

Unveiling the Potential of BenzylethyleneAryl-Urea Scaffolds for Designing of new Onco Immunomodulating Agents

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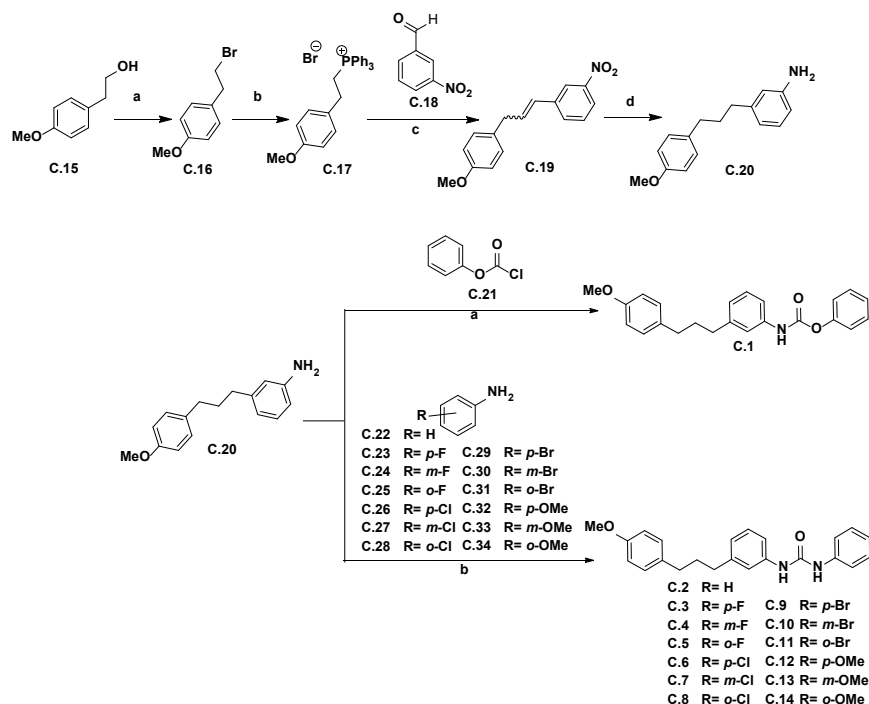
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Experimental procedure



1-(Bromomethyl)-4-methoxybenzene (C.16)

To a solution of 2-(4-methoxyphenyl)ethan-1-ol **C.15** (3.88 g, 25.3 mmol) in toluene (33 mL) was added PBr_3 (856 μL , 8.8 mmol, 0.35 eq) under nitrogen atmosphere and the resulting mixture was refluxed for 2 hr. After cooling to room temperature the mixture was washed with an aqueous saturated solution of $\text{Na}_2\text{S}_2\text{O}_3/\text{NaHCO}_3$ (1:1) (3 x 20 mL), dried over MgSO_4 and concentrated *in vacuo* to give 5.12 g (94 %) of compound **C.16** as a clear oil.

(4-Methoxyphenethyl)triphenylphosphonium bromide (C.17)

To a solution of 1-(2-bromoethyl)-4-methoxybenzene **C.16** (5.12 g, 23.80 mmol) in EtOH (240 mL) was added PPh_3 (7.00 g, 26.20 mmol, 1.1 eq). The mixture was refluxed for 6 days under nitrogen atmosphere. Then, the solvent was removed *in vacuo* and the crude product was purified on silica gel chromatography using dichloromethane and dichloromethane:MeOH (9:1) to give 9.44 g (83%) of **C.17** as a clear oil.

(*E/Z*)-1-(3-(4-Methoxyphenyl)prop-1-en-1-yl)-3-nitrobenzene (C.19)

To a solution of (4-methoxyphenethyl)triphenylphosphonium bromide **C.17** (3.11 g, 6.51 mmol) in dichloromethane (40 mL) was added 3-nitrobenzaldehyde **C.18** (994 mg, 6.51 mmol), K₂CO₃ (7.16 mmol, 1.1 eq) and 18-crown-6 (310 mg, 0.18 eq). The mixture was refluxed for 24 h and then filtered and concentrated *in vacuo*. The crude product was purified on silica gel chromatography using Hexanes:AcOEt (9:1) to give 1.38 g (79 %) of compound **C.19** as an orange oil.

