

Property Based Optimisation of Glucokinase Activators – Discovery of the Phase IIb Clinical Candidate AZD1656

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Experimental references

Glucokinase Enzyme Assay

Enzymatic activity of recombinant human pancreatic GK was measured by incubating GK, ATP and glucose. The rate of product formation was determined by coupling the assay to a G-6-P dehydrogenase, NADP/NADPH system and measuring the linear increase with time of optical density at 340nm. For further details see K. Brocklehurst *et al.* (*Diabetes* **2004**, *53*, 535-541).

Oral Glucose Tolerance Test

Oral glucose tolerance tests were done on conscious Zucker obese fa/fa rats (age 12-13 weeks or older) fed a high fat diet (45 % kcal fat) for at least two weeks prior to experimentation. The animals were fasted for 2 hours before use for experiments. A test compound or a vehicle was given orally 120 minutes before oral administration of a glucose solution at a dose of 2 g/kg body weight. Blood glucose levels were measured using a Accucheck glucometer from tail bled samples taken at different time points before and after administration of glucose (time course of 60 minutes). A time curve of the blood glucose levels was generated and the area-under-the-curve (AUC) for 120 minutes was calculated (the time of glucose administration being time zero). Percent reduction in glucose excursion was determined using the AUC in the vehicle-control group as zero percent reduction.

Secondary Screening Assays

Protocols for generating solubility and logD data are described in D. Buttar, N. Colclough, S. Gerhardt *et al.* *Bioorg. and Medicinal Chemistry* 2010, **18**, 7486.

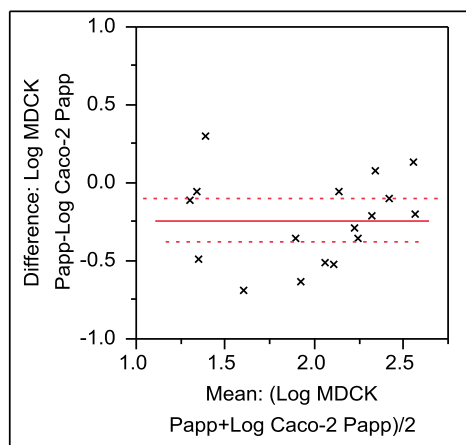
Solubilities quoted are measured on amorphous material unless otherwise stated.

The in vitro permeability were generated as described in G. Camenisch, J. Alsenz, H. van de Waterbeemd, G. Folkers, *Eur. J. Pharm. Sci.*, 1998, **6**, 313.

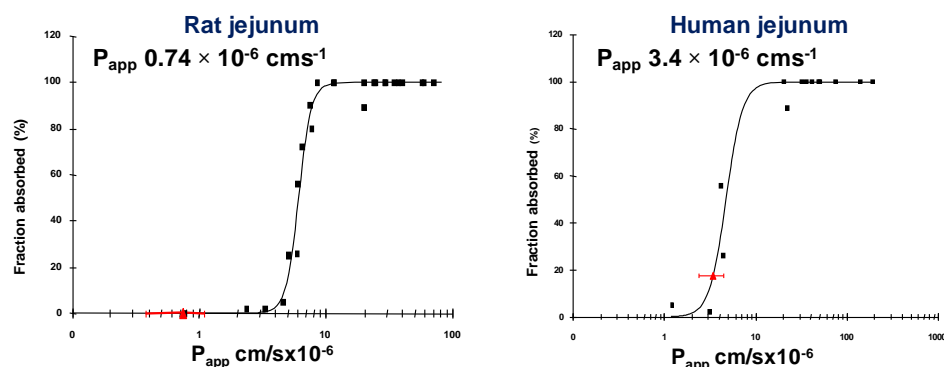
The hERG assay used to generate the data is described in M. H. Bridgland-Taylor, A. C. Hargreaves, A. Easter *et al.* *J. Pharmacological and Toxicological Methods* 2006, **54**, 189.

Comparison of MDCK vs Caco-2 Papp values

Difference vs. mean plot shows values are generally comparable and correlate with each other (r value 0.81), Caco-2 values are greater than those from MDCK by 0.24 log units on average.



Ussing Chamber Experiments on AZD1092



Synthesis

All solvents and chemicals used were reagent grade. Anhydrous solvents were purchased from Aldrich. Flash column chromatography was carried out using prepacked silica cartridges (from 4 g up to 330 g) from Redisep, Biotage, or Crawford and eluted using an Isco Companion system. Purity and characterization of compounds were established by a combination of liquid chromatography-mass spectrometry (LC-MS), high performance liquid chromatography (HPLC), and NMR analytical techniques and was >95% for all test compounds. ^1H NMR were recorded on a Varian Gemini 2000 (300 MHz) or a Bruker Avance DPX400 (400 MHz) and were determined in CDCl_3 or $\text{DMSO}-d_6$. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) (0.00 ppm) or solvent peaks as the internal reference. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. Merck-precoated thin layer chromatography (TLC) plates (silica gel 60 F254, 0.25 mm, art. 5715) were used for TLC analysis.

3-[[4-(Azetidin-1-ylcarbonyl)phenyl]oxy]-5-[[1*S*]-2-hydroxy-1-methylethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide

3-[[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy]-5-[[1*S*]-2-hydroxy-1-methylethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (104 mg, 0.215 mmol) was dissolved in methanol (3 mL) and THF (3 mL).

Triethylamine (65 mg, 0.644 mmol) was added and the flask evacuated and purged with nitrogen (3 times). 10% Palladium on carbon (25 mg) was added and the flask further evacuated and finally purged with hydrogen gas.

The reaction mixture was stirred at ambient temperature for 16 hours until completion. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was removed by filtration, the filtrate concentrated *in vacuo* and dissolved in ethyl acetate (10 mL), washed with water ($2 \times 10 \text{ mL}$, saturated aqueous sodium chloride solution (10 mL) and dried (MgSO_4) to give the product (95 mg). ^1H NMR (d_6 -DMSO): 1.22 (d, 3H), 2.24 (m, 2H), 3.51 (m, 2H), 3.76 (s, 3H), 4.02 (m, 2H), 4.30 (br s, 2H), 4.56 (m, 1H), 4.84 (t, 1H), 6.53 (d, 1H), 6.80 (m, 1H), 7.06 (d, 2H), 7.21 (m, 1H), 7.43 (m, 1H), 7.57 (m, 1H), 7.66 (d, 2H), 10.83 (br s, 1H). MS m/z 451 ($\text{M}+\text{H}$)⁺.

3-[[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy]-5-[[1*S*]-2-hydroxy-1-methylethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide

To a mixture of 3-((1*S*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-1-methylethoxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (215 mg, 0.53 mmol) and 1-(3-chloro-4-fluorobenzoyl) azetidine (135 mg, 0.63 mmol) in DMF (2.0 mL) was added potassium carbonate (146 mg, 1.06 mmol) and the stirred mixture heated at 160 °C in a microwave reactor for 120 minutes. The mixture was allowed to reach ambient temperature and pressure then reduced in volume. The residue was purified by column chromatography, eluting with 0-20% methanol in DCM, afforded the product (130 mg). ^1H NMR (CDCl_3): 1.22 (d, 3H), 2.14 (m, 2H), 3.50 (m, 2H), 3.76 (s, 3H), 4.05 (m, 2H), 4.33 (m, 2H), 4.56 (m, 1H), 4.84 (t, 1H), 6.53 (d, 1H), 6.78 (m, 1H), 7.12 (m, 2H), 7.42 (s, 1H), 7.59 (m, 2H), 7.80 (m, 1H), 10.84 (br s, 1H). MS m/z 485/487 ($\text{M}+\text{H}$)⁺.

1-(3-Chloro-4-fluorobenzoyl)azetidine

To a solution of 3-chloro-4-fluorobenzoic acid (1.74 g, 10.0 mmol) in DCM (50 mL) was added oxalyl chloride (1.05 mL, 12.0 mmol) and DMF (1 drop). The mixture was stirred at ambient temperature for 16 hours and the DCM and excess oxalyl chloride evaporated *in vacuo*. The residual acid chloride and azetidine hydrochloride (1.12 g, 12 mmol) were dissolved in DCM (25 mL) and triethylamine (4.18 mL, 30 mmol) added to the mixture, which was stirred at ambient temperature for 2 hours. The DCM was evaporated *in vacuo*, and the residue partitioned between ethyl acetate (100 mL) and 1*N* hydrochloric acid (50 mL). The ethyl acetate layer was washed sequentially with saturated aqueous sodium hydrogen carbonate and brine, dried (MgSO_4), and

evaporated. The residue was crystallized from ethyl acetate / isohexane to give the product (1.64 g). ¹H NMR (CDCl₃): 2.4 (m, 2H), 4.2-4.4 (m, 4H), 7.2 (m, 1H), 7.55 (m, 1H), 7.7 (m, 1H).

3-((1S)-2-[[tert-Butyl(dimethyl)silyl]oxy]-1-methylethoxy)-5-hydroxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide
3-((1S)-2-[[tert-Butyl(dimethyl)silyl]oxy]-1-methylethoxy)-5-(phenylmethyl)oxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide (1.8 g, 3.64 mmol) was dissolved in methanol (50 mL) and the flask evacuated and purged with nitrogen (3 times). 10% Palladium on carbon (0.2 g) was added and the flask further evacuated and purged with hydrogen gas. The reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was removed by filtration, and the filtrate concentrated *in vacuo* to give the product (1.45 g). ¹H NMR (d₆-DMSO): 0.02 (d, 6H), 0.83 (s, 9H), 1.18 (d, 3H), 3.66 (m, 2H), 3.72 (s, 3H), 4.51 (m, 1H), 6.42 (m, 1H), 6.52 (m, 1H), 6.90 (s, 1H), 7.02 (s, 1H), 7.55 (m, 1H), 9.58 (br s, 1H), 10.59 (br s, 1H). MS *m/z* 406 (M+H)⁺

3-((1S)-2-[[tert-Butyl(dimethyl)silyl]oxy]-1-methylethoxy)-5-(phenylmethyl)oxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide

DIPEA (4.06 g, 23.4 mmol) was added to a suspension of 3-((phenylmethyl)oxy)-5-((1S)-2-[[tert-butyl(dimethyl)silyl]oxy]-1-methylethoxy) benzoic acid (2.43 g, 5.84 mmol), 1-methyl-1H-pyrazole-3-amine (0.85 g, 8.76 mmol) and HATU (4.66 g, 12.3 mmol) in DMF (50 mL) and stirred at ambient temperature for 16 hours. The resultant mixture was partially reduced *in vacuo*, poured onto water (100 mL) and extracted with diethyl ether (2 × 50 mL). The extracts were washed with water and brine then dried (MgSO₄), filtered and reduced to an opaque gum which partially crystallized. The crude product was purified by column chromatography, eluting with 0-100% ethyl acetate in isohexane, to give the product as a colourless oil (1.87 g). ¹H NMR (d₆-DMSO): 0.02 (d, 6H), 0.84 (s, 9H), 1.21 (d, 3H), 3.68 (d, 2H), 3.76 (s, 3H), 4.58 (m, 1H), 5.13 (s, 2H), 6.56 (m, 1H), 6.70 (m, 1H), 7.18 (s, 1H), 7.24 (s, 1H), 7.29-7.46 (m, 5H), 7.57 (m, 1H), 10.74 (br s, 1H). MS *m/z* 496 (M+H)⁺

3-((Phenylmethyl)oxy)-5-((1S)-2-[[tert-butyl(dimethyl)silyl]oxy]-1-methylethoxy) benzoic acid

Methyl 3-((1S)-2-[[tert-butyl(dimethyl)silyl]oxy]-1-methylethoxy)-5-[(phenylmethyl)oxy]benzoate (3.0 g, 6.98 mmol) was dissolved in THF (50 mL) and water (10 mL) and lithium hydroxide monohydrate (586 mg, 13.95 mmol) added. The resultant mixture was heated with stirring at 45°C for 2 hours, then at ambient temperature for 16 hours, and at 45°C for a further 4 hours. Water (40 mL) was added and the solvent removed *in vacuo*. The resultant solution was acidified carefully with 1M citric acid (2 equivalents), washed with water and brine then dried (MgSO₄), filtered and evaporated *in vacuo* to give the product as a colourless gum (2.58 g). ¹H NMR (d₆-DMSO): 0.02 (d, 6H), 0.84 (s, 9H), 1.17 (d, 3H), 3.66 (m, 2H), 4.43 (m, 1H), 5.05 (s, 2H), 6.56 (br s, 1H), 7.10 (br s, 1H), 7.17 (br s, 1H), 7.25-7.44 (m, 5H), 7.60 (br s, 1H).

Methyl 3-((1S)-2-[[tert-butyl(dimethyl)silyl]oxy]-1-methylethoxy)-5-[(phenylmethyl)oxy] benzoate

(2R)-1-[[tert-Butyl(dimethyl)silyl]oxy]propan-2-ol (3.31 g, 17.4 mmol) was added to a solution of methyl 3-hydroxy-5-[[phenylmethyl]oxy]benzoate (3.00 g, 11.6 mmol) in THF (50 mL) at 0°C followed by addition of triphenylphosphine (4.57 g, 17.4 mmol) then DIAD (3.43 mL, 17.4 mmol) and the reaction was warmed to RT and stirred for 16 h. The reaction was quenched with water (100 mL) and diethyl ether (400 mL) and the organic layer was separated then dried (MgSO₄) and evaporated. Purification by column chromatography, eluting with 1:15 to 1:5 ethyl acetate:hexane, afforded the product as a colourless oil (4.00 g, 80%). ¹H NMR (CDCl₃): 0.03 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.29 (d, 3H), 3.63 (dd, 1H), 3.78 (dd, 1H), 3.92 (s, 3H), 4.44 (m, 1H), 5.08 (s, 2H), 6.77 (m, 1H), 7.40 (m, 7H)

(2R)-1-[[tert-Butyl(dimethyl)silyl]oxy]propan-2-ol

tert-Butyl(dimethyl)silyl chloride (5.90 g, 39.5 mmol) was added to a solution of (2R)-propane-1,2-diol (3.00 g, 39.5 mmol) in DCM (100 mL) followed by diisopropylethylamine (7.10 g, 55.3 mmol) and the reaction was stirred under argon for 72 h. The reaction was diluted with diethyl ether (500 mL) and water (140 mL) and the organic layer was separated then dried (MgSO₄), filtered and evaporated. Purification by column chromatography, eluting with 1:15 to 1:10 ethyl acetate: hexane, afforded the product as a colourless oil (6.00 g, 80%). ¹H NMR (CDCl₃): 0.10 (m, 6H), 0.92 (s, 9H), 1.14 (d, 3H), 2.42 (d, 1H), 3.38 (dd, 1H), 3.60 (dd, 1H), 3.82 (m, 1H).

