

## Experimental Section

**Abbreviations:**  $P_{\text{HPLC}}$ , purity determined by HPLC; TLC, thick-layer chromatography; TOFMS, time-of-flight mass spectrometry.

**Chemistry.** All reactions were monitored by thin-layer chromatography carried out on 0.2 mm E. Merck silica gel plates (60F-254) using UV light as a visualizing agent. Chromatography was undertaken using silica gel 60 (230-400 mesh ASTM) from Macherey-Nagel. Thick-layer chromatography (TLC) was performed using silica gel from Merck, from which the compounds were extracted by the following solvent system:  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ , 75:25:10. All melting points were determined on a Büchi melting point apparatus and were uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained using a Bruker 300 MHz spectrometer, chemical shifts ( $\delta$ ) were expressed in ppm relative to TMS used as an internal standard. Mass spectra were recorded on a time-of-flight (TOF) plasma desorption spectrometer using a Californium source. The purity of final compounds was verified by two types of high pressure liquid chromatography (HPLC): C18 vydac (C18V) and C18 nucleosil (C18N) columns. Analytical HPLC was performed on a Shimadzu system equipped with a UV detector set at 254 nm. Compounds were dissolved in EtOH and injected through a 50  $\mu\text{L}$  loop. The following eluent systems were used: A ( $\text{H}_2\text{O}/\text{TFA}$ , 100:0.05) and B ( $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{TFA}$ , 80:20:0.05). HPLC retention times (HPLC  $t_R$ ) were obtained, at flow rates of 1 mL/min, using the following conditions: a gradient run from 100% eluent A during 5 min, then to 100% eluent B over the next 25 min. 4,7-dichloroquinoline was obtained from Acros, PyBroP from Novabiochem and other reagents from Acros, Aldrich and Lancaster.

**Procedure for chlorhydrate salts.** To a solution of compound **1-21** (1 eq.) in MeOH was added trimethylchlorosilane (1 eq.). After stirring the mixture for 15 minutes at room temperature, the solvent was evaporated to yield the desired chlorhydrate.

**Method A: General Procedure for the Synthesis of Compounds 2-19.** To a solution of compound **1** (150 mg, 0.5 mmol, 1 eq.) in 10 mL of DMF were added the appropriate halogenocarboxylic acid (0.5 mmol, 1 eq.), PyBroP (235 mg, 0.5 mmol, 1 eq) and 1-ethylpiperidine (140  $\mu$ L, 1 mmol, 2 eq.). After stirring the mixture at room temperature for 12 h, the appropriate amine (2 mmol, 4 eq.) was added. Further stirring of the mixture at reflux for 5 h was followed by evaporation of solvent with the residue being taken up in 15 mL of  $\text{CH}_2\text{Cl}_2$  and washed with aqueous  $\text{NaHCO}_3$  1 M and brine. The organic layer was separated, dried over  $\text{MgSO}_4$ , the solvent evaporated and the residue purified by TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 90:10 to 60:40) to yield the desired product.

**Method B: General Procedure for the Synthesis of Compounds 25-33.** At  $0^\circ\text{C}$ , to a solution of compound **8** (150 mg, 0.35 mmol, 1 eq.) in 10 mL of dry  $\text{CH}_2\text{Cl}_2$  were added the appropriate halogenocarboxylic acid (0.53 mmol, 1.5 eq.), DMAP (130 mg, 1.05 mmol, 3 eq.) and DCC (145 mg, 0.7 mmol, 2 eq.). After stirring at room temperature for 18 h, the mixture was cooled to  $-20^\circ\text{C}$  and filtered. The appropriate amine (3.55 mmol, 10 eq.) and 1-ethylpiperidine (194  $\mu$ L, 1.42 mmol, 4 eq.) were then introduced to the filtrate. At reflux the mixture was stirred for 18 h, before being washed with aqueous  $\text{NaHCO}_3$  1 M and brine. The organic layer was separated, dried over  $\text{MgSO}_4$ , the solvent evaporated and the residue purified by TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 95:5 to 85:15) to yield the desired product.

