Supporting information

1,3-Disubstituted Ureas Functionalized with Ether Groups are Potent Inhibitors of the Soluble Epoxide Hydrolase with Improved Pharmacokinetic Properties

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Syntheses:

1-Adamantan-1-yl-3-(2-hydroxyethyl)urea (**1**)

^{1}H NMR δ ($CDCl_3$) 1.67 (6H, brs), 1.96 (6H, brs), 2.07 (3H, brs), 3.16 (1H, s), 3.30 (2H, q, *J* = 6.9 Hz), 3.69 (2H, t, *J* = 6.9 Hz), 4.24 (1H, s), 4.58 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{13}H_{22}N_2O_2$ $[M + H]^+$ 239.17, found $[M + H]^+$ 239.17, mp 169-171°C.

1-Adamantan-1-yl-3-(2-heptyloxyethyl)urea (**2**)

^{1}H NMR δ ($CDCl_3$) 0.89 (3H, t, *J* = 6.9 Hz), 1.27-1.32 (8H, m), 1.57 (2H, quint, *J* = 6.9 Hz), 1.67 (6H, brs), 1.96 (6H, brs), 2.05 (3H, brs), 3.30 (2H, q, *J* = 6.9 Hz), 3.41-3.48 (4H, m), 4.40 (1H, s), 4.53 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{20}H_{36}N_2O_2$ $[M + H]^+$ 337.28, found $[M + H]^+$ 337.28, mp 61°C.

1-Adamantan-1-yl-3-(3-hydroxypropyl)urea (**3**)

^{1}H NMR δ ($CDCl_3$) 1.58-1.67 (8H, m), 1.95 (6H, brs), 2.07 (3H, brs), 3.32 (2H, q, *J* = 6.9 Hz), 3.64 (2H, t, *J* = 6.9 Hz), 4.19 (1H, s), 4.41 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{14}H_{24}N_2O_2$ $[M + H]^+$ 253.18, found $[M + H]^+$ 253.20, mp 181°C.

1-Adamantan-1-yl-3-(3-hexyloxypropyl)urea (**4**)

^{1}H NMR δ ($CDCl_3$) 0.89 (3H, t, *J* = 6.9 Hz), 1.27-1.32 (6H, m), 1.54-1.78 (10H, m), 1.95 (6H, brs), 2.05 (3H, brs), 3.23 (2H, q, *J* = 6.9 Hz), 3.43 (2H, t, *J* = 6.9 Hz), 3.49 (2H, t, *J* = 6.9 Hz), 4.06 (1H, s), 4.55 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{20}H_{36}N_2O_2$ $[M + H]^+$ 337.28, found $[M + H]^+$ 337.26, mp 99-101°C.

1-Adamantan-1-yl-3-(4-hydroxybutyl)urea (**5**)

^{1}H NMR δ ($CDCl_3$) 1.57-1.60 (4H, m), 1.66 (6H, brs), 1.96 (6H, brs), 2.07 (3H, brs), 3.18 (2H,q, *J* = 6.9 Hz), 3.68 (2H, t, *J* = 6.9 Hz), 4.14 (1H, s), 4.39 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{15}H_{26}N_2O_2$ $[M + H]^+$ 267.20, found $[M + H]^+$ 267.21, mp 250°C.

1-Adamantan-1-yl-3-(4-pentyloxybutyl)urea (**6**)

^{1}H NMR δ ($CDCl_3$) 0.91 (3H, t, *J* = 6.9 Hz), 1.27-1.32 (4H, m), 1.54-1.74 (12H, m), 1.96 (6H, brs), 2.06 (3H, brs), 3.14 (2H, q, *J* = 6.9 Hz), 3.39-3.45 (4H, m), 4.01 (1H, s), 4.26 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{20}H_{36}N_2O_2$ $[M + H]^+$ 337.28, found $[M + H]^+$ 337.27, mp 67-70°C.

1-Adamantan-1-yl-3-(6-hydroxyhexyl)urea (**9**)

^{1}H NMR δ ($CDCl_3$) 1.40-1.47 (2H, m), 1.52-1.59 (4H, m), 1.67 (6H, brs), 1.96 (6H, brs), 2.08 (3H, brs), 3.14 (2H, q, *J* = 6.9 Hz), 3.66 (2H, t, *J* = 6.9 Hz), 4.25 (2H, brs). LC-MS (ESI) *m/z* calcd for $C_{17}H_{30}N_2O_2$ $[M + H]^+$ 295.23, found $[M + H]^+$ 295.25, mp 115-118°C.

