

Supplementary information for

The synthesis of tertiary amides from anionically-activated trifluoromethyl groups

Gavin O'Mahony* and Andrew Pitts

AstraZeneca R&D Mölndal, Pepparedsleden 1, 43183 Mölndal, Sweden

gavin.omahony@astrazeneca.com

General experimental information

Commercially-available reagents were used without further purification. Thin-layer chromatography was performed using Merck silica gel 60 F₂₅₄ plates and visualized under a UV lamp at 254 nm. Proton and carbon-13 NMR spectra were recorded on Varian Inova 500 and 400 machines (at 500 MHz and 400 MHz respectively). Unless otherwise stated, NMR spectra were recorded in the solvent stated with non-deuterated solvent used as internal reference. Data for ¹H-NMR spectra are reported as follows: chemical shift (δ , ppm), multiplicity, integration and coupling constants (Hz). Data for ¹³C-NMR spectra are reported in terms of chemical shift (δ , ppm). High resolution mass spectrometry was performed by Compound Management, Lead Generation Department, AstraZeneca R&D Mölndal. Analytical HPLC was performed using an Agilent 1100 series HPLC system with UV diode array detector coupled to a Waters 2700 Sample Manager and a Waters Micromass ZQ ESI mass spectrometer, using the following method: Sunfire C₁₈ column (5 μ m particle size, 3 mm internal diameter, 50 mm long), pH3 aq buffer (10 mmol formic acid, 1 mmol ammonium formate), 3 min gradient H₂O/ACN (95/5% to 5/95%). Retention times are given in minutes. Low resolution MS results were obtained using a Waters ZQ ESI mass spectrometer. Flash column chromatography was performed using prepacked Biotage SNAP columns on a Biotage SP4 system using HPLC grade solvents. Microwave experiments were performed in sealed Biotage microwave vials using a Biotage Initiator microwave with sample changer and infrared temperature sensor. Compounds were named using the AutoNom add-in for MDL ISIS Draw 2.5.

Procedure A. The trifluoromethyl compound (1 equiv) and the secondary amine (2 equiv) were dissolved in dioxane (9 mL) and then 1 M sodium hydroxide (3 equiv) was added. The mixture was stirred at 75 °C and allowed to cool to rt on completion by LCMS.

(2-Hydroxy-phenyl)-piperidin-1-yl methanone (9a)¹ Followed procedure A, used 2-(trifluoromethyl)phenol **4a** (504 mg, 3.11 mmol) and piperidine (0.614 mL, 6.22 mmol). Reaction time: 3.5 h. Water (20 mL) was added and the solution was acidified to pH 1 with 1 M hydrochloric acid and the dioxane removed under reduced pressure. The product was extracted into DCM (3 x 30 mL) yielding an orange/brown gum on evaporation of the solvent. This was redissolved in DCM and washed with water and brine. Removal of solvent *in vacuo* afforded a light yellow solid (571 mg, 89%).

¹H NMR (500 MHz, CDCl₃) δ 9.64 (s, 1H), 7.32-7.24 (m, 1H), 7.21 (d, J = 6.2, 1H), 7.00-6.90 (m, 1H), 6.82 (dd, J = 5.6, 8.3, 1H), 3.62 (s, 4H), 1.68 (s, 2H), 1.62 (s, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 170.8, 158.8, 132.5, 128.4, 118.7, 118.1, 47.0, 26.3, 24.7.

LCMS retention time (min) 1.45.

MS (ESI) C₁₂H₁₅NO₂ [M + H] calculated 206.2, found 206.2.

HRMS (ESI) C₁₂H₁₅NO₂ [M + H] calculated 206.1181, found 206.1200.

N,N-Diethyl-2-hydroxy-benzamide (10a)² Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (503 mg, 3.10 mmol) and diethylamine (0.645 mL, 6.20 mmol). Reaction time: 5 h. The solution slowly turned yellow and a white precipitate formed. The solution was acidified with 1 M hydrochloric acid and the dioxane removed under reduced pressure forming a gummy orange/brown solid. This was redissolved in DCM (3 x 30 mL) and washed with water, followed by separation of the organic phase and evaporation to give a yellow oil (614 mg). This was redissolved in DCM (50 mL) and washed with water followed by brine. After evaporation, a yellow oil remained (551 mg, 92%). This was purified by flash chromatography (MeOH/DCM, 5:95) yielding a white solid (385 mg, 64%).

^1H NMR (500MHz, CDCl_3) δ , 9.61 (s, 1H), 7.25-7.21 (m, 2H), 6.92 (d, $J = 8.21$ Hz, 1H), 6.80 (t, $J = 7.52$, 1H), 3.47 (q, $J = 7.08$ Hz, 4H), 1.22 (t, $J = 7.10$ Hz, 6H).

^{13}C NMR (126MHz, CDCl_3) δ 171.4, 158.1, 158.0, 132.1, 127.5, 118.8, 117.9, 42.2, 13.6.

LCMS retention time (min) 1.40.

MS (ESI) $\text{C}_{11}\text{H}_{15}\text{NO}_2$ [M + H] calculated 194.1, found 194.2.

HRMS (ESI) $\text{C}_{11}\text{H}_{15}\text{NO}_2$ [M + H] calculated 194.1181, found 194.1183.

(2-Hydroxy-phenyl)-pyrrolidin-1-yl-methanone (11a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (506 mg, 3.12 mmol) and pyrrolidine (0.515 mL, 6.24 mmol). Reaction time: 18.5 h. The dioxane was removed *in vacuo* and water (20 mL) was added. The mixture was basified to pH 14 with 1 M aq sodium hydroxide and washed with DCM. The aqueous layer was acidified with 1 M hydrochloric acid and extracted with DCM (3 x 30 mL). The combined organic layers were passed through a phase separator to remove traces of water and then evaporated to give a light brown solid (575 mg, 96%) which was not further purified.

^1H NMR (500 MHz, CDCl_3) δ 11.23 (s, 1H), 7.45 (dd, $J = 1.4, 7.9$ Hz, 1H), 7.30 (dt, $J = 9.4, 25.5$ Hz, 1H), 6.96 (d, $J = 8.3$ Hz, 1H), 6.87-6.77 (m, 1H), 3.69 (s, 4H), 1.93 (s, 4H).

