2H), 5.58–5.74 (bs, 2H), 6.72–6.83 (m, 3H), 7.12–7.20 (m, 1H), 7.21–7.40 (m, 10H) ppm. LRMS: *m/z* 459 [M + H]⁺.

Sulfamic acid 2-cyclopentyl-ethyl ester (56). Chlorosulfonyl isocyanate (275 mL, 3.15 mol) at 0 °C was treated with formic acid (119 mL, 3.15 mol) dropwise and the resulting suspension stirred at 0 °C for 20 min. The mixture was diluted with dichloromethane (875 mL) and warmed to room temperature for 1 h. The mixture was cooled to 0 °C and treated with a solution of 2-cyclopentyl ethanol (240 g, 2.1 mol) and pyridine (255 mL, 3.15 mol) in dichloromethane (2.1 L), maintaining a temperature below 7 °C. After 2 h, the mixture was concentrated in vacuo and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic layer was separated, washed with brine, dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with heptane:ethyl acetate (90:10–50:50, by volume) to give **56** as a colorless oil, 276 g, 95% yield.

8-Oxa-7-thia-6-aza-spiro[4.5]decane-7,7-dioxide (57). Sulfamate **56** (276 g, 1.43 mol) in dichloromethane (7.1 L) at room temperature was treated with magnesium oxide (132.5 g, 3.29 mol), iodobenzene diacetate (507 g, 1.57 mol) and rhodium acetate dimer (12.6 g, 0.028 mol) and stirred for 18 h. The mixture was filtered through Celite and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel, eluting with heptane:ethyl acetate (90:10–50:50, by volume) to give **57** as a white solid, 205 g, 75% yield. ¹H NMR (400 MHz, CDCl₃) δ: 1.63–1.78 (m, 4H), 1.79–2.00 (m, 4H), 2.00–2.11 (m, 2H), 4.64–4.67 (m, 2H), 4.71 (s, 1H) ppm. LRMS: *m/z* 214 [M + Na]⁺.

7,7-Dioxo-8-oxa-7-thia-6-aza-spiro[4.5]decane-6-carboxylic acid *tert*-butyl ester (58). Cyclic sulfamate **57** (1.0 g, 5.23 mmol), di-*tert*-butyl dicarbonate (1.36 g, 6.24 mmol), triethylamine (1.06 g, 10.5

mmol) and 4-dimethylaminopyridine (126 mg, 1.03 mmol) in dichloromethane (50 mL) were stirred together at room temperature for 3 h. The mixture was washed with saturated aqueous ammonium chloride solution (50 mL), dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with pentane:ethyl acetate (100:0–80:20, by volume) to give **58** as a colorless oil, 700 mg, 46% yield. ^1H NMR (400 MHz, CDCl_3) δ : 1.48 (s, 9H), 1.48–1.66 (m, 2H), 1.82–1.96 (m, 4H), 2.17–2.33 (m, 4H), 4.57–4.63 (m, 2H) ppm.

4-(1-Amino-cyclopentyl)-2,2-diphenyl-butyronitrile (59). The title compound was prepared from compound **58** using a similar method to that described for **37**, to give **59**, 67% yield. ^1H NMR (400 MHz, CDCl_3) δ : 1.43–1.58 (m, 4H), 1.58–1.67 (m, 4H), 1.72–1.80 (m, 2H), 2.49–2.60 (m, 2H), 7.25–7.46 (m, 10H) ppm. LRMS: m/z 305 $[\text{M} + \text{H}]^+$.

4-[1-(3-Hydroxy-azetidin-1-yl)-cyclopentyl]-2,2-diphenyl-butyronitrile (60). The title compound was prepared from **59** using a similar method to that described for **38**, to give **60**, 52% yield. ^1H NMR (400 MHz, CDCl_3) δ : 1.25–1.38 (m, 2H), 1.39–1.64 (m, 6H), 1.65–1.78 (m, 2H), 2.42–2.55 (m, 2H), 2.86–2.97 (m, 2H), 3.36–3.40 (m, 2H), 4.29–4.40 (m, 1H), 7.25–7.48 (m, 10H) ppm. LRMS: m/z 361 $[\text{M} + \text{H}]^+$.

Methanesulfonic acid 1-[1-(3-cyano-3,3-diphenyl-propyl)-cyclopentyl]-azetidin-3-yl ester (61). The title compound was prepared from **60** using a similar method to that described for **39**, to give **61**, 59% yield. ^1H NMR (400 MHz, CDCl_3) δ : 1.25–1.67 (m, 10H), 2.42–2.52 (m, 2H), 3.00 (s, 3H), 3.15–3.26 (m, 2H), 3.40–3.55 (m, 2H), 4.95–5.05 (m, 1H), 7.27–7.45 (m, 10H) ppm. LRMS: m/z 439 $[\text{M} + \text{H}]^+$.

4-{1-[3-(3-Methoxy-phenoxy)-azetidin-1-yl]-cyclopentyl}-2,2-diphenyl-butyronitrile (62). The title compound was prepared from mesylate **61** and 3-methoxyphenol, using a similar method to that described for **40**, to give **62**, 73% yield. ^1H NMR (400 MHz, CDCl_3) δ : 1.25–1.38 (m, 2H), 1.40–1.65 (m, 6H), 1.66–1.76 (m, 2H), 2.46–2.57 (m, 2H), 3.06–3.16 (m, 2H), 3.48–3.57 (m, 2H), 3.78 (s, 3H),

4.64–4.72 (m, 1H), 6.34 (s, 1H), 6.33–6.37 (m, 1H), 6.48–6.53 (m, 1H), 7.13–7.19 (m, 1H), 7.27–7.46 (m, 10H) ppm. LRMS: m/z 467 [M + H]⁺.

4-{1-[3-(3-Methoxy-phenoxy)-azetidin-1-yl]-cyclopentyl}-2,2-diphenyl-butylamide (63). The title compound was prepared from **62** using a similar nitrile hydrolysis method to that described for **4**, to give **63**, 48% yield. ¹H NMR (400 MHz, CDCl₃) δ: 1.22–1.70 (m, 10H), 2.46–2.53 (m, 2H), 3.07–3.15 (m, 2H), 3.47–3.59 (m, 2H), 3.77 (s, 3H), 4.63–4.73 (m, 1H), 5.44–5.60 (bm, 2H), 6.33 (s, 1H), 6.33–6.36 (m, 1H), 6.48–6.53 (m, 1H), 7.11–7.18 (m, 1H), 7.20–7.40 (m, 10H) ppm. LRMS: m/z 485 [M + H]⁺.

4-{1-[3-(3-Hydroxy-phenoxy)-azetidin-1-yl]-cyclopentyl}-2,2-diphenyl-butylamide (64). The title compound was prepared from **63** using a similar method to that described for (*S*)-**11**, to give **64**, 53% yield. ¹H NMR (400 MHz, CDCl₃) δ: 1.31–1.47 (m, 6H), 1.48–1.60 (m, 2H), 1.63–1.77 (m, 2H), 2.45–2.54 (m, 2H), 3.22–3.28 (m, 2H), 3.73–3.80 (m, 2H), 4.75–4.83 (m, 1H), 5.40–5.55 (bm, 1H), 6.24 (s, 1H), 6.36–6.39 (m, 1H), 6.48–6.55 (m, 1H), 6.56–6.67 (bm, 1H), 7.08–7.7.16 (m, 1H), 7.17–7.38 (m, 10H) ppm. LRMS: m/z 471 [M + H]⁺. Anal. (C₃₀H₃₄N₂O₃·1.3H₂O) C, H, N.

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