1-Adamantan-1-yl-3-(6-propyloxyhexyl)urea (**10**)

^{1}H NMR δ ($CDCl_3$) 0.91 (3H, t, *J* = 6.9 Hz), 1.34-1.38 (4H, m), 1.48-1.74 (12H, m), 1.96 (6H, brs), 2.06 (3H, brs), 3.10 (2H, q, *J* = 6.9 Hz), 3.35-3.42 (4H, m), 4.08 (2H, brs). LC-MS (ESI) *m/z* calcd for $C_{20}H_{36}N_2O_2$ $[M + H]^+$ 337.28, found $[M + H]^+$ 337.28, mp 81-83°C.

1-Adamantan-1-yl-3-[5-(2-methylpentyloxy)pentyl]urea (**12**)

^{1}H NMR δ ($CDCl_3$) 0.89 (3H, t, *J* = 6.9 Hz), 1.33-1.38 (4H, m), 1.48-1.68 (16H, m), 1.96 (6H, brs), 2.06 (3H, brs), 3.14 (2H, q, *J* = 6.9 Hz), 3.26-3.28 (2H, m), 3.39 (2H, t, *J* = 6.9 Hz), 4.01 (1H, s), 4.10 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{22}H_{40}N_2O_2$ $[M + H]^+$ 365.31, found $[M + H]^+$ 365.30, mp 49-50°C, Anal. ($C_{22}H_{40}N_2O_2$) C, H, N.

1-Adamantan-1-yl-3-[5-(3-propoxypropoxy)pentyl]urea (**13**)

To a suspension of 60% sodium hydride (2.1 g, 52.5 mmol) and 1,3-dihydroxypropane (2.0 g, 26.2 mmol) in DMF (30 mL) was added dropwise 1-bromopropane (2.23 g, 26.2 mmol) at 0ºC After stirring for 3 hrs, water (30 mL) was poured into the reaction mixture, and this mixture was stirred for 10 min. The product was then extracted with ether (90 mL), and the organic solution was washed with water (60 mL x 2), dried over $MgSO_4$ and evaporated to give 3-propoxy-1-propanol (0.55 g, 4.70 mmol) in 18% yield. To a suspension of 60% sodium hydride (0.12 g, 3.05 mmol) in DMF (6 mL) was added this alkylated propanol in DMF (2 mL) at room temperature. After stirring for 20 min, **I** (1.0 g, 3.05 mmol) was added to this reaction mixture at room temperature, and the reaction was stirred overnight. The product was extracted with ether (30 mL), and the organic layer was washed with water (30 mL), dried over $MgSO_4$, and concentrated. The residue was purified with column chromatography eluting with hexane and ethyl acetate (2:1) to afford **13** (0.23 g, 25%) as an oil. ^{1}H NMR δ ($CDCl_3$) 0.91 (3H, t, J = 6.9 Hz), 1.34-1.42 (2H, m), 1.45-1.55 (2H, m), 1.58-1.66 (10H, m), 1.84 (2H, quint, J = 6.9 Hz), 1.95 (6H, brs), 2.06 (3H, brs), 3.10 (2H, q, J = 6.9 Hz), 3.35-3.51 (8H, m), 4.09 (1H, s), 4.20 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{22}H_{40}N_2O_3$ $[M + H]^+$ 381.30, found $[M + H]^+$ 381.32, Anal. ($C_{22}H_{40}N_2O_3$) C, H, N.

Compound **14** was synthesized with the same procedure used for the preparation of **13** using 1,4-dihydroxybutane instead of 1,3-dihydroxypropane.

1-Adamantan-1-yl-3-[5-(4-propoxybutoxy)pentyl]urea (**14**)

^{1}H NMR δ ($CDCl_3$) 0.91 (3H, t, J = 6.9 Hz), 1.34-1.42 (2H, m), 1.45-1.55 (2H, m), 1.58-1.66 (14H, m), 1.96 (6H, brs), 2.06 (3H, brs), 3.10 (2H, q, J = 6.9 Hz), 3.35-3.46 (8H, m), 4.09 (1H, s), 4.18 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{23}H_{42}N_2O_3$ $[M + H]^+$ 395.32, found $[M + H]^+$ 395.35, Anal.

