**SUPPORTING INFORMATION**

# Naphthyl and coumarinyl biaryl piperazine derivatives as highly potent human β-secretase inhibitors. Design, synthesis, enzymatic BACE-1 and cell assays

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## Experimental section

General procedures: Unless otherwise noted, starting materials and reagents were obtained from commercial suppliers and were used without purification. Methylene dichloride ($CH_2Cl_2$) was distilled over $P_2O_5$ just prior to use. Acetonitrile was of anhydrous quality from commercial suppliers (Aldrich, Carlo Erba Reagents). Melting points were determinated on an Electrothermal IA-9100 digital, all temperature are given in degrees Celsius and are uncorrected. $^1$H NMR spectra were recorded at 250 MHz on a Brüker AC-250 spectrometer. Chemical shifts are expressed as δ units (part per million) downfield from TMS (tetramethylsilane). Electro-spray mass spectra were obtained on a Waters Micromass ZMD spectrometer by direct injection of the sample solubilized in acetonitrile. Elemental analyses were within ± 0.4% of theorical values for all compounds. All reactions were monitored by thin-layer chromatography. Analytical thin layer chromatographies (TLC) were performed using silica gel plates 0.2 mm thick ($60F_{254}$ Merck). Preparative flash column chromatographies were carried out on silica gel (230-400 mesh, G60 Merck).

**4-(4-Bromo-2-nitro-phenyl)-morpholine (1a).** To a mixture of 2,5-dibromonitrobenzene (4.0 g, 14.2 mmol), triethylamine (1 mL, 7.2 mmol) in *i*-PrOH (15 mL) was added morpholine (2.5 mL, 28.4 mmol). The resulting mixture was stirred at 70°C for 24 hours. The reaction mixture was cooled to room temperature, and then concentrated under reduced pressure. The brown residue was purified by chromatography on silica gel. Elution with increasing proportions of EtOAc-cHex (1:3 to 1:1) gave the desired compound **1a** (3.0 g, 73%) as an orange oil. $R_f$ 0.18 (cHex:EtOAc, 3:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 3.02 (t, 4H, J= 4.5 Hz, NC*H*$_2$CH$_2$O), 3.82 (t, 4H, J= 4.5 Hz, NCH$_2$C*H*$_2$O), 7.02 (d, 1H, J= 8.8 Hz, Ar*H*), 7.58 (dd, 1H, J= 2.3 and 8.8 Hz, Ar*H*), 7.91 (d, 1H, J= 2.3 Hz, Ar*H*). ESI-MS m/z $[M+H]^+$= 287.

**4-(4-Bromo-2-nitro-phenyl)-1-*tert*-butoxycarbonyl-piperazine (1b).** To a mixture of 2,5-dibromonitrobenzene (0.50 g, 1.8 mmol), triethylamine (250 µL, 1.8 mmol) in *i*-PrOH (10 mL) was added 1-*tert*-butoxycarbonyl-piperazine (0.67 g, 3.6 mmol). The resulting mixture was stirred at 70°C for 24 hours. The reaction mixture was cooled to room temperature, and then concentrated under reduced pressure. The brown residue was purified by chromatography on silica gel. Elution with increasing proportions of EtOAc-cHexane (1:3 to 1:1) gave the desired compound **1b** (0.50 g, 72%) as an orange oil. $R_f$ 0.79 (cHex:EtOAc, 1:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.46 (s, 9H, C*H*$_3$ , *t*Bu), 2.98 (t, 4H, J= 4.7 Hz, NC*H*$_2$CH$_2$NBoc), 3.57 (t, 4H, J= 4.7 Hz, NCH$_2$C*H*$_2$NBoc), 7.01 (d, 1H, J= 8.9 Hz, Ar*H*), 7.58 (dd, 1H, J= 2.4 and 8.9 Hz, Ar*H*), 7.91 (d, 1H, J= 2.4 Hz, Ar*H*). ESI-MS m/z $[M+H]^+$= 386.

**1-Benzyl-4-(4-bromo-2-nitro-phenyl)-piperazine (1c).** To a mixture of 2,5-dibromonitrobenzene (1.0 g, 3.6 mmol) in *i*-PrOH (15 mL) was added 1-benzylpiperazine (0.96 g, 5.4 mmol). The resulting mixture was stirred at 70°C for 24 hours. The reaction mixture was cooled to room temperature, and then concentrated under reduced pressure. The brown residue was purified by chromatography on silica gel. Elution with increasing proportions of EtOAc-cHexane (1:5 to 1:3) gave the desired compound **1c** (1.16 g, 85%) as a yellow oil. $R_f$ 0.51 (cHexane:EtOAc, 1:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.59 (t, J= 4.8 Hz, 4H, NCH$_2$C*H*$_2$NCH$_2$Ph), 3.06 (t, J= 4.8 Hz, 4H, NC*H*$_2$CH$_2$NCH$_2$Ph ), 3.56 (s, 2H, NC*H*$_2$Ph), 7.01 (d, J= 8.7 Hz, Ar*H*), 7.28-7.34 (m, 5H, Ar*H*), 7.54 (dd, J= 8.7 and 2.4 Hz, 1H, Ar*H*), 7.89 (d, J= 2.4 Hz, 1H, Ar*H*). ESI-MS m/z $[M+H]^+$= 376.

**4-(2-Amino-4-bromo-phenyl)-morpholine (2a).** Zinc dust (3.4 g, 52.3 mmol) was added to a stirred solution of **1a** (3.0 g, 10.4 mmol) in THF (60 mL) followed by $KH_2PO_4$ (20

mL, 1 M). The resulting mixture was stirred at 80°C for 24 hours. The reaction mixture was cooled to room temperature, filtered and evaporated to a small volume. The mixture was extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, with EtOAc-cHexane as eluant (1:6), giving aniline **2a** (1.7 g, 63%) as a pale yellow foam. M.p. 123°. $R_f$ 0.53 (EtOAc:cHexane, 1:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.59 (bs, 4H, $NCH_2CH_2O$), 2.89 (t, J= 4.8 Hz, 4H, $NCH_2CH_2O$), 4.01 (brs, 2H, $NH_2$), 6.78-6.87 (m, 3H). ESI-MS m/z $[M+H]^+$= 257.

**4-(2-Amino-4-bromo-phenyl)-1-*tert*-butoxycarbonyl-piperazine (2b).** Zinc dust (4.4 g, 66.8 mmol) was added to a stirred solution of **1b** (5.2 g, 13.4 mmol) in THF (60 mL) followed by $KH_2PO_4$ (20 mL, 1 M). The resulting mixture was stirred at 80°C for 24 hours. The reaction mixture was cooled to room temperature, filtered and evaporated to a small volume. The mixture was extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, with EtOAc-toluene as eluant (6:1), giving aniline **2b** (3 g, 63%) as a yellow oil. $R_f$ 0.42 (EtOAc:toluene, 1:6). $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.48 (s, 9H, $CH_3$, *t*Bu), 2.81 (t, 4H, J= 4.7 Hz, $CH_2CH_2$NBoc), 3.56 (br s, 4H, $CH_2CH_2$NBoc), 4.08 (br s, 2H, $NH_2$), 6.81-6.87 (m, 3H, Ar*H*). ESI-MS m/z $[M+H]^+$= 356.

**1-Benzyl-4-(2-amino-4-bromo-phenyl)-piperazine** (**2c).** Zinc dust (1.9 g, 28.6 mmol) was added to a stirred solution of **1b** (2.2 g, 5.7 mmol) in THF (30 mL) followed by $KH_2PO_4$ (10 mL, 1 M). The resulting mixture was stirred at 80°C for 24 hours. The reaction mixture was cooled to room temperature, filtered and evaporated to a small volume. The mixture was extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, with EtOAc-toluene as eluant (6:1), giving aniline **2c** (1.7 g, 86%) as a yellow powder. M.p. 85°. $R_f$ 0.66 (EtOAc:cHex, 1:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.62 (brs, 4H, $NCH_2CH_2NCH_2Ph$), 2.91 (t, 4H, J= 4.7Hz, $NCH_2CH_2NCH_2Ph$), 3.59 (s, 2H, $NCH_2Ph$), 4.00 (brs, 1H, $NH_2$), 6.82-6.85 (m, 3H, Ar*H*), 7.29-7.36 (m, 5H, Ar*H*). ESI-MS m/z $[M+H]^+$= 346.