^{13}C NMR (126MHz, CDCl_3) δ 170.4, 160.5, 133.0, 128.4, 118.2, 118.0, 117.5, 50.8, 47.4, 27.0, 24.4.

LCMS retention time (min) 1.34.

MS (ESI) $\text{C}_{11}\text{H}_{13}\text{NO}_2$ [M + H] calculated 192.2, found 192.2.

HRMS (ESI) $\text{C}_{11}\text{H}_{13}\text{NO}_2$ [M + H] calculated 192.1024, found 192.1032.

(2-Hydroxy-phenyl)-morpholin-4-yl-methanone (12a)³ Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (515 mg, 3.18 mmol) and morpholine (0.554 mL, 6.35 mmol). Reaction time: 1.2 h. The solution was acidified with 1 M hydrochloric acid and the dioxane removed under reduced pressure. The residual solution was diluted with water and extracted with DCM (3 x 30 mL). The combined organic extracts were passed through a phase separator to remove traces of water. The solvent was removed *in vacuo* to yield a white solid (652mg, 99%) which was not further purified.

^1H NMR (500 MHz, CDCl_3) δ 9.52 (s, 1H), 7.34 (t, $J = 7.8$, 1H), 7.23 (dd, $J = 1.3, 7.8$, 1H), 7.01 (d, $J = 8.3$, 1H), 6.86 (t, $J = 7.5$, 1H), 3.74 (s, 8H).

^{13}C NMR (126 MHz, CDCl_3) δ 171.1, 159.3, 133.1, 128.4, 118.9, 118.4, 116.8, 67.1, 46.6.

LCMS retention time (min) 1.09.

MS (ESI) $\text{C}_{11}\text{H}_{13}\text{NO}_3$ [M + H] calculated 208.2, found 208.1.

HRMS (ESI) $\text{C}_{11}\text{H}_{13}\text{NO}_3$ [M + H] calculated 208.0973, found 208.0977.

(2-Hydroxy-phenyl)-(4-methyl-piperazin-1-yl)-methanone (13a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (501 mg, 3.09 mmol) and 1-methylpiperazine (0.688 mL, 6.18 mmol). Reaction time: 2.5 h. The mixture turned yellow on heating. 1 M hydrochloric acid was added, the dioxane was removed under reduced pressure and the aqueous layer washed with DCM (30 mL). The aqueous layer was neutralized to pH 7 with 1 M aq sodium

hydroxide and extracted with DCM (3 x 30 mL). These combined extracts were passed through a phase separator to remove traces of water and concentrated under reduced pressure to afford the desired product (460 mg, 68%).

^1H NMR (500 MHz, CDCl_3) δ 7.33-7.25 (m, 1H), 7.21 (dd, $J = 1.5, 7.7$ Hz, 1H), 6.94 (d, $J = 8.3$ Hz, 1H), 6.88-6.78 (m, 1H), 3.76 - 3.69 (m, 4H), 2.50-2.35 (m, 4H), 2.30 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 170.8, 158.6, 132.6, 128.6, 118.9, 118.1, 117.9, 67.3, 55.2, 46.2.

LCMS retention time (min) 0.20.

MS (ESI) $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$ [$\text{M} + \text{H}$] calculated 221.3, found 221.2.

HRMS (ESI) $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2 \cdot \text{C}_2\text{H}_6\text{OS}$ (DMSO adduct) [$\text{M} + \text{H}$] calculated 299.1429, found 299.1450.

(2-Hydroxy-phenyl)-(4-hydroxy-piperidin-1-yl)-methanone (14a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (506 mg, 3.12 mmol) and piperidin-4-ol (631 mg, 6.24 mmol). Reaction time: 20 h. The mixture was acidified to pH 1 with 1 M hydrochloric acid before removing the dioxane *in vacuo*. The mixture was then extracted with ethyl acetate (3 x 30 mL) and the organics concentrated under reduced pressure. The residue was then dissolved in the minimum amount of water before freeze-drying to give soft white crystals (525mg) which were impure. This crude product was purified by flash chromatography (MeOH/DCM, 5:95) affording a white solid (343mg, 50%).

^1H NMR (500 MHz, CDCl_3) δ 9.61 (s, 1H), 7.33 (t, $J = 7.8$ Hz, 1H), 7.24 (dd, $J = 1.3, 7.8$ Hz, 2H), 7.01 (d, $J = 8.3$ Hz, 1H), 6.85 (t, $J = 7.5$ Hz, 1H), 4.11-3.95 (m, 3H), 3.54-3.35 (m, 2H), 2.03-1.87 (m, 2H), 1.68-1.59 (m, 2H).

^{13}C NMR (150MHz, CDCl_3) δ 171.2, 159.4, 132.9, 128.4, 118.8, 118.4, 117.2, 67.1, 43.2, 34.5.

LCMS retention time (min) 0.78.

MS (ESI) $\text{C}_{12}\text{H}_{15}\text{NO}_3$ [$\text{M} + \text{H}$] calculated 222.1, found 222.2.

HRMS (ESI) $\text{C}_{12}\text{H}_{15}\text{NO}_3$ [$\text{M} + \text{H}$] calculated 222.1130, found 222.1116.

(2-Hydroxy-phenyl)-(2-methyl-piperidin-1-yl)-methanone (15a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (501 mg, 3.09 mmol) and 2-methylpiperidine (0.730 mL, 6.18 mmol). Reaction time: 20 h. Minimum 1M hydrochloric acid was used to acidify the mixture to pH 1 followed by extraction with DCM (3 x 30 mL). The combined organic layers were passed through a phase separator to remove traces of water yielding a very pale brown solid (586 mg, 86%). Removal of the solvent *in vacuo* gave a residue which was purified by flash chromatography (MeOH/DCM, 5:95) to afford a white solid (470 mg, 70%).