($C_{23}H_{42}N_2O_3$) C, H, N.

1-Adamantan-1-yl-3-(5-{2-[2-(4-ethylphenoxy)ethoxy]ethoxy}pentyl)urea (**17**)

^{1}H NMR δ ($CDCl_3$) 1.20 (3H, t, *J* = 6.9 Hz), 1.40 (2H, quint, *J* = 6.9 Hz), 1.50 (2H, quint, *J* = 6.9 Hz), 1.55-1.65 (8H, m), 1.95 (6H, brs), 2.05 (3H, brs), 2.56 (2H, q, *J* = 6.9 Hz), 3.08 (2H, t, *J* = 6.9 Hz), 3.45 (2H, t, *J* = 6.9 Hz), 3.59 (2H, t, *J* = 6.9 Hz), 3.64 (2H, t, *J* = 6.9 Hz), 3.72 (2H, t, *J* = 6.9 Hz), 3.86 (2H, t, *J* = 6.9 Hz), 4.11 (2H, q, *J* = 6.9 Hz), 4.20 (2H, s), 6.84 (2H, d, *J* = 6.9 Hz), 7.10 (2H, d, *J* = 6.9 Hz). LC-MS (ESI) *m/z* calcd for $C_{22}H_{44}N_2O_4$ $[M + H]^+$ 473.33, found $[M + H]^+$ 473.33, mp 71°C, Anal. ($C_{22}H_{44}N_2O_4$) C, H, N.

1-Adamantan-1-yl-3-(5-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}pentyl)urea (**18**)

^{1}H NMR δ ($CDCl_3$), 1.36-1.43 (2H, m), 1.45-1.52 (2H, m), 1.55-1.60 (2H, m), 1.66 (6H, brs), 1.95 (6H, brs), 2.05 (3H, brs), 3.12 (2H, q, *J* = 6.9 Hz), 3.38 (3H, s), 3.46 (2H, t, *J* = 6.9 Hz), 3.54-3.58 (4H, m), 3.63-3.67 (8H, m), 4.28 (1H, s), 4.36 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{23}H_{42}N_2O_5$ $[M + H]^+$ 427.31, found $[M + H]^+$ 427.40, Anal. ($C_{23}H_{42}N_2O_5$) C, H, N.

1-Adamantan-1-yl-3-[5-(3-morpholin-4-yl-propoxy)pentyl]urea (**19**)

^{1}H NMR δ ($CDCl_3$) 1.34-1.41 (2H, m), 1.47-1.59 (4H, m), 1.66 (6H, brs), 1.76 (2H, qintet, *J* = 6.9 Hz), 1.95 (6H, brs), 2.05 (3H, brs), 2.45 (6H, brs), 3.10 (2H, q, *J* = 6.9 Hz), 3.37-3.46 (4H, m), 3.71-3.74 (4H, m), 4.04 (1H, s), 4.14 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{23}H_{41}N_3O_3$ $[M + H]^+$ 408.31, found $[M + H]^+$ 408.30, Anal. ($C_{23}H_{41}N_3O_3$) C, H, N.

N-(2-{2-[5-(3-Adamantan-1-yl-ureido)pentyloxy]ethoxy}ethyl)methanesulfonamide (**20**)

^{1}H NMR δ ($CDCl_3$) 1.34-1.41 (2H, m), 1.46-1.54 (2H, m), 1.60-1.69 (8H, m), 1.95 (6H, brs),

2.06 (3H, brs), 2.91 (3H, brs), 3.13 (2H, q, *J* = 6.9 Hz), 3.24 (2H, t, *J* = 6.9 Hz), 3.43 (2H, t, *J* = 6.9 Hz), 3.58-3.65 (4H, m), 3.76 (2H, t, *J* = 6.9 Hz), 4.18 (1H, s), 4.32 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{21}H_{39}N_3O_5S$ $[M + H]^+$ 446.26, found $[M + H]^+$ 446.31, Anal. ($C_{21}H_{39}N_3O_5S$) C, H, N.