**{4-Bromo-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-morpholine (3a).** To a solution of **2a** (210 mg, 0.81 mmol) in methylene chloride (10 mL) with DIEA (210 µL, 1.21 mmol) was added 1-naphthoyl chloride (200 mg, 1.05 mmol). The reaction mixture was stirred for 4 hours at room temperature. The mixture was extracted with water (15 mL), the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, with EtOAc-cHexane eluant (1:9) giving **3c** (300 mg, 90%) as a yellow solid. M.p. 172°. $R_f$ 0.61 (EtOAc:cHexane, 1:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.86 (t, 4H, J= 4.4 Hz, $NCH_2CH_2O$), 3.70 (t, 4H, J= 4.4 Hz, $NCH_2CH_2O$), 7.08 (d, 1H, J= 8.4 Hz, Ar*H*), 7.27 (dd, 1H, J= 2.2 and 8.4 Hz, Ar*H*), 7.51-7.60 (m, 3H, Ar*H*), 7.71-7.75 (m, 1H, Ar*H*), 7.91-7.95 (m, 1H, Ar*H*), 8.01 (d, 1H, J= 8.2 Hz, Ar*H*), 8.44-8.48 (m, 1H, Ar*H*), 8.9 3 (d, 1H, J= 2.2 Hz, Ar*H*), 9.15 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 411.

**1-{4-Bromo-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-4-*tert*-butoxycarbonyl piperazine (3b).** To a solution of **2b** (150 mg, 0.42 mmol) in methylene chloride (5 mL) with DIEA (110 µL, 0.63 mmol) was added 1-naphthoyl chloride (104 mg, 0.55 mmol). The reaction mixture was stirred for 4 hours at room temperature. The mixture was extracted with water (10 mL), the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, with EtOAc-cHexane eluant (1:9) giving **3b** (180 mg, 84%) as a colourless oil. $R_f$ 0.59 (EtOAc:cHexane, 1:2). $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.45 (s, 9H, $CH_3$, *t*Bu), 2.81 (t, 4H, J= 4.7 Hz, $NCH_2CH_2$NBoc), 3.43 (brs,

4H, $NCH_2CH_2NBoc$), 7.04 (d, 1H, J= 8.4 Hz, Ar*H*), 7.24 (dd, 1H, J= 2.3 and 8.4 Hz, Ar*H*), 7.51-7.60 (m, 3H, Ar*H*), 7.70-7.84 (m, 1H, Ar*H*), 7.91-7.95 (m, 1H, Ar*H*), 7.99 (d, 1H, J= 8.2 Hz, Ar*H*), 8.43-8.47 (m, 1H, Ar*H*), 8.92 (d, 1H, J= 2.3 Hz, Ar*H*), 9.10 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 510.

**4-Benzyl-1-{4-bromo-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-piperazine (3c).** To a solution of **2c** (1.8 g, 5.2 mmol) in methylene chloride (20 mL) with DIEA (1.4 mL, 7.8 mmol) was added 1-naphthoyl chloride (1.3 g, 6.8 mmol). The reaction mixture was stirred for 4 hours at room temperature. The mixture was extracted with water (20 mL), the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, with EtOAc-cHexane eluant (1:6) giving **3c** (2.0 g, 75%) as a white powder. M.p. 147°. $R_f$ 0.31 (EtOAc:cHexane, 1:9). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.49 (brs, 4H, $NCH_2CH_2NCH_2Ph$), 2.89 (t, 4H, J= 4.7 Hz, $NCH_2CH_2NCH_2Ph$), 3.48 (s, 2H, $NCH_2Ph$), 7.08 (d, 1H, J= 8.5 Hz, Ar*H*), 7.24 (dd, 1H, J= 2.3 and 8.5 Hz, Ar*H*), 7.29-7.33 (m, 5H, Ar*H*), 7.52-7.61 (m, 3H, Ar*H*), 7.71-7.75 (m, 1H, Ar*H*), 7.93-7.95 (m, 1H, Ar*H*), 8.02 (d, 1H, J= 8.2 Hz, Ar*H*), 8.47-8.51 (m, 1H, Ar*H*), 8.91 (d, 1H, J= 2.3 Hz, Ar*H*), 9.17 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 500.

**1-{4-Bromo-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-piperazine (3d).** To a stirred suspension of the appropriate N-benzyl compound **3c** (1.0 g, 2 mmol) and an equal weight of 10% Pd-C in dry methanol (10 mL), anhydrous ammonium formate (630 mg, 10 mmol) was added in a single portion under nitrogen. The resulting mixture was stirred at relux temperature and the reaction was monitored by TLC. After completion, the catalyst was removed by filtration through celite, washed with methyle chloride (10 mL). The solvent was removed under reduced pressure, the crude product was purified by chromatography on silica gel with DCM, 0.5% MeOH as eluent, to yield the desired compound **3d** (0.8 g, 97%) as a yellow oil. $R_f$ 0.09 (EtOAc:cHexane, 2:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 3.08 (brs, 4H, $NCH_2CH_2NH$), 3.19 (brs, 4H, $NCH_2CH_2NH$), 7.19 (d, 1H, J= 8.4 Hz, Ar*H*), 7.40 (dd, 1H, J= 2.3 and 8.4 Hz, Ar*H*), 7.58-7.64 (m, 3H, Ar*H*), 7.77-7.80 (m, 1H, Ar*H*), 8.02-8.05 (m, 1H, Ar*H*), 8.09 (d, 1H, J= 8.2 Hz, Ar*H*), 8.22 -8.26 (m, 1H, Ar*H*), 8.43 (d, 1H, J= 2.3 Hz, Ar*H*), 8.77 (brs, 2H, N*H*), 9.78 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 410.

**1-{4-Bromo-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-4-(2-hydroxyethyl)-piperazine (3e).** 2-Bromoethanol (5.0 µL, 0.070 mmol) was added to a vigorous stirred mixture of **3d** (34 mg, 0.065) and anhydrous $K_2CO_3$ (18 mg, 0.13 mmol) in dry acetonitrile (5 mL). The suspension was refluxed for 10 hours under nitrogen. The solvent was then removed under reduced pressure. The crude product was dissolved in $CH_2Cl_2$ (5 mL) and extracted with water (2x5 mL), the organic layer was dried over $MgSO_4$, and then purified by chromatography on silica gel, using methylene chloride-methanol (9:1) as eluent, to yield the compound **3e** (27 mg, 92%) as a white powder. M.p. 88°. $R_f$ 0.55 ($CH_2Cl_2$:MeOH, 5:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.53 (brs, 6H, $NCH_2CH_2OH$ and $NCH_2CH_2NCH_2CH_2OH$), 2.91 (brs, 4H, $NCH_2CH_2NCH_2CH_2OH$), 3.62 (t, 2H, J= 4.3 Hz, $NCH_2CH_2OH$), 7.08 (d, 1H, J= 8.4 Hz, Ar*H*), 7.25 (dd, 1H, J= 2.2 and 8.4 Hz, Ar*H*), 7.51-7.60 (m, 3H, Ar*H*), 7.71 (d, 1H, J= 7.0 Hz, Ar*H*), 7.91-7.95 (m, 1H, Ar*H*), 8.00 (d, 1H, J= 8.3 Hz, Ar*H*), 8.45-8.48 (m, 1H, Ar*H*), 8.92 (d, 1H, J= 2.2 Hz, Ar*H*), 9.10 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 454.