Methyl 3-hydroxy-5-[[phenylmethyl]oxy]benzoate

To a stirred solution of methyl 3,5-dihydroxybenzoate (1.00 kg, 5.95 mol) in DMF (6 L) was added potassium carbonate (910 g, 9 mol), and the suspension stirred at ambient temperature under argon. To this was added benzyl bromide (1.44 kg, 8.42 mol) slowly over 1 hour, with a slight exotherm, and the reaction mixture stirred overnight at ambient temperature. The reaction was quenched cautiously with ammonium chloride solution (5 L) followed by water (35 L). The aqueous suspension was extracted with DCM (1 × 3 L and 2 × 5 L). The combined extracts were washed with water (10 L) and dried overnight (MgSO₄). The solution was evaporated *in vacuo*, and the crude product chromatographed in 3 batches (flash column, 3 × 2 kg silica, eluting with a gradient consisting of hexane containing 10% DCM, to neat DCM, to DCM containing 50% ethyl acetate) to eliminate starting material. The crude eluant was further chromatographed in 175 g batches (Amicon HPLC, 5 kg normal-phase silica, eluting with isohexane containing 20% v/v of ethyl acetate) to give the product (323 g,

21%). ¹H NMR (d₆-DMSO): 3.8 (s, 3H), 5.1 (s, 2H), 6.65 (m, 1H), 7.0 (m, 1H), 7.05 (m, 1H), 7.3-7.5 (m, 5H), 9.85 (br s, 1H).

3-[[4-(Azetidin-1-ylcarbonyl)phenyl]oxy]-N-(1-ethyl-1H-pyrazol-3-yl)-5-[[[(1S)-2-hydroxy-1-methylethyl]oxy]benzamide

A solution of 3-[[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy]-N-(1-ethyl-1H-pyrazol-3-yl)-5-[[[(1S)-2-hydroxy-1-methylethyl]oxy]benzamide (246 mg, 0.504 mmol) and triethylamine (0.42 mL, 3.02 mmol) in THF (6 mL) and methanol (6 mL) was evacuated and purged with argon (x3). Palladium on carbon (10% w/w, 52 mg) was added and reaction mixture was evacuated and finally filled with hydrogen gas. The reaction mixture was left to stir at ambient temperature under hydrogen for 2 hours. The catalyst was removed by filtration and mixture partitioned between ethyl acetate and 1M hydrochloric acid solution. The organic phase was dried (MgSO₄) and concentrated *in vacuo* to give the product (170 mg, 73%). ¹H NMR (CDCl₃): 1.25 (d, 3H), 1.45 (t, 3H), 2.35 (m, 2H), 3.75 (m, 2H), 4.1 (q, 2H), 4.3 (m, 4H), 4.6 (m, 1H), 6.8 (m, 2H), 7.0 (d, 2H), 7.1 (s, 1H), 7.3 (s, 1H), 7.35 (s, 1H), 7.65 (d, 2H), 8.6 (s, 1H). MS *m/z* 464 (M+H)⁺

3-[[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy]-N-(1-ethyl-1H-pyrazol-3-yl)-5-[[[(1S)-2-hydroxy-1-methylethyl]oxy]benzamide

A suspension of 3-[[[(1S)-2-[[[(1,1-dimethylethyl)(dimethyl)silyl]oxy]-1-methylethyl]oxy]-N-(1-ethyl-1H-pyrazol-3-yl)-5-hydroxybenzamide (200 mg, 0.477 mmol), potassium carbonate (132 mg, 2.0 equiv) and 1-(3-Chloro-4-fluorobenzoyl)azetidine (123 mg, 1.2 equiv) in acetonitrile (2 mL) was heated in a microwave reactor at 160°C for 15 hours. The reaction mixture was quenched with ethyl acetate / aqueous ammonium chloride solution and the aqueous phase extracted twice with ethyl acetate. The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was then purified by column chromatography, eluting with ethyl acetate, to give product as a white foam (135 mg, 59%). ¹H NMR (CDCl₃): 1.29 (d, 3H), 1.45 (t, 3H), 2.01 (br. s, 1H), 2.38 (m, 2H), 3.75 (m, 2H), 4.07 (q, 2H), 4.26 (br. s, 2H), 4.36 (br. s, 2H), 4.55 (m, 1H), 6.72 (s, 1H), 6.78 (s, 1H), 7.02 (d, 2H), 7.25 (s, 1H), 7.33 (s, 1H), 7.52 (d, 1H), 7.80 (s, 1H), 8.38 (br. s, 1H). MS *m/z* 497 (M-H)⁻

3-[[[(1S)-2-[[[(1,1-Dimethylethyl)(dimethyl)silyl]oxy]-1-methylethyl]oxy]-N-(1-ethyl-1H-pyrazol-3-yl)-5-hydroxybenzamide

A solution of 3-[[[(1S)-2-[[[(1,1-dimethylethyl)(dimethyl)silyl]oxy]-1-methylethyl]oxy]-N-(1-ethyl-1H-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (2.40 g, 4.71 mmol) and THF (80 mL) was evacuated and purged with Argon (x3). Palladium on carbon (10%, 422 mg) was added and reaction mixture was evacuated and finally purged with hydrogen gas. Reaction mixture was left to stir at ambient temperature under hydrogen for 16 hours. Pd/C was removed by filtration and the filtrate concentrated *in vacuo* to give the product as a colourless oil (1.87 g, 95%). ¹H NMR (CDCl₃): 0.01 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 1.27 (d, 3H), 1.49 (t, 3H), 3.64 (dd, 1H), 3.78 (dd, 1H), 4.10 (q, 2H), 4.43 (m, 1H), 6.60 (s, 1H), 6.81 (s, 1H), 6.98 (s, 1H), 7.00 (s, 1H), 7.37 (s, 1H), 8.61 (br. s, 1H). MS *m/z* 420 (M+H)⁺, 418 (M-H)⁻.

3-[[[(1S)-2-[[[(1,1-Dimethylethyl)(dimethyl)silyl]oxy]-1-methylethyl]oxy]-N-(1-ethyl-1H-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide

DIPEA (3.11 mL, 18.03 mmol) was added to a solution of 3-[(phenylmethyl)oxy]-5-((1S)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-1-methylethoxy) benzoic acid (3.00 g, 7.21 mmol), HATU (3.41 g, 9.01 mmol) and 1-ethyl-1H-pyrazol-3-amine (1.20 g, 10.8 mmol) in DMF (10 mL). The resulting mixture was stirred at ambient temperature for 3 hours. The DMF was removed *in vacuo*. The solvent was evaporated and the residue was dissolved in 5% w/v citric acid (50 mL), ethyl acetate (30 mL) and diethyl ether (30 mL) and the organic layer was further washed with sat. aqueous NaHCO₃ (30 mL) and brine (30 mL). The organic layer was separated, then dried (MgSO₄), filtered and evaporated. The residue was purified by column chromatography, eluting with 1:5 to 1:2 ethyl acetate:hexanes, to afford the product as a colourless oil (2.40 g, 65%). ¹H NMR (CDCl₃): 0.01 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.24 (d, 3H), 1.42 (t, 3H), 3.62 (dd, 1H), 3.75 (dd, 1H), 4.01 (q, 2H), 4.40 (m, 1H), 5.03 (s, 2H), 6.67 (s, 1H), 6.78 (s, 1H), 6.97 (s, 1H), 7.04 (s, 1H), 7.33 (m, 6H), 8.38 (br. s, 1H). MS *m/z* 510 (M+H)⁺, 508 (M-H)⁻.

3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1S)-2-hydroxy-1-methylethoxy]-N-(5-methylpyrazin-2-yl)benzamide

DIPEA (0.4 mL, 2.08 mmol) was added to a suspension of 4-(3-[(1S)-2-hydroxy-1-methylethoxy]-5-[(5-methylpyrazin-2-yl)amino]carbonyl)phenoxy)benzoic acid (110 mg, 0.26 mmol), HATU (210 mg, 0.55 mmol) and azetidine hydrochloride (49 mg, 0.52 mmol) in DMF (3 mL) and the mixture stirred at RT for 24 hours. Water (30 mL) was added and the mixture extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine, dried (MgSO₄), and evaporated to a residue which was chromatographed on silica, eluting with 5% methanol in ethyl acetate, to give the product (55 mg). ¹H NMR (CDCl₃): 1.30 (d, 3H), 2.35 (m, 2H), 2.57 (s, 2H), 3.77 (m, 2H), 4.20-4.40 (brm, 4H), 4.57 (m, 1H), 6.80 (m, 1H), 7.03 (d, 2H), 7.12 (m, 1H), 7.30 (m, 1H), 7.64 (d, 2H), 8.11 (s, 1H), 8.42 (brs, 1H), 9.51 (s, 1H); MS *m/z* 463 (M+H)⁺

4-(3-[(1S)-2-Hydroxy-1-methylethoxy]-5-[(5-methylpyrazin-2-yl)amino]carbonyl)phenoxy)benzoic acid

A solution of ethyl 4-(3-[(1*S*)-2-hydroxy-1-methylethoxy]-5-[[5-methylpyrazin-2-yl]amino]carbonyl]phenoxy)benzoate (0.4 g, 0.88 mmol) in THF (16 mL) was added to a solution of lithium hydroxide monohydrate (0.19 g, 4.43 mmol) in water (8 mL). The mixture was stirred at RT for 72 hours and the THF removed *in vacuo*. The aqueous layer was acidified with 1M hydrochloric acid (10 mL), and the solid precipitate collected by filtration, washed with water and dried *in vacuo* to give the product (0.22 g). The material was used without further purification. MS *m/z* 424 (M+H)⁺

Ethyl 4-(3-[(1S)-2-hydroxy-1-methylethoxy]-5-[[5-methylpyrazin-2-yl]amino]carbonyl]phenoxy)benzoate
Caesium carbonate (8.45 g, 26 mmol) was added to a mixture of 3-hydroxy-5-[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide (4 g, 13 mmol) and ethyl 4-fluorobenzoate (2.33 g, 13 mmol) in dimethylacetamide (70 mL) and the stirred mixture heated at 130 °C for 72 hours. The mixture was allowed to cool to RT and ethyl acetate (100 mL) added. The mixture was washed with water (5 × 40mL), brine (40 mL), dried (MgSO₄), filtered and reduced *in vacuo*. The residue was chromatographed on silica, eluting with a gradient of 50% ethyl acetate in isohexane, to give the product (0.18 g). ¹H NMR (CDCl₃): 1.33 (d, 3H), 1.40 (t, 3H), 2.62 (s, 3H), 3.75 (m, 2H), 4.39 (q, 2H), 4.60 (m, 1H), 6.83 (m, 1H), 7.05 (d, 2H), 7.19 (m, 1H), 7.27 (m, 1H), 7.39 (m, 1H), 8.05 (d, 2H), 8.18 (m, 1H), 8.98 (brs, 1H), 9.65 (m, 1H). MS *m/z* 452(M+H)⁺

3-Hydroxy-5-[[[(1S)-2-hydroxy-1-methylethyl]oxy]-N-(5-methylpyrazin-2-yl)benzamide
Trimethylsilyl iodide (6.06 mL, 42.75 mmol) was added to a solution of 3-hydroxy-5-[[[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy]-*N*-(5-methylpyrazin-2-yl)benzamide (2.71 g, 8.55 mmol) in dry acetonitrile (150 mL) and stirred for 24 h. Methanol (30 mL) was added to quench the reaction and stirred for 10 mins. 10% w/v Aqueous sodium thiosulfate pentahydrate (20 mL) was added to the mixture and the organic solvents removed *in vacuo*. The residue was brought to pH5 with 1M hydrochloric acid and ethyl acetate (80 mL) added. A yellow solid (1.4 g) was separated by filtration. The aqueous filtrate was reextracted into ethyl acetate (2 × 80 mL) and the combined organic layers dried (MgSO₄), filtered and the solvents removed *in vacuo*. This residue was combined with the yellow solid obtained above and purified by column chromatography, eluting with 5% to 10% methanol in DCM, to give the product (1.70 g). ¹H NMR (d₆-DMSO): 1.21 (d, 3H), 2.50 (s, 3H), 3.40-3.60 (m, 2H), 4.45 (sex, 1H), 4.80 (t, 1H), 6.50 (s, 1H), 6.97 (s, 1H), 7.08 (s, 1H), 8.32 (s, 1H), 9.21 (s, 2H), 9.63 (s, 1H), 10.80 (brs, 1H). MS *m/z* 304 (M+H)⁺

3-Hydroxy-5-[[[(1S)-1-methyl-2-(methyloxy)ethyl]oxy]-N-(5-methylpyrazin-2-yl)benzamide
3-[[[(1*S*)-1-Methyl-2-(methyloxy)ethyl]oxy]-*N*-(5-methylpyrazin-2-yl)-5-[(phenylmethyl)oxy]benzamide (4.5 g, 11 mmol) was dissolved in ethanol (35 mL) and THF (35 mL) and the flask evacuated and purged with argon (3 times). 10% Palladium on carbon (0.45 g) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at ambient temperature for 20 hours until completion. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was removed by filtration through celite, and the filtrate concentrated *in vacuo* to give the product (3.21 g). ¹H NMR (d₆-DMSO): 1.23 (d, 3H), 2.45 (s, 3H), 3.28 (s, 3H), 3.48 (m, 2H), 4.65 (m, 1H), 6.51 (s, 1H), 6.97 (s, 1H), 7.10 (s, 1H), 8.34 (s, 1H), 9.22 (s, 1H), 9.70 (s, 1H), 10.89 (br s, 1H). MS *m/z* 318 (M+H)⁺