**Method C: General Procedure for the Synthesis of Compounds 34-36.** At  $0^\circ\text{C}$ , to a solution of compound **8** (150 mg, 0.35 mmol, 1 eq.) in 10 mL of dry  $\text{CH}_2\text{Cl}_2$  were added the appropriate acid (0.53 mmol, 1.5 eq.), DMAP (130 mg, 1.05 mmol, 3 eq.) and DCC (145 mg, 0.7 mmol, 2 eq.). After stirring at room temperature for 18 h, the mixture was cooled to  $-20^\circ\text{C}$  and filtered, the filtrate washed with aqueous  $\text{NaHCO}_3$  1 M and brine. The organic layer was separated, dried over  $\text{MgSO}_4$ , the solvent evaporated and the residue purified by TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 90:10 to 85:15) to yield the desired product.

**Method D: General Procedure for the Synthesis of Benzylpiperazine Derivatives.** At 0°C, to a solution of piperazine (600 mg, 7.0 mmol, 5 eq.) in 20 mL of dry CH<sub>2</sub>Cl<sub>2</sub> was added the appropriate benzaldehyde (1.4 mmol, 1 eq.) and, after stirring at room temperature for 1 h, NaHB(OAc)<sub>3</sub> (590 mg, 2.8 mmol, 2 eq.). Following further stirring of the mixture at room temperature for 18 h, aqueous NaHCO<sub>3</sub> 1 M was introduced and the mixture left for 15 min, the organic layer was separated and the aqueous layer washed with CH<sub>2</sub>Cl<sub>2</sub>. Then the organic layers were mixed and dried over MgSO<sub>4</sub>, the solvent was evaporated and the residue purified by TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 90:10) to yield the desired product.

**Method E: General Procedure for the Synthesis of Compounds 38-66.** At 0°C, to a solution of compound 37 (100 mg, 0.24 mmol, 1 eq.) in 10 mL of dry CH<sub>2</sub>Cl<sub>2</sub> was added the appropriate amine (0.24 mmol, 1 eq.) and, after stirring at room temperature for 1 h, NaHB(OAc)<sub>3</sub> (100 mg, 0.47 mmol, 2 eq.). Following further stirring at room temperature for 18 h, aqueous NaHCO<sub>3</sub> 1 M was introduced and the mixture was left to stir for 15 min. The organic layer was then separated and the aqueous layer washed with CH<sub>2</sub>Cl<sub>2</sub>. The organic layers were combined, washed with brine, separated and dried over MgSO<sub>4</sub>. The solvent was evaporated and the residue purified by TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 93:7 to CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH, 80:20:1) to yield the desired product.

**3-Amino-5-(7-chloro-quinolin-4-ylamino)-phenylmethanol (1).** At 0°C, to a solution of 4,7-dichloroquinoline (1.88 g, 9.5 mmol, 1 eq.) in 50 mL of EtOH was added *N*-methylmorpholine (1.2 mL, 10.9 mmol, 1.2 eq.). After stirring the mixture at 0°C for 1 h, a solution of 3,5-diaminobenzyl alcohol dihydrochloride (2 g, 9.5 mmol, 1 eq.) in 10 mL of a EtOH/CHCl<sub>3</sub> 1:1 mixture was introduced. Following further stirring at 0°C for 2 h and at room temperature for 72 h, the mixture was filtered and the precipitate washed by ether to yield compound 1 as a yellow solid (2.5 g, 88% yield); R<sub>f</sub> 0.15 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1); mp > 250°C; HPLC (C18V) P<sub>HPLC</sub> 100%, t<sub>R</sub> 10.55 min; HPLC (C18N) P<sub>HPLC</sub> 99%, t<sub>R</sub> 12.87 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.06 (s, 1 H, NH), 8.78 (d, *J* = 9.2 Hz, 1 H, Ar-H), 8.52 (d, *J* = 7.0 Hz, 1 H, Ar-H), 8.10 (d, *J* = 2.0 Hz, 1