**1-{4-(Phenyl)-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-4-*tert*-butoxy carbonyl piperazine (4b)** Phenyl boronic acid (132 mg, 1.1 mmol) was dissolved in anhydrous 1,3-dioxane (30 mL). The appropriate bromo derivative **3b** (500 mg, 1 mmol) was dissolved in anhydrous dioxane (30 mL) and the two solutions were mixed with dppf (17 mg,

0.03 mmol), dppf-$Pd^{II}$ (25 mg, 0.03 mmol), and KOAc (300 mg, 3 mmol). The resulting suspension was refluxed for 72 hours. The dioxane was removed under reduced pressure and the catalysts were removed by filtration through silica gel. The crude product was purified by flash chromatography with cHex-EtOAc (9:1) as eluent, to yield the desired compound **4b** as a white oil (180 mg, 36 %). $R_f$ 0.26 (EtOAc: cHexane, 1:9). $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.45 (s, 9H, C*H*$_3$, *t*Bu), 2.81 (t, 4H, J= 4.7 Hz, NC*H*$_2$CH$_2$NBoc), 3.43 (brs, 4H, NCH$_2$C*H*$_2$NBoc), 7.27-7.35 (m, 8H, Ar*H*), 7.42 (d, 2H, J= 8.5 Hz, Ar*H*), 7.75-7.78 (m, 1H, Ar*H*), 7.91-7.93 (m, 1H, Ar*H*), 8.02 (d, 1H, J= 8.3 Hz, Ar*H*), 8.50-8.54 (m, 1H, Ar*H*), 8.98 (brs, 1H, Ar*H*), 9.20 (brs, 1H, N*H*C(O)) ESI-MS m/z $[M+H]^+$= 508.

**4-Benzyl-1-{4-(phenyl)-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-piperazine (4c).** Phenyl boronic acid (270 mg, 2.2 mmol) was dissolved in anhydrous 1,3-dioxane (40 mL). The appropriate bromo derivative **3c** (1 g, 2 mmol) was dissolved in anhydrous dioxane (30 mL) and the two solutions were mixed with dppf (34 mg, 0.06 mmol), dppf-$Pd^{II}$ (50 mg, 0.06 mmol), and KOAc (590 mg, 6 mmol). The resulting suspension was refluxed for 72 hours. The dioxane was removed under reduced pressure and the catalysts were removed by filtration through silica gel. The crude product was purified by flash chromatography with cHex-EtOAc (9:1) as eluent, to yield the desired compound **4c** as a white powder (800 mg, 80 %). M.p. 156°. $R_f$ 0.23 (EtOAc: cHexane, 1:9). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.51 (brs, 4H, NCH$_2$C*H*$_2$NCH$_2$Ph), 2.96 (t, 4H, J= 4.7 Hz, NC*H*$_2$CH$_2$NCH$_2$Ph), 3.49 (s, 2H, NC*H*$_2$Ph), 7.27-7.35 (m, 8H, Ar*H*), 7.42 (d, 2H, J= 8.5 Hz, Ar*H*), 7.53-7.63 (m, 5H, Ar*H*), 7.75-7.78 (m, 1H, Ar*H*), 7.91-7.93 (m, 1H, Ar*H*), 8.02 (d, 1H, J= 8.3 Hz, Ar*H*), 8.50-8.54 (m, 1H, Ar*H*), 8.98 (brs, 1H, Ar*H*), 9.20 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 498.

**1-{4-(Phenyl)-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-piperazine (4d).** To a stirred suspension of the appropriate N-Benzyl compound **4c** (800 mg, 1.5 mmol) and an equal weight of 10% Pd-C in dry methanol (75 mL), anhydrous ammonium formate (475 mg, 7.5 mmol) was added in a single portion under nitrogen. The resulting reaction mixture was stirred at reflux temperature. After completion of reaction, the catalyst was removed by filtration through celite, which was then washed with 2x40 mL of chloroform. The combined organic filtrates were concentrated under reduced pressure and the crude product was purified by chromatography on silica gel with DCM, 0.5% MeOH as eluent, to yield **4d** as a white powder (540 mg, 88%). M.p. 118°. $R_f$ 0.45 (MeOH: $CH_2Cl_2$, 1:9). $^1$H-NMR ($CDCl_3$) $\delta_H$ 3.03 (brs, 8H, NC*H*$_2$C*H*$_2$NH), 4.32 (brs, 1H, NCH$_2$CH$_2$N*H*), 7.31-7.41 (m, 2H, Ar*H*), 7.43-7.49 (m, 2H, Ar*H*), 7.55-7.59 (m, 3H, Ar*H*), 7.67-7.71 (brd, 2H, Ar*H*), 7.75 (dd, 1H, J= 1.3 and 7.0 Hz, Ar*H*), 7.91-7.95 (m, 2H, Ar*H*), 8.00 (brd, 1H, Ar*H*), 8.46-8.50 (m, 1H, Ar*H*), 9.00 (brs, 1H, Ar*H*), 9.06 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 408.

**1-{4-(Phenyl)-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-4-(2-hydroxyethyl) piperazine (5a).** 2-Bromoethanol (9 µL, 0.12 mmol) was added to a vigorous stirred mixture of **4d** (50 mg, 0.12 mmol) and anhydrous potassium carbonate (38 mg, 0.27 mmol) in dry acetonitrile (6 mL), and then the suspension was refluxed for 10 hours under nitrogen. After that time, the suspension was concentrated. The crude product was purified by chromatography (2% methanol in methylene chloride) to give **5a** (42 mg, 77%) as a white solid. M.p. 183°. $R_f$ 0.65 (MeOH: $CH_2Cl_2$, 1:9). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.51-2.57 (m, 6H, NCH$_2$C*H*$_2$NC*H*$_2$CH$_2$OH), 2.74 (brs, 1H, NCH$_2$CH$_2$O*H*), 2.98 (t, 4H, J= 4.7 Hz, NC*H*$_2$CH$_2$NCH$_2$CH$_2$OH), 3.62 (t, 2H, J= 5.3 Hz, NCH$_2$C*H*$_2$OH), 7.28-7.41 (m, 2H, Ar*H*), 7.43-7.48 (m, 2H, Ar*H*), 7.52-7.60 (m, 3H, Ar*H*), 7.69-7.72 (brd, 2H, Ar*H*), 7.77 (dd, 1H, J= 1.3 and 7.0 Hz, Ar*H*), 7.91-7.95 (m, 2H, Ar*H*), 7.99-8.02 (brd, 1H, Ar*H*), 8.50-8.54 (m, 1H, Ar*H*), 9.02 (brs, 1H, Ar*H*), 9.16 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 452.

**1-{4-(Phenyl)-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-4-(ethyl-aceto) piperazine (5b).** Ethyl-bromo acetate (20 µL, 0.17 mmol) was added to a vigorous stirred mixture of **4d** (70 mg, 0.17 mmol) and anhydrous potassium carbonate (56 mg, 0.40 mmol) in dry acetonitrile (7mL), and then the suspension was refluxed for 10 hours under nitrogen. After that time, the suspension was concentrated. The crude product was chromatographied with cyclohexane-ethyl acetate (9/1) as eluent to give **5b** (40 mg, 47%) as a white oil. $R_f$ 0.42 (EtOAc:cHexane, 1:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.25 (t, 3H, $NCH_2CO_2CH_2CH_3$), 2.65 (brs, 4H, $NCH_2CH_2NCH_2CO_2Et$), 3.03 (t, 4H, J= 4.7 Hz, $NCH_2CH_2NCH_2CO_2Et$), 3.20 (s, 2H, $NCH_2CO_2Et$), 4.17 (q, 2H, $NCH_2CO_2CH_2CH_3$), 7.29-7.40 (m, 2H, Ar*H*), 7.42-7.48 (m, 2H, Ar*H*), 7.53-7.60 (m, 3H, Ar*H*), 7.68-7.72 (brd, 2H, Ar*H*), 7.77 (dd, 1H, J= 1.3 and 7.0 Hz, Ar*H*), 7.91-7.95 (m, 2H, Ar*H*), 7.99-8.02 (brd, 1H, Ar*H*), 8.51-8.55 (m, 1H, Ar*H*), 9.01 (brs, 1H, Ar*H*), 9.20 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 494.