7-[2-(2-Ethoxyethoxy)ethoxy]heptanoic acid adamantan-1-ylamide (**22**)

To a mixture of sodium hydride (0.53 g, 13.2 mmol) and diethylene glycol monoethyl ether (1.70 g, 12.6 mmol) was added dropwise 7-bromoheptanoic acid ethyl ester (3.0 g, 12.6 mmol) in DMF (20 mL) at room temperature. After stirring for 5 hrs, water (50 mL) was poured into the reaction mixture. The product was extracted with ether (60 mL), and the organic solution was dried over $MgSO_4$ and concentrated. The residue was purified using silica gel column chromatography eluting with hexane and ethyl acetate (3:1) to give 7-[2-(2-ethoxyethoxy)]ethoxyheptanoic acid ethyl ester (1.46g, 40%). Then, this ester intermediate was added to an aqueous solution of 1N NaOH (5 mL) in ethanol (15 mL) at room temperature. This mixture was stirred for 3 hrs, and the ethanol solvent was evaporated. The residue was neutralized using an aqueous solution of 1N HCl, and the product was extracted with ether (30 mL). The ether layer was washed with water (30 ml), dried over $MgSO_4$, and concentrated to give 7-[2-(2-ethoxyethoxy)]ethoxyheptanoic acid (1.27 g, 96%). To a solution of the above acid intermediate (0.40 g, 1.53 mmol) and DMAP (0.19 g, 1.53 mmol) in dichloromethane (10 mL) was added 1-adamantylamine (0.23 g, 1.53 mmol) at room temperature. After stirring for 10 min, EDCI (0.29 g, 1.53 mmol) was added portionwise to the mixture. The reaction was stirred for 3 hrs, and an aqueous solution of 1N HCl (15 mL) was poured into the reaction mixture. The product was extracted with ether (40 mL), and the organic solution was washed with water (40 mL), dried over $MgSO_4$, and concentrated. This residue was purified using silica gel column chromatography eluting hexane and ethyl acetate (1:1) to afford compound **22** (0.59g, 97%) as an oil. ^{1}H NMR δ ($CDCl_3$) 1.21 (3H, t, *J* = 6.9 Hz), 1.32-1.34 (6H, m), 1.49-1.61

(2H, m), 1.67 (6H, brs), 1.99 (6H, brs), 2.05-2.07 (5H, m), 3.45 (2H, q, J = 6.9 Hz), 3.50-3.65 (10H, m), 5.19 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{23}H_{41}NO_4$ $[M + H]^+$ 396.30, found $[M + H]^+$ 396.50, Anal. ($C_{23}H_{41}NO_4$) C, H, N.

2-Adamantan-1-yl-*N*-{5-[2-(2-ethoxyethoxy)ethoxy]pentyl}acetamide (**23**)

To a solution of di-(*tert*-butyl) dicarbonate (2.0 g, 9.16 mmol) in dioxane (20 mL) was added 5-amino-1-pentanol (0.95 g, 9.16 mmol) at room temperature. After stirring for 3 hrs, the product was extracted with ether (50 mL X 2), and the organic solutions were washed with water (50 mL), dried over $MgSO_4$, and concentrated. The residue was purified using silica gel column chromatography eluting with hexane and ethyl acetate (1:1) to provide the corresponding *tert*-butoxycarbonylated amino alcohol (1.8 g, 97%). A solution of this intermediate (0.5 g, 2.46 mmol) in DMF (1.5 mL) was added to a mixture of sodium hydride (0.15 g, 3.69 mmol), 2-(ethoxyethoxy)ethyl bromide (0.58 g, 2.95 mmol), and sodium iodide (catalytic amount) in DMF (10 mL). After stirring overnight at room temperature, water (50 mL) was poured into the reaction mixture. The product was extracted with ether (60 mL), and the organic layer was dried over $MgSO_4$ and evaporated. The residue was purified using silica gel column chromatography (hexane:ethyl acetate = 1:1) to give *tert*-butoxycarbonylated amino ether (0.22 g, 28%). A solution of this intermediate in dioxane (10 mL) was treated with a solution of 4N HCl in dioxane (2 mL) at room temperature, and the mixture was stirred for 1 hr. Then the solvent was evaporated to dryness, and the residue solid was dissolved in dichloromethane (15 mL) and treated with triethylamine (0.07 g, 0.69 mmol). To this solution was added 1-adamantylacetic acid (0.14 g, 0.69 mmol) and DMAP (80 mg, 0.69 mmol) at room temperature. After stirring for 10 min, EDCI (0.14 g, 0.69 mmol) was added to the reaction mixture, and the reaction was further stirred for 3 hrs. An aqueous solution of 1N HCl (15 mL) was poured into the reaction mixture. The product was extracted with