H, Ar-H), 7.84 (dd,  $J = 9.1, 2.1$  Hz, 1 H, Ar-H), 6.92 (s, 2 H, Ar-H), 6.85 (s, 1 H, Ar-H), 6.82 (d,  $J = 7.0$  Hz, 1 H, Ar-H), 4.47 (s, 2 H, CH<sub>2</sub>), 3.60 (s, 2 H, NH<sub>2</sub>), 2.70 (s, 1 H, OH); TOFMS  $m/z$  299.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-2-(4-methyl-piperidin-1-yl)-acetamide (2).**

Compound 2 was prepared from chloroacetic acid (48 mg, 0.5 mmol, 1 eq.) and 4-methylpiperidine (240  $\mu$ L, 2 mmol, 4 eq.) by method A and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 90:10) as a yellow solid (110 mg, 50% yield);  $R_f$  0.55 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1); mp 226°C (hydrochloride); HPLC (C18V)  $P_{HPLC}$  99%,  $t_R$  12.69 min; HPLC (C18N)  $P_{HPLC}$  100%,  $t_R$  14.46 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  9.66 (s, 1 H, CONH), 9.08 (s, 1 H, NH), 8.43 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.40 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 7.85 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.63 (s, 1 H, Ar-H), 7.52 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.26 (s, 1 H, Ar-H), 6.99 (s, 1 H, Ar-H), 6.93 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.22 (t,  $J = 5.7$  Hz, 1 H, OH), 4.45 (d,  $J = 5.7$  Hz, 2 H, CH<sub>2</sub>), 2.77-2.74 (m, 2 H, piperidine), 2.70-2.68 (m, 2 H, piperidine), 1.51-1.47 (m, 2 H, piperidine), 1.31-1.20 (m, 3 H, piperidine), 0.85 (d,  $J = 5.9$  Hz, 3 H, CH<sub>3</sub>); TOFMS  $m/z$  438.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-3-(4-methyl-piperidin-1-yl)-propanamide (3).**

Compound 3 was prepared from 3-bromopropanoic acid (77 mg, 0.5 mmol, 1 eq.) and 4-methylpiperidine (240  $\mu$ L, 2 mmol, 4 eq.) by method A and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 80:20) as a yellow solid (55 mg, 25% yield);  $R_f$  0.25 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8:2); mp 145°C (hydrochloride); HPLC (C18V)  $P_{HPLC}$  90%,  $t_R$  12.84 min; HPLC (C18N)  $P_{HPLC}$  92%,  $t_R$  14.70 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  10.22 (s, 1 H, CONH), 9.11 (s, 1 H, NH), 8.47 (d,  $J = 5.5$  Hz, 1 H, Ar-H), 8.44 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 7.89 (d,  $J = 2.0$  Hz, 1 H, Ar-H), 7.62 (s, 1 H, Ar-H), 7.56 (dd,  $J = 8.8, 2.0$  Hz, 1 H, Ar-H), 7.25 (s, 1 H, Ar-H), 7.00 (s, 1 H, Ar-H), 6.97 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 5.25 (t,  $J = 5.6$  Hz, 1 H, OH), 4.48 (d,  $J = 5.5$  Hz, 2 H, CH<sub>2</sub>), 2.88-2.85 (m, 2 H, piperidine), 2.63-2.61 (m, 2 H, piperidine), 2.27 (m, 2 H, CH<sub>2</sub>), 1.98 (m, 2 H, CH<sub>2</sub>), 1.61-1.59 (m, 2 H, piperidine), 1.35-1.20 (m, 3 H, piperidine), 0.87 (d,  $J = 6.3$  Hz, 3 H, CH<sub>3</sub>); TOFMS  $m/z$  452.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-5-(4-methyl-piperidin-1-yl)-pentanamide**