3-[[[(1S)-1-Methyl-2-(methyloxy)ethyl]oxy]-N-(5-methylpyrazin-2-yl)-5-[(phenylmethyl)oxy]benzamide
DMF (2 drops) was added to a solution of 3-[[[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy]-5-[(phenylmethyl)oxy]benzoic acid (6.0 g, 19.0 mmol) and oxalyl chloride (1.99 mL, 22.8 mmol) in DCM (40 mL). The mixture was stirred at ambient temperature for 2 hours and the DCM and excess oxalyl chloride evaporated *in vacuo*. The residual acid chloride was dissolved in DCM and added dropwise to 2-amino-5-methylpyrazine (2.28 g, 19.8 mmol) and pyridine (2.56 mL, 38 mmol) in DCM (40 mL), at 0°C. The mixture was stirred at ambient temperature for 24 hours. The DCM was evaporated *in vacuo*, and the residue partitioned between ethyl acetate (100 mL) and 1N hydrochloric acid (50 mL). The ethyl acetate layer was washed sequentially with saturated aqueous sodium hydrogen carbonate (50 mL) and brine (50 mL), dried (MgSO₄), and evaporated *in vacuo*. The residue was chromatographed on silica, eluting with a gradient of 30-100% ethyl acetate in isohexane, to give the product (7.6 g). ¹H NMR (CDCl₃): 1.32 (d, 3H), 2.55 (s, 3H), 3.40 (s, 3H), 3.50-3.62 (m, 2H), 4.60 (m, 1H), 5.10 (s, 2H), 6.75 (s, 1H), 7.09 (m, 1H), 7.13 (m, 1H), 7.32-7.46 (m, 5H), 8.13 (s, 1H), 8.38 (s, 1H), 9.55 (s, 1H). MS *m/z* 408 (M+H)⁺

3-[(1S)-2-Methoxy-(1-methylethyl)oxy]-5-[[phenylmethyl]oxy]benzoic acid

A solution of methyl 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-[[phenylmethyl]oxy] benzoate (77.4 mmol) in a mixture of THF (232 mL) and methanol (232 mL) was treated with a solution of 2M sodium hydroxide (232 mmol), and the reaction mixture stirred for 4 hours at ambient temperature. The resulting solution was diluted with water (250 mL) and most of the organic solvent removed *in vacuo*. The resulting suspension was washed with diethyl ether (3 × 200 mL) and the organic washings discarded. The resulting aqueous solution was acidified to pH 4 with 2M hydrochloric acid solution and extracted with ethyl acetate (2 × 200 mL). The extracts were combined, washed with brine, dried (MgSO₄), and evaporated to give the product (99% yield). ¹H NMR (d₆-DMSO): 1.20 (d, 3H), 3.46 (m, 2H), 4.64 (m, 1H), 5.15 (s, 2H), 6.83 (app t, 1H), 7.06 (s, 1H), 7.13 (s, 1H), 7.30-7.49 (m, 5H), 12.67 (br s, 1H)

Methyl 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-[[phenylmethyl]oxy]benzoate

To a solution of methyl 3-hydroxy-5-([phenylmethyl]oxy)benzoate (30.0 g; 116 mmol) in DCM (1.2L) was added polymer-supported triphenylphosphine (77.3g of 3 mmol/g loading, 232 mmol). DIAD (24.3 mL 140 mmol) was added dropwise at 0°C, the mixture stirred at 0°C – 5°C for 30 minutes then treated with (*R*)-(-)-1-methoxy-2-propanol (16.7 mL; 174 mmol). The mixture was stirred at ambient temperature for 16 hours, filtered, washing the residue with DCM (2×50 mL). The filtrate and washings were combined, and evaporated to a residue which was stirred in diethyl ether (400 mL), filtered and evaporated to a residue which was chromatographed on silica with 10% ethyl acetate in hexane as eluant to give the desired compound (24.6 g). ¹H NMR (d6-DMSO): 3.26 (s, 3H), 3.44 (m, 2H), 3.82 (s, 3H), 4.63 (m, 1H), 5.14 (s, 2H), 6.85 (s, 1H), 7.05 (s, 1H), 7.11 (s, 1H), 7.30-7.47 (m, 5H).

3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1S)-2-hydroxy-1-methylethoxy]-N-(1-isopropyl-1H-pyrazol-3-yl)benzamide

3-[4-(Azetidin-1-ylcarbonyl)-2-chlorophenoxy]-5-[(1S)-2-hydroxy-1-methylethoxy]-N-(1-isopropyl-1H-pyrazol-3-yl)benzamide (0.33 g, 0.644 mmol) was dissolved in methanol (4 mL) and THF (4 mL) and the flask evacuated and purged with argon (3 times). 10% Palladium on carbon (0.033 g) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at ambient temperature for 20 hours. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was removed by filtration through celite, and the filtrate concentrated *in vacuo*. The residue was chromatographed on silica eluting with a gradient of 0-100% ethyl acetate in isohexane to give the product (0.15 g). ¹H NMR (CDCl₃): 1.30 (d, 3H), 1.45 (d, 6H), 2.20 (brs, 1H), 2.35 (quin, 2H), 3.71 (m, 2H), 4.20-4.40 (brm, 5H), 4.54 (m, 1H), 6.77 (m, 2H), 7.00 (d, 2H), 7.08 (m, 1H), 7.23 (m, 1H), 7.34 (m, 1H), 7.63 (d, 2H), 8.49 (brs, 1H); MS *m/z* 479 (M+H)⁺

3-[4-(Azetidin-1-ylcarbonyl)-2-chlorophenoxy]-5-[(1S)-2-hydroxy-1-methylethoxy]-N-(1-isopropyl-1H-pyrazol-3-yl)benzamide

Potassium carbonate (182 mg, 1.32 mmol) was added to a mixture of 3-((1S)-2-([*tert*-butyl(dimethyl)silyl]oxy)-1-methylethoxy)-5-hydroxy-N-(1-isopropyl-1H-pyrazol-3-yl)benzamide (350 mg, 0.81 mmol) and 1-(3-Chloro-4-fluorobenzoyl)azetidine (181 mg, 0.85 mmol) in acetonitrile (5 mL) and the stirred mixture heated at 160°C in a microwave reactor for 15 hours. The mixture was allowed to reach ambient temperature and pressure and reduced *in vacuo*. The residual oil was partitioned between ethyl acetate (50 mL) and water (50 mL). The ethyl acetate layer was separated, washed with brine, dried (MgSO₄) and evaporated to a residue which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the product (331 mg). ¹H NMR (CDCl₃): 1.28 (d, 3H), 1.46 (d, 6H), 2.05 (brs, 1H), 2.38 (quin, 2H), 3.75 (m, 2H), 4.20-4.40 (brm, 5H), 4.55 (m, 1H), 6.71 (m, 1H), 7.01 (m, 2H), 7.25 (m, 2H), 7.31 (m, 1H), 7.51 (d, 1H), 7.79 (d, 1H), 8.39 (brs, 1H). MS *m/z* 513, 515 (M+H)⁺

3-((1S)-2-([tert-Butyl(dimethyl)silyl]oxy)-1-methylethoxy)-5-hydroxy-N-(1-isopropyl-1H-pyrazol-3-yl)benzamide

A solution of 3-(benzyloxy)-5-((1S)-2-([*tert*-butyl(dimethyl)silyl]oxy)-1-methylethoxy)-N-(1-isopropyl-1H-pyrazol-3-yl)benzamide (1.97 g, 3.77 mmol) and THF (70 mL) was evacuated and purged three times with argon. Palladium on carbon (10% w/w, 400 mg) was added and reaction mixture was evacuated and finally purged with hydrogen gas. Reaction mixture was left to stir at ambient temperature under hydrogen for 16 hours. Pd/C was removed by filtration and concentrated *in vacuo* to give the product as a colourless oil (1.58 g, 97%). ¹H NMR (CDCl₃): 0.02 (s, 3H), 0.04 (s, 3H), 0.85 (s, 9H), 1.27 (d, 3H), 1.53 (s, 3H), 1.55 (s, 3H), 3.63 (dd, 1H), 3.77 (dd, 1H), 4.41 (m, 1H), 6.60 (s, 1H), 6.81 (s, 1H), 7.00 (s, 1H), 7.07 (s, 1H), 7.38 (s, 1H), 8.78 (br. s, 1H). MS *m/z* 434 (M+H)⁺, 432 (M-H)⁻.

3-(Benzyloxy)-5-((1S)-2-([tert-butyl(dimethyl)silyl]oxy)-1-methylethoxy)-N-(1-isopropyl-1H-pyrazol-3-yl)benzamide

DIPEA (3.11 mL, 18.03 mmol) was added to a solution of 3-([phenylmethyl]oxy)-5-((1S)-2-([*tert*-butyl(dimethyl)silyl]oxy)-1-methylethoxy) benzoic acid (3.00 g, 7.21 mmol), HATU (3.12 g, 8.21 mmol) and 1-isopropyl-1H-pyrazol-3-amine (1.13 g, 9.01 mmol) in DMF (10 mL). The resulting mixture was stirred at ambient temperature for 16 hours. The DMF was removed *in vacuo*. The solvent was evaporated and the residue was dissolved in 5% w/v citric acid (50 mL) and ethyl acetate (30 mL) and diethyl ether (30 mL) and the organic layer was further washed with sat. aqueous sodium bicarbonate solution (30 mL) and brine (30 mL). The organic layer was separated, then dried (MgSO₄), filtered and evaporated. The residue was purified by column chromatography, eluting with 1:4 to 1:3 ethyl acetate:hexanes, afforded the product as a colourless oil (2.40 g, 65%). ¹H NMR (CDCl₃): 0.01 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 1.24 (d, 3H), 1.49 (s, 3H), 1.51 (s, 3H), 3.64 (dd, 1H), 3.78 (dd, 1H), 4.39 (m, 1H), 4.46 (m, 1H), 5.09 (s, 2H), 6.70 (s, 1H), 6.78 (s, 1H), 7.02 (s, 1H), 7.08 (s, 1H), 7.35 (m, 6H), 8.32 (br. s, 1H). MS *m/z* 524 (M+H)⁺, 522 (M-H)⁻.

1-Isopropyl-1H-pyrazol-3-amine

2-Chloroacrylonitrile (3.41 mL, 42.59 mmol) was added at RT to a stirring solution of *N*-isopropylhydrazine hydrochloride (4.71 g, 42.6 mmol), potassium carbonate (11.8 g, 85.2 mmol) in water (50 mL). The reaction was warmed to 45 °C for 4 hours before cooling back to RT. The aqueous layer was then extracted with ethyl

acetate (5 × 30 mL) and the combined organic layers were dried (MgSO₄), treated with activated charcoal, filtered and evaporated. The residue was purified by chromatography, eluting with 67%-100% ethyl acetate in hexanes, to afford the product (3.08 g, 58%) as a 6:1 mixture of authentic product to regioisomeric product as an oil. The material was used without further purification. ¹H NMR (CDCl₃): 1.42 (m, 6H), 3.58 (br. s, 2H), 4.25 (sept, 1H), 5.58 (d, 1H), 7.15 (d, 1H).

3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1S)-2-hydroxy-1-methylethoxy]-N-1H-pyrazol-3-ylbenzamide

A suspension of 4-{3-[(1S)-2-hydroxy-1-methylethoxy]-5-[(1H-pyrazol-3-ylamino)carbonyl]phenoxy}benzoic acid (130 mg, 0.327 mmol), HATU (156 mg, 0.41 mmol), azetidine hydrochloride (38 mg, 0.41 mmol) and DIPEA (0.143 mL; 0.82 mmol) in DMF (2 mL) was stirred at ambient temperature for 16 hours. Water was added to the reaction mixture and it was extracted into ethyl acetate (3 × 30 mL). The organic phases were combined, washed with brine solution and dried (MgSO₄). The filtrate was concentrated *in vacuo* and the residue purified by column chromatography, eluting with 0-50% methanol in DCM, to give the product as a colourless foam (65 mg, 46%). ¹H NMR (d₆-DMSO): 1.2 (d, 3H), 2.2 (s, 2H), 2.95 (s, 6H), 3.2 (s, 3H), 3.5 (m, 2H), 4.0 (m, 2H), 4.3 (m, 2H), 4.6 (m, 1H), 4.80 (t, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 7.05 (d, 2H), 7.2 (s, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 7.65 (d, 2H), 10.8 (s, 1H). MS *m/z* 437 (M+H)⁺, 435 (M-H)⁺.

4-{3-[(1S)-2-Hydroxy-1-methylethoxy]-5-[(1H-pyrazol-3-ylamino)carbonyl]phenoxy}benzoic acid

A solution of ethyl 4-{3-[(1S)-2-hydroxy-1-methylethoxy]-5-[(1H-pyrazol-3-ylamino)carbonyl]phenoxy}benzoate (175 mg, 0.4 mmol) in THF (5 mL) and water (1 mL) was treated with 1N sodium hydroxide solution (3 mL) and the reaction stirred at RT for 16 hours. The solvent was removed *in vacuo* and the pH adjusted to 3-4 by the addition of 1N citric acid solution. The white precipitate was collected by filtration and dried *in vacuo* to give the product as a white solid (138 mg, 85%). ¹H NMR (d₆-DMSO): 1.2 (d, 3H), 3.25 (s, 3H obscured by water peak), 3.5 (m, 2H), 4.55 (m, 1H), 4.80 (t, 1H), 6.6 (d, 1H), 6.8 (app s, 1H), 7.1 (d, 2H), 7.2 (s, 1H), 7.4 (s, 1H), 7.6 (d, 1H), 8.0 (d, 2H), 10.8 (s, 1H). MS *m/z* 398 (M+H)⁺, 396 (M-H)⁺.