3-(3-(4-Methoxyphenyl)propyl)aniline (C.20)

A solution of (*E/Z*)-1-(3-(4-methoxyphenyl)prop-1-en-1-yl)-3-nitrobenzene **C.19** (860 mg, 3.19 mmol) in AcOEt (19 mL) was added to a mixture of Pd/C (10%, 172 mg) in AcOEt (3.5 mL). The resulting mixture was stirred overnight under H₂ atmosphere and then filtered through Celite yielding 602 mg (78 %) of compound **C.19** as a brown oil.

(Phenyl (3-((4-methoxybenzyl)oxy)phenyl)carbamate) (C.1)

A solution of 3-(3-(4-methoxyphenyl)propyl)aniline **C.20** (361 mg, 1.5 mmol) in dry THF (7.5 mL) was cooled at 0 °C and then anhydrous pyridine (301 µL, 3.74 mmol) and phenyl chloroformate **C.21** (291 µL, 2.25 mmol) were added. The resulting mixture was stirred under nitrogen atmosphere for 20 min at 0°C and at room temperature for 1 h. Then, water (7.5 mL) and 1M aqueous HCl (3.75 mL) were added and the mixture was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic phases were washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo* and the residue was purified on silica gel chromatography using Hexanes:Ethyl acetate (9:1) as eluent yielding 384 mg (71 %) of carbamate **C.1** as a white solid.

Analytical NMR spectra

1-(2-Bromoethyl)-4-methoxybenzene (C.16). Yield 94%; clear oil; ¹H NMR (400 MHz, CDCl₃) δ 7.15 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 3.55 (t, J = 7.6 Hz, 2H), 3.13 (t, J = 7.6 Hz, 2H).; ¹³C NMR (100 MHz, CDCl₃) δ 158.52 (C), 130.97 (C), 129.59 (2CH), 113.97 (2CH), 55.18 (CH₃), 38.53 (CH₂), 33.29 (CH₂).

(4-Methoxyphenethyl)triphenylphosphonium bromide (C.17). Yield 94%; clear oil; ¹H NMR (400 MHz, CDCl₃) δ 7.89 – 7.76 (m, 9H), 7.73 – 7.66 (m, 6H), 7.22 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 4.16 – 4.05 (m, 2H), 3.75 (s, 3H), 3.07 – 2.95 (m, 2H).; ¹³C NMR (100 MHz, CDCl₃) δ 158.65 (C), 135.00 (3CH, d, J = 3.0 Hz), 133.77 (6CH, d, J = 10.1 Hz), 130.47 (6CH, d, J = 12.6 Hz), 130.14 (C, d, J = 13.6 Hz), 129.70 (2CH), 118.22 (3C, d, J = 85.7 Hz), 114.27 (2CH), 55.29 (CH₃), 27.61 (CH₂, d, J = 3.7 Hz), 24.87 (CH₂, d, J = 47.4 Hz).

(Z)-1-(3-(4-Methoxyphenyl)prop-1-en-1-yl)-3-nitrobenzene + (E)-1-(3-(4-methoxyphenyl)prop-1-en-1-yl)-3-nitrobenzene (42:58) (C.19). Yield 91%; orange oil; ¹H NMR (400 MHz, CDCl₃) δ 8.23 – 8.16 (m, 2H), 8.12 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H-cis), 8.05 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H-trans), 7.64 (ddd, J = 7.7, 3.3, 2.1 Hz, 2H), 7.52 (t, J = 7.9 Hz, 1H-cis), 7.45 (t, J = 8.0 Hz, 1H-trans), 7.17 (d, J = 8.7 Hz, 2H-trans), 7.14 (d, J = 8.8 Hz, 2H-cis), 6.89 (d, J = 8.7 Hz, 2H-trans), 6.87 (d, J = 8.6 Hz, 2H-cis), 6.60 (d, J = 11.5 Hz, 1H-cis), 6.51 (dd, J = 15.3, 9.2 Hz, 1H-trans), 6.46 (d, J = 15.9 Hz, 1H-trans), 6.04 (dt, J = 11.5, 7.6 Hz, 1H-cis), 3.82 (s, 3H-trans), 3.81 (s, 3H-cis), 3.61 (dd, J = 7.6, 1.6 Hz, 2H-cis), 3.54 (d, J = 5.7 Hz, 2H-trans).; ¹³C NMR (100 MHz, CDCl₃) δ 158.29 (C), 158.20 (C), 148.60 (C), 148.29 (C), 139.32 (C), 138.82 (C), 134.57 (CH), 134.02 (CH), 133.29 (CH), 131.88 (CH), 131.78 (C), 131.20 (C), 129.63 (2CH), 129.31 (CH), 129.17 (CH), 129.13 (2CH), 128.49 (CH), 127.40 (CH), 123.45 (CH), 121.62 (CH), 121.60 (CH), 120.67 (CH), 114.10 (2CH), 114.07 (2CH), 55.28 (CH₃), 55.26 (CH₃), 38.34 (CH₂), 33.65 (CH₂); HR ESMS *m/z* 292.0956 [M-Na]⁺. Calc. for C₁₆H₁₅NO₃ 292.0950.