^1H NMR (500 MHz, CDCl_3) δ 9.56 (s, 1H), 7.35 - 7.27 (m, 1H), 7.21 (dd, $J = 1.5, 7.7$ Hz, 1H), 7.03-6.93 (m, 1H), 6.88-6.78 (m, 1H), 4.72 (s, 1H), 4.15 (d, $J = 13.1$ Hz, 1H), 3.10 (td, $J = 2.3, 13.4$ Hz, 1H), 1.79-1.63 (m, 4H), 1.63-1.46 (m, 2H), 1.31 (d, $J = 7.0$ Hz, 3H).

^{13}C (126 MHz, CDCl_3) δ 171.0, 159.0, 132.4, 128.0, 118.7, 118.3, 118.2, 48.1, 41.5, 30.7, 26.3, 19.1, 16.3.

LCMS retention time (min) 1.34.

MS (ESI) C₁₃H₁₇NO₂ [M + H] calculated 220.1, found 220.4.

HRMS (ESI) C₁₃H₁₇NO₂ [M + H] calculated 220.1137, found 220.1317.

2-Hydroxy-N-isopropyl-N-methylbenzamide (16a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (501mg, 3.09 mmol) and N-methylpropan-2-amine (0.642 mL, 6.18 mmol). Reaction time: 20.5 h. The dioxane was removed *in vacuo* and the product was extracted with DCM (3 x 30 mL). The combined organic layers were passed through a phase separator to remove traces of water and the solvents removed *in vacuo* to afford a yellow oil which was dried under vacuum. This was purified by flash chromatography (ethyl acetate/heptane, 20-50% gradient) affording a white solid (420 mg, 70%).

¹H NMR (500 MHz, CDCl₃) δ 9.73 (s, 1H), 7.33-7.21 (m, 2H), 6.97 (d, J = 8.2 Hz, 1H), 6.83 (t, J = 7.5 Hz, 1H), 4.61 (s, 1H), 2.96 (s, 3H), 1.23 (d, J = 6.7, 6H).

¹³C NMR (126Hz, CDCl₃) δ 171.7, 158.9, 132.4, 128.2, 118.6, 118.5, 118.1, 48.2, 29.7, 20.0.

LCMS retention time (min) 1.11.

MS (ESI) C₁₁H₁₅NO₂ [M + H] calculated 194.3, found 194.4.

HRMS (ESI) C₁₁H₁₅NO₂ [M + H] calculated 194.1181, found 194.1168.

N-Cyclohexyl-2-hydroxy-N-methylbenzamide (17a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (503 mg, 3.10 mmol) and N-methylcyclohexanamine (0.809 mL, 6.21 mmol). Reaction time: 20.5 h. The red/orange solution was then cooled, acidified with 1M hydrochloric acid to pH 1 and the dioxane removed *in vacuo*. A precipitate formed which was collected by filtration affording the product as a white solid after drying (539 mg, 75%).

¹H NMR (500 MHz, CDCl₃) δ 9.82 (s, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.26 (d, J = 6.3 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.84 (t, J = 7.5 Hz, 1H), 4.20 (s, 1H), 3.00 (s, 3H), 1.83 (t, J = 13.7 Hz, 4H), 1.68 (d, J = 13.2 Hz, 1H), 1.61-1.50 (m, 2H), 1.36 (q, J = 13.2 Hz, 2H), 1.19-1.05 (m, 1H).

¹³C NMR (150.9 MHz, CDCl₃) δ 171.4, 159.1, 132.4, 128.1, 118.4, 118.1, 118.0, 67.1, 56.3, 30.2, 25.6, 25.5.

LCMS retention time (min) 1.41.

MS (ESI) C₁₄H₁₉NO₂ [M + H] calculated 234.3, found 234.4.

HRMS (ESI) C₁₄H₁₉NO₂ [M + H] calculated 234.1494, found 234.1486.

(2-Hydroxyphenyl)(3-hydroxypyrrolidin-1-yl)methanone (18a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (503 mg, 3.10 mmol) and pyrrolidin-3-ol (0.516 mL, 6.21 mmol). Reaction time: for 4 h, and turned deep orange on heating. The solution was acidified to pH 1 with 1M hydrochloric acid and the product extracted using DCM (3 x 30 mL) giving soft, dark yellow needles. Minor impurities were removed by filtration through a silica gel plug (eluted with 5:95 MeOH/DCM). Concentration under reduced pressure afforded a thick yellow oil which crystallized on drying under vacuum affording sticky white needles (482 mg, 75%).

¹H NMR (500 MHz, CDCl₃) δ 7.40 (s, 1H), 7.31 (t, J = 7.8 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.82 (t, J = 7.6 Hz, 1H), 4.48 (s, 1H), 3.90 (s, 1H), 3.82-3.74 (m, 1H), 3.71 (s, 1H), 3.61 (d, J = 12.1 Hz, 1H), 1.98 (s, 2H).

^{13}C NMR (75 MHz, CDCl_3 , 50 °C) δ 170.7, 160.0, 133.1, 128.4, 118.4, 118.0, 117.7, 70.1, 56.9, 46.9, 34.0.

LCMS retention time (min) 0.75.

MS (ESI) $\text{C}_{14}\text{H}_{19}\text{NO}_2$ [M + H] calculated 208.1, found 208.2.

HRMS (ESI) $\text{C}_{14}\text{H}_{19}\text{NO}_2$ [M + H] calculated 208.0973, found 208.0962.

2-Hydroxy-N,N-diisopropylbenzamide (19a)⁴ Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (503 mg, 3.10 mmol) and diisopropylamine (0.876 mL, 6.21 mmol). Reaction time: 20.5 hours. A small amount of a white precipitate was filtered off and the filtrate was acidified to pH 1 with 1M hydrochloric acid and evaporated to dryness. The residue was purified by flash chromatography (5:95 MeOH/DCM). Salicylic acid remained as an impurity, so the white solid was dissolved in water and the pH adjusted to 9 and the product extracted into DCM (3 x 30 mL). Concentration under reduced pressure afforded a white solid (42 mg, 6%).

^1H NMR (500 MHz, CDCl_3) δ 9.28 (s, 1H), 7.26 (t, J = 7.1 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.83 (t, J = 7.5 Hz, 1H), 3.92 (s, 2H), 1.38 (d, J = 4.6 Hz, 12H).