(4). Compound 4 was prepared from 5-bromovaleric acid (91 mg, 0.5 mmol, 1 eq.) and 4-methylpiperidine (240  $\mu$ L, 2 mmol, 4 eq.) by method A and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 75:25) as a yellow solid (50 mg, 21% yield);  $R_f$  0.15 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 7:3); mp 182°C (hydrochloride); HPLC (C18V)  $P_{\text{HPLC}}$  98%,  $t_R$  13.26 min; HPLC (C18N)  $P_{\text{HPLC}}$  100%,  $t_R$  14.93 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.93 (s, 1 H, CONH), 9.11 (s, 1 H, NH), 8.48 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.46 (d,  $J = 9.2$  Hz, 1 H, Ar-H), 7.90 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.64 (s, 1 H, Ar-H), 7.57 (dd,  $J = 9.0, 2.3$  Hz, 1 H, Ar-H), 7.28 (s, 1 H, Ar-H), 7.00 (s, 1 H, Ar-H), 6.97 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.27 (bs, 1 H, OH), 4.49 (s, 2 H,  $\text{CH}_2$ ), 2.78-2.75 (m, 2 H, piperidine), 2.34-2.22 (m, 4 H,  $\text{CH}_2$ ), 1.84-1.76 (m, 2 H, piperidine), 1.58-1.44 (m, 6 H, piperidine and  $\text{CH}_2$ ), 1.23-1.20 (m, 1 H, piperidine), 1.12-1.08 (m, 2 H, piperidine), 0.87 (d,  $J = 6.4$  Hz, 3 H,  $\text{CH}_3$ ); TOFMS  $m/z$  452.5 ( $\text{M}^+$ ).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-6-(4-methyl-piperidin-1-yl)-hexanamide**

(5). Compound 5 was prepared from 6-bromohexanoic acid (98 mg, 0.5 mmol, 1 eq.) and 4-methylpiperidine (240  $\mu$ L, 2 mmol, 4 eq.) by method A and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 75:25) as a yellow solid (40 mg, 16% yield);  $R_f$  0.30 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 6:4); HPLC (C18V)  $P_{\text{HPLC}}$  99%,  $t_R$  13.54 min; HPLC (C18N)  $P_{\text{HPLC}}$  100%,  $t_R$  15.22 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.98 (s, 1 H, CONH), 9.07 (s, 1 H, NH), 8.43 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.40 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 7.84 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.60 (s, 1 H, Ar-H), 7.51 (dd,  $J = 9.0, 2.0$  Hz, 1 H, Ar-H), 7.24 (s, 1 H, Ar-H), 6.95 (s, 1 H, Ar-H), 6.92 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 4.43 (s, 2 H,  $\text{CH}_2$ ), 4.21 (bs, 1 H, OH), 2.88-2.83 (m, 2 H, piperidine), 2.35-2.26 (m, 4 H,  $\text{CH}_2$ ), 2.04-1.98 (m, 2 H, piperidine), 1.48-1.43 (m, 6 H, piperidine and  $\text{CH}_2$ ), 1.31-1.14 (m, 5 H, piperidine and  $\text{CH}_2$ ), 0.82 (d,  $J = 6.3$  Hz, 3 H,  $\text{CH}_3$ ); TOFMS  $m/z$  494.5 ( $\text{M}^+$ ).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-8-(4-methyl-piperidin-1-yl)-octanamide**