3-(3-(4-Methoxyphenyl)propyl)aniline (C.20). Yield 78%; brown oil; ¹H NMR (400 MHz, CDCl₃) δ 7.12 (d, J = 8.8 Hz, 2H), 7.10 – 7.05 (m, 1H), 6.85 (d, J = 8.7 Hz, 2H), 6.62 (d, J = 7.8 Hz, 1H), 6.57 – 6.52 (m, 2H), 3.81 (s, 3H), 3.52 (s, 2H), 2.64 – 2.52 (m,

4H), 1.98 – 1.85 (m, 2H).; ¹³C NMR (100 MHz, CDCl₃) δ 157.64 (C), 146.30 (C), 143.56 (C), 134.40 (C), 129.23 (2CH), 129.09 (CH), 118.77 (CH), 115.22 (CH), 113.66 (2CH), 112.57 (CH), 55.16 (CH₃), 35.30 (CH₂), 34.46 (CH₂), 32.93 (CH₂); HR ESMS *m/z* 242.1540 [M-H]⁺. Calc. for C₁₆H₁₉NO 242.1545.

Phenyl (3-(3-(4-methoxyphenyl)propyl)phenyl)carbamate (C.1). Yield 71%; white solid; m.p. 89-91°C; ¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.29 (m, 2H), 7.26 (s, 1H), 7.22 – 7.10 (m, 5H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.96 – 6.83 (m, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 3.72 (s, 3H), 2.61 – 2.48 (m, 4H), 1.86 (tt, *J* = 9.1, 6.9 Hz, 2H).; ¹³C NMR (100 MHz, CDCl₃) δ 157.69 (C), 151.63 (C), 150.56 (C), 143.60 (C), 137.31 (C), 134.21 (C), 129.35 (2CH), 129.27 (2CH), 128.96 (CH), 125.63 (CH), 124.08 (CH), 121.62 (2CH), 118.78 (CH), 116.18 (CH), 113.72 (2CH), 55.21 (CH₃), 35.32 (CH₂), 34.44 (CH₂), 33.00 (CH₂).; IR *v*_{max} (cm⁻¹) 3296 (N-H), 1706 (C=O), 1545 (N-H amide), 1202, 1172, 1028 (C-O).; HR ESMS *m/z* 384.1579 [M-Na]⁺. Calc. for C₂₃H₂₃NO₃ 384.1576.

1-(3-(3-(4-Methoxyphenyl)propyl)phenyl)-3-phenylurea (C.2). Yield 52%; white solid; m.p. 157-159°C; ¹H NMR (400 MHz, DMSO) δ 8.60 (s, 1H), 8.57 (s, 1H), 7.45 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.32 (d, *J* = 1.7 Hz, 1H), 7.30 – 7.21 (m, 3H), 7.17 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.00 – 6.92 (m, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 7.4 Hz, 1H), 3.72 (s, 3H), 2.54 (dd, *J* = 13.4, 5.7 Hz, 4H), 1.84 (dq, *J* = 15.3, 7.7 Hz, 2H).; ¹³C NMR (100 MHz, DMSO) δ 157.34 (C), 152.48 (C), 142.55 (C), 139.68 (C), 139.62 (C), 133.74 (C), 129.14 (2CH), 128.71 (2CH), 128.61 (CH), 121.85 (CH), 121.72 (CH), 118.14 (2CH), 118.02 (CH), 115.68 (CH), 113.67 (2CH), 54.91 (CH₃), 34.74 (CH₂), 33.77 (CH₂), 32.82 (CH₂).; IR *v*_{max} (cm⁻¹) 3299 (N-H), 1643 (C=O), 1554 (N-H amide), 1446 (N-C=O), 1242, 1041 (C-O).; HR ESMS *m/z* 383.1728 [M-Na]⁺. Calc. for C₂₃H₂₄N₂O₂ 383.1736.