Ethyl 4-{3-[(1S)-2-hydroxy-1-methylethoxy]-5-[(1H-pyrazol-3-ylamino)carbonyl]phenoxy}benzoate

Trimethylsilyl iodide (0.27 mL) was added dropwise under argon to a solution of *tert*-butyl 3-({3-[4-(ethoxycarbonyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]benzoyl}amino)-1H-pyrazole-1-carboxylate (167 mg, 0.38 mmol) in acetonitrile (5 mL) and stirred at ambient temperature for 16 hours. Sodium thiosulfate solution was added to quench the reaction and the reaction mixture was extracted into ethyl acetate (3 × 25 mL). Organic phases were combined and dried (MgSO₄) and the filtrate was concentrated *in vacuo* to give a clear oil (180 mg), which was not purified further. MS *m/z* 426 (M+H)⁺, 424 (M-H)⁺.

tert-Butyl 3-({3-[4-(ethoxycarbonyl)phenoxy]-5-[(1S)-2-methoxy-1-methylethoxy]benzoyl}amino)-1H-pyrazole-1-carboxylate

tert-Butyl 3-({3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]benzoyl}amino)-1H-pyrazole-1-carboxylate (391 mg, 1 mmol), ethyl-4-boronic acid benzoate (388 mg, 2.0 equiv), copper (II) acetate (363 mg, 2.0 equiv) and triethylamine (0.7 mL; 5.0 equiv) were suspended in dry DCM over freshly activated powdered 4A molecular sieves (ca. 1 g) for 7 hours under an ambient atmosphere. Reaction mixture filtered through diatomaceous earth was washed with DCM (x3). Filtrate concentrated *in vacuo*, taken up in ethyl acetate and washed with 1M hydrochloric acid, saturated sodium hydrogen carbonate, saturated brine and dried (MgSO₄) and evaporated. The residue was purified by column chromatography, eluting with 0-50% ethyl acetate in isohexane to give the product (210 mg, 39%). ¹H NMR (CDCl₃): 1.3 (d, 3H), 1.4 (t, 3H), 1.6 (s, 9H), 3.4 (s, 3H), 3.5 (m, 2H), 4.35 (q, 2H), 4.5 (m, 1H), 6.8 (s, 1H), 7.0 (d, 2H), 7.05 (s, 2H), 7.2 (s, 1H), 8.0 (s, 1H), 8.05 (d, 2H), 9.2 (s, br, 1H). MS *m/z* 440 (M+H)⁺.

tert-Butyl 3-({3-hydroxy-5-[(1S)-2-methoxy-1-methylethoxy]benzoyl}amino)-1H-pyrazole-1-carboxylate

A solution of *tert*-butyl 3-({3-(benzyloxy)-5-[(1S)-2-methoxy-1-methylethoxy]benzoyl}amino)-1H-pyrazole-1-carboxylate (23 g, 47.8 mmol) in THF (140 mL) and ethanol (140 mL) was evacuated and purged three times with nitrogen. 10% Palladium on carbon (2.3 g, 10% w/w) was added and reaction mixture was evacuated and finally purged with hydrogen gas. The reaction mixture was left to stir at ambient temperature under a hydrogen balloon for 16 hours. Pd/C was filtered through diatomaceous earth and the filtrate concentrated *in vacuo* to give the product as a white foam (18 g, 97%). ¹H NMR (d₆-DMSO): 1.2 (d, 3H), 1.55 (s, 9H), 3.25 (s, 3H obscured by water peak), 3.4-3.5 (m, 2H), 4.7 (m, 1H), 6.5 (s, 1H), 6.95 (d, 1H), 7.0 (s, 1H), 7.1 (s, 1H), 8.2 (d, 1H), 9.65 (s, 1H), 11.2 (s, br, 1H). MS *m/z* 392 (M+H)⁺.

tert-Butyl 3-({3-(benzyloxy)-5-[(1S)-2-methoxy-1-methylethoxy]benzoyl}amino)-1H-pyrazole-1-carboxylate

To a suspension of 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-[[phenylmethyl]oxy]benzoic acid (20.7 g, 65.6 mmol), HATU (31.2 g, 82.0 mmol) and *tert*-butyl 3-amino-1H-pyrazole-1-carboxylate (15.0 g, 82.0 mmol) in DMF (30 mL) was added DIPEA (28.5 mL, 164 mmol) and reaction mixture stirred for 16 hours at ambient temperature. Water (250 mL) was then added to reaction mixture and extracted into diethyl ether (3x150 mL). The organic layer was washed with saturated brine solution, dried (MgSO₄) and evaporated. The residue crystallised on standing. These crystals were ashed with isohexane to give product (23.4 g, 73%). *m/z* 482 (M+H)⁺.

tert-Butyl 3-amino-1H-pyrazole-1-carboxylate

1*H*-Pyrazol-3-amine (428 mg, 5.15 mmol) was dissolved in DMF (5 mL) at 0 °C and treated with sodium hydride (206 mg, 5.15 mmol) followed by stirring for a further 30 min. Warmed di-*tert*-butyl dicarbonate (1.12 g, 5.15 mmol) was then slowly added via syringe over 5 min and the reaction was allowed to warm to RT and stirred for a further 2 h. The reaction mixture added to saturated aqueous sodium hydrogencarbonate (50 mL) and ethyl acetate (100 mL). The organic layer was separated then dried (MgSO₄), filtered and evaporated. Purification by column chromatography (eluting with 1:1 ethyl acetate:hexanes to neat ethyl acetate) afforded the product as a white solid (117 mg, 18%). ¹H NMR (CDCl₃): 1.62 (s, 9H), 4.00 (br s, 2H), 5.81 (d, 1H), 7.82 (d, 1H).

*3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-hydroxy-1-methylethoxy]-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide*

10% Hydrochloric acid (2 mL) was added to a solution of 3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-((1*S*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-1-methylethoxy)-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide (580 mg, 1.0 mmol) in methanol (20 mL). The reaction was stirred at ambient temperature for 1 hour, saturated sodium bicarbonate solution added and the methanol evaporated. The aqueous residue was taken to pH2 by addition of hydrochloric acid (2N) and extracted with ethyl acetate. The extracts were combined, washed with brine, dried (MgSO₄), filtered, and evaporated *in vacuo* to give the crude product (275 mg) which was recrystallised from ethyl acetate (mp 159-160°C). ¹H NMR □ (CDCl₃): 1.3 (d, 3H), 2.4 (m, 2H), 2.5 (s, 3H), 3.75 (d, 2H), 4.2 – 4.4 (m, 4H), 4.6 (m, 1H), 6.8 (s, 1H), 7.0 (d, 1H), 7.2 (s, 1H), 7.25 (s, 1H), 7.3 (s, 1H), 7.65 (d, 2H). MS *m/z* 468 (M+H)⁺.

*3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-[[tert-butyl(dimethyl)silyl]oxy]-1-methylethoxy]-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide*

DIPEA (0.5 mL, 3.0 mmol) was added to a suspension of 3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-((1*S*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-1-methylethoxy)benzoic acid (485 mg, 1.0 mmol), HATU (495 mg, 1.3 mmol) and 5-amino-3-methyl-1,2,4 thiadiazole (345 mg, 3.0 mmol) in DMF (6 mL). The resulting mixture was stirred at ambient temperature for 16 hours, water (90 mL) was added and the mixture extracted with ethyl acetate. The organic layer was washed with brine, dried (MgSO₄), filtered and evaporated *in vacuo* to give the crude product which was chromatographed on silica, eluting with 75% ethyl acetate in isohexane, to give the product (580 mg). MS *m/z* 583 (M+H)⁺.

*3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1*S*)-2-[[tert-butyl(dimethyl)silyl]oxy]-1-methylethoxy]benzoic acid*

3-[4-(Azetidin-1-ylcarbonyl)-2-chlorophenoxy]-5-((1*S*)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-1-methylethoxy)benzoic acid (3.08 g, 5.93 mmol) was dissolved in methanol (30 mL) and THF (30 mL). Triethylamine (2 mL) was added and the flask evacuated and purged three times with nitrogen. 10% Palladium on carbon (200 mg) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at ambient temperature for 16 hours LC-MS showed only 26% required product. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was removed by filtration, and the flask containing the filtrate evacuated and purged with nitrogen (3 times). Fresh 10% Palladium on carbon (200 mg) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at ambient temperature for a further 16 hours LC-MS showed complete reaction. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was filtered off, the filtrate concentrated *in vacuo* and dissolved in diethylether (50 mL), washed with water (20 mL), 1N citric acid (20 mL), saturated aqueous sodium chloride solution (20 mL) and dried (MgSO₄) to give the product (2.16 g). ¹H NMR (CDCl₃): 0.0 (d, 6H), 0.85 (s, 9H), 1.25 (d, 3H), 2.35 (m, 2H), 3.6-3.8 (m, 2H), 4.15-4.4 (d, 4H), 4.45 (m, 1H), 6.8 (s, 1H), 7.0 (d, 2H), 7.25 (s, 1H), 7.4 (s, 1H), 7.65 (d, 2H). MS *m/z* 486 (M+H)⁺.

*3-[4-(Azetidin-1-ylcarbonyl)-2-chlorophenoxy]-5-[(1*S*)-2-[[tert-butyl(dimethyl)silyl]oxy]-1-methylethoxy]benzoic acid*

To a stirred solution of 3-[4-(Azetidin-1-ylcarbonyl)-2-chlorophenoxy]-5-((1*S*)-2-hydroxy-1-methylethoxy)benzoic acid (5.3g, 13 mmol) and imidazole (8.9g, 130 mmol) in DMF (65 mL) was added *tert*-butyldimethylsilyl chloride (11.8g, 7.8 mmol) The mixture was stirred at ambient temperature for 24 hours, poured onto water (975 mL) and extracted with ether (3 × 250 mL). The combined ether extracts were washed with brine (100 mL), dried (MgSO₄) and evaporated *in vacuo* to a residue which was taken up in ether (50 mL) and treated with saturated sodium hydrogen carbonate solution (50 mL). The mixture was stirred at ambient temperature for 30 minutes, the aqueous layer separated and taken to pH6 with concentrated hydrochloric acid, extracted with ether (3 × 50 mL), the combined ether extracts washed with brine (25 mL), dried (MgSO₄) and evaporated *in vacuo* to a residue which was chromatographed on silica with 0 - 20% methanol in ethyl acetate as eluant to give the product (1.7g). ¹H NMR (CDCl₃): 0.00 (s, 3H), 0.03 (s, 3H), 0.94 (s, 9H), 1.28 (d, 3H), 2.35 (quin, 2H), 3.60-3.80 (m, 2H), 4.20-4.38 (brm, 4H), 4.46 (m, 1H), 6.75 (s, 1H), 6.92 (d, 1H), 7.21 (m, 1H), 7.38 (m, 1H), 7.44 (m, 1H), 7.70 (s, 1H). MS *m/z* 520 (M+H)⁺.

*3-[4-(Azetidin-1-ylcarbonyl)-2-chlorophenoxy]-5-[(1*S*)-2-hydroxy-1-methylethoxy]benzoic acid*

To a stirred solution of methyl-3-[4-(Azetidin-1-ylcarbonyl)-2-chlorophenoxy]-5-((1*S*)-2-hydroxy-1-methylethoxy)benzoate (2.9g, 6.91 mmol) in THF (30 mL) was added a solution of lithium hydroxide

monohydrate (290mg, 6.91 mmol) in water (15 mL) and the mixture stirred at ambient temperature for 24 hours. The THF was evaporated *in vacuo*, the aqueous residue acidified with citric acid and extracted with ethyl acetate (3 × 25 mL), the combined ethyl acetate extracts washed with brine, dried (MgSO₄) and evaporated *in vacuo* to give the product (1.8g). ¹H NMR (CDCl₃): 1.35(d, 3H), 2.38 (quin, 2H), 3.75 (m, 2H), 4.30 (br m, 4H), 4.52 (m, 1H), 6.79 (m, 1H), 6.98 (d, 1H), 7.24 (m, 1H), 7.41 (m, 1H), 7.50 (dd, 1H), 7.78 (m, 1H). MS *m/z* 406 (M+H)⁺.

Methyl-3-[4-(Azetidin-1-ylcarbonyl)-2-chlorophenoxy]-5-((1S)-2-hydroxy-1-methylethoxy)benzoate

Potassium carbonate (4.14g, 30.0 mmol) was added to a mixture of methyl-3-((1S)-2-hydroxy-1-methylethoxy)-5-hydroxy-benzoate (3.4g, 15.0 mmol) and 1-(3-Chloro-4-fluorobenzoyl)azetidine (3.2g, 15.0 mmol) in DMA (70 mL) and the stirred mixture heated at 120°C for 72 hours. The mixture was allowed to cool to ambient temperature, poured onto water (1.05L) and extracted with ethyl acetate (3 × 250 mL). The combined ethyl acetate extracts were washed with brine, dried (MgSO₄), and evaporated to give the product which was used without further purification (5.9g). MS *m/z* 420 (M+H)⁺.

Methyl-3-((1S)-2-hydroxy-1-methylethoxy)-5-hydroxy-benzoate

To a stirred solution of methyl-3-((1S)-2-methoxy-1-methylethoxy)-5-hydroxy-benzoate (11.6g, 48.3 mmol) in acetonitrile (240 mL) was added iodotrimethylsilane (35.0 mL, 242 mmol) and the mixture stirred at ambient temperature for 4 hours. Methanol (100 mL) was added and stirring continued for a further 30 minutes, then the mixture treated with saturated potassium carbonate solution (100 mL) and saturated sodium thiosulphate (100 mL) and stirred for a further 20 minutes. The acetonitrile and methanol were evaporated *in vacuo*, the aqueous residue acidified with 2M hydrochloric acid and extracted with ethyl acetate (3 × 100 mL). The combined ethyl acetate extracts were washed with brine, dried (MgSO₄) and evaporated *in vacuo* to a residue which was chromatographed on silica with 0%-100% ethyl acetate in hexane as eluant to give the product (6.1g). ¹H NMR (d₆-DMSO): 1.18 (d, 3H), 3.4-3.55 (m, 2H), 3.8 (s, 3H), 4.35 (sex, 1H), 4.8 (t, 1H), 6.57 (m, 1H), 6.90 (m, 2H), 9.75 (s, 1H); *m/z* 225 (M-H)⁻.