(6). Compound 6 was prepared from 8-bromooctanoic acid (112 mg, 0.5 mmol, 1 eq.) and 4-methylpiperidine (240  $\mu$ L, 2 mmol, 4 eq.) and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 60:40) as a yellow solid (40 mg, 15%

yield);  $R_f$  0.20 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 6:4); HPLC (C18V)  $P_{\text{HPLC}}$  98%,  $t_R$  14.68 min; HPLC (C18N)  $P_{\text{HPLC}}$  97%,  $t_R$  16.39 min;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  9.88 (s, 1 H, CONH), 9.06 (s, 1 H, NH), 8.43 (d,  $J = 5.6$  Hz, 1 H, Ar-H), 8.40 (d,  $J = 9.5$  Hz, 1 H, Ar-H), 7.84 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.59 (s, 1 H, Ar-H), 7.51 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.23 (s, 1 H, Ar-H), 6.94 (s, 1 H, Ar-H), 6.92 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.25 (bs, 1 H, OH), 4.43 (s, 2 H,  $\text{CH}_2$ ), 2.77-2.74 (m, 2 H, piperidine), 2.25-2.10 (m, 4 H,  $\text{CH}_2$ ), 1.78-1.70 (m, 2 H, piperidine), 1.36-1.30 (m, 6 H, piperidine and  $\text{CH}_2$ ), 1.26-1.23 (m, 6 H,  $\text{CH}_2$ ), 1.05-0.98 (m, 3 H, piperidine), 0.80 (d,  $J = 6.4$  Hz, 3 H,  $\text{CH}_3$ ); TOFMS  $m/z$  522.5 ( $\text{M}^+$ ).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-12-(4-methyl-piperidin-1-yl)-**

**dodecanamide (7).** Compound 7 was prepared from 12-bromododecanoic acid (140 mg, 0.5 mmol, 1 eq.) and 4-methylpiperidine (240  $\mu\text{L}$ , 2 mmol, 4 eq.) by method A and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 60:40) as a yellow solid (30 mg, 10% yield);  $R_f$  0.15 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 6:4); mp 89°C (hydrochloride); HPLC (C18V)  $P_{\text{HPLC}}$  94%,  $t_R$  18.28 min; HPLC (C18N)  $P_{\text{HPLC}}$  94%,  $t_R$  20.13 min;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  9.93 (s, 1 H, CONH), 9.11 (s, 1 H, NH), 8.48 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.45 (d,  $J = 10.6$  Hz, 1 H, Ar-H), 7.90 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.65 (s, 1 H, Ar-H), 7.57 (dd,  $J = 9.1, 2.2$  Hz, 1 H, Ar-H), 7.28 (s, 1 H, Ar-H), 7.00 (s, 1 H, Ar-H), 6.97 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.20 (bs, 1 H, OH), 4.49 (s, 2 H,  $\text{CH}_2$ ), 2.79-2.76 (m, 2 H, piperidine), 2.30-2.13 (m, 4 H,  $\text{CH}_2$ ), 1.81-1.77 (m, 2 H, piperidine), 1.57-1.49 (m, 6 H, piperidine and  $\text{CH}_2$ ), 1.31-1.29 (m, 14 H,  $\text{CH}_2$ ), 1.24-1.10 (m, 3 H, piperidine), 0.87 (d,  $J = 6.4$  Hz, 3 H,  $\text{CH}_3$ ); TOFMS  $m/z$  578.5 ( $\text{M}^+$ ).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-2-piperidin-1-yl-acetamide (8).** Compound 8 was prepared from compound 1 (2 g, 6.7 mmol, 1 eq.), chloroacetic acid (630 mg, 6.7 mmol, 1 eq.) and piperidine (2 mL, 20 mmol, 3 eq.) by method A and was obtained after column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 90:10) as a yellow solid (2.57 g, 91% yield);  $R_f$  0.10 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 9:1); mp 206°C (hydrochloride); HPLC (C18V)  $P_{\text{HPLC}}$  98%,  $t_R$  11.85 min; HPLC (C18N)  $P_{\text{HPLC}}$  100%,  $t_R$  13.91 min;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  9.67 (s, 1 H, CONH), 9.08 (s, 1 H, NH), 8.43 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.40 (d,  $J = 9.1$  Hz, 1 H,