1-(4-Fluorophenyl)-3-(3-(3-(4-methoxyphenyl)propyl)phenyl)urea (C.3). Yield 91%; white solid; m.p. 181-183°C; ¹H NMR (400 MHz, DMSO) δ 8.63 (s, 1H), 8.56 (s, 1H), 7.45 (dd, *J* = 9.2, 4.9 Hz, 2H), 7.31 (t, *J* = 1.7 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 7.14 – 7.05 (m, 4H), 6.87 – 6.82 (m, 2H), 6.80 (d, *J* = 7.4 Hz, 1H), 3.72 (s, 3H), 2.57 – 2.52 (m, 4H), 1.89 – 1.76 (m, 2H).; ¹³C NMR (100 MHz, DMSO) δ 157.86 (s), 157.80 (C, *J* = 238.0 Hz), 153.10 (C), 143.06 (C), 140.11 (C), 136.55 (C), 134.26 (C), 129.66 (2CH), 129.12 (CH), 122.40 (CH), 120.43 (2CH, *d*, *J* = 7.7 Hz), 118.60 (CH),

116.26 (CH), 115.71 (2CH, d, J = 22.2 Hz), 114.19 (2CH), 55.43 (CH₃), 35.25 (CH₂), 34.29 (CH₂), 33.33 (CH₂).; 19F NMR (377 MHz, DMSO) δ -121.58; IR ν_{max} (cm⁻¹) 3292 (N-H), 1637 (C=O), 1561 (N-H amide), 1508 (N-C=O), 1212, 1041 (C-O).; HR ESMS m/z 401.1636 [M-Na]⁺. Calc. for C₂₃H₂₃N₂O₂F 401.1642.

1-(3-Fluorophenyl)-3-(3-(3-(4-methoxyphenyl)propyl)phenyl)urea (C.4). Yield 88%; white solid; m.p. 154°C; 1H NMR (400 MHz, DMSO); δ 8.87 (s, 1H), 8.67 (s, 1H), 7.49 (dt, J = 12.1, 2.3 Hz, 1H), 7.32 (t, J = 2.0 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.23 (tt, J = 4.5, 2.2 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 7.12 (d, J = 8.6 Hz, 2H), 7.11 – 7.07 (m, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.83 – 6.80 (m, 1H), 6.80 – 6.72 (m, 1H), 3.72 (s, 3H), 2.55 (t, J = 7.6 Hz, 4H), 1.90 – 1.77 (m, 2H).; 13C NMR (100 MHz, DMSO) δ 162.37 (C, J = 240.7 Hz), 157.35 (C), 152.34 (C), 142.59 (C), 141.60 (C, d, J = 11.4 Hz), 139.34 (C), 133.74 (C), 130.22 (CH, d, J = 9.8 Hz), 129.15 (2CH), 128.64 (CH), 122.11 (CH), 118.20 (CH), 115.87 (CH), 113.85 (CH, d, J = 2.6 Hz), 113.67 (2CH), 108.01 (CH, d, J = 21.4 Hz), 104.79 (CH, d, J = 26.5 Hz), 54.91 (CH₃), 34.72 (CH₂), 33.77 (CH₂), 32.81 (CH₂).; 19F NMR (377 MHz, DMSO) δ -112.31; IR ν_{max} (cm⁻¹) 3292 (N-H), 1640 (C=O), 1554 (N-H amide), 1508 (N-C=O), 1245, 1143, 1035 (C-O).; HR ESMS m/z 401.1640 [M-Na]⁺. Calc. for C₂₃H₂₃N₂O₂F 401.1642.