^{13}C NMR (151 MHz, CDCl_3) δ 171.2, 158.1, 131.7, 126.9, 120.7, 118.8, 118.1, 49.2, 21.2.

LCMS retention time (min) 1.38.

MS (ESI) $\text{C}_{13}\text{H}_{19}\text{NO}_2$ [M + H] calculated 222.2, found 222.4.

HRMS (ESI) $\text{C}_{13}\text{H}_{19}\text{NO}_2$ [M + H] calculated 222.1494, found 222.1489.

2-Hydroxy-N-methyl-N-phenylbenzamide (20a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (504 mg, 3.11 mmol) and N-methylaniline (0.674 mL, 6.22 mmol). Reaction time: 30 mins. Water (20 mL) was added to the tan reaction solution which turned white with brown immiscible globules. On acidification to pH 1 with 1M hydrochloric acid, the solution became clear but the precipitate remained. The product was extracted with DCM (3 x 30 mL) and the brown globules dissolved in the organic layer. The combined organic layers were passed through a phase separator to remove traces of water. The solvent was removed *in vacuo* affording a brown oil which was dried under vacuum. Further impurities were removed by filtration through a silica gel plug (eluted with DCM) affording the purified product (557 mg, 79%).

^1H NMR (500 MHz, CDCl_3) δ 10.90 (s, 1H), 7.33 (t, J = 7.6 Hz, 2H), 7.24 (d, J = 7.5 Hz, 1H), 7.16 (t, J = 7.1 Hz, 1H), 7.12 (d, J = 7.4 Hz, 2H), 6.93 (d, J = 8.1 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.39 (t, J = 7.6 Hz, 1H), 3.49 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 171.7, 160.9, 145.4, 132.9, 130.6, 129.9, 127.4, 126.9, 118.0, 117.9, 116.2, 39.5.

LCMS retention time (min) 1.32.

MS (ESI) $\text{C}_{14}\text{H}_{13}\text{NO}_2$ [M + H] calculated 228.1, found 228.4.

HRMS (ESI) $\text{C}_{14}\text{H}_{13}\text{NO}_2$ [M + H] calculated 228.1024, found 228.1014.

2-Hydroxy-N-methyl-N-o-tolylbenzamide (21a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (502 mg, 3.10 mmol) and methyl-*o*-tolyl-amine (0.765 mL, 6.19 mmol). Reaction time: 5 h. The solution was acidified to pH 1 with 1 M hydrochloric acid and the product extracted with DCM (3 x 30 mL). The combined organic layers were passed

through a phase separator to remove traces of water and the solvent removed *in vacuo*. Baseline impurities were removed by filtration through a silica gel plug, eluting with DCM, affording an orange solid which was further purified by flash chromatography (10:90 MeOH/DCM) affording a light orange solid (388 mg, 52%).

^1H NMR (600 MHz, CDCl_3) δ 11.28 (s, 1H), 7.23-7.14 (m, 3H), 7.13-7.06 (m, 2H), 6.88 (d, J = 8.2 Hz, 1H), 6.56 (d, J = 7.8 Hz, 1H), 6.32 (t, J = 7.4 Hz, 1H), 3.35 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 171.7, 160.9, 143.96, 143.95, 133.0, 132.0, 129.5, 128.4, 128.0, 127.8, 118.0, 117.8, 116.4, 38.7, 17.8.

LCMS retention time (min) 1.48.

MS (ESI) $\text{C}_{15}\text{H}_{15}\text{NO}_2$ [M + H] calculated 242.1, found 242.3.

HRMS (ESI) $\text{C}_{15}\text{H}_{15}\text{NO}_2$ [M + H] calculated 242.1181, found 242.1167.

N-(4-Chlorophenyl)-2-hydroxy-N-methylbenzamide (22a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (505 mg, 3.12 mmol) and 4-chloro-N-methylaniline (0.755 mL, 6.23 mmol). Reaction time: 6 h. Water (20mL) was added to the colorless solution and the mixture adjusted to pH 1 with 1 M hydrochloric acid, causing a white flaky solid to precipitate. The mixture was extracted with DCM (3 x 30 mL) and the combined organic layers were passed through a phase separator to remove traces of water. The solvent was removed *in vacuo* affording a yellow/brown solid. The residue was purified by flash chromatography (5:95 MeOH/DCM) affording a white solid (555 mg, 67%).

^1H NMR (600 MHz, CDCl_3) δ 10.66 (s, 1H), 7.25 (d, J = 8.7 Hz, 2H), 7.19-7.09 (m, 1H), 7.01 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.3 Hz, 1H), 6.66 (dd, J = 1.2 Hz, 8.0 Hz, 1H), 6.42 (t, J = 7.6 Hz, 1H), 3.42 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 171.7, 160.7, 143.9, 113.1, 132.9, 130.4, 130.0, 128.1, 118.17, 118.16, 116.1, 39.4.

LCMS retention time (min) 1.55.

MS (ESI) $\text{C}_{14}\text{H}_{12}\text{ClNO}_2$ [M + H] calculated 262.1, found 262.7.

HRMS (ESI) $\text{C}_{14}\text{H}_{12}\text{ClNO}_2$ [M + H] calculated 262.0635, found 262.0645.

2-Hydroxy-N-(4-methoxyphenyl)-N-methylbenzamide (23a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (503 mg, 3.10 mmol) and 4-methoxy-N-methylaniline (851 mg, 6.21 mmol). Reaction time: 3.5 h. Water (20 mL) was added and then the solution was acidified with 1 M hydrochloric acid to pH 1. The mixture was extracted with DCM (3 x 30 mL) affording a dark green organic layer (the aqueous layer had a black tint). The combined organic layers were passed through a phase separator to remove traces of water. Removal of the solvent *in vacuo* afforded a brown/green solid (766 mg, 96%).

^1H NMR (600 MHz, CDCl_3) δ 10.96 (s, 1H), 7.13 (t, J = 7.2 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.2 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 7.9 Hz, 1H), 6.39 (t, J = 7.5 Hz, 1H), 3.77 (s, 3H), 3.42 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 171.6, 160.8, 158.6, 138.2, 132.8, 130.5, 127.9, 117.99, 117.95, 116.3, 115.0, 55.7, 39.8.