**1-{4-(Phenyl)-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-4-[1-(5-phthalimido)-pentyl] piperazine (5c).** N-(5-bromopentyl) phthalimide (44 mg, 0.15 mmol) was added to a vigorous stirred mixture of **4d** (60 mg, 0.14 mmol) and anhydrous potassium carbonate (50 mg, 0.35 mmol) in dry acetonitrile (7mL), and then the suspension was refluxed for 10 hours under nitrogen. After that time, the suspension was concentrated. The crude product was chromatographied with methylene chloride-methanol (9/1) as eluent to give **5c** (90 mg, 99%) as a aple yellow neddles. M.p. 72°. $R_f$ 0.60 (MeOH: $CH_2Cl_2$, 1:9). $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.32-1.38 (m, 2H), 1.47-1.58 (m, 2H), 1.64-1.75 (m, 2H), 2.28-2.34 (m, 2H), 2.49 (brs, 4H, $NCH_2CH_2N(CH_2)_5$-phthalimide), 2.96 (t, 4H, J= 4.7 Hz, $NCH_2CH_2N(CH_2)_5$- phthalimide), 3.68 (t, 2H, J= 7.1 Hz), 7.27-7.40 (m, 2H, Ar*H*), 7.42-7.48 (m, 2H, Ar*H*), 7.53-7.60 (m, 3H, Ar*H*), 7.68-7.72 (m, 4H, Ar*H*), 7.73-7.80 (m, 1H, Ar*H*), 7.82-7.85 (m, 2H, Ar*H*), 7.91-7.94 (m, 2H, Ar*H*), 7.99-8.02 (brd, 1H, Ar*H*), 8.52-8.57 (m, 1H, Ar*H*), 9.02 (brs, 1H, Ar*H*), 9.20 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 623.

**4-[1-(5-Amino)-pentyl]-1-{4-(phenyl)-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-piperazine (5d).** Compound **5c** (75 mg, 0.12 mmol) was dissolved in warm ethanol (5mL), hydrazine monohydrate (10 mg, 0.18 mmol) was added, and the solution was refluxed for 3 hours, cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the residue was diluted with $NaHCO_3$ and extracted with methylene chloride. The organic layer was dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography with methylene chloride-methanol (9/1) as eluent to give the compound **5d** (50 mg, 84%) as brown oil. $R_f$ 0.09 (MeOH: $CH_2Cl_2$, 1:9). $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.26-1.36 (m, 2H), 1.42-1.53 (m, 4H), 2.30 (m, 2H), 2.49 (brs, 4H, $NCH_2CH_2N(CH_2)_5NH_2$), 2.71 (t, 2H, J= 6.9 Hz), 2.98 (t, 4H, J= 4.7 Hz, $NCH_2CH_2N(CH_2)_5NH_2$), 3.49 (brs, 2H, $NCH_2CH_2N(CH_2)_5NH_2$), 7.29 (d, 1H, J= 8.3 Hz, Ar*H*), 7.36-7.40 (m, 1H, Ar*H*), 7.46 (t, 2H, J= 7.3 Hz, Ar*H*), 7.53-7.61 (m, 3H, Ar*H*), 7.69-7.72 (m, 2H, Ar*H*), 7.77-7.79 (m, 1H, Ar*H*), 7.92-7.95 (m, 2H, Ar*H*), 8.01 (d, 1H, J= 8.2 Hz, Ar*H*), 8.52-8.56 (m, 1H, Ar*H*), 9.02 (brs, 1H, Ar*H*), 9.22 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 493.

**(*S*)-(-)-1-{4-(Phenyl)-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-4-[1-(3-phenyl)-propan-3-ol]-piperazine (5e).** (*S*)-(-)-3-Chloro-1-phenyl-1-propanol (17 mg, 0.09 mmol) was added to a vigorous stirred mixture of **4d** (40 mg, 0.09 mmol) and anhydrous potassium carbonate (31mg, 0.22 mmol) in dry acetonitrile (5mL), and then the suspension was stirred at room temperature for 10 hours under nitrogen. After that time, the suspension was concentrated. The crude product was chromatographied with methylene chloride-

methanol (9/1) as eluent to give **5e** (42 mg, 86%) as a yellow oil. $R_f$ 0.64 (MeOH: $CH_2Cl_2$, 1:9). $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.86-1.90 (m, 2H), 2.51-2.74 (m, 5H), 3.03 (t, 4H, J= 4.7 Hz, NC*H*$_2$CH$_2$NCH$_2$CH$_2$CH(Ph)OH), 3.36-3.49 (m, 1H), 4.92-4.95 (m, 1H), 7.27-7.39 (m, 8H, Ar*H*), 7.43-7.49 (m, 2H, Ar*H*), 7.52-7.62 (m, 3H, Ar*H*), 7.70 (brd, 2H, Ar*H*), 7.77 (dd, 1H, J= 1.3 and 7.0 Hz, Ar*H*), 7.91-7.95 (m, 2H, Ar*H*), 7.99 (brd, 1H, Ar*H*), 8.50-8.54 (m, 1H, Ar*H*), 9.02 (brs, 1H, Ar*H*), 9.14 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 542. $[\alpha]^{20}_D$ = - 24° (c = 1.10, $CHCl_3$).

**(*R*)-(+)-1-{4-(Phenyl)-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-4-[1-(3-phenyl)-propan-3-ol]-piperazine (5f).** (*R*)-(+)-3-Chloro-1-phenyl-1-propanol (17 mg, 0.09 mmol) was added to a vigorous stirred mixture of **4d** (40 mg, 0.09 mmol) and anhydrous potassium carbonate (31mg, 0.22 mmol) in dry acetonitrile (5mL), and then the suspension was stirred at room temperature for 12 hours under nitrogen. After that time, the suspension was concentrated. The crude product was purified by chromatography with methylene chloride- methanol (9:1) as eluent to give **5f** (25 mg, 51%) as a white oil. $R_f$ 0.64 (MeOH: $CH_2Cl_2$, 1:9). $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.83-1.90 (m, 2H), 2.52-2.74 (m, 5H), 3.03 (t, 4H, J= 4.7 Hz, NC*H*$_2$CH$_2$NCH$_2$CH$_2$CH(Ph)OH), 3.36-3.49 (m, 1H), 4.93-4.98 (m, 1H), 7.25-7.39 (m, 8H, Ar*H*), 7.43-7.49 (m, 2H, Ar*H*), 7.52-7.62 (m, 3H, Ar*H*), 7.70 (brd, 2H, Ar*H*), 7.77 (dd, 1H, J= 1.3 and 7.0 Hz, Ar*H*), 7.91-7.95 (m, 2H, Ar*H*), 8.09 (brd, 1H, Ar*H*), 8.49-8.53 (m, 1H, Ar*H*), 9.02 (brs, 1H, Ar*H*), 9.13 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 542. $[\alpha]^{20}_D$ = + 19.5° (c = 1.07, $CHCl_3$).

**1-{4-(Phenyl)-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-4-benzoyl-piperazine (6a). 4d** (50 mg, 0.12mmol) was dissolved in methylene chloride (5 mL) with DIEA (30µL, 0.16 mmol). To this solution, benzoyl chloride (17 µL, 0.14 mmol) was added. The reaction mixture was stirred for 2 hours at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography with cyclohexane-ethyl acetate (9/1) as eluent to give the desired compound **6a** (56 mg, 91%) as a white powder. M.p. 91°. $R_f$ 0.44 (EtOAc:cHexane, 1:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.98 (brs, 4H, NC*H*$_2$CH$_2$NC(O)Ph), 3.60 (brs, 4H, NCH$_2$C*H*$_2$NC(O)Ph), 7.18 (d, 1H, J= 7.2 Hz, Ar*H*), 7.27-7.40 (m, 8H, Ar*H*), 7.44-7.53 (m, 3H, Ar*H*), 7.60-7.62 (m, 2H, Ar*H*), 7.68 (dd, 1H, J= 1.3 and 7.0 Hz, Ar*H*), 7.84-7.87 (m, 1H, Ar*H*), 7.91-7.95 (brd, 2H, Ar*H*), 8.38-8.41 (m, 1H, Ar*H*), 8.94 (brs, 1H, Ar*H*), 9.03 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 512.