Methyl-3-((1S)-2-methoxy-1-methylethoxy)-5-hydroxy-benzoate

A solution of methyl 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-[[phenylmethyl]oxy]benzoate (50.7 g, 154 mmol) in THF (200 mL) and ethanol (200 mL) was evacuated and purged three times with nitrogen. 10% Palladium on carbon (5.0 g, 10% w/w) was added and reaction mixture was evacuated and finally purged with hydrogen gas. Reaction mixture was left to stir at ambient temperature under a hydrogen balloon for 2 days. The catalyst was filtered through diatomaceous earth and the filtrate concentrated *in vacuo* to give the product (38.0 g). ¹H NMR □ (CDCl₃): 1.32(d, 3H), 3.41 (s, 3H), 3.55-3.65 (m, 2H), 3.92 (s, 3H), 4.60 (m, 1H), 6.65 (m, 1H), 7.15 (m, 1H), 7.19 (m, 1H); *m/z* 239 (M-H)⁻.

3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-[(1S)-2-hydroxy-1-methylethoxy]-N-1,3-thiazol-2-ylbenzamide 5

10% Hydrochloric acid (1 mL) was added to a solution of 3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-((1S)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-1-methylethoxy)-N-1,3-thiazol-2-ylbenzamide (284 mg, 0.5 mmol) in methanol (10 mL). The reaction was stirred at RT for 1 hour, saturated sodium bicarbonate solution added and the methanol evaporated. The aqueous residue was taken to pH 2 and extracted with ethyl acetate. The extracts were combined, washed with brine, dried (MgSO₄), filtered, and evaporated *in vacuo* to give the crude product which was chromatographed on silica, eluting with 1% methanol in ethyl acetate, to give the product (113 mg). ¹H NMR (CDCl₃): 1.3 (d, 3H), 2.4 (m, 2H), 3.75 (d, 2H), 4.2 – 4.4 (m, 4H), 4.6 (m, 1H), 6.8 (s, 1H), 7.0 (m, 3H), 7.2 (s, 1H), 7.3 (d, 1H), 7.4 (s, 1H), 7.65 (d, 2H). *m/z* 454 (M+H)⁺.

3-[4-(Azetidin-1-ylcarbonyl)phenoxy]-5-((1S)-2-[[tert-butyl(dimethyl)silyl]oxy]-1-methylethoxy)-N-1,3-thiazol-2-ylbenzamide

DIPEA (0.25 mL, 1.5 mmol) was added to a suspension of 3-[4-(azetidin-1-ylcarbonyl)phenoxy]-5-((1S)-2-[[*tert*-butyl(dimethyl)silyl]oxy]-1-methylethoxy)benzoic acid (243 mg, 0.5 mmol), HATU (248 mg, 0.65 mmol) and 2-amino-1,3 thiazole (150 mg, 1.5 mmol) in DMF (3 mL). The resulting mixture was stirred at RT for 16 hours, water (45 mL) was added and the mixture extracted with ethyl acetate. The extracts were combined, washed with brine, dried (MgSO₄), filtered and evaporated *in vacuo* to give the crude product which was chromatographed on silica, eluting with 75% ethyl acetate in isohexane, to give the product (284 mg). MS *m/z* 568 (M+H)⁺.

3-[[4-(Azetidin-1-ylcarbonyl)phenyl]oxy]-5-[(1S)-2-methoxy-1-methylethyl]oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide

To a suspension of 4-[(3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-[(1-methyl-1H-pyrazol-3-yl)amino]carbonyl)phenyl]oxy]benzoic acid (212 mg), HATU (400 mg) and azetidine hydrochloride (98 mg) in DMF (10mL), was added DIPEA (0.35mL) and the mixture stirred at ambient temperature for 24 hours. Water (30mL) was added and the mixture extracted with ethyl acetate (3 × 15mL). The combined organic extracts were washed with brine, dried (MgSO₄), and evaporated to a residue which was chromatographed on silica eluting with a gradient of 0-50% methanol in ethyl acetate to give the product (130 mg). ¹H NMR (CDCl₃): 1.30 (d, 3H), 2.38 (m, 2H), 3.39 (s, 3H), 3.48-3.60 (m, 2H), 3.78 (s, 3H), 4.20-4.40 (m, 4H), 4.58 (m, 1H), 6.78 (m, 2H), 7.00 (d, 2H), 7.08 (s, 1H), 7.22 (s, 1H), 7.28 (s, 1H), 7.63 (d, 2H), 8.72 (s, 1H). MS *m/z* 464 (M+H)⁺.

4-[(3-[(1S)-2-Methoxy-(1-methylethyl)oxy])-5-[(1-methyl-1H-pyrazol-3-yl)amino]carbonyl]phenyl]oxy]benzoic acid

A solution of ethyl 4-[(3-[(1S)-2-methoxy-(1-methylethyl)oxy])-5-[(1-methyl-1H-pyrazol-3-yl)amino]carbonyl]phenyl]oxy]benzoate (5.45g) in THF (200 mL) was added to a solution of lithium hydroxide monohydrate (2.52g) in water (100mL). The mixture was stirred at ambient temperature for 48 hours and the THF removed *in vacuo*. The aqueous layer was acidified with 1M hydrochloric acid (60mL), and the solid precipitate collected by filtration, washed with water and dried *in vacuo* to give the product (5g). ¹H NMR (d₆-DMSO): 1.22 (d, 3H), 3.26 (s, 3H), 3.45 (m, 2H), 3.75 (s, 3H), 4.71 (m, 1H), 6.51 (m, 1H), 6.84 (m, 1H), 7.08 (d, 2H), 7.24 (m, 1H), 7.44 (s, 1H), 7.57 (m, 1H), 7.95 (d, 2H), 10.84 (br s, 1H), 12.80 (br s, 1H); MS *m/z* 426 (M+H)⁺.

Ethyl 4-[(3-[(1S)-2-methoxy-(1-methylethyl)oxy])-5-[(1-methyl-1H-pyrazol-3-yl)amino]carbonyl]phenyl]oxy]benzoate

A solution of 3-hydroxy-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide (10.0g), 4-ethoxycarbonylphenylboronic acid (9.4g), copper (II) acetate (9g), triethylamine (23mL) and freshly activated 4Å molecular sieves (36g) in dichloromethane (500mL) was stirred at ambient temperature and under ambient atmosphere for 2 days. The reaction mixture was filtered through celite, washed with dichloromethane (2 × 50mL), the dichloromethane removed *in vacuo* and the residual oil partitioned between ethyl acetate (500mL) and 1M hydrochloric acid (200mL). The ethyl acetate layer was separated, washed sequentially with aqueous sodium hydrogen carbonate solution and brine, dried (MgSO₄), and evaporated to a residue which was chromatographed on silica eluting with a gradient of 50-100% ethyl acetate in isohexane to give the product (5.47g). ¹H NMR □ (CDCl₃): 1.3 (m, 3H), 1.41 (t, 3H), 3.39 (s, 3H), 3.49 (m, 1H), 3.58 (m, 1H), 3.78 (s, 3H), 4.38 (q, 2H), 4.58 (m, 1H), 6.79 (m, 2H), 7.01-7.1 (m, 3H), 7.26 (m, 2H), 8.01 (m, 2H), 8.61 (br s, 1H); MS *m/z* 454 (M+H)⁺.

3-Hydroxy-5-[(1S)-2-methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide

To a solution of 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (7.07g) in THF (50mL) and methanol (50mL) was added 10% palladium on carbon (727mg) as a slurry in THF (1 mL) and methanol (1 mL). The mixture was placed under vacuum and stirred under an atmosphere of hydrogen for 70 hours. The mixture was filtered through diatomaceous earth, and the diatomaceous earth washed with methanol (2 × 100 mL), followed by evaporation *in vacuo*. The residues were dissolved in ethyl acetate (10 mL), treated with isohexane (40 mL), the solid collected by filtration and washed with isohexane (50 mL) to afford the product (5.17g) which was used without further purification. ¹H NMR (d₆-DMSO): 1.22 (d, 3H), 3.28 (s, 3H, obscured by water), 3.38-3.53 (m, 2H), 3.76 (s, 3H), 4.65 (m, 1H), 6.44 (m, 1H), 6.54 (m, 1H), 6.93 (s, 1H), 7.04 (s, 1H), 7.57 (m, 1H), 9.63 (br s, 1H), 10.60 (s, 1H). MS *m/z* 306 (M+H)⁺, 304 (M-H)⁻.

3-[(1S)-2-methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide

A solution of 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid (8.73g) in dichloromethane (150 mL) was cooled to 0 °C. Oxalyl chloride (4.81 mL) and DMF (0.15mL) were slowly added with stirring. The mixture was allowed to warm to ambient temperature and stirred for 16 hours, following which the organics were removed *in vacuo*, and the residues azeotroped with toluene (75mL). The crude material was dissolved in dichloromethane (75 mL) and slowly added to a stirred suspension of 1-methyl-1H-pyrazol-3-amine (3.35g) and diisopropylethylamine (14.4 mL) in dichloromethane (75 mL). The mixture was stirred at ambient temperature for 18 hours before the organics were evaporated *in vacuo* and the residue dissolved in ethyl acetate (150 mL). The organics were washed with 1M aqueous hydrochloric acid (100 mL) and brine (50 mL), and dried (MgSO₄), before evaporation *in vacuo* to give crude material. This was chromatographed (eluting with 30 to 90% ethyl acetate in isohexane), and evaporated *in vacuo* to afford the product (7.07g). ¹H NMR (d₆-DMSO): 1.23 (d, 3H), 3.28 (s, 3H, obscured by water), 3.40-3.52 (m, 2H), 3.77 (s, 3H), 4.70 (m, 1H), 5.03 (s, 2H), 6.56 (m, 1H), 6.71 (m, 1H), 7.18 (s, 1H), 7.24 (s, 1H), 7.32-7.47 (br m, 5H), 7.58 (m, 1H), 10.73 (s, 1H). MS *m/z* 396 (M+H)⁺.

3-[[4-(Azetidin-1-ylcarbonyl)phenyl]oxy]-5-(1-methylethoxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide

To a suspension of 4-[(3-[(1-methylethyl)oxy])-5-[(1-methyl-1H-pyrazol-3-yl)amino]carbonyl]phenyl]oxy]benzoic acid (300 mg), HATU (600 mg) and azetidine hydrochloride (150 mg) in DMF (5mL), was added DIPEA (0.56mL) and the mixture stirred at ambient temperature for 24 hours. Water (30 mL) was added and the mixture extracted with ethyl acetate (3 × 15mL). The combined organic extracts were washed with brine, dried (MgSO₄), and evaporated to a residue which was chromatographed on silica eluting with ethyl acetate to give the product (120 mg). ¹H NMR (d₆-DMSO): 1.30 (d, 6H), 2.25 (m, 2H), 3.78 (s, 3H), 4.05 (m, 2H), 4.43 (m, 2H), 4.75 (sept, 1H), 6.58 (s, 1H), 7.09 (d, 2H), 7.23 (s, 1H), 7.44 (s, 1H), 7.60 (s, 1H), 7.69 (d, 2H), 10.80 (br, 1H). MS *m/z* 435 (M+H)⁺.

4-[(3-[(1-methylethyl)oxy])-5-[(1-methyl-1H-pyrazol-3-yl)amino]carbonyl]phenyl]oxy]benzoic acid

A solution of ethyl 4-[(3-[(1-methylethyl)oxy])-5-[(1-methyl-1H-pyrazol-3-yl)amino]carbonyl]phenyl]oxy]benzoate (14.74g) in THF (580 mL) was added to a solution of lithium

hydroxide monohydrate (7.31g) in water (290mL). The mixture was stirred at ambient temperature for 48 hours and the THF removed *in vacuo*. The aqueous layer was acidified with 1M hydrochloric acid (175mL), and the solid precipitate collected by filtration, washed with water and dried *in vacuo* to give the product (12.6g). ¹H NMR (d₆-DMSO): 1.28 (d, 6H), 3.78 (s, 3H), 4.71 (sept, 1H), 6.54 (m, 1H), 6.81 (m, 1H), 7.09 (d, 2H), 7.24 (s, 1H), 7.42 (s, 1H), 7.59 (m, 1H), 7.98 (d, 2H), 10.85 (br s, 1H), 12.80 (br s, 1H). MS *m/z* 396 (M+H)⁺.

Ethyl 4-[(3-[(1-methylethyl)oxy])-5-[(1-methyl-1H-pyrazol-3-yl)amino]carbonyl]phenyl]oxy]benzoate

To a mixture of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazolo-3-yl)benzamide (1.0 g) and ethyl-4-fluorobenzoate (672 mg) in DMF (18 mL) was added potassium carbonate (1.0 g) and the stirred mixture heated at 115° C for 24 hours. The mixture was cooled to ambient temperature, diethyl ether (100 mL) was added and the mixture washed with water (3 × 50mL), brine (50 mL), dried (MgSO₄) and evaporated *in vacuo* to a residue which was chromatographed on silica, eluting with a gradient of 50% ethyl acetate in isohexane to give the product (0.6 g). ¹H NMR (CDCl₃): 1.35 (m, 9H), 3.78 (s, 3H), 4.36 (q, 2H), 4.58 (m, 1H), 6.71 (m, 1H), 6.80 (m, 1H), 7.05 (m, 3H), 7.21 (m, 1H), 7.28 (m, 1H), 8.03 (d, 2H), 8.51 (s, 1H). MS *m/z* 424 (M+H)⁺.