Ar-H), 7.85 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.63 (s, 1 H, Ar-H), 7.51 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.26 (s, 1 H, Ar-H), 6.99 (s, 1 H, Ar-H), 6.93 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 5.22 (t,  $J = 5.5$  Hz, 1 H, OH), 4.45 (d,  $J = 5.5$  Hz, 2 H, CH<sub>2</sub>), 3.02 (s, 2 H, CH<sub>2</sub>), 2.40 (t,  $J = 4.9$  Hz, 4 H, piperidine), 1.55-1.47 (m, 4 H, piperidine), 1.35 (d,  $J = 4.8$  Hz, 2 H, piperidine); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)  $\delta$  144.29, 128.31, 127.05, 120.09, 119.36, 117.00, 115.21, 101.16, 57.87, 53.81, 52.15, 23.05, 21.94; TOFMS  $m/z$  424.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-2-(4-methyl-piperazin-1-yl)-acetamide (9).**

Compound **9** was prepared from chloroacetic acid (48 mg, 0.5 mmol, 1 eq.) and *N*-methylpiperazine (215  $\mu$ L, 2 mmol, 4 eq.) by method A and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 70:30) as a yellow solid (70 mg, 32% yield); R<sub>f</sub> 0.10 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 7:3); mp 183°C (hydrochloride); HPLC (C18V) P<sub>HPLC</sub> 100%,  $t_R$  11.37 min; HPLC (C18N) P<sub>HPLC</sub> 100%,  $t_R$  13.29 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  9.71 (s, 1 H, CONH), 9.08 (s, 1 H, NH), 8.43 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.40 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 7.85 (d,  $J = 2.1$  Hz, 1 H, Ar-H), 7.62 (s, 1 H, Ar-H), 7.52 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.25 (s, 1 H, Ar-H), 6.99 (s, 1 H, Ar-H), 6.93 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.22 (bs, 1 H, OH), 4.45 (s, 2 H, CH<sub>2</sub>), 3.08 (s, 2 H, CH<sub>2</sub>), 2.50-2.44 (m, 8 H, piperazine), 2.19 (s, 3 H, NCH<sub>3</sub>); TOFMS  $m/z$  439.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-2-morpholin-4-yl-acetamide (10).**

Compound **10** was prepared from chloroacetic acid (48 mg, 0.5 mmol, 1 eq.) and morpholine (175  $\mu$ L, 2 mmol, 4 eq.) by method A and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 90:10) as a yellow solid (140 mg, 66% yield); R<sub>f</sub> 0.45 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1); mp 232°C (hydrochloride); HPLC (C18V) P<sub>HPLC</sub> 98%,  $t_R$  14.00 min; HPLC (C18N) P<sub>HPLC</sub> 100%,  $t_R$  16.37 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  9.76 (s, 1 H, CONH), 9.08 (s, 1 H, NH), 8.43 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.40 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 7.85 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.63 (s, 1 H, Ar-H), 7.51 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.27 (s, 1 H, Ar-H), 6.99 (s, 1 H, Ar-H), 6.93 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.25 (bs, 1 H, OH), 4.45 (s, 2 H, CH<sub>2</sub>), 3.58 (t,  $J = 4.5$  Hz, 4 H, morpholine), 3.08 (s, 2 H, CH<sub>2</sub>), 2.47 (t,  $J = 4.6$  Hz, 4 H, morpholine); TOFMS  $m/z$  426.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-2-(4-hydroxy-piperidin-1-yl)-acetamide**