**1-{4-(4'-Chlorophenyl)-2-[(naphthalene-1-carbonyl)-amino]-phenyl}-4-{(5-dithiolan)-pentanoyl}-piperazine (6b). 4d** (50 mg, 0.12 mmol), racemic (+/-)-α-Lipoic acid (47 mg, 0.22 mmol), DCC (47 mg, 0.22 mmol), HOBt (30 mg, 0.22 mmol), and DMAP (28 mg, 0.22 mmol) were stirred in dry DCM (6 mL) at room temperature for 10 hours. After this time, the insoluble residue was filtered off and washed with 2x5 mL of DCM. The filtrate was concentrated and the resulting crude residue was purified by column chromatography with DCM, 0.5% MeOH as eluent, to yield **6b** as a white solid (60 mg, 84%) as a white powder. M.p. 82°. $R_f$ 0.83 (MeOH: $CH_2Cl_2$, 1:9). $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.42-1.54 (m, 2H), 1.60-1.76 (m, 4H), 1.84-1.98 (m, 1H), 2.33 (t, 2H, J= 7.3 Hz), 2.40-2.53 (m, 1H), 2.91 (t, 4H, J= 4.7 Hz, NC*H*$_2$CH$_2$NC(O)-(CH$_2$)$_4$-dithiolan), 3.10-3.20 (m, 2H), 3.47-3.66 (m, 5H), 7.24 (d, 1H, J= 8.3 Hz, Ar*H*), 7.37-7.41 (m, 1H, Ar*H*), 7.46 (t, 2H, J= 7.3 Hz, Ar*H*), 7.55-7.61 (m, 3H, Ar*H*), 7.68-7.71 (d, 2H, Ar*H*), 7.77 (dd, 1H, J= 1.3 and 7.0 Hz, Ar*H*), 7.92-7.96 (m, 2H, Ar*H*), 8.00 (brd, 1H, J= Hz, Ar*H*), 8.47-8.51 (m, 1H, Ar*H*), 9.03 (brs, 1H, Ar*H*), 9.12 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 596.

**Coumarin-3-carboxylic acid or 2-oxo-2*H*-chromene-3-carboxylic acid (7).** A mixture of salicylaldehyde, 2-hydroxy-benzaldehyde, (1.22 g, 10.0 mmol), Meldrum's acid (1.44 g, 10.0 mmol), piperidinium acetate (30 mg, 0.2 mmol) and ethanol (10 mL) was stirred at room temperature for 20 minutes, and then refluxed for 2 hours. The reaction mixture was allowed to cool down to room temperature. The crystallized product was filtered, washed three times with ethanol, and dried in vacuo to give quantitativelly the desired compound **7** as yellow needles (1.9 g, quantitative) as yellow neddles. M.p. 188°. $R_f$ 0.12 (cHex-EtOAc, 2:1). $^1$H-NMR (DMSO$d_6$) $\delta_H$ 7.38 (dd, 1H, J= 1.0 and 7.5 Hz, Ar*H*), 7.41-7.45 (m, 1H, Ar*H*), 7.69-7.76 (m, 1H, Ar*H*), 7.90 (dd, 1H, J= 1.6 and 7.7 Hz, Ar*H*), 8.73 (s, 1H, $H_4$), 13.12 (brs, 1H, COO*H*). ESI-MS m/z $[M+H]^+$= 191.

**8-Methoxy-coumarin-3-carboxylic acid or 8-methoxy-2-oxo-2*H*-chromene-3-carboxylic acid (8).** A mixture of 2-hydroxy-3-methoxy-benzaldehyde (1.50 g, 10.0 mmol), Meldrum's acid (1.44 g, 10.0 mmol), piperidinium acetate (30 mg, 0.2 mmol) and ethanol (10 mL) was stirred at room temperature for 20 minutes, and then refluxed for 2 hours. The reaction mixture was allowed to cool down to room temperature. The crystallized product was filtered, washed three times with ethanol, and dried in vacuo to give quantitativelly the desired compound as yellow needles (2.2 g, quantitative) as yellow neddles. M.p. 182°. $R_f$ 0.09 (cHex-EtOAc, 2:1). $^1$H-NMR (DMSO$d_6$) $\delta_H$ 3.89 (s, 3H, OC$H_3$), 7.25-7.41 (m, 3H, Ar*H*), 8.67 (s, 1H, $H_4$), 13.40 (brs, 1H, COO*H*). ESI-MS m/z $[M+H]^+$= 221.

**{4-Bromo-2-[(2-Oxo-2*H*-chromene-3-carbonyl)-amino]-phenyl}-morpholine (9a).** Coumarin-3-carboxylic acid **7** (350 mg, 1.90 mmol) and the amino moiety **2a** (400 mg, 1.56 mmol) were dissolved in anhydrous pyridine (10 mL). The solution was cooled to -15°C and phosphorus oxychloride (160 µL, 1.72 mmol) was added dropwise under vigorous stirring. The reaction mixture was stirred at -15°C for at least 30 min. The solution was then stirred 12 hours at room temperature. The reaction was quenched by addition of crushed ice/water (30 mL). The desired compound was extracted into AcOEt (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography to lead to the desired compound **9a** (200 mg, 30%) as yellow neddles. M.p. 222°. $R_f$ 0.48 (cHex-EtOAc, 1:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.90 (t, 4H, J= 4.5 Hz, NC$H_2$C$H_2$O), 3.99 (t, 4H, J= 4.5 Hz, NC$H_2$C$H_2$O), 7.10 (d, 1H, J= 8.4 Hz, Ar*H*), 7.25 (dd, 1H, J= 2.3 and 8.4 Hz, Ar*H*), 7.42-7.47 (m, 2H, Ar*H*), 7.68-7.78 (m, 2H, Ar*H*), 8.83 (d, 1H, J= 2.3 Hz, Ar*H*), 9.01 (s, 1H, Ar*H*), 11.67 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 429.

**1-{4-Bromo-2-[(2-Oxo-2*H*-chromene-3-carbonyl)-amino]-phenyl}-4-*tert*-butoxycarbonyl piperazine (9b).** Coumarin-3-carboxylic acid **7** (240 mg, 1.25 mmol) and the amino moiety **2b** (370 mg, 1.04 mmol) were dissolved in anhydrous pyridine (10 mL). The solution was cooled to -15°C and phosphorus oxychloride (110 µL, 1.14 mmol) was added dropwise under vigorous stirring. The reaction mixture was stirred at -15°C for at least 30 min. The solution was then stirred 12 hours at room temperature. The reaction was quenched by addition of crushed ice/water (30 mL). The desired compound was extracted into AcOEt (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography to lead to the desired compound **9b** (390 mg, 71%) as a yellow powder. M.p. 230°. $R_f$ 0.66 (Toluene-EtOAc, 6:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.48 (s, 9H, $CH_3$, *t*Bu), 2.87 (brs, 4H, NC$H_2$C$H_2$NBoc), 3.73 (brs, 4H, NC$H_2$C$H_2$NBoc), 7.09-7.24 (m, 4H, Ar*H*), 7.37-7.45 (m, 3H, Ar*H*), 7.66-7.76 (m, 3H, Ar*H*), 8.61 (d, 1H, J= 2.3 Hz, Ar*H*), 9.03 (s, 1H, Ar*H*), 11.69 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 528.