LCMS retention time (min) 1.32.

MS (ESI) $\text{C}_{15}\text{H}_{15}\text{NO}_3$ [M + H] calculated 258.1, found 258.5.

HRMS (ESI) C₁₅H₁₅NO₃ [M + H] calculated 258.1130, found 258.1136.

(3,4-Dihydroquinolin-1(2H)-yl)(2-hydroxyphenyl)methanone (24a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (505mg, 3.12 mmol) and 1,2,3,4-tetrahydroquinoline (830 mg, 6.23 mmol). Reaction time: 5 h. The green reaction mixture was adjusted to pH 14 with 1 M aq sodium hydroxide and the brown/yellow precipitate extracted with DCM (3 x 30 mL). The combined organic layers were passed through a phase separator to remove traces of water. The solvent was then removed *in vacuo* and the residue purified by flash chromatography (5:95 MeOH/DCM) affording a white solid. Washing with diethyl ether and drying afforded the product (473 mg, 60%).

¹H NMR (600 MHz, CDCl₃) δ 10.40 (s, 1H), 7.23 (dd, J = 5.8, 9.7 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.04 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.93 (t, J = 7.7 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.52 (t, J = 7.6 Hz, 1H), 3.90 (t, J = 6.6 Hz, 2H), 2.82 (t, J = 6.6 Hz, 2H), 2.04 (p, J = 6.6 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 171.7, 160.6, 139.6, 133.4, 132.2, 130.4, 128.7, 126.3, 125.5, 118.3, 116.9, 44.8, 26.9, 24.3.

LCMS retention time (min) 1.49.

MS (ESI) C₁₆H₁₅NO₂ [M + H] calculated 254.1, found 254.3.

HRMS (ESI) C₁₆H₁₅NO₂ [M + H] calculated 254.1181, found 254.1176.

2-Hydroxy-N-methyl-N-(pyridin-2-yl)benzamide (25a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (503 mg, 3.10 mmol) and N-methylpyridin-2-amine (0.638 mL, 6.21 mmol). Reaction time: 2.5 h. Water (20 mL) was added and the solution acidified to pH 8 using 1 M hydrochloric acid. The dioxane was then removed *in vacuo* and the product extracted using DCM (3 x 30 mL). The combined organic layers were passed through a phase separator to remove traces of water. The solvents were removed *in vacuo* affording a colorless oil which was purified by flash chromatography (2:98 MeOH/DCM) affording a white solid (126 mg, 18%).

¹H NMR (600 MHz, CDCl₃) δ 10.40 (s, 1H), 8.43 (dd, J = 1.1, 4.8 Hz, 1H), 7.46 (td, J = 1.8, 7.9 Hz, 1H), 7.17-7.10 (m, 1H), 7.10-7.04 (m, 1H), 6.88 (d, J = 7.9 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.61 (dd, J = 1.4, 8.0 Hz, 1H), 6.39 (t, J = 7.2 Hz, 1H), 3.51 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 172.4, 160.4, 157.2, 149.4, 138.2, 133.3, 130.2, 121.9, 121.7, 118.3, 118.1, 116.8, 36.7.

LCMS retention time (min) 1.06.

MS (ESI) C₁₃H₁₂N₂O₂ [M + H] calculated 229.1, found 229.1.

HRMS (ESI) C₁₃H₁₂N₂O₂ [M + H] calculated 229.0977, found 229.0972.

2-Hydroxy-N-methyl-N-pyridin-3-yl-benzamide (26a) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (508 mg, 3.13 mmol) and N-methylpyridin-3-amine (678 mg, 6.27 mmol). Reaction time: 48 h. The solution turned dark brown on heating. Water (20 mL) was added before removing the dioxane *in vacuo*. The aqueous layer was basified with 1 M aq sodium hydroxide and washed with DCM (30 mL). The aqueous layer was then acidified with 1 M hydrochloric acid and washed with DCM (30 mL). The aqueous layer was then adjusted to pH 9 with 1 M aq sodium hydroxide and extracted with DCM (3 x 30 mL). The combined organic extracts were passed through a phase separator to remove traces of water. The solvents were removed *in vacuo* and the residue freeze-dried overnight. Purification by flash chromatography (MeOH/DCM, gradient 1:99-8:92) afforded a white solid (83 mg, 12%).

^1H NMR (500 MHz, CDCl_3) δ 10.44 (s, 1H), 8.49-8.35 (m, 2H), 7.47-7.37 (m, 1H), 7.28-7.20 (m, 1H), 7.19-7.09 (m, 1H), 6.87 (d, J = 8.3 Hz, 1H), 6.68 (dd, J = 1.3, 7.9 Hz, 1H), 6.46 (t, J = 7.6 Hz, 1H), 3.48 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 171.7, 159.8, 147.8 (2C), 142.0, 134.0, 133.1, 130.2, 124.1, 118.5, 118.1, 116.7, 39.1.

LCMS retention time (min) 0.84.

MS (ESI) $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$ [$\text{M} + \text{H}$] calculated 229.1, found 229.1.

HRMS (ESI) $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$ [$\text{M} + \text{H}$] calculated 229.0977, found 229.0967.

Piperazine-1,4-diylbis((2-hydroxyphenyl)methanone) (28) Followed Procedure A, used 2-(trifluoromethyl)phenol **4a** (509 mg, 3.14 mmol) and piperazine (135 mg, 1.57 mmol). Reaction time: 8 h. The mixture was added to water (20 mL) and filtered to yield a fine white solid which was dried under vacuum affording the product (401 mg, 78%).

^1H NMR (500 MHz, DMSO-d_6) δ 9.86 (s, 2H), 7.20 (t, J = 6.9, 2H), 7.12 (d, J = 7.1, 2H), 6.83 (dd, J = 7.7, 16.4, 4H), 3.60 (s, 4H), 3.25 (s, 4H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 167.9, 154.0, 130.9, 128.9, 124.3, 119.7, 116.4.

LCMS retention time (min) 1.05.

MS (ESI) $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4$ [$\text{M} + \text{H}$] calculated 327.1, found 327.2.