(11). Compound **11** was prepared from chloroacetic acid (48 mg, 0.5 mmol, 1 eq.) and 4-hydroxypiperidine (202 mg, 2 mmol, 4 eq.) by method A and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 80:20) as a yellow solid (120 mg, 54% yield); R<sub>f</sub> 0.50 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 91°C (hydrochloride); HPLC (C18V) P<sub>HPLC</sub> 96%, t<sub>R</sub> 11.17 min; HPLC (C18N) P<sub>HPLC</sub> 97%, t<sub>R</sub> 13.03 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.21 (s, 1 H, CONH), 9.35 (s, 1 H, NH), 8.46-8.41 (m, 2 H, Ar-H), 7.87 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.62 (s, 1 H, Ar-H), 7.57 (dd, *J* = 9.0, 2.1 Hz, 1 H, Ar-H), 7.26 (s, 1 H, Ar-H), 7.03 (s, 1 H, Ar-H), 6.93 (d, *J* = 5.6 Hz, 1 H, Ar-H), 5.29 (t, *J* = 5.3 Hz, 1 H, OH), 4.82 (s, 1 H, OH), 4.46 (d, *J* = 5.3 Hz, 2 H, CH<sub>2</sub>), 3.10-3.04 (m, 4 H, piperidine), 2.93-2.91 (m, 1 H, piperidine), 2.84 (s, 2 H, CH<sub>2</sub>), 1.68-1.66 (m, 4 H, piperidine); TOFMS m/z 440.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-2-pyrrolidin-1-yl-acetamide** (12).

Compound **12** was prepared from chloroacetic acid (48 mg, 0.5 mmol, 1 eq.) and pyrrolidine (167 μL, 2 mmol, 4 eq.) by method A and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 90:10) as a yellow solid (105 mg, 51% yield); R<sub>f</sub> 0.30 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1); mp 195°C (hydrochloride); HPLC (C18V) P<sub>HPLC</sub> 100%, t<sub>R</sub> 14.04 min; HPLC (C18N) P<sub>HPLC</sub> 100%, t<sub>R</sub> 13.44 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.78 (s, 1 H, CONH), 9.13 (s, 1 H, NH), 8.50 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.47 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.91 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.70 (s, 1 H, Ar-H), 7.58 (dd, *J* = 9.0, 2.2 Hz, 1 H, Ar-H), 7.35 (s, 1 H, Ar-H), 7.05 (s, 1 H, Ar-H), 7.00 (d, *J* = 5.4 Hz, 1 H, Ar-H), 5.28 (t, *J* = 5.8 Hz, 1 H, OH), 4.50 (d, *J* = 5.7 Hz, 2 H, CH<sub>2</sub>), 3.25 (s, 2 H, CH<sub>2</sub>), 2.60-2.57 (m, 4 H, pyrrolidine), 1.75-1.72 (m, 4 H, pyrrolidine); TOFMS m/z 410.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-2-thiazolidin-1-yl-acetamide** (13).

Compound **13** was prepared from chloroacetic acid (48 mg, 0.5 mmol, 1 eq.) and thiazolidine (158 μL, 2 mmol, 4 eq.) by method A and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 90:10) as a yellow solid (50 mg, 23% yield); R<sub>f</sub> 0.80 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1); mp 181°C (hydrochloride); HPLC (C18V) P<sub>HPLC</sub> 100%, t<sub>R</sub> 14.67 min; HPLC

(C18N) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 14.31 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.87 (s, 1 H, CONH), 9.05 (s, 1 H, NH), 8.40 (d, *J* = 5.4 Hz, 1 H, Ar-H), 8.37 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.81 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.61 (s, 1 H, Ar-H), 7.48 (dd, *J* = 9.0, 2.2 Hz, 1 H, Ar-H), 7.27 (s, 1 H, Ar-H), 6.96 (s, 1 H, Ar-H), 6.90 (d, *J* = 5.3 Hz, 1 H, Ar-H), 5.18 (bs, 1 H, OH), 4.41 (s, 2 H, CH<sub>2</sub>), 4.01 (s, 2 H, thiazolidine), 3.11 (s, 2 H, CH<sub>2</sub>), 3.01 (t, *J* = 6.4 Hz, 4 H, thiazolidine), 2.77 (t, *J* = 6.4 Hz, 4 H, thiazolidine); TOFMS *m/z* 428.5 (M<sup>+</sup>).