1-(2-Fluorophenyl)-3-(3-(3-(4-methoxyphenyl)propyl)phenyl)urea (C.5). Yield 92%; white solid; m.p. 152°C; 1H NMR (400 MHz, DMSO); δ 9.00 (s, 1H), 8.49 (d, J = 2.5 Hz, 1H), 8.15 (td, J = 8.3, 1.7 Hz, 1H), 7.32 (t, J = 1.7 Hz, 1H), 7.27 – 7.21 (m, 2H), 7.20 – 7.14 (m, 2H), 7.12 (d, J = 8.6 Hz, 2H), 7.04 – 6.95 (m, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.82 (m, 1H), 3.72 (s, 3H), 2.60 – 2.52 (m, 4H), 1.90 – 1.76 (m, 2H).; 13C NMR (100 MHz, DMSO) δ 157.35 (C), 152.14 (C), 151.96 (C, d, J = 241.1 Hz), 142.68 (C), 139.36 (C), 133.75 (C), 129.15 (2CH), 128.72 (CH), 127.54 (d, J = 10.3 Hz), 124.44 (s), 122.35 (d, J = 7.5 Hz), 122.12 (s), 120.54 (C), 117.94 (CH), 115.61 (CH), 114.89 (CH, d, J = 19.1 Hz), 113.68 (2CH), 54.92 (CH₃), 34.73 (CH₂), 33.77 (CH₂), 32.81 (CH₂).; 19F NMR (377 MHz, DMSO) δ -129.80; IR ν_{max} (cm⁻¹) 3302 (N-H), 1647 (C=O), 1554 (N-H amide), 1508 (N-C=O), 1238, 1196, 1047 (C-O).; HR ESMS m/z 401.1639 [M-Na]⁺. Calc. for C₂₃H₂₃N₂O₂F 401.1641.

1-(4-Chlorophenyl)-3-(3-(3-(4-methoxyphenyl)propyl)phenyl)urea (C.6). Yield 66%; white solid; m.p. 179-182°C; ¹H NMR (400 MHz,DMSO); δ 8.75 (s, 1H), 8.61 (s, 1H), 7.48 (d, J = 9.0 Hz, 2H), 7.34 – 7.28 (m, 3H), 7.25 – 7.21 (m, 1H), 7.18 (t, J = 7.7 Hz, 1H), 7.12 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.83 – 6.79 (m, 1H), 3.72 (s, 3H), 2.55 (t, J = 7.7 Hz, 4H), 1.89 – 1.78 (m, 2H).; ¹³C NMR (100 MHz, DMSO) δ 157.34(C), 152.38 (C), 142.57(C), 139.43(C), 138.70 (C), 133.74 (C), 129.14 (2CH), 128.62 (C), 128.54 (2CH), 122.54(CH), 122.03 (CH), 119.67 (2CH), 118.15 (CH), 115.81 (CH), 113.67 (2CH), 54.91 (CH₃), 34.71 (CH₂), 33.76 (CH₂), 32.80 (CH₂).; IR ν_{max} (cm⁻¹) 3289 (N-H), 1637 (C=O), 1558 (N-H amide), 1505 (N-C=O), 1244, 1044 (C-O).; HR ESMS *m/z* 417.1339 [M-Na]⁺. Calc. for C₂₃H₂₃N₂O₂Cl 417.1346.

1-(3-Chlorophenyl)-3-(3-(3-(4-methoxyphenyl)propyl)phenyl)urea (C.7). Yield 69%; white solid; m.p. 143-147°C; ¹H NMR (400 MHz,DMSO); δ 8.83 (s, 1H), 8.66 (s, 1H), 7.72 (t, J = 1.9 Hz, 1H), 7.33 (t, J = 1.7 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.27 – 7.22 (m, 2H), 7.22 – 7.16 (m, 1H), 7.13 (d, J = 8.7 Hz, 2H), 7.01 (ddd, J = 7.6, 2.1, 1.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 6.84 – 6.79 (m, 1H), 3.73 (s, 3H), 2.55 (t, J = 7.6 Hz, 4H), 1.91 – 1.77 (m, 2H).; ¹³C NMR (100 MHz, DMSO) δ 157.87 (C), 152.85 (C), 143.11 (C), 141.80 (C), 139.85 (C), 134.25 (C), 133.67 (C), 130.83 (CH), 129.67 (2CH), 129.15 (CH), 122.65 (CH), 121.85 (CH), 118.75 (CH), 118.01 (CH), 117.09 (CH), 116.41 (CH), 114.19 (2CH), 55.43 (CH₃), 35.24 (CH₂), 34.29 (CH₂), 33.33 (CH₂).; IR ν_{max} (cm⁻¹) 3299 (N-H), 1637 (C=O), 1547 (N-H amide), 1511 (N-C=O), 1244, 1035 (C-O).; HR ESMS *m/z* 417.1341 [M-Na]⁺. Calc. for C₂₃H₂₃N₂O₂Cl 417.1346.