HRMS (ESI) $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4$ [$\text{M} + \text{H}$] calculated 327.1345, found 327.1325.

(4-Hydroxyphenyl)(piperidin-1-yl)methanone (30)⁵ Followed Procedure A, used 4-(trifluoromethyl)phenol **29** (505 mg, 3.12 mmol) and piperidine (0.615 mL, 6.23 mmol). Reaction time: 48 h. A pellet of sodium hydroxide was added after 47 h. The dioxane was removed under reduced pressure and the remaining basic aqueous layer was washed with DCM (30 mL) before acidification to pH 1 with 1 M hydrochloric acid. A white precipitate formed (505 mg, 79%) and was collected by filtration. Additional product was isolated from a DCM extraction (3 x 30 mL) of the filtrate. The organics were dried over magnesium sulfate and concentrated under reduced pressure. Both crops of product were combined to afford the product as a white solid (564 mg, 88%).

^1H NMR (600 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.17 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 3.38 (s, 4H), 1.55 (d, J = 5.0 Hz, 2H), 1.44 (s, 4H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 169.8, 159.1, 129.5, 127.4, 115.5, 43.2, 26.3, 24.8.

LCMS retention time (min) 1.08.

MS (ESI) $\text{C}_{12}\text{H}_{15}\text{NO}_2$ [$\text{M} + \text{H}$] calculated 206.1, found 206.3.

HRMS (ESI) $\text{C}_{12}\text{H}_{15}\text{NO}_2$ [$\text{M} + \text{H}$] calculated 206.1181, found 206.1160.

(4-Hydroxyphenyl)(morpholino)methanone (31) Followed Procedure A, used 4-(trifluoromethyl)phenol **29** (508 mg, 3.13 mmol) and morpholine (0.547 mL, 6.27 mmol). Reaction time: 16 h, the reaction solution turned light yellow on heating. Water (20 mL) was added, the dioxane removed *in vacuo* and the remaining aqueous solution adjusted to pH 1 with 1 M hydrochloric acid. The product was extracted with DCM (3 x 30 mL), and the

combined organic extracts passed through a phase separator to remove traces of water. Removal of the solvent *in vacuo* afforded a white solid (565 mg, 87%).

^1H NMR (500 MHz, CDCl_3) δ 8.69 (s, 1H), 7.22 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 3.71 (br. s, 8H).

^{13}C NMR (151 MHz, CDCl_3) δ 171.7, 159.1, 129.4, 125.6, 115.8, 67.3, 67.1, 48.4, 43.4.

LCMS retention time (min) 0.77.

MS (ESI) $\text{C}_{11}\text{H}_{13}\text{NO}_3$ [M + H] calculated 208.1, found 208.1.

HRMS (ESI) $\text{C}_{12}\text{H}_{15}\text{NO}_2$ [M + H] calculated 208.0974, found 208.0960.

4-Hydroxy-N-methyl-N-phenylbenzamide (32) Followed Procedure A, used 4-(trifluoromethyl)phenol **29** (504 mg, 3.11 mmol) and N-methylaniline (0.674 mL, 6.22 mmol). Reaction time: 1 h. Water (20 mL) was added and the dioxane removed *in vacuo* before adjusting to pH 14 with 1 M aq sodium hydroxide and washing with DCM (30 mL). The aq layer was then acidified with 1 M hydrochloric acid to pH 1 and a khaki precipitate formed which was collected by filtration and dried. The filtrate was further extracted with DCM (3 x 30 mL) and the combined organic extracts passed through a phase separator to remove traces of water. Removal of the solvent *in vacuo* yielded additional product. Both crops were combined and dried under vacuum (562 mg, 80%).

^1H NMR (600 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.23 (t, J = 7.8 Hz, 2H), 7.11 (t, J = 7.4 Hz, 1H), 7.09-7.02 (m, 4H), 6.51 (d, J = 8.6 Hz, 2H), 3.29 (s, 3H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 170.0, 159.2, 146.0, 131.2, 129.7, 127.5, 127.1, 126.7, 115.0, 36.8.

LCMS retention time (min) 1.20.

MS (ESI) $\text{C}_{14}\text{H}_{13}\text{NO}_2$ [M + H] calculated 228.1, found 228.2.

HRMS (ESI) $\text{C}_{14}\text{H}_{13}\text{NO}_2$ [M + H] calculated 228.1025, found 228.1004.

4-Hydroxy-N-(4-methoxyphenyl)-N-methylbenzamide (33) Followed Procedure A, used 4-(trifluoromethyl)phenol **29** (506 mg, 3.12 mmol) and 4-methoxy-N-methylaniline (856 mg, 6.24 mmol). Reaction time: 1 h. The dioxane was removed *in vacuo* and the aqueous solution adjusted to pH 14 using 1 M aq sodium hydroxide and washed with DCM (30 mL). The lime green organic washings were discarded and the aqueous layer adjusted to pH 1 with 1 M hydrochloric acid, causing a white solid to precipitate. This was collected by filtration and dried under vacuum affording the product (665 mg, 83%).

^1H NMR (600 MHz, DMSO-d_6) δ 9.68 (s, 1H), 7.05 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.51 (d, J = 8.6 Hz, 2H), 3.66 (s, 3H), 3.24 (s, 3H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 170.0, 159.0, 157.9, 138.8, 131.1, 128.7, 127.3, 114.9, 114.9, 55.9, 39.0.

LCMS retention time (min) 1.20.

MS (ESI) $\text{C}_{15}\text{H}_{15}\text{NO}_3$ [M + H] calculated 258.1, found 258.4.

HRMS (ESI) $\text{C}_{14}\text{H}_{13}\text{NO}_2$ [M + H] calculated 258.1130, found 258.1107.