**4-Benzyl-1-{4-bromo-2-[(2-Oxo-2*H*-chromene-3-carbonyl)-amino]-phenyl}-piperazine (9c).** Coumarin-3-carboxylic acid **7** (55 mg, 0.29mmol) and the amino moiety **2c** (100 mg, 0.29 mmol) were dissolved in anhydrous pyridine (4 mL). The solution was cooled to -15°C and phosphorus oxychloride (30 µL, 0.32 mmol) was added dropwise under vigorous stirring. The reaction mixture was stirred at -15°C for at least 30 min. The solution was then stirred 12 hours at room temperature. The reaction was quenched by addition of crushed ice/water (10 mL). The desired compound was extracted into AcOEt (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography to lead to the desired compound **9c** (100 mg, 70%) as a yellow powder. M.p. 190°. $R_f$ 0.27 (cHex-EtOAc, 2:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.77 (brs, 4H, $NCH_2CH_2NCH_2Ph$), 2.93 (brs, 4H, $NCH_2CH_2NCH_2Ph$), 3.65 (s, 2H, $NCH_2Ph$), 7.09 (d, 1H, J= 8.4 Hz, Ar*H*), 7.23 (dd, 1H, J= 2.3 and 8.4 Hz, Ar*H*), 7.28-7.48 (m, 7H, Ar*H*), 7.67-7.77 (m, 2H, Ar*H*), 8.81 (d, 1H, J= 2.3 Hz, Ar*H*), 9.01 (s, 1H, Ar*H*), 11.57 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 518.

**1-{4-Bromo-2-[(2-Oxo-2*H*-chromene-3-carbonyl)-amino]-phenyl}-piperazine as a TFA salt (9d).** To a stirred solution of the appropriate N-Boc compound **9c** (60 mg, 0.11 mmol) in dry $CH_2Cl_2$ (10 mL), trifluoroacetic acid (TFA) (90 µL, 1.1 mmol) was added dropwise under nitrogen at 0°C. The reaction mixture was stirred overnight at room temperature. After completion, the solvent and excess TFA were removed under reduced pressure, the corresponding trifluoroacetic acid salt was identified as the desired compound **9d** (60 mg, 97%) as a TFA salt. $R_f$ 0.09 (EtOAc:cyclohexane, 2:1). $^1$H-NMR ($DMSOd_6$) $\delta_H$ 3.06 (brs, 4H, $NCH_2CH_2NH$.TFA), 3.32 (brs, 4H, $NCH_2CH_2NH$.TFA), 7.26-7.38 (m, 2H, Ar*H*), 7.48-7.58 (m, 2H, Ar*H*), 7.83 (t, 1H, J= 8.1 Hz, Ar*H*), 8.10 (d, 1H, J= 6.7 Hz, Ar*H*), 8.72 (d, 1H, J= 2.2 Hz, Ar*H*), 8.85 (brs, 2H, $NCH_2CH_2NH$.TFA), 9.10 (s, 1H, Ar*H*), 11.53 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 428.

**1-{4-Bromo-2-[(2-Oxo-2*H*-chromene-3-carbonyl)-amino]-phenyl}-4-(2-hydroxyethyl)-piperazine (9e).** 2-Bromoethanol (4.5 µL, 0.061 mmol) was added to a vigorous stirred mixture of **9d** (30 mg, 0.055 mmol) and anhydrous $K_2CO_3$ (20 mg, 0.14 mmol) in dry acetonitrile (5 mL). The suspension was refluxed for 10 hours under nitrogen. The solvent was then removed under reduced pressure. The crude product was dissolved in $CH_2Cl_2$ (5 mL) and extracted with water (2x 5 mL), the organic layer was dried over $MgSO_4$, and then purified by chromatography on silica gel, using methylene chloride-methanol (9:1) as eluent, to yield the compound **9e** (20 mg, 77%) as a brown oil. $R_f$ 0.45 ($CH_2Cl_2$: MeOH, 5:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.76 (brs, 2H, $NCH_2CH_2OH$), 2.89 (brs, 4H, $NCH_2CH_2$ $NCH_2CH_2OH$), 2.96 (brs, 4H, $NCH_2CH_2NCH_2CH_2OH$), 3.67-3.73 (m, 2H, $NCH_2CH_2OH$), 7.10 (d, 1H, J= 8.3 Hz, Ar*H*), 7.25 (dd, 1H, J= 2.2 and 8.3 Hz, Ar*H*), 7.42-7.46 (m, 2H, Ar*H*), 7.67-7.76 (m, 2H, Ar*H*), 8.82 (d, 1H, J= 2.2 Hz, Ar*H*), 9.01 (s, 1H, Ar*H*), 11.56 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 472.

**{4-Bromo-2-[(8-methoxy-2-Oxo-2*H*-chromene-3-carbonyl)-amino]-phenyl}-morpholine (10a).** Coumarin-3-carboxylic acid **8** (410 mg, 1.90 mmol) and the amino moiety **2a** (400 mg, 1.56 mmol) were dissolved in anhydrous pyridine (10 mL). The solution was cooled to -15°C and phosphorus oxychloride (160 µL, 1.72 mmol) was added dropwise under vigorous stirring. The reaction mixture was stirred at -15°C for at least 30 min. The solution was then stirred 12 hours at room temperature. The reaction was quenched by addition of crushed ice/water (30 mL). The desired compound was extracted into AcOEt (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated

under reduced pressure. The crude material was purified by flash chromatography to lead to the desired compound **10a** (150 mg, 21%) as a yellow powder. M.p. 229°. $R_f$ 0.41 (cHex-EtOAc, 1:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.89 (t, 4H, J= 4.5 Hz, NC*H*$_2$CH$_2$O), 3.98 (t, 4H, J= 4.5 Hz, NCH$_2$C*H*$_2$O), 4.01 (s, 3H, OC*H*$_3$), 7.06 (d, 1H, J= 8.4 Hz, Ar*H*), 7.20-7.35 (m, 5H, Ar*H*), 8.83 (d, 1H, J= 2.3 Hz, Ar*H*), 8.98 (s, 1H, Ar*H*), 11.70 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 459.

**1-{4-Bromo-2-[(8-methoxy-2-Oxo-2*H*-chromene-3-carbonyl)-amino]-phenyl}-4-*tert*-butoxycarbonyl piperazine (10b).** 8-Methoxy-coumarin-3-carboxylic acid **8** (300 mg, 1.35 mmol) and the amino moiety **2b** (400 mg, 1.12 mmol) were dissolved in anhydrous pyridine (10 mL). The solution was cooled to -15°C and phosphorus oxychloride (115 µL, 1.23 mmol) was added dropwise under vigorous stirring. The reaction mixture was stirred at -15°C for at least 30 min. The solution was then stirred 12 hours at room temperature. The reaction was quenched by addition of crushed ice/water (30 mL). The desired compound was extracted into AcOEt (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography to lead to the desired compound **10b** (390 mg, 64%) as a yellow powder. M.p. 241°. $R_f$ 0.39 (cHex-EtOAc, 2:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.49 (s, 9H,, $CH_3$, *t*Bu), 2.83 (brs, 4H, NC*H*$_2$CH$_2$NBoc), 3.71 (brs, 4H, NCH$_2$C*H*$_2$NBoc), 4.00 (s, 3H, OC*H*$_3$), 7.02 (d, 1H, J= 8.3 Hz, Ar*H*), 7.21-7.24 (m, 1H, Ar*H*), 7.29-7.34 (m, 2H, Ar*H*), 8.83 (d, 1H, J= 2.3 Hz, Ar*H*), 8.98 (s, 1H, Ar*H*), 11.73 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 558.