1-(2-Chlorophenyl)-3-(3-(3-(4-methoxyphenyl)propyl)phenyl)urea (C.8). Yield 92%; white solid; m.p. 134-136°C; ¹H NMR (400 MHz,DMSO); δ 9.34 (s, 1H), 8.26 (s, 1H), 8.16 (dd, J = 8.3, 1.5 Hz, 1H), 7.45 (dd, J = 8.0, 1.4 Hz, 1H), 7.33 (t, J = 1.7 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.27 – 7.23 (m, 1H), 7.20 (t, J = 7.7 Hz, 1H), 7.12 (d, J = 8.7 Hz, 2H), 7.02 (ddd, J = 8.0, 7.4, 1.6 Hz, 1H), 6.85 (d, J = 8.2 Hz, 2H), 6.83 – 6.81 (m, 1H), 3.72 (s, 3H), 2.55 (td, J = 7.8, 4.0 Hz, 4H), 1.91 – 1.76 (m, 2H).; ¹³C NMR (100 MHz, DMSO) δ 157.35 (C), 152.07 (C), 142.66 (C), 139.37 (C), 135.96 (C), 133.73 (C), 129.14 (3CH), 128.73 (CH), 127.50 (CH), 123.19 (CH), 122.18 (CH), 121.83 (C), 121.26 (CH), 118.02 (CH), 115.68 (CH), 113.68 (2CH), 54.91 (CH₃), 34.72 (CH₂), 33.76 (CH₂), 32.80 (CH₂).; IR ν_{max} (cm⁻¹) 3266 (N-H), 1647 (C=O), 1561 (N-H amide), 1508 (N-C=O),

1249, 1041 (C-O).; HR ESMS m/z 417.1340 $[M-Na]^+$. Calc. for $C_{23}H_{23}N_2O_2Cl$ 417.1346.

1-(4-Bromophenyl)-3-(3-(3-(4-methoxyphenyl)propyl)phenyl)urea (C.9). Yield 51%; white solid; m.p. 191-196°C; 1H NMR (400 MHz, DMSO); δ 8.75 (s, 1H), 8.61 (s, 1H), 7.43 (s, 4H), 7.31 (d, $J = 1.6$ Hz, 1H), 7.25 – 7.20 (m, 1H), 7.18 (t, $J = 7.7$ Hz, 1H), 7.12 (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 6.81 (d, $J = 7.5$ Hz, 1H), 3.72 (s, 3H), 2.54 (dd, $J = 13.0, 5.2$ Hz, 4H), 1.91 – 1.76 (m, 2H).; ^{13}C NMR (100 MHz, DMSO) δ 156.29 (C), 151.29 (C), 141.52 (C), 138.36 (C), 138.09 (C), 132.69 (C), 130.39 (2CH), 128.09 (2CH), 127.58 (CH), 121.00 (CH), 119.03 (2CH), 117.11 (CH), 114.77 (CH), 112.62 (2CH), 112.04 (C), 53.86 (CH₃), 33.67 (CH₂), 32.72 (CH₂), 31.75 (CH₂).; IR ν_{max} (cm⁻¹) 3296 (N-H), 1640 (C=O), 1548 (N-H amide), 1508 (N-C=O), 1244, 1041 (C-O).; HR ESMS m/z 461.0838 $[M-Na]^+$. Calc. for $C_{23}H_{23}N_2O_2Br$ 461.0841.