2-Phenyl-4-(trifluoromethyl)-1H-imidazole (5)⁶⁻⁸ 3,3-dibromo-1,1,1-trifluoropropan-2-one (1079 mg, 4 mmol) and sodium acetate (328 mg, 4 mmol) were dissolved in water (1 mL) and heated to 100 °C for 45 mins. The mixture was added to a solution of benzaldehyde (424 mg, 4 mmol) and ammonium hydroxide (7 mL) in methanol (35 mL) and the resulting mixture stirred at rt for 40 minutes and then heated to reflux for 1.5 h and then stirred at rt overnight. The mixture was concentrated under reduced pressure and the residue partitioned between water (25 mL) and DCM (2 x 45 mL). The combined organic extracts were passed through a phase separator to remove traces of water and concentrated under reduced pressure affording a pale yellow solid. Purification by flash chromatography (20 to 30% ethyl acetate in heptane) afforded the product as a white solid (508 mg, 59%).

¹H NMR (500 MHz, DMSO-d₆) δ 13.17 (s, 1H), 7.96 (d, J = 7.4 Hz, 2H), 7.90 (s, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.41 (t, J = 7.3 Hz, 1H).

¹³C NMR (151 MHz, DMSO-d₆) δ 148.0, 131.4, 131.2, 130.1, 129.8, 129.5, 126.0, 123.9, 122.1, 119.6.

¹⁹F NMR (282 MHz, DMSO-d₆) δ -61.14 (s, 3F).

LCMS retention time (min) 1.36.

MS (ESI) C₁₀H₇F₃N₂ [M + H] calculated 213.2, found 213.4.

(2-Phenyl-1H-imidazol-4-yl)(piperidin-1-yl)methanone (34) Followed Procedure A, used 2-phenyl-4-(trifluoromethyl)-1H-imidazole **5** (509 mg, 2.40 mmol) and piperidine (0.474 mL, 4.80 mmol). Reaction time: 8 h. A small amount of 1 M aq sodium hydroxide was used to rinse the reaction flask and maintain pH 13-14 for extraction with DCM (3 x 30 mL). The combined organic layers were passed through a phase separator to remove traces of water. Removal of the solvent *in vacuo* yielded a yellow oil. This was purified by flash chromatography (4:96 MeOH/DCM) affording a light yellow solid. This washed with diethyl ether and dried affording the product (560 mg, 91%).

¹H NMR (300 MHz, DMSO-d₆, 80 °C) δ 12.66 (s, 1H), 7.97 (d, J = 6.6 Hz, 2H), 7.56 (s, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.35 (t, J = 7.3 Hz, 1H), 3.82 (s, 4H), 1.71-1.47 (m, 6H).

¹³C NMR (75MHz, DMSO-d₆, 80 °C) δ 163.1, 145.5, 138.6, 131.1, 129.3, 129.1, 126.0, 123.1, 45.8, 26.6, 25.0.

LCMS retention time (min) 1.18.

MS (ESI) C₁₅H₁₇N₃O [M + H] calculated 256.2, found 256.5.

HRMS (ESI) C₁₅H₁₇N₃O [M + H] calculated 256.1450, found 256.1450.

Morpholino(2-phenyl-1H-imidazol-4-yl)methanone (35) Followed Procedure A, used 2-phenyl-4-(trifluoromethyl)-1H-imidazole **5** (501 mg, 2.36 mmol) and morpholine (0.412 mL, 4.72 mmol). Reaction time: 1 h. The dioxane and most of the water were removed *in vacuo* and the remaining aqueous solution was freeze-dried to give a lime green residue. This was purified by flash chromatography (4:96 MeOH/DCM) affording the product as a white solid (519 mg, 85%).

¹H NMR (300 MHz, DMSO-d₆, 80 °C) δ 12.74 (s, 1H), 7.96 (d, J = 7.3 Hz, 2H), 7.64 (s, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 3.93 (s, 4H), 3.65 (t, J = 5.2 Hz, 4H).

^{13}C NMR (75 MHz, DMSO- d_6 , 80 °C) δ 162.8, 146.1, 130.9, 129.3, 129.2, 126.1, 124.7, 67.2, 45.5.

LCMS retention time (min) 0.94.

MS (ESI) $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_2$ [M + H] calculated 258.1, found 258.4.

HRMS (ESI) $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_2$ [M + H] calculated 258.1242, found 258.1229.

N-Methyl-N,2-diphenyl-1H-imidazole-4-carboxamide (36) Followed Procedure A, used 2-phenyl-4-(trifluoromethyl)-1H-imidazole **5** (506 mg, 2.38 mmol) and N-methylaniline (0.517 mL, 4.77 mmol). Reaction time: 1 h. A small amount of 1 M aq sodium hydroxide was used to rinse the reaction flask and maintain pH 13-14. The mixture was extracted with DCM. The extracts were passed through a phase separator to remove traces of water and the solvent removed *in vacuo* affording a brown oil. This was purified by flash chromatography (3:97 MeOH/DCM) affording a brown solid (590 mg, 89%).

^1H NMR (300 MHz, DMSO- d_6 , 80 °C) δ 12.61 (s, 1H), 7.91 (s, 2H), 7.50-7.23 (m, 9H), 3.41 (s, 3H).

^{13}C NMR (75 MHz, DMSO- d_6 , 80 °C) δ 162.3, 146.8, 145.4, 130.7, 129.9, 129.2, 129.1, 128.2, 127.8, 126.3, 38.6.

LCMS retention time (min) 1.20.

MS (ESI) $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}$ [M + H] calculated 278.1, found 278.5.

HRMS (ESI) $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}$ [M + H] calculated 278.1293, found 278.1277.

N-(4-Methoxyphenyl)-N-methyl-2-phenyl-1H-imidazole-4-carboxamide (37) Followed Procedure A, used 2-phenyl-4-(trifluoromethyl)-1H-imidazole **5** (510 mg, 2.40 mmol) and 4-methoxy-N-methylaniline (659 mg, 4.81 mmol). Reaction time: 3 h. The mixture was extracted with DCM (3 x 30 mL) and the combined organic layers passed through a phase separator to remove traces of water. Removal of the solvent *in vacuo* afforded a dark green solid which was purified by flash chromatography (3:97 MeOH/DCM) affording a brown solid (676 mg, 92%).

^1H NMR (300 MHz, DMSO- d_6 , 80 °C) δ 12.58 (s, 1H), 7.94 (s, 2H), 7.49-7.28 (m, 4H), 7.23 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H), 3.35 (s, 3H).