ether (40 mL), and the organic solution was washed with water (40 mL), dried over $MgSO_4$, and concentrated. This residue was purified using silica gel column chromatography eluting hexane and ethyl acetate (1:1) to afford compound **23** (0.26 g, 97%) as an oil. ^{1}H NMR δ ($CDCl_3$), 1.21 (3H, t, *J* = 6.9 Hz), 1.38-1.41 (6H, m), 1.49-1521 (2H, m), 1.61 (6H, brs), 1.82 (2H, brs), 1.90 (6H, brs), 1.96 (3H, brs), 3.23 (2H, q, *J* = 6.9 Hz), 3.43-3.64 (10H, m), 5.41 (1H, s). LC-MS (ESI) *m/z* calcd for $C_{23}H_{41}NO_4$ $[M + H]^+$ 396.30, found $[M + H]^+$ 396.50, Anal. ($C_{23}H_{41}NO_4$) C, H, N.

1-Adamantan-1-yl-3-{4-[2-(2-ethoxyethoxy)ethoxy]cyclohexyl}urea (**25**)

A mixture of 1-adamantyl isocyanate (10.0 g, 56.4 mmol), *trans*-4-aminocyclohexanol hydrochloride (12.6 g, 84.6 mmol), and triethylamine (12.3 mL, 84.6 mmol) in dry DMF (80 mL) was stirred at room temperature for 12 hrs, and to the reaction mixture was poured an aqueous solution of 1N HCl (60 mL) at 0°C. After 30 min stirring, the solid product crystalized was filtered, and washed with water (80 mL) and ethyl acetate (50 mL). The resulting solid was dried in the vacuum oven at 50°C to give 1-adamantan-1-yl-3-(4-hydroxycyclohexyl)urea **IV** (16.4 g, 100%) as a white solid. To a suspension of 60% sodium hydride (4.11 g, 102 mmol) in dry DMF (50 mL) was added a solution of **IV** (10.0 g, 34.2 mmol) at room temperature. After stirring for 30 min, **II** (10.1 g, 51.3 mmol) was added to the reaction at room temperature. The reaction was stirred for 12 hrs, and water (90 mL) was poured into the reaction mixture. The product was extracted with ether (50 mL X 2), and the ether solution was dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel eluting hexane and ethyl acetate (1:1) to afford **25** (5.31 g, 35%) as a solid. Purified compound was recrystalized in ethyl acetate, and dried in the vacuum oven for 2 days. ^{1}H NMR δ ($CDCl_3$) 1.10 (2H, q, *J* = 6.9 Hz), 1.21 (3H, t, *J* = 6.9 Hz), 1.37 (2H, q, *J* = 6.9 Hz), 1.66 (6H, brs), 1.96 (6H, brs), 2.00-2.02 (4H, m), 2.06 (3H, s), 3.23-3.25 (1H, m), 3.48-3.54 (3H, m), 3.57-3.65 (8H, m), 3.98 (2H, s). ^{13}C-NMR δ ($CDCl_3$): 29.51, 30.64, 31.58, 36.40,

42.49, 48.52, 50.91, 66.62, 67.52, 69.79, 70.67, 70.85, 156.4. IR: 1625 cm^{-1}, 2908 cm^{-1}, 3346 cm^{-1}. LC-MS (ESI) *m/z* calcd for $C_{23}H_{40}N_2O_4$ $[M + H]^+$ 409.30, found $[M + H]^+$ 409.30, mp 155°C, Anal. ($C_{23}H_{40}N_2O_4$) C, H, N.

1-Adamantan-1-yl-3-[4-(3-morpholin-4-yl-propoxy)cyclohexyl]urea (**26**)

To a solution of 4-(3-hydroxypropyl)morpholine (2.11 g, 14.5 mmol) and triphenylphosphine (4.19 g, 15.9 mmol) in THF (30 mL) was added carbon tetrabromide (5.30 g, 15.9 mmol) at 0°C. After stirring overnight, water (40 mL) was poured into the reaction mixture. The organic layer dissolving the product was extracted with an aqueous solution of 1N HCl (30 mL). Then the acidic solution was neutralized with an aqueous solution of 1N NaOH, and the product was extracted with ethyl acetate (30 mL X 3). The organic layer was combined, dried over $MgSO_4$, and concentrated to give 4-(3-bromopropyl)morpholine (1.63 g, 54%).