**4-Benzyl-1-{4-bromo-2-[(8-methoxy-2-Oxo-2*H*-chromene-3-carbonyl)-amino]-phenyl}-piperazine (10c).** 8-Methoxy-coumarin-3-carboxylic acid **8** (35 mg, 0.16 mmol) and the amino moiety **2c** (50 mg, 0.14 mmol) were dissolved in anhydrous pyridine (4 mL). The solution was cooled to -15°C and phosphorus oxychloride (20 µL, 0.17 mmol) was added dropwise under vigorous stirring. The reaction mixture was stirred at -15°C for at least 30 min. The solution was then stirred 12 hours at room temperature. The reaction was quenched by addition of crushed ice/water (10 mL). The desired compound was extracted into AcOEt (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography to lead to the desired compound **10c** (30 mg, 40%) as a yellow powder. M.p. 232°. $R_f$ 0.31 (cHex-EtOAc, 2:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.79 (brs, 4H, NCH$_2$C*H*$_2$NCH$_2$Ph), 2.94 (brs, 4H, NC*H*$_2$CH$_2$NCH$_2$Ph), 3.66 (s, 2H, NC*H*$_2$Ph), 4.03 (s, 3H, OC*H*$_3$), 7.07 (d, 1H, J= 8.4 Hz, Ar*H*), 7.23 (dd, 1H, J= 2.3 and 8.4 Hz, Ar*H*), 7.28-7.34 (m, 5H, Ar*H*), 7.40-7.42 (m, 2H, Ar*H*), 8.81 (d, 1H, J= 2.3 Hz, Ar*H*), 8.98 (s, 1H, Ar*H*), 11.59 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 548.

**1-{4-Bromo-2-[(8-methoxy-2-Oxo-2*H*-chromene-3-carbonyl)-amino]-phenyl}-piperazine as a TFA salt (10d).** To a stirred solution of the appropriate N-Boc compound **10c** (100 mg, 0.18 mmol) in dry $CH_2Cl_2$ (10 mL), trifluoroacetic acid (TFA) (140 µL, 1.8 mmol) was added dropwise under nitrogen at 0°C. The reaction mixture was stirred overnight at room temperature. After completion, the solvent and excess TFA were removed under reduced pressure, the corresponding trifluoroacetic acid salt was identified as the desired compound **10d** (102 mg, 99%) as TFA salt. $R_f$ 0.08 (EtOAc:cHexane, 2:1). $^1$H-NMR ($DMSOd_6$) $\delta_H$ 3.05 (t, 4H, J= 4.4 Hz, NC*H*$_2$CH$_2$NH), 3.34 (brs, 4H, NCH$_2$C*H*$_2$NH), 3.96 (s, 3H, OC*H*$_3$), 7.30 (d, 1H, J= 8.5 Hz, Ar*H*), 7.35 (dd, 1H, J= 2.2 and 8.5 Hz, Ar*H*), 7.43 (d, 1H, J= 7.5 Hz, Ar*H*), 7.48-7.52 (m, 1H, Ar*H*),7.61-7.66 (m, 1H, Ar*H*), 8.71(d, 1H, J= 2.2 Hz, Ar*H*), 8.70 (brs, 2H, NCH$_2$CH$_2$N*H*.TFA), 9.06 (s, 1H, Ar*H*), 11.58 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 458.

**1-{4-Bromo-2-[(8-methoxy-2-Oxo-2*H*-chromene-3-carbonyl)-amino]-phenyl}-4-(2-hydroxyethyl)-piperazine (10e).** 2-Bromoethanol (6.3 µL, 0.090 mmol) was added to a vigorous stirred mixture of **10d** (46 mg, 0.081 mmol) and anhydrous $K_2CO_3$ (28 mg, 0.20 mmol) in dry acetonitrile (6 mL). The suspension was refluxed for 10 hours under nitrogen. The solvent was then removed under reduced pressure. The crude product was dissolved in $CH_2Cl_2$ (5 mL) and extracted with water (2x 5 mL), the organic layer was dried over $MgSO_4$, and then purified by chromatography on silica gel, using methylene chloride-methanol (9:1) as eluent, to yield the compound **10e** (40 mg, 97%) as a pale yellow solid. M.p. 219°. $R_f$ 0.65 ($CH_2Cl_2$: MeOH, 5:1). $^1$H-NMR ($DMSOd_6$) $\delta_H$ 2.76 (brs, 2H, NC*H*$_2$CH$_2$OH), 3.16 (brs, 4H, NCH$_2$C*H*$_2$NCH$_2$CH$_2$OH), 3.36 (brs, 4H, NC*H*$_2$CH$_2$NCH$_2$CH$_2$OH), 3.79 (brs, 2H, NCH$_2$C*H*$_2$OH), 3.96 (s, 3H, OC*H*$_3$), 7.29 (d, 1H, J= 8.3 Hz, Ar*H*), 7.36 (dd, 1H, J= 2.2 and 8.3 Hz, Ar*H*), 7.42-7.46 (m, 2H, Ar*H*), 7.67-7.76 (m, 1H, Ar*H*), 8.74 (d, 1H, J= 2.2 Hz, Ar*H*), 9.07 (s, 1H, Ar*H*), 11.50 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 502.

**1-{4-(Phenyl)-2-[(2-Oxo-2*H*-chromene-3-carbonyl)-amino]-phenyl}-4-*tert*-butoxycarbonyl piperazine (11b).** Phenyl boronic acid (30 mg, 0.23 mmol) was dissolved in anhydrous 1,3-dioxane (10 mL). The appropriate bromo derivative **9b** (100 mg, 0.19 mmol) was dissolved in anhydrous dioxane (10 mL) and the two solutions were mixed with dppf (5 mg, 0.006 mmol), dppf-Pd$^{II}$ (10 mg, 0.006 mmol), and KOAc (56 mg, 0.57 mmol). The resulting suspension was refluxed for 72 hours. The dioxane was removed under reduced pressure and the catalysts were removed by filtration through silica gel. The crude product was purified by flash chromatography with cHex-EtOAc (9:1) as eluent, to yield the desired compound **11b** as a yellow powder (45 mg, 45 %). M.p. 224°. $R_f$ 0.76 (EtOAc:cHexane, 1:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 1.45 (s, 9H, $CH_3$, *t*Bu), 2.98 (brs, 4H, NC*H*$_2$CH$_2$NBoc), 3.92 (brs, 4H, NCH$_2$C*H*$_2$NBoc), 7.23-7.26 (m, 1H, Ar*H*), 7.32-7.47 (m, 7H, Ar*H*), 7.56-7.69 (m, 2H, Ar*H*), 7.71-7.78 (m, 2H, Ar*H*), 8.92 (d, 1H, J= 2.0 Hz, Ar*H*), 9.05 (s, 1H, Ar*H*), 11.75 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 526.

**4-Benzyl-1-{4-(phenyl)-2-[(2-Oxo-2*H*-chromene-3-carbonyl)-amino]-phenyl}-piperazine (11c).** Phenyl boronic acid (175 mg, 1.43 mmol) was dissolved in anhydrous 1,3-dioxane (20 mL). The appropriate bromo derivative **9c** (370 mg, 0.720 mmol) was dissolved in anhydrous dioxane (10 mL) and the two solutions were mixed with dppf (12 mg, 0.022 mmol), dppf-Pd$^{II}$ (20 mg, 0.022 mmol), and KOAc (210 mg, 2.1 mmol). The resulting suspension was refluxed for 72 hours. The dioxane was removed under reduced pressure and the catalysts were removed by filtration through silica gel. The crude product was purified by flash chromatography with cHex-EtOAc (9:1) as eluent, to yield the desired compound **11c** as a yellow powder (190 mg, 51 %). M.p. 235°. $R_f$ 0.61 (EtOAc: cHexane, 1:1). $^1$H-NMR ($CDCl_3$) $\delta_H$ 2.79 (brs, 4H, NCH$_2$C*H*$_2$NCH$_2$Ph), 3.00 (t, 4H, J= 4.7 Hz, NC*H*$_2$CH$_2$NCH$_2$Ph), 3.66 (s, 2H, NC*H*$_2$Ph), 7.29-7.44 (m, 10H, Ar*H*), 7.46-7.49 (m, 2H, Ar*H*), 7.57 (d, 2H, J= 8.7 Hz, Ar*H*), 7.67-7.75 (m, 2H, Ar*H*), 8.89 (d, 1H, J= 1.7 Hz, Ar*H*), 9.03 (s, 1H, Ar*H*), 11.60 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 516.