^{13}C NMR (75 MHz, DMSO- d_6 , 80 °C) δ 159.3, 138.0, 129.4, 129.2, 129.1, 126.4, 115.4, 56.2, 38.7.

LCMS retention time (min) 1.20.

MS (ESI) $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$ [M + H] calculated 308.1, found 308.5.

HRMS (ESI) $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$ [M + H] calculated 308.1399, found 308.1388.

Procedure B. 2-(Trifluoromethyl)aniline (1 equiv) and the secondary amine (2 equiv) were dissolved in dioxane (9 mL) and 1 M aq sodium hydroxide (3 equiv) in a 20 mL microwave vial. The vial was capped and heated to 195 or 200 °C for 360 min (fixed hold time on) in a single node microwave reactor (Biotage Initiator).

(2-Aminophenyl)(piperidin-1-yl)methanone (9b) Followed Procedure B, used 2-(trifluoromethyl)aniline **4b** (0.390 mL, 3.10 mmol) and piperidine (0.613 mL, 6.21 mmol). Water (20 mL) was added to the mixture the pH adjusted to 7 with 1 M hydrochloric acid. The mixture was extracted with DCM (3 x 30 mL) and the combined organic extracts passed through a phase separator to remove traces of water. The solvent was removed under reduced pressure affording an orange oil that was purified by flash chromatography (3:97 MeOH/DCM) affording the product as a yellow solid (439 mg, 69%).

^1H NMR (600 MHz, CDCl_3) δ 7.01 (t, J = 7.4 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 6.66-6.49 (m, 2H), 4.26 (s, 2H), 3.42 (br. s, 4H), 1.53 (d, J = 4.3 Hz, 2H), 1.46 (s, 4H).

^{13}C NMR (151 MHz, CDCl_3) δ 169.9, 145.7, 130.4, 127.7, 120.6, 117.3, 116.7, 48.7, 43.7, 26.4, 24.8.

LCMS retention time (min) 1.18.

MS (ESI) $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}$ [M + H] calculated 205.1, found 205.3.

HRMS (ESI) $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}$ [M + H] calculated 205.1341, found 205.1328.

(2-Aminophenyl)(morpholino)methanone (10b) Followed Procedure B, used 2-(trifluoromethyl)aniline **4b** (0.390 mL, 3.10 mmol) and morpholine (0.541 mL, 6.21 mmol). The reaction vial was rinsed with minimal water the mixture adjusted to pH 5 with 1 M hydrochloric acid. The mixture was extracted with DCM (3 x 30 mL) and the combined organic extracts passed through a phase separator to remove traces of water. The solvents were removed under reduced pressure affording a yellow oil that was purified by flash chromatography (3:97 MeOH/DCM) affording a colorless oil (347 mg, 54%).

^1H NMR (600 MHz, CDCl_3) δ 7.03 (t, J = 7.4 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 6.57 (d, J = 7.5 Hz, 2H), 4.34 (s, 2H), 3.56 (s, 4H), 3.49 (s, 4H).

^{13}C NMR (151 MHz, CDCl_3) δ 170.1, 146.0, 130.9, 128.1, 119.2, 117.4, 116.9, 67.1, 45.3.

LCMS retention time (min) 0.86.

MS (ESI) $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$ [M + H] calculated 207.1, found 207.1.

HRMS (ESI) $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$ [M + H] calculated 207.1133, found 207.1129.

2-Amino-N-methyl-N-phenylbenzamide (11b)⁹ Followed Procedure B, used 2-(trifluoromethyl)aniline **4b** (0.390 mL, 3.10 mmol) and N-methylaniline (0.672 mL, 6.21 mmol). The vial was rinsed with minimal water and 1 M hydrochloric acid added to adjust to pH 7. The mixture was extracted with DCM (3 x 30 mL) and the combined organic extracts passed through a phase separator to remove traces of water. Removal of the solvents under reduced pressure and purification by flash chromatography (5:95 MeOH/DCM) afforded a sticky brown oil that solidified on drying under high vacuum (100 mg, 14%).

^1H NMR (600 MHz, CDCl_3) δ 7.19 (t, J = 7.8 Hz, 2H), 7.09 (t, J = 7.4 Hz, 1H), 7.04 (d, J = 7.5 Hz, 2H), 6.94 (t, J = 7.7 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 6.29 (t, J = 7.5 Hz, 1H), 4.56 (s, 2H), 3.45 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 171.3, 147.1, 145.2, 130.6, 129.9, 129.3, 126.6, 126.5, 119.9, 116.8, 116.6, 38.1.

LCMS retention time (min) 1.31.

MS (ESI) C₁₄H₁₄N₂O [M + H] calculated 227.1, found 227.2.

HRMS (ESI) C₁₄H₁₄N₂O [M + H] calculated 227.1184, found 227.1168.

2-Amino-N-(4-methoxyphenyl)-N-methylbenzamide (12b) Followed Procedure B, used 2-(trifluoromethyl)aniline **4b** (0.390 mL, 3.10 mmol) and 4-methoxy-N-methylaniline (851 mg, 6.21 mmol). The pH of the mixture was adjusted to 7 and the mixture extracted with DCM (3 x 30 mL) and the combined organic extracts passed through a phase separator to remove traces of water. Removal of the solvent *in vacuo* afforded a brown oil that was purified by flash chromatography (MeOH/DCM 2:98 to 5:95) affording the product as a brown oil (285 mg, 36%).

¹H NMR (600 MHz, CDCl₃) δ 7.00-6.86 (m, 3H), 6.75-6.66 (m, 3H), 6.56 (d, J = 8.1 Hz, 1H), 6.31 (t, J = 7.5 Hz, 1H), 4.59 (s, 2H), 3.68 (s, 3H), 3.40 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 171.3, 158.0, 146.8, 138.1, 130.4, 129.7, 127.6, 120.2, 116.9, 116.6, 114.5, 55.5, 38.4.

LCMS retention time (min) 1.31.

MS (ESI) C₁₅H₁₆N₂O₂ [M + H] calculated 257.3, found 257.2.

HRMS (ESI) C₁₅H₁₆N₂O₂ [M + H] calculated 257.1290, found 257.1288.

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