1-(3-Bromophenyl)-3-(3-(3-(4-methoxyphenyl)propyl)phenyl)urea (C.10). Yield 34%; white solid; m.p. 141-144°C; 1H NMR (400 MHz, DMSO); δ 8.81 (s, 1H), 8.65 (s, 1H), 7.86 (t, $J = 1.9$ Hz, 1H), 7.32 (t, $J = 1.5$ Hz, 1H), 7.29 (dd, $J = 8.2, 2.0$ Hz, 1H), 7.26 – 7.22 (m, 1H), 7.22 – 7.20 (m, 1H), 7.20 – 7.16 (m, 1H), 7.16 – 7.13 (m, 1H), 7.12 (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 6.81 (s, 1H), 3.72 (s, 3H), 2.55 (t, $J = 7.6$ Hz, 4H), 1.90 – 1.78 (m, 2H).; ^{13}C NMR (100 MHz, DMSO) δ 157.34 (C), 152.31 (C), 142.59 (C), 141.41 (C), 139.31 (C), 133.73 (C), 130.62 (CH), 129.15 (2CH), 128.63 (CH), 124.24 (CH), 122.14 (CH), 121.67 (C), 120.34 (CH), 118.24 (CH), 116.97 (CH), 115.89 (CH), 113.67 (2CH), 54.91 (CH₃), 34.72 (CH₂), 33.76 (CH₂), 32.81 (CH₂).; IR ν_{max} (cm⁻¹) 3296 (N-H), 1637 (C=O), 1554 (N-H amide), 1508 (N-C=O), 1244, 1037 (C-O).; HR ESMS m/z 461.0839 $[M-Na]^+$. Calc. for $C_{23}H_{23}N_2O_2Br$ 461.0841.

1-(2-Bromophenyl)-3-(3-(3-(4-methoxyphenyl)propyl)phenyl)urea (C.11). Yield 64%; white solid; m.p. 137-140°C; 1H NMR (400 MHz, DMSO); δ 9.40 (s, 1H), 8.09 (s, 1H), 8.07 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.61 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.37 – 7.30 (m, 2H), 7.29 – 7.23 (m, 1H), 7.20 (t, $J = 7.7$ Hz, 1H), 7.12 (d, $J = 8.7$ Hz, 2H), 6.97 (ddd, $J = 8.0, 7.4, 1.6$ Hz, 1H), 6.84 (d, $J = 8.7$ Hz, 2H), 6.83 – 6.80 (m, 1H), 3.72 (s, 3H), 2.55 (td, $J = 7.9, 3.6$ Hz, 4H), 1.91 – 1.78 (m, 2H).; ^{13}C NMR (100 MHz, DMSO) δ 157.34 (C), 152.12 (C), 142.65 (C), 139.41 (C), 137.07 (C), 133.73 (C), 132.41 (CH), 129.14 (2CH),

128.71 (CH), 127.99 (CH), 123.95 (CH), 122.17 (2CH), 118.05 (CH), 115.70 (CH), 113.67 (2CH), 112.95 (C), 54.91 (CH₃), 34.72 (CH₂), 33.76 (CH₂), 32.80 (CH₂).; IR ν_{max} (cm⁻¹) 3270 (N-H), 1643 (C=O), 1558 (N-H amide), 1508 (N-C=O), 1249, 1041 (C-O).; HR ESMS m/z 461.0842 [M-Na]⁺. Calc. for C₂₃H₂₃N₂O₂Br 461.0841.

1-(4-Methoxyphenyl)-3-(3-(3-(4-methoxyphenyl)propyl)phenyl)urea (C.12). Yield 34%; white solid; m.p. 181-183°C; ¹H NMR (400 MHz, DMSO); δ 8.48 (s, 1H), 8.40 (s, 1H), 7.34 (d, J = 9.1 Hz, 2H), 7.30 (t, J = 1.7 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.19 – 7.14 (m, 1H), 7.12 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 9.0 Hz, 3H), 6.84 (d, J = 8.6 Hz, 3H), 6.78 (d, J = 7.4 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 2.59 – 2.52 (m, 4H), 1.88 – 1.77 (m, 2H).; ¹³C NMR (100 MHz, DMSO) δ 154.42 (C), 152.68 (C), 142.50 (C), 139.81 (C), 133.75 (C), 132.70 (C), 129.14 (2CH), 128.57 (CH), 121.65 (CH), 119.97 (2CH), 117.92 (CH), 115.58 (CH), 113.94 (2CH), 113.67 (2CH), 55.14 (CH₃), 54.91 (CH₃), 34.74 (CH₂), 33.77 (CH₂), 32.82 (CH₂).; IR ν_{max} (cm⁻¹) 3289 (N-H), 1633 (C=O), 1554 (N-H amide), 1508 (N-C=O), 1238, 1179, 1021 (C-O).; HR ESMS m/z 391.2024 [M-H]⁺. Calc. for C₂₄H₂₆N₂O₃ 391.2022.