To a suspension of 60% sodium hydride (0.94 g, 23.5 mmol) in dry DMF (50 mL) was added a solution of **IV** (2.29 g, 7.83 mmol) at room temperature. After stirring for 30 min, the above bromide (1.63 g, 7.88 mmol) was added to the reaction at room temperature. The reaction was stirred for 12 hrs, and then reaction mixture was washed with water (40 mL). The product was extracted with ether (50 mL), and the organic layer was extracted with an aqueous solution of 1N HCl (30 mL). The acidic solution was neutralized by adding an aqueous solution of 1N NaOH, and the product was extracted with ether (30 mL X 2), dried over $MgSO_4$, and concentrated. The residue was recrystalized in hexane and dried in the vacuum over for 2 days to afford pure **26**. ^{1}H NMR δ ($CDCl_3$) 1.11 (2H, q, *J* = 6.9 Hz), 1.33 (2H, q, *J* = 6.9 Hz), 1.63-1.67 (8H, m), 1.74 (2H, quintet, *J* = 6.9 Hz), 1.96 (6H, brs), 2.00-2.02 (4H, m), 2.06 (3H, s), 2.42 (6H, brs), 3.12-3.21 (1H, m), 3.48 (4H, t, *J* = 6.9 Hz), 3.87 (1H, s), 3.90 (1H, s), 3.94 (1H, brs). ^{13}C-NMR δ ($CDCl_3$): 29.52, 30.71, 31.60, 36.39, 42.49, 48.50, 50.96, 53.68, 55.91, 66.37, 66.95, 156.3. IR: 1627 cm^{-1}, 2906 cm^{-1}, 3348 cm^{-1}.

LC-MS (ESI) *m/z* calcd for $C_{24}H_{41}N_3O_3$ $[M + H]^+$ 420.31, found $[M + H]^+$ 420.45, mp 178°C, Anal. ($C_{24}H_{41}N_3O_3$) C, H, N.

1-Adamantan-1-yl-3-{4-[2-(2-ethoxyethoxy)ethoxy]phenyl}urea (**28**)

To a solution of 1-adamantyl isocyanate (10.0 g, 56 mmol) in DMF (100 mL) was added portionwise 4-aminophenol (9.24 g, 85 mmol) at 0ºC. After stirring overnight at room temperature, an aqueous solution of 1N HCl (100 mL) and water (50 mL) was added to the reaction mixture at 0ºC, and the mixture was stirred for 30 min. The product crystallized was filtered, washed with water (100 mL) and hexane (100 mL), and dried in the vacuum oven at 45ºC to afford 1-adamantan-1-yl-3-(4-hydroxyphenyl)urea in approximately 95% yield. To a suspension of sodium hydride (4.20 g, 0.10 mol) in DMF (70 mL) was added this phenol intermediate (10.0 g, 35 mmol) at 0ºC. After stirring for 30 min, a solution of 2-(ethoxyethoxy)ethyl bromide (10.3 g, 52 mmol) in DMF (4 mL) was added dropwise to this reaction mixture at 0ºC, and the reaction was stirred overnight at room temperature. Water (40 mL) was poured into the reaction, and the product was extracted with ether (100 mL). The organic solution was washed with water (100 mL), dried over $MgSO_4$, and concentrated. The residue was purified using column chromatography eluting hexane and ethyl acetate (3:1) to provide **28** as a white solid in 90% yield.

^{1}H NMR δ ($CDCl_3$), 1.21 (3H, t, *J* = 6.9 Hz), 1.66 (6H, brs), 1.96 (6H, brs), 2.06 (3H, brs), 3.54 (2H, q, *J* = 6.9 Hz), 3.62 (2H, t, *J* = 6.9 Hz), 3.72 (2H, t, *J* = 6.9 Hz), 3.85 (2H, t, *J* = 6.9 Hz), 4.11 (2H, t, *J* = 6.9 Hz), 4.40 (1H, s), 5.96 (1H, s), 6.85 (2H, d, *J* = 6.9 Hz), 7.14 (2H, d, *J* = 6.9 Hz). ^{13}C-NMR δ ($CDCl_3$): 15.13, 29.48, 36.33, 42.20, 51.21, 66.70, 67.66, 69.72, 69.83, 70.87, 115.3, 124.3, 131.4, 155.2, 155.8. IR: 1628 cm^{-1}, 2907 cm^{-1}, 3330 cm^{-1}. LC-MS (ESI) *m/z* calcd for $C_{23}H_{34}N_2O_4$ $[M + H]^+$ 403.25, found $[M + H]^+$ 403.24, mp 105°C, Anal. ($C_{24}H_{41}N_3O_3$) C, H, N.