3-Hydroxy-5-[(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide

To a solution of 3-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (51.0 g) in THF (500 mL) and methanol (500 mL) was added 10% palladium on carbon (5.1 g) as a slurry in THF (1 mL) and methanol (1 mL). The mixture was placed under vacuum and stirred under an atmosphere of hydrogen for 20 hours. The mixture was filtered through diatomaceous earth, and the diatomaceous earth washed with methanol (2 × 100 mL), followed by evaporation *in vacuo*. The residues were treated with ethyl acetate (100 mL), the solid collected by filtration and washed with isohexane (50 mL) to afford the product (30.5 g) which was used without further purification. ¹H NMR (d₆-DMSO): 1.30 (d, 6H), 3.78 (s, 3H), 4.68 (sept, 1H), 6.47 (m, 1H), 6.60 (s, 1H), 6.94 (s, 1H), 7.05 (s, 1H), 7.60 (s, 1H), 10.63 (s, 1H). MS *m/z* 276 (M+H)⁺.

3-[(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide

A solution of 3-[(1-methylethyl)oxy]-5-[[phenylmethyl]oxy]benzoic acid (40.0 g) in dichloromethane (700 mL) was cooled to 0°C. Oxalyl chloride (14.6 mL) and DMF (0.15 mL) were slowly added with stirring. The mixture was allowed to warm to ambient temperature and stirred for 4 hours, following which the organics were removed *in vacuo*, and the residues azeotroped with toluene (75 mL). The crude material was dissolved in dichloromethane (300 mL) and slowly added to a stirred suspension of 1-methyl-1*H*-pyrazol-3-amine (14.25 g) and triethylamine (41.0 mL) in dichloromethane (300 mL). The mixture was stirred at ambient temperature for 18 hours, before the organics were evaporated *in vacuo* and the residue dissolved in ethyl acetate (400 mL). The organics were washed with 1M aqueous hydrochloric acid (200 mL), saturated aqueous sodium hydrogen carbonate (200 mL) and brine (100 mL) and dried (MgSO₄) before evaporation *in vacuo* to give crude material. This was chromatographed on silica, eluting with a gradient of 30% to 90% ethyl acetate in isohexane, to give the product (51.0g). ¹H NMR (CDCl₃): 1.30 (d, 6H), 3.61 (s, 3H), 4.50 (sept, 1H), 5.01 (s, 2H), 6.66 (m, 1H), 6.88 (m, 1H), 7.00 (m, 1H), 7.06 (m, 1H), 7.24 (m, 1H), 7.39 (m, 5H), 9.50 (s, 1H). MS *m/z* 366 (M+H)⁺.

3-[(1-methylethyl)oxy]-5-[[phenylmethyl]oxy]benzoic acid

To a solution of methyl 3-[(1-methylethyl)oxy]-5-[[phenylmethyl]oxy] benzoate (37.0g) in a mixture of THF (300 mL) and methanol (300 mL) was added a solution of 2M sodium hydroxide (300 mL), and the reaction mixture heated under reflux for 45 minutes. The resulting solution was diluted with water (250 mL) and most of the organic solvent removed *in vacuo*. The resulting suspension was washed with diethyl ether (3 × 200 mL) and the organic washings discarded. The resulting aqueous solution was acidified to pH4 with 2M hydrochloric acid solution and extracted with ethyl acetate (2 × 300 mL). The combined extracts were washed with brine, dried (MgSO₄), and evaporated to give the product (33.5g). ¹H NMR (d₆-DMSO): 1.26 (d, 6H), 4.59-4.69 (m, 1H), 5.15 (s, 2H), 6.80 (app t, 1H), 7.04 (m, 1H), 7.12 (m, 1H), 7.33-7.46 (m, 5H), 12.95 (s, 1H).

Methyl 3-[(1-methylethyl)oxy]-5-[[phenylmethyl]oxy]benzoate

To a solution of methyl 3-hydroxy-5-[[phenylmethyl]oxy]benzoate (25.0 g) and benzyl bromide (24.5 g) in DMF (250 mL) was added potassium carbonate (40.4 g). The stirred mixture was heated at 60° C for 5 hours, cooled to ambient temperature, the DMF evaporated *in vacuo* to a residue which was taken up in ethyl acetate (500 mL), washed with water (3 × 100 mL) and brine (150 mL), dried (MgSO₄) and evaporated *in vacuo* to give the product (37.0 g). ¹H NMR (d₆-DMSO): 1.26 (d, 6H), 3.84 (s, 3H), 4.66 (m, 1H), 5.12 (s, 2H), 6.84 (t, 1H), 7.05 (t, 1H), 7.13 (m, 1H), 7.31-7.46 (m, 5H).

Methyl 3-hydroxy-5-[(1-methylethyl)oxy]benzoate

To a solution of methyl 3,5-dihydroxybenzoate (16.8 g) and 2-iodopropane (17.0 g) in DMF (180 mL) was added potassium carbonate (27.2 g). The mixture was stirred at ambient temperature for 16 hours, poured onto water (1.0 L), extracted with diethyl ether (3 × 500 mL), washed with water (3 × 100 mL), brine (150 mL), dried (MgSO₄) and evaporated *in vacuo* to a residue which was treated with toluene (40 mL), stirred for 16 hours, filtered and the filtrates evaporated *in vacuo* to a residue which was chromatographed on silica, eluting with a gradient of 10% -15% ethyl acetate in isohexane to give the product (7.92g). ¹H NMR (d₆-DMSO): 1.26 (d, 6H), 3.8 (s, 3H), 4.5-4.6 (m, 1H), 6.55 (m, 1H), 7.85 (m, 1H), 7.95 (m, 1H), 9.80 (s, 1H).

3-[[4-(Azetidin-1-ylcarbonyl)phenyl]oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yl]benzamide

A mixture of 3-[[4-(azetidin-1-ylcarbonyl)phenyl]oxy]-5-hydroxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide (0.26 g, 0.66 mmol), (3R)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate (241 mg, 0.99 mmol) and potassium carbonate (229 mg, 1.66 mmol) in acetonitrile (5 mL) was stirred in a microwave reactor at 160°C for 3 hours. The solvent was removed *in vacuo* and ethyl acetate (50 mL) added. The organics were washed with water (40 mL), brine (40 mL), dried (MgSO₄), filtered and the solvent removed *in vacuo* to give a yellow foam which was chromatographed on silica, eluting with a gradient of 0-5% methanol in ethyl acetate, to give the product (104 mg). ¹H NMR (CDCl₃): 2.18 (m, 1H), 2.25 (m, 1H), 2.48 (quin, 2H), 3.78 (s, 3H), 3.92 (m, 1H), 4.01 (m, 3H), 4.20-4.40 (m, 4H), 4.96 (m, 1H), 6.72 (s, 1H), 6.80 (s, 1H), 7.04 (d, 2H), 7.11 (s, 1H), 7.19 (s, 1H), 7.28 (m, 1H), 7.63 (d, 2H), 8.61 (s, 1H). MS *m/z* 463 (M+H)⁺.

(3R)-Tetrahydrofuran-3-yl 4-methylbenzenesulfonate

4-Toluene sulfonyl chloride (1.65 g, 8.63 mmol) was added to a solution of *R*-3-hydroxytetrahydrofuran (0.8 g, 9.08 mmol) and pyridine (0.88 mL, 10.9 mmol) in DCM (15 mL). The reaction was stirred at RT for 72 hours. Water (10 mL) and 1M hydrochloric acid (1 mL) were added and the mixture extracted with DCM (15 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄), filtered and reduced *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with a gradient of 0-50% ethyl acetate in isohexane, to give the product (1.0 g). ¹H NMR (CDCl₃): 2.13 (m, 2H), 2.47 (s, 3H), 3.80-3.95 (m, 4H), 5.15 (m, 1H), 7.37 (d, 2H), 7.81 (d, 2H).

3-[[4-(Azetidin-1-ylcarbonyl)phenyl]oxy]-5-hydroxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide

A solution of 3-[[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (1.00 g, 1.93 mmol), 10% by weight palladium on carbon (0.10 g) and triethylamine (0.81 mL, 5.79 mmol), in ethanol (50 mL), was allowed to stir at RT under a hydrogen atmosphere for 16 hours. The solution was filtered through Celite® and washed through with methanol (100 mL). The solution was concentrated *in vacuo*, the residue dissolved in ethanol (50 mL) and 10% by weight palladium on carbon (0.10 g) and triethylamine (0.81 mL, 5.79 mmol) added. The reaction was stirred at RT under a hydrogen atmosphere for 48 hours. The solution was filtered through Celite® and washed through with methanol (100 mL). The filtrate was concentrated *in vacuo* to give the product (0.73 g). ¹H NMR (CDCl₃): 2.27 (quin, 2H), 3.69 (s, 3H), 4.20 (d, 4H), 6.59 (t, 1H), 6.67 (d, 1H), 6.88 (d, 2H), 6.94 (t, 1H), 7.08 (t, 1H), 7.20 (s, 1H), 7.50 (d, 2H), 8.69 (s, 1H). MS *m/z* 393 (M+H)⁺.

3-[[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide

DIPEA (2.1 mL, 11.24 mmol) was added to a suspension of 3-[[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy]-5-[(phenylmethyl)oxy]benzoic acid (1.23 g, 2.81 mmol), HATU (2.23 g, 5.90 mmol) and 3-amino-1-methylpyrazole (0.54 mg, 5.62 mmol) in DMF (15 mL). The resulting mixture was stirred at RT for 24 hours. The DMF was removed *in vacuo*. Water (50 mL) was added and the mixture extracted with ethyl acetate (3 × 50 mL). The extracts were combined and washed with brine (50 mL), dried (MgSO₄), filtered, and evaporated *in vacuo* to give the crude product which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the product (1.0 g). ¹H NMR (CDCl₃): 2.38 (quin, 2H), 3.79 (s, 3H), 4.20-4.40 (m, 4H), 5.07 (s, 2H), 6.78 (m, 2H), 6.99 (d, 1H), 7.05 (m, 1H), 7.28 (m, 2H), 7.39 (m, 5H), 7.48 (dd, 1H), 7.78 (d, 1H), 8.43 (brs, 1H). MS *m/z* 517 (M+H)⁺.

3-[[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy]-5-[(phenylmethyl)oxy]benzoic acid

Lithium hydroxide monohydrate (0.27g, 6.5mol) in water (10 mL) was added to a solution of methyl 3-[[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy]-5-[(phenylmethyl)oxy]benzoate (1.17 g, 2.6 mmol) in THF (20 mL) and the reaction mixture stirred for 2.5 hours at RT. The THF was removed *in vacuo* and the aqueous residue washed with ethyl acetate (20 mL). The aqueous layer was adjusted to pH3 with 1M hydrochloric acid and extracted with ethyl acetate (2 × 50 mL). The combined extracts were washed with brine (50 mL), dried (MgSO₄), filtered, and evaporated to give the product (0.9 g). ¹H NMR (CDCl₃): 2.39 (quin, 2H), 4.20-4.40 (m, 4H), 5.08 (s, 2H), 6.82 (m, 1H), 6.99 (d, 1H), 7.29 (m, 1H), 7.38 (m, 5H), 7.51 (m, 2H), 7.78 (m, 1H). MS *m/z* 438 (M+H)⁺.

Methyl 3-[[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy]-5-[(phenylmethyl)oxy]benzoate

A mixture of methyl 3-hydroxy-5-[[phenylmethyl]oxy]benzoate (1.54 g, 5.96 mmol), potassium carbonate (1.64 g, 11.91 mmol) and 1-[(3-chloro-4-fluorophenyl)carbonyl]azetidine (0.85 g, 3.97 mmol) in DMF (20 mL) was heated at 120°C for 24 hours. The DMF was removed *in vacuo*, water (50 mL) added and the mixture extracted with ethyl acetate (3 × 50 mL). The extracts were combined and washed with brine (100 mL), dried (MgSO₄), filtered, and evaporated *in vacuo* to give the crude product which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the product. (1.17 g). ¹H NMR (CDCl₃): 2.38 (quin, 2H), 4.20-4.40 (m, 4H), 5.08 (s, 2H), 6.82 (m, 1H), 6.98 (d, 1H), 7.30 (m, 1H), 7.38 (m, 5H), 7.50 (m, 2H), 7.78 (m, 1H). MS *m/z* 452 (M+H)⁺.

1-[(3-Chloro-4-fluorophenyl)carbonyl]azetidine

To a solution of 3-chloro-4-fluorobenzoic acid (1.74 g, 10.0 mmol) in DCM (50 mL) was added oxalyl chloride (1.05 mL, 12.0 mmol) and DMF (1 drop). The mixture was stirred at RT for 16 hours and the DCM and excess oxalyl chloride evaporated *in vacuo*. The residual acid chloride and azetidine hydrochloride (1.12 g, 12 mmol) were taken up in DCM (25 mL) and triethylamine (4.18 mL, 30 mmol) added to the mixture, which was stirred at RT for 2 hours. The DCM was evaporated *in vacuo*, and the residue partitioned between ethyl acetate (100 mL) and 1N hydrochloric acid (50 mL). The ethyl acetate layer was washed sequentially with saturated aqueous sodium hydrogen carbonate and brine, dried (MgSO₄), and evaporated. The residue was crystallized from ethyl acetate and isohexane to give the product (1.64 g). ¹H NMR (CDCl₃): 2.4 (m, 2H), 4.2-4.4 (m, 4H), 7.2 (m, 1H), 7.55 (m, 1H), 7.7 (m, 1H).