1-(3-Methoxyphenyl)-3-(3-(3-(4-methoxyphenyl)propyl)phenyl)urea (C.13). Yield 90%; white solid; m.p. 107-110°C; ¹H NMR (400 MHz, DMSO) δ 8.62 (s, 1H), 8.56 (s, 1H), 7.31 (t, J = 1.6 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.20 – 7.14 (m, 3H), 7.12 (d, J = 8.7 Hz, 2H), 6.92 (dd, J = 8.1, 1.9 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 7.4 Hz, 1H), 6.54 (ddd, J = 8.2, 2.5, 0.8 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 2.58 – 2.52 (m, 4H), 1.84 (dq, J = 15.3, 7.7 Hz, 2H).; ¹³C NMR (100 MHz, DMSO) δ 159.67 (C), 157.34 (C), 152.41 (C), 142.57 (C), 140.92 (C), 139.55 (C), 133.74 (C), 129.46 (CH), 129.14 (2CH), 128.61 (CH), 121.90 (CH), 118.05 (CH), 115.72 (CH), 113.67 (2CH), 110.45 (CH), 107.20 (CH), 103.88 (CH), 54.91 (CH₃), 54.89 (CH₃), 34.74 (CH₂), 33.77 (CH₂), 32.83 (CH₂).; IR ν_{max} (cm⁻¹) 3282 (N-H), 1640 (C=O), 1551 (N-H amide), 1508 (N-C=O), 1241, 1153, 1038 (C-O).; HR ESMS m/z 391.2024 [M-H]⁺. Calc. for C₂₄H₂₆N₂O₃ 391.2022.

1-(2-Methoxyphenyl)-3-(3-(3-(4-methoxyphenyl)propyl)phenyl)urea (C.14). Yield 78%; white solid; m.p. 82-85°C; ¹H NMR (400 MHz, DMSO) δ 9.24 (s, 1H), 8.19 (s, 1H), 8.14 (dd, J = 7.8, 1.8 Hz, 1H), 7.33 (t, J = 1.6 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.18 (t, J =

7.7 Hz, 1H), 7.12 (d, $J = 8.6$ Hz, 2H), 7.01 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.94 (td, $J = 7.7, 1.8$ Hz, 1H), 6.88 (td, $J = 8.1, 2.1$ Hz, 1H), 6.84 (d, $J = 8.7$ Hz, 2H), 6.80 (d, $J = 7.5$ Hz, 1H), 3.87 (s, 3H), 3.72 (s, 3H), 2.55 (t, $J = 7.6$ Hz, 4H), 1.90 – 1.76 (m, 2H).; ^{13}C NMR (100 MHz, DMSO) δ 157.34 (C), 152.35 (C), 147.59 (C), 142.58 (C), 139.79 (C), 133.75 (C), 129.14 (2CH), 128.70 (C), 128.65 (CH), 121.77 (CH), 121.67 (CH), 120.50 (CH), 118.25 (CH), 117.76 (CH), 115.42 (CH), 113.67 (2CH), 110.68 (CH), 55.73 (CH₃), 54.90 (CH₃), 34.76 (CH₂), 33.78 (CH₂), 32.82 (CH₂).; IR ν_{max} (cm⁻¹) 3302 (N-H), 1647 (C=O), 1541 (N-H amide), 1515 (N-C=O), 1244, 1218, 1172, 1021 (C-O).; HR ESMS m/z 391.2015 [M-H]⁺. Calc. for C₂₄H₂₆N₂O₃ 391.2022.

Graphical NMR spectra