**1-{4-(Phenyl)-2-[(2-Oxo-2*H*-chromene-3-carbonyl)-amino]-phenyl}-piperazine (11d).** To a stirred solution of the appropriate N-Boc compound **11b** (37 mg, 0.070 mmol) in dry $CH_2Cl_2$ (5 mL), trifluoroacetic acid (TFA) (55 µL, 0.70 mmol) was added dropwise under nitrogen at 0°C. The reaction mixture was stirred overnight at room temperature. After completion, the solvent and excess TFA were removed under reduced pressure, the corresponding trifluoroacetic acid salt was identified as the desired compound **11d** (4 mg, 13%) as a TFA salt. $R_f$ 0.06 (EtOAc:cHexane, 2:1). $^1$H-NMR ($CD_3OD$) $\delta_H$ 3.13 (brt, 4H, J=

4.7 Hz, NC*H*$_2$CH$_2$NH), 3.00 (brt, 4H, J= 4.7 Hz, NCH$_2$C*H*$_2$NH), 7.39-7.51 (m, 8H, Ar*H*), 7.61-7.64 (m, 2H, Ar*H*), 7.75-7.84 (m, 1H, Ar*H*), 7.91 (dd, 1H, J= 1.6 and 8.1 Hz, Ar*H*), 8.80 (brs, 1H, NCH$_2$CH$_2$N*H*.TFA), 8.85 (d, 1H, J= 2.0 Hz, Ar*H*), 9.06 (s, 1H, Ar*H*), 11.50 (brs, 1H, N*H*C(O)). ESI-MS m/z $[M+H]^+$= 426.

**Table of elemental analyses**

| Compound | Formula | Calculated | Found |
|---|---|---|---|
| **1a** | $C_{10}H_{11}BrN_2O_3$ | C 41.83, H 3.86, N 9.76 | C 41.46, H 4.12, N 10.05 |
| **1b** | $C_{15}H_{20}BrN_3O_4$ | C 46.64, H 5.22, N 10.88 | C 46.31, H 5.49, N 11.10 |
| **1c** | $C_{17}H_{18}BrN_3O_2$ | C 54.27, H 4.82, N 11.17 | C 54.60, H 4.51, N 10.92 |
| **2a** | $C_{10}H_{13}BrN_2O$ | C 46.71, H 5.10, N 10.89 | C 46.42, H 5.32, N 10.61 |
| **2b** | $C_{15}H_{22}BrN_3O_2$ | C 50.57, H 6.22, N 11.79 | C 50.87, H 6.22, N 11.42 |
| **2c** | $C_{17}H_{20}BrN_3$ | C 58.97, H 5.82, N 12.14 | C 59.31, H 5.43, N 12.39 |
| **3a** | $C_{21}H_{19}BrN_2O_2$ | C 61.32, H 4.66, N 6.81 | C 61.69, H 4.93 N 7.12 |
| **3b** | $C_{26}H_{28}BrN_3O_3$ | C 61.18, H 5.53, N 8.23 | C 61.34, H 5.81 N 8.54 |
| **3c** | $C_{28}H_{26}BrN_3O$ | C 67.20, H 5.24, N 8.40 | C 67.54, H 5.02 N 8.76 |
| **3d** | $C_{21}H_{20}BrN_3O$ | C 61.47, H 4.91, N 10.24 | C 61.98, H 5.24 N 10.49 |
| **3e** | $C_{23}H_{24}BrN_3O_2$ | C 60.80, H 5.32, N 9.25 | C 61.12, H 5.02 N 9.54 |
| **4b** | $C_{32}H_{33}N_3O_3$ | C 75.71, H 6.55, N 8.28 | C 75.43, H 6.59 N 7.99 |
| **4c** | $C_{34}H_{31}N_3O$ | C 82.06, H 6.28, N 8.46 | C 81.98, H 6.09 N 8.26 |
| **4d** | $C_{27}H_{25}N_3O$ | C 79.58, H 6.18, N 10.31 | C 79.64, H 6.27 N 10.13 |
| **5a** | $C_{29}H_{29}N_3O_2$ | C 77.13, H 6.47, N 9.31 | C 77.57, H 6.22 N 9.45 |
| **5b** | $C_{31}H_{31}N_3O_3$ | C 75.43, H 6.33, N 8.51 | C 75.79, H 6.47 N 8.63 |
| **5c** | $C_{40}H_{38}N_4O_3$ | C 77.15, H 6.15, N 9.00 | C 76.89, H 5.99 N 8.86 |
| **5d** | $C_{32}H_{36}N_4O$ | C 78.01, H 7.37, N 11.37 | C 78.22, H 7.05 N 11.69 |
| **5e** | $C_{36}H_{35}N_3O_2$ | C 79.82, H 6.51, N 7.76 | C 79.53, H 6.71 N 7.62 |
| **5f** | $C_{36}H_{35}N_3O_2$ | C 79.76, H 6.46, N 7.56 | C 79.22, H 6.69 N 7.44 |
| **6a** | $C_{34}H_{29}N_3O_2$ | C 79.78, H 5.67, N 8.21 | C 79.62, H 5.46 N 8.06 |
| **6b** | $C_{35}H_{37}N_3O_2S_2$ | C 70.55, H 6.26, N 7.05 | C 70.43, H 6.48 N 6.97 |

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|---|---|---|---|
| **7** | $C_{10}H_6O_4$ | C 63.16, H 3.18 | C 63.37, H 3.04 |
| **8** | $C_{11}H_8O_5$ | C 60.00, H 3.66 | C 60.37, H 3.41 |
| **9a** | $C_{20}H_{17}BrN_2O_4$ | C 55.96, H 3.99, N 6.53 | C 56.21, H 3.62 N 6.32 |
| **9b** | $C_{25}H_{26}BrN_3O_5$ | C 56.83, H 4.96, N 7.95 | C 57.13, H 4.71 N 8.31 |
| **9c** | $C_{27}H_{24}BrN_3O_3$ | C 62.56, H 4.67, N 8.11 | C 62.77, H 4.29 N 8.37 |
| **9d** | $C_{22}H_{19}BrF_3N_3O_5$ | C 48.72, H 3.53, N 7.75 | C 48.99, H 3.31 N 7.91 |
| **9e** | $C_{22}H_{22}BrN_3O_4$ | C 55.94, H 4.69, N 8.90 | C 56.21, H 4.39 N 8.63 |
| **10a** | $C_{21}H_{19}BrN_2O_5$ | C 54.92, H 4.17, N 6.10 | C 55.31, H 4.34 N 6.47 |
| **10b** | $C_{26}H_{28}BrN_3O_6$ | C 55.92, H 5.05, N 7.52 | C 55.63, H 5.29 N 7.78 |
| **10c** | $C_{28}H_{26}BrN_3O_4$ | C 61.32, H 4.78, N 7.66 | C 61.75, H 4.93 N 8.12 |
| **10d** | $C_{23}H_{21}BrF_3N_3O_6$ | C 48.27, H 3.70, N 7.34 | C 48.39, H 3.41 N 7.59 |
| **10e** | $C_{23}H_{24}BrN_3O_5$ | C 54.99, H 4.82, N 8.36 | C 54.70, H 4.99 N 8.72 |
| **11b** | $C_{31}H_{31}N_3O_5$ | C 70.84, H 5.95, N 7.95 | C 70.81, H 6.12 N 7.87 |
| **11c** | $C_{33}H_{29}N_3O_3$ | C 76.86, H 5.63, N 8.14 | C 76.95, H 5.49 N 7.93 |
| **11d** | $C_{28}H_{24}F_3N_3O_5$ | C 62.34, H 4.44, N 7.72 | C 62.19, H 4.14 N 7.91 |