3-[[4-(Azetidin-1-ylcarbonyl)phenyl]oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-[(tetrahydro-2H-pyran-4-yl)oxy]benzamide 18

A mixture of 3-[[4-(azetidin-1-ylcarbonyl)phenyl]oxy]-5-hydroxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide (0.15 g, 0.38 mmol), tetrahydro-2H-pyran-4-yl 4-methylbenzenesulfonate (147 mg, 0.57 mmol) and potassium carbonate (132 mg, 0.97 mmol) in acetonitrile (5 mL) was stirred in a 'Biotage initiator Microwave' at 160°C for 3 hours. The solvent was removed *in vacuo* and ethyl acetate (50 mL) added. The organics were washed with water (40 mL), brine (40 mL), dried (MgSO₄), filtered and the solvent removed *in vacuo* to give a yellow foam which was chromatographed on silica, eluting with a gradient of 0-5% methanol in ethyl acetate, to give the product (37 mg). ¹H NMR (CDCl₃): 1.80 (m, 2H), 2.05 (m, 2H), 2.38 (quin, 2H), 3.60 (m, 2H), 3.82 (s, 3H), 3.99 (m, 2H), 4.20-4.40 (m, 4H), 4.56 (m, 1H), 6.78 (m, 2H), 7.04 (d, 2H), 7.08 (s, 1H), 7.22 (s, 1H), 7.28 (m, 1H), 7.68 (d, 2H), 8.39 (s, 1H). MS *m/z* 477 (M+H)⁺.

Tetrahydro-2H-pyran-4-yl 4-methylbenzenesulfonate

4-Toluene sulfonyl chloride (1.65 g, 8.63 mmol) was added to a solution of 4-hydroxytetrahydropyran (0.93 g, 9.08 mmol) and pyridine (0.88 mL, 10.9 mmol) in DCM (15 mL). The reaction was stirred at RT for 72 hours. Water (10 mL) and 1M hydrochloric acid (1 mL) were added and the mixture extracted with DCM (15 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄), filtered and reduced *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with a gradient of 0-50% ethyl acetate in isohexane, to give the product (1.2 g). ¹H NMR (CDCl₃): 1.78 (m, 2H), 1.89 (m, 2H), 2.47 (s, 3H), 3.50 (m, 2H), 3.90 (m, 2H), 4.73 (m, 1H), 7.37 (d, 2H), 7.82 (d, 2H).

3-[[4-(Azetidin-1-ylcarbonyl)phenyl]oxy]-5-[[2-fluoro-1-(fluoromethyl)ethyl]oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide

A solution of 3-[[4-(azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy]-5-[[2-fluoro-1-(fluoromethyl)ethyl]oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide (0.125 g, 0.25 mmol) and triethylamine (0.104 mL, 0.74 mmol) in ethanol (10 mL) was evacuated and the atmosphere replaced with argon (3 times). 10% Palladium on carbon (12 mg) was added and the vessel again evacuated and the atmosphere replaced with argon (3 times) and finally evacuated and the atmosphere replaced with hydrogen. The mixture was stirred at RT overnight. The reaction mixture was filtered through Celite®, washed with methanol (50 mL) and the solvents were removed *in vacuo*. The residual solid was chromatographed on silica, eluting with ethyl acetate, to give the product (58 mg). ¹H NMR (CDCl₃): 2.29 (quin, 2H), 3.70 (s, 3H), 4.22 (m, 4H), 4.60 (m, 5H), 6.71 (d, 1H), 6.76 (t, 1H), 6.95 (d, 2H), 7.06 (s, 1H), 7.20 (m, 1H), 7.21 (d, 1H), 7.59 (m, 2H), 8.59 (s, 1H). MS *m/z* 471 (M+H)⁺.

3-[[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy]-5-[[2-fluoro-1-(fluoromethyl)ethyl]oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide

A solution of 3-[[2-fluoro-1-(fluoromethyl)ethyl]oxy]-5-hydroxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide (350 mg, 1.12 mmol), 1-[(3-chloro-4-fluorophenyl)carbonyl]azetidine (253 mg, 1.18 mmol) and potassium carbonate (388 mg, 2.81 mmol) in acetonitrile (5 mL) was heated in a microwave reactor at 160°C for 6 hours. The acetonitrile was removed *in vacuo* and the residue dissolved in ethyl acetate (25 mL), washed with water (25 mL), brine (25 mL), dried (MgSO₄) and evaporated to a residue which was chromatographed on silica, eluting with ethyl acetate, and then chromatographed by preparative HPLC on C18 reversed phase, eluting with 5-95% acetonitrile (+0.2% TFA) in water (+0.2% TFA), to give the required product (125 mg).

¹H NMR (CDCl₃): 2.31 (quin, 2H), 3.82 (s, 3H), 4.18 (t, 2H), 4.30 (t, 2H), 4.58 (m, 2H), 4.69 (m, 2H), 4.89 (m, 1H), 6.76 (t, 1H), 6.90 (d, 1H), 6.98 (s, 1H), 7.00 (s, 1H), 7.30 (d, 1H), 7.33 (t, 1H), 7.45 (d, 1H), 7.47 (d, 1H), 7.71 (d, 1H), 10.24 (s, 1H). MS *m/z* 505 (M+H)⁺.

3-[[2-Fluoro-1-(fluoromethyl)ethyl]oxy]-5-hydroxy-N-(1-methyl-1H-pyrazol-3-yl)benzamide

A solution of 3-[[2-fluoro-1-(fluoromethyl)ethyl]oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (2.46 g, 6.13 mmol) and 10% by weight palladium on carbon (0.246 g) in ethanol (100 mL) was allowed to stir at RT, under a hydrogen atmosphere overnight. The solution was filtered through Celite® and the cake washed with methanol (100 mL). The solution was evaporated to give the product (1.78 g). ¹H NMR (d₆-DMSO): 3.78 (s, 3H), 4.72 (m, 4H), 4.97 (m, 1H), 6.57 (d, 2H), 7.03 (s, 1H), 7.16 (s, 1H), 7.59 (s, 1H). MS *m/z* 312 (M+H)⁺.

3-[[2-Fluoro-1-(fluoromethyl)ethyl]oxy]-N-(1-methyl-1H-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide

A solution 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid (3.00 g, 9.31 mmol), 3-amino-1-methylpyrazole (1.83 g, 18.6 mmol), HATU (4.60 g, 12.1 mmol) and DIPEA (3.25 mL, 18.6 mmol) in DMF (12 mL) was stirred at RT overnight. Water (150 mL) was added and the solution partitioned with ethyl acetate (250 mL). The ethyl acetate layer was separated, washed with brine and dried (MgSO₄), and evaporated to a residue which was chromatographed on silica, eluting with 50% ethyl acetate in isohexane, to give the desired product (2.46 g). ¹H NMR (CDCl₃): 3.69 (s, 3H), 4.57 (m, 5H), 5.00 (s, 2H), 6.70 (t, 1H), 6.74 (d, 1H), 7.01 (t, 1H), 7.08 (t, 1H), 7.21 (d, 1H), 7.30 (m, 5H), 8.68 (s, 1H). MS *m/z* 402 (M+H)⁺.

3-{[2-Fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid

A solution of lithium hydroxide monohydrate (2.32 g, 55.1 mmol) in water (100 mL) was added to a solution of methyl 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoate (7.41 g, 22.0 mmol) in THF (200 mL) and the mixture allowed to stir at RT overnight. The THF was removed *in vacuo* and the resulting solution partitioned between water (100 mL) and ethyl acetate (250 mL). The ethyl acetate layer was separated, washed with brine and dried (MgSO₄). The aqueous layer was then adjusted to pH 7 by addition of 1M hydrochloric acid and extracted with ethyl acetate (75 mL). The ethyl acetate layer was separated, washed with brine and dried (MgSO₄). The ethyl acetate layers were combined and evaporated to give the required product (6.40 g). ¹H NMR (d₆-DMSO): 4.74 (m, 4H), 5.08 (s, 2H), 6.67 (s, 1H), 6.67 (s, 1H), 7.23 (s, 1H), 7.37 (m, 5H). MS *m/z* 231 (M-H)⁻.

Methyl 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoate

DIAD (7.63 mL, 38.7 mmol) was added in a drop wise fashion to a solution of methyl 3-hydroxy-5-[(phenylmethyl)oxy]benzoate (5.00 g, 19.4 mmol), 1,3-difluoropropan-2-ol (3 mL, 38.7 mmol), and triphenylphosphine (10.16 g, 38.7 mmol) in THF (100 mL) under an inert atmosphere at 0°C. The solution was allowed to reach RT and left to stir for 2 days. The THF was removed *in vacuo* and the residual oil slurried with a mixture of 20% ethyl acetate in isohexane. After allowing to stir for 90 minutes, the mixture was filtered and the filtrate evaporated. The residual was oil chromatographed on silica, eluting with 30% ethyl acetate in isohexane, to give the product (7.41 g). ¹H NMR (d₆-DMSO): 3.85 (s, 3H), 4.71 (m, 4H), 5.03 (m, 1H), 5.17 (s, 2H), 7.01 (t, 1H), 7.20 (m, 2H), 7.40 (m, 5H); *m/z* 335 (M-H)⁻.

3-[4-[(Azetidin-1-yl)carbonyl]phenoxy]-5-[(1S)-2-(methoxy)-1-methylethoxy]-N-(5-methylpyrazin-2-yl)benzamide

To a stirred solution of 3-{[4-(Azetidin-1-ylcarbonyl)phenyl]oxy}-5-[(1S)-2-hydroxy-1-methylethyl]oxy]-benzoic acid (193 mg, 0.5 mmol) in dichloromethane (10 mL) under an atmosphere of nitrogen was added 1-chloro-N,N,2-trimethyl-1-propenylamine (0.08 mL, 0.6 mmol) and the mixture stirred at ambient temperature for 1 hour. To the stirred solution was added 5-methylpyrazin-2-amine (109 mg, 1.0 mmol) and pyridine (0.08 mL, 1.0 mmol) and the mixture stirred at ambient temperature for 30 minutes. The dichloromethane was evaporated *in vacuo* to a residue which was taken up in ethyl acetate (20 mL), washed with water (2 × 10 mL), 1N citric acid solution (10 mL), brine (10 mL), dried (MgSO₄) and evaporated *in vacuo* to a residue which was chromatographed on silica with 60% - 100% ethyl acetate in hexane as eluant to give the product (176 mg). ¹H NMR (CDCl₃): 1.30 (d, 3H), 2.35 (m, 2H), 2.57 (s, 3H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 4.20-4.40 (brm, 4H), 4.55-4.65 (m, 1H), 6.83 (s, 1H), 7.04 (d, 2H), 7.15 (s, 1H), 7.3 (s, 1H), 7.65 (d, 2H), 8.15 (s, 1H), 8.38 (brs, 1H), 9.51 (s, 1H). MS *m/z* 477 (M+H)⁺.

3-{[4-(Azetidin-1-ylcarbonyl)phenyl]oxy}-5-[(1S)-2-hydroxy-1-methylethyl]oxy]-benzoic acid

3-{[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-[(1S)-2-methoxy-1-methylethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzoic acid (2.4 g, 5.7 mmol) was dissolved in ethanol (30 mL) and THF (30 mL). Triethylamine (2.23 mg, 22.0 mmol) was added and the flask evacuated and purged with nitrogen (3 times). 10% Palladium on carbon (240 mg) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at ambient temperature for 16 hours until completion. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was removed by filtration, the filtrate concentrated *in vacuo* and dissolved in ethyl acetate (50 mL), washed with water (2 × 10mL, saturated aqueous sodium chloride solution (10 mL) and dried (MgSO₄) to give the product (1.19 g). ¹H NMR (CDCl₃): 1.32 (d, 3H), 2.3-2.4 (m, 2H), 3.40 (s, 3H), 3.51-3.57 (m, 2H), 4.26-4.35 (brm, 4H), 4.59 (m, 1H), 6.82 (s, 1H), 6.95 (d, 2H), 7.26 (s, 1H), 7.35 (s, 1H), 7.66 (d, 2H). MS *m/z* 386 (M+H)⁺.

3-{[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-[(1S)-2-methoxy-1-methylethyl]oxy]-benzoic acid

To a mixture of 3-[(1S)-2-methoxy-1-methylethoxy]-5-hydroxy-benzoate (3.6 g, 15.0 mmol) and 1-(3-chloro-4-fluorobenzoyl) azetidine (3.2 g, 15.0 mmol) in DMA (65.0 mL) under an atmosphere of nitrogen was added cesium carbonate (9.77 g, 30.0 mmol) and the stirred mixture heated at 120°C for 16 hours. The mixture was cooled to ambient temperature, treated with diethyl ether (100 mL), washed with water (3 x 50 mL), brine (50 mL), dried (MgSO₄) and evaporated *in vacuo* to a residue which was chromatographed on silica with 50% ethyl acetate in hexane as eluant to give methyl-3-{[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-[(1S)-2-methoxy-1-methylethyl]oxy}-benzoate (1.92g). *m/z* 434 (M+H)⁺. The aqueous washings above were acidified to pH4 with citric acid, extracted with ethyl acetate (3 × 75 mL), the combined ethyl acetate extracts washed with brine, dried (MgSO₄) and evaporated *in vacuo* to give the product (2.4 g). ¹H NMR (CDCl₃): 1.32 (d, 3H),

2.37 (m, 2H), 3.40 (s, 3H), 3.51-3.57 (m, 2H), 4.26-4.35 (brm, 4H), 4.59 (m, 1H), 6.82 (s, 1H), 6.99 (d, 1H), 7.26 (s, 1H), 7.44 (s, 1H), 7.51 (d, 1H), 7.78 (s, 1H). MS m/z 420 (M+H)⁺

3-[[5-(1-Azetidinylcarbonyl)-3-chloro-2-pyridinyl]oxy]-5-[[[(1S)-1-methyl-2-(methyloxy)ethyl]oxy]-N-(5-methylpyrazin-2-yl)benzamide

Cesium carbonate (489 mg, 1.5 mmol) was added to a solution of 3-hydroxy-5-[[[(1S)-1-methyl-2-(methyloxy)ethyl]oxy]-N-(5-methylpyrazin-2-yl)benzamide (159 mg, 0.5 mmol) and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (173 mg, 0.75 mmol) in acetonitrile (5 mL) and the stirred mixture heated at 120 °C in a microwave reactor for 1 hour. The mixture was cooled to RT and ambient pressure, the acetonitrile evaporated *in vacuo*, the residue partitioned between water (25 mL) and ethyl acetate (50 mL), the organic layer washed with brine, dried (MgSO₄) and evaporated to a residue which was chromatographed on silica, eluting with 75% ethyl acetate in isohexane to give the desired product (206 mg). ¹H NMR (CDCl₃): 1.3 (d, 3H), 2.3 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 – 3.55 (m, 2H), 4.1 – 4.35 (m, 4H), 4.55 (m, 1H), 6.9 (d, 1H), 7.2 (d, 1H), 7.35 (s, 1H), 8.05 (s, 1H), 8.1 (s, 1H), 8.2 (d, 1H), 8.3 (s, 1H) and 9.45 (s, 1H). MS m/z 512 (M+H)⁺.