Compounds **27** and **29** were prepared using the above method from the corresponding urea

phenol (1-adamantan-1-yl-3-(3-hydroxyphenyl)urea for **27** or 1-adamantan-1-yl-3-(4-hydroxy-phenyl)urea for **29**) and bromide (2-(ethoxyethoxy)ethyl bromide for **27** or 3-morpholinopropyl bromide for **29**)

1-Adamantan-1-yl-3-{3-[2-(2-ethoxyethoxy)ethoxy]phenyl}urea (**27**)

^{1}H NMR δ ($CDCl_3$) 1.24 (3H, t, *J* = 6.9 Hz), 1.67 (6H, brs), 1.99 (6H, brs), 2.05 (3H, brs), 3.57 (2H, q, *J* = 6.9 Hz), 3.64 (2H, t, *J* = 6.9 Hz), 3.71 (2H, t, *J* = 6.9 Hz), 3.83 (2H, t, *J* = 6.9 Hz), 4.10 (2H, t, *J* = 6.9 Hz), 4.85 (1H, s), 6.54-6.58 (2H, m), 6.84-6.91 (2H, m), 7.13 (1H, t, *J* = 6.9 Hz). LC-MS (ESI) *m/z* calcd for $C_{23}H_{34}N_2O_4$ $[M + H]^+$ 403.25, found $[M + H]^+$ 403.24, Anal. ($C_{23}H_{34}N_2O_4$) C, H, N.

1-Adamantan-1-yl-3-[4-(3-morpholin-4-yl-propoxy)phenyl]urea (**29**)

^{1}H NMR δ ($CDCl_3$), 1.66 (6H, brs), 1.95-1.98 (8H, m), 2.05 (3H, brs), 2.49 (6H, brs), 3.74 (4H, brs), 3.99 (2H, t, *J* = 6.9 Hz), 4.37 (1H, s), 5.90 (1H, s), 6.84 (2H, d, *J* = 6.9 Hz), 7.15 (2H, d, *J* = 6.9 Hz). LC-MS (ESI) *m/z* calcd for $C_{24}H_{35}N_3O_3$ $[M + H]^+$ 414.27, found $[M + H]^+$ 414.24, mp 191ºC Anal. ($C_{24}H_{35}N_3O_3$) C, H, N.

Elemental Analyses

(only key compounds included)

Compd.	Calculated (%)				Found (%)			
	C	H	N	F	C	H	N	F
7	68.53	10.06	9.99		68.55	10.10	9.92	
8	71.38	10.78	8.32		71.41	10.79	8.29	
11	72.48	11.06	7.68		72.48	11.01	7.61	
12	72.48	11.06	7.68		72.50	11.11	7.60	
13	69.43	10.59	7.36		69.36	10.49	7.40	
14	70.01	10.73	7.10		70.11	10.73	7.05	
15	66.33	10.17	7.06		66.91	10.21	7.04	
16	58.65	8.28	6.22	12.65	58.89	8.34	6.23	12.58
17	71.15	9.38	5.93		71.20	9.33	5.91	
18	64.76	9.92	6.57		64.79	9.98	6.50	
19	67.78	10.14	10.31		67.70	10.01	10.51	
20	56.60	8.82	9.43		56.68	8.84	9.47	
21	59.56	9.32	9.47		59.56	9.35	9.51	
22	69.83	10.45	3.54		69.89	10.51	3.51	
23	69.83	10.45	3.54		69.81	10.42	3.57	
24	72.88	10.56	7.73		72.95	10.65	7.69	
25	67.61	9.87	6.86		67.45	9.97	6.81	
26	68.70	9.85	10.01		68.66	9.98	9.90	
27	68.63	8.51	6.96		68.59	8.58	6.90	
28	68.63	8.51	6.96		68.53	8.61	6.88	
29	69.70	8.53	10.16		69.62	8.64	10.06	