5-(Azetidin-1-ylcarbonyl)-2,3-dichloropyridine

DMF (2 drops) was added to a solution of 5,6-dichloronicotinic acid (1.22 g, 6.35 mmol) and oxalyl chloride (0.67 mL, 7.62 mmol) in DCM (20 mL) and 2M hydrogen chloride in ether (3.15 mL, 6.35 mmol). The mixture was stirred at RT for 4 hours and the DCM and excess oxalyl chloride evaporated *in vacuo*. The residual acid chloride was dissolved in DCM (10 mL) and added to a mixture of azetidine hydrochloride (0.66 g, 6.99 mmol) and triethylamine (2.14 mL, 13.97 mmol) in DCM (10 mL) then stirred at RT for 24 hours. The DCM was evaporated *in vacuo*, and the residue partitioned between ethyl acetate (100 mL) and 1M citric acid (50 mL). The ethyl acetate layer was washed sequentially with saturated aqueous sodium hydrogen carbonate (50 mL) and brine (50 mL), dried (MgSO₄), and the solvent removed *in vacuo* to give a residue which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the product (0.89 g). ¹H NMR (CDCl₃): 2.43 (quin, 2H), 4.21 - 4.44 (m, 4H), 8.11 (d, 1H), 8.53 (d, 1H). MS m/z 231 (M+H)⁺

3-Hydroxy-5-[[[(1S)-1-methyl-2-(methyloxy)ethyl]oxy]-N-(5-methylpyrazin-2-yl)benzamide

10% Palladium on charcoal (700 mg) was added to a solution of 3-[[[(1S)-1-methyl-2-(methyloxy)ethyl]oxy]-N-(5-methylpyrazin-2-yl)-5-[(phenylmethyl)oxy]benzamide (7.0 g, 17.2 mmol) in ethanol (125 mL) and the mixture stirred at RT under a hydrogen atmosphere for 4 hours. The catalyst was removed by filtration and the ethanol evaporated *in vacuo*. The residue was crystallised from ethyl acetate to give the product (4.22 g). ¹H NMR (CDCl₃): 1.25 (d, 3H), 2.5 (s, 3H), 3.3 (s, 3H), 3.4 – 3.5 (m, 2H), 4.5 (m, 1H), 6.3 (br, 1H), 6.55 (s, 1H), 6.9 (s, 1H), 6.95 (s, 1H), 8.05 (s, 1H), 8.45 (s, 1H) and 9.5 (s, 1H). MS m/z 318 (M+H)⁺.

3-[[[(1S)-1-Methyl-2-(methyloxy)ethyl]oxy]-N-(5-methylpyrazin-2-yl)-5-[(phenylmethyl)oxy]benzamide

Oxalyl chloride (2.1 mL, 24.0 mmol) was added to a solution of 3-[(1S)-2-methoxy-(1-methylethyl)oxy]-5-[[phenylmethyl]oxy]benzoic acid (6.32 g, 20.0 mmol) in DCM (100 mL) and the mixture stirred at RT for 4 hours. The mixture was evaporated *in vacuo* to a residue, which was taken up in DCM (25 mL) and added to a stirred mixture of 2-amino-5-methylpyrazine (2.29 g, 21.0 mmol) and pyridine (1.94 mL, 24.0 mmol) in DCM (100 mL) at 5°C - 10°C. The mixture was stirred at RT for 18 hours, the DCM evaporated *in vacuo*. The residue was partitioned between water (50 mL) and ethyl acetate (150 mL), the organic layer washed with brine, dried (MgSO₄) and evaporated to a residue, which was chromatographed on silica, eluting with 50% ethyl acetate in isohexane, to give the product (7.0 g). ¹H NMR (CDCl₃): 1.3 (d, 3H), 2.5 (s, 3H), 3.3 (s, 3H), 3.4 – 3.5 (m, 2H), 4.5 (m, 1H), 5.0 (s, 2H), 6.7 (s, 1H), 7.0 (s, 1H), 7.05 (s, 1H), 7.35 (m, 5H), 8.05 (s, 1H), 8.3 (s, 1H) and 9.5 (s, 1H). MS m/z 408 (M+H)⁺.

3-[[5-(1-Azetidinylcarbonyl)-2-pyrazinyl]oxy]-5-[[[(1S)-1-methyl-2-(methyloxy)ethyl]oxy]-N-(5-methylpyrazin-2-yl)benzamide

Cesium carbonate (489 mg, 1.5 mmol) was added to a solution of 3-hydroxy-5-[[[(1S)-1-methyl-2-(methyloxy)ethyl]oxy]-N-(5-methylpyrazin-2-yl)benzamide (159 mg, 0.5 mmol) and 5-(azetidin-1-ylcarbonyl)-2-chloropyrazine (148 mg, 0.75 mmol) in acetonitrile (5 mL) and the stirred mixture heated at 120 °C in a microwave reactor for 1 hour. The mixture was cooled to RT and ambient pressure, the acetonitrile evaporated *in vacuo*, the residue partitioned between water (25 mL) and ethyl acetate (50 mL), the organic layer washed with brine, dried (MgSO₄) and evaporated to a residue which was chromatographed on silica, eluting with ethyl acetate to give the desired product (185 mg). ¹H NMR (CDCl₃): 1.3 (d, 3H), 2.3 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 – 3.55 (m, 2H), 4.1 – 4.35 (m, 4H), 4.55 (m, 1H), 6.9 (d, 1H), 7.2 (d, 1H), 7.35 (s, 1H), 8.05 (s, 1H), 8.1 (s, 1H), 8.2 (d, 1H), 8.3 (s, 1H) and 9.45 (s, 1H). MS m/z 512 (M+H)⁺.

5-(azetidin-1-ylcarbonyl)-2-chloropyrazine

Oxalyl chloride (1.55 mL, 17.48 mmol), followed by DMF (2 drops), was added to a mixture of 5-chloropyrazine-2-carboxylic acid (2.31 g, 14.57 mmol) in DCM (40 mL). The reaction was stirred at RT for 2 hours after which time the volatiles were removed *in vacuo*. The residue was taken up DCM (40 mL) and azetidine (1.08 mL, 16.03 mmol) and triethylamine (4.46 mL, 32.06 mmol) added. The mixture was stirred at RT for 72 hours. The volatiles were removed *in vacuo* and ethyl acetate (100 mL) added to the residue. The

organics were washed with water (100 mL), citric acid (50 mL), saturated sodium bicarbonate solution (50 mL), brine (50 mL), dried (MgSO₄), filtered and the solvent removed *in vacuo* to give a yellow solid. The residue was chromatographed on silica, eluting with a gradient of 50 -100% ethyl acetate in *iso*-hexane, to give the product (2.38 g). ¹H NMR (CDCl₃): 2.35 - 2.42 (2H, m), 4.26 (2H, t), 4.67 (2H, t), 8.52 (1H, d), 9.09 (1H, d). MS *m/z* 198 (M+H)⁺.

5-Chloropyrazine-2-carboxylic acid

To a solution of methyl-5-chloropyrazine-2-carboxylate (120 mg, 0.70 mmol) in a mixture of acetonitrile (2 mL) and DMF (1 mL) was added lithium chloride (295 mg, 6.95 mmol). The suspension was heated to 160°C for 5 mins in a microwave reactor after which time the reaction was diluted with water (10 mL). Saturated sodium bicarbonate solution (20 mL) was added and the aqueous layered extracted twice with ethyl acetate (30 mL). The combined organics were discarded and the aqueous layer adjusted to pH 4 with 1N hydrochloric acid. The aqueous phase was extracted twice with ethyl acetate (20 mL) and the combined organics washed with water (2 × 20 mL), brine (10 mL), dried (MgSO₄) and evaporated to give the product as a colourless solid (68 mg). ¹H NMR (CDCl₃): 7.20 (1H, br s), 8.72 (1H, s), 9.21 - 9.21 (1H, m). MS *m/z* 157 (M-H)⁺.

3-[[5-(1-Azetidinylcarbonyl)-2-pyridinyl]oxy]-5-[[[(1S)-1-methyl-2-(methyloxy)ethyl]oxy]-N-(5-methylpyrazin-2-yl)benzamide

Cesium carbonate (489 mg, 1.5 mmol) was added to a solution of 3-hydroxy-5-[[[(1S)-1-methyl-2-(methyloxy)ethyl]oxy]-N-(5-methylpyrazin-2-yl)benzamide (159 mg, 0.5 mmol) and 5-(azetidin-1-ylcarbonyl)-2-chloropyridine (147 mg, 0.75 mmol) in acetonitrile (5 mL) and the stirred mixture heated at 120°C in a microwave reactor for 1 hour. The mixture was cooled to RT and ambient pressure, the acetonitrile evaporated *in vacuo*, the residue partitioned between water (25 mL) and ethyl acetate (50 mL), the organic layer washed with brine, dried (MgSO₄) and evaporated to a residue which was chromatographed on silica, eluting with 75% ethyl acetate in isohexane to give the desired product (135 mg). ¹H NMR (CDCl₃): 1.3 (d, 3H), 2.3 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 - 3.55 (m, 2H), 4.15 - 4.35 (m, 4H), 4.55 (m, 1H), 6.8 (d, 1H), 6.95 (d, 1H), 7.2 (s, 1H), 7.35 (s, 1H), 8.0 (dd, 1H), 8.05 (s, 1H), 8.35 (d, 1H), 8.5 (s, 1H) and 9.5 (s, 1H). MS *m/z* 478 (M+H)⁺.

5-(Azetidin-1-ylcarbonyl)-2-chloropyridine

DMF (2 drops) was added to a solution of 6-chloronicotinic acid (1.00 g, 6.35 mmol) and oxalyl chloride (0.67 mL, 7.62 mmol) in DCM (20 mL) and 2M hydrogen chloride in ether (3.15 mL, 6.35 mmol). The mixture was stirred at RT for 4 hours and the DCM and excess oxalyl chloride evaporated *in vacuo*. The residual acid chloride was dissolved in DCM (10 mL) and added to a mixture of azetidine hydrochloride (0.66 g, 6.99 mmol) and triethylamine (2.14 mL, 13.97 mmol) in DCM (10 mL) then stirred at RT for 24 hours. The DCM was evaporated *in vacuo*, and the residue partitioned between ethyl acetate (100 mL) and 1M citric acid (50 mL). The ethyl acetate layer was washed sequentially with saturated aqueous sodium hydrogen carbonate (50 mL) and brine (50 mL), dried (MgSO₄), and the solvent removed *in vacuo* to give a residue which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the product. (0.73 g). ¹H NMR (CDCl₃): 2.43 (quin, 2H), 4.2-4.4 (brm, 4H), 7.42 (d, 1H), 7.97 (d, 1H), 8.63 (s, 1H). MS *m/z* 197 (M+H)⁺.

3-[[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy]-5-[[[(1S)-1-methyl-2-(methyloxy)ethyl]oxy]-N-(5-methylpyrazin-2-yl)benzamide

Cesium carbonate (489 mg, 1.5 mmol) was added to a solution of 3-hydroxy-5-[[[(1S)-1-methyl-2-(methyloxy)ethyl]oxy]-N-(5-methylpyrazin-2-yl)benzamide (159 mg, 0.5 mmol) and 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (181 mg, 0.75 mmol) and bromotris(triphenylphosphine)copper (93 mg, 0.1 mmol) in DMA (5 mL) and the stirred mixture heated at 160°C in a microwave reactor for 4 hours. The mixture was cooled to RT and ambient pressure, partitioned between water (75 mL) and ethyl acetate (50 mL), the organic layer washed with brine, dried (MgSO₄) and evaporated *in vacuo*. The residue was chromatographed on silica, eluting with ethyl acetate. The residue was crystallised from ether to give the product (45 mg). ¹H NMR (CDCl₃): 1.3 (d, 3H), 2.3 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 - 3.55 (m, 2H), 4.2 (t, 2H), 4.55 (m, 1H), 4.65 (t, 2H), 6.75 (d, 1H), 7.05 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 8.0 (s, 1H), 8.05 (d, 1H), 8.25 (d, 1H), 8.3 (s, 1H) and 9.45 (s, 1H). MS *m/z* 478 (M+H)⁺.

2-(Azetidin-1-ylcarbonyl)-5-bromopyridine

DMF (2 drops) was added to a solution of 5-bromopicolinic acid (1.22 g, 6.35 mmol) and oxalyl chloride (0.67 mL, 7.62 mmol) in DCM (20 mL) and 2M hydrogen chloride in ether (3.15 mL, 6.35 mmol). The mixture was stirred at RT for 4 hours and the DCM and excess oxalyl chloride evaporated *in vacuo*. The residual acid chloride was dissolved in DCM (10 mL) and added to a mixture of azetidine hydrochloride (0.66 g, 6.99 mmol) and triethylamine (2.14 mL, 13.97 mmol) in DCM (10 mL) then stirred at RT for 24 hours. The DCM was evaporated *in vacuo*, and the residue partitioned between ethyl acetate (100 mL) and 1M citric acid (50 mL). The ethyl acetate layer was washed sequentially with saturated aqueous sodium hydrogen carbonate (50 mL) and brine (50 mL), dried (MgSO₄), and the solvent removed *in vacuo* to give a residue which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the product.

(0.89 g) ^1H NMR (CDCl_3): 2.35(quin, 2H), 4.25 (t, 2H), 4.70 (t, 2H), 7.93 (d, 1H), 8.03 (d, 1H), 8.63 (s, 1H).
MS m/z 241, 243 ($\text{M}+\text{H}$) $^+$.