**2-Tert-butylamino-N-[3-(7-chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-acetamide (14).**

Compound **14** was prepared from chloroacetic acid (48 mg, 0.5 mmol, 1 eq.) and *tert*-butylamine (210 μL, 2 mmol, 4 eq.) by method A and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 80:20) as a yellow solid (120 mg, 58% yield); R<sub>f</sub> 0.45 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 186°C (hydrochloride); HPLC (C18V) P<sub>HPLC</sub> 96%, *t*<sub>R</sub> 11.74 min; HPLC (C18N) P<sub>HPLC</sub> 96%, *t*<sub>R</sub> 13.62 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.07 (s, 1 H, CONH), 9.49 (s, 1 H, NH), 8.54 (d, *J* = 9.1 Hz, 1 H, Ar-H), 8.47 (d, *J* = 5.5 Hz, 1 H, Ar-H), 7.92 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.69 (s, 1 H, Ar-H), 7.60 (dd, *J* = 9.1, 2.2 Hz, 1 H, Ar-H), 7.33 (s, 1 H, Ar-H), 7.08 (s, 1 H, Ar-H), 6.96 (d, *J* = 5.5 Hz, 1 H, Ar-H), 5.37 (t, *J* = 5.4 Hz, 1 H, OH), 4.49 (d, *J* = 5.1 Hz, 2 H, CH<sub>2</sub>), 3.96 (s, 2 H, CH<sub>2</sub>), 2.87 (bs, 1 H, NH), 1.30 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>); TOFMS *m/z* 412.5 (M<sup>+</sup>).

**N-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-2-diethylamino-acetamide (15).** Compound **15** was prepared from chloroacetic acid (48 mg, 0.5 mmol, 1 eq.) and diethylamine (207 μL, 2.5 mmol, 4 eq.) by method A and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 85:15) as a yellow solid (90 mg, 56% yield); R<sub>f</sub> 0.80 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 168°C (hydrochloride); HPLC (C18V) P<sub>HPLC</sub> 98%, *t*<sub>R</sub> 11.69 min; HPLC (C18N) P<sub>HPLC</sub> 97%, *t*<sub>R</sub> 13.40 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.82 (s, 1 H, CONH), 9.12 (s, 1 H, NH), 8.44 (d, *J* = 5.4 Hz, 1 H, Ar-H), 8.40 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.85 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.65 (s, 1 H, Ar-H), 7.53 (dd, *J* = 9.0, 2.2 Hz, 1 H, Ar-H), 7.25 (s, 1 H, Ar-H), 7.01 (s, 1 H, Ar-H), 6.94 (d, *J* = 5.4 Hz, 1 H, Ar-H), 5.20 (bs, 1 H, OH), 4.46 (s, 2 H, CH<sub>2</sub>), 3.27 (s, 2 H, CH<sub>2</sub>), 2.66 (q, *J* = 7.1 Hz, 4 H, N(CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>), 1.01 (t, *J* = 7.1 Hz, 6 H, N(CH<sub>2</sub>-CH<sub>3</sub>)<sub>2</sub>); TOFMS *m/z* 412.5 (M<sup>+</sup>).

**2-Benzylamino-N-[3-(7-chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-acetamide (16).** Compound 16 was prepared from chloroacetic acid (48 mg, 0.5 mmol, 1 eq.) and benzylamine (218  $\mu$ L, 2 mmol, 4 eq.) by method A and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 85:15) as a yellow solid (120 mg, 54% yield);  $R_f$  0.85 (method A) and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 85:15) as a yellow solid (120 mg, 54% yield);  $R_f$  0.85 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8.5:1.5); mp > 250°C (hydrochloride); HPLC (C18V)  $P_{\text{HPLC}}$  100%,  $t_R$  13.28 min; HPLC (C18N)  $P_{\text{HPLC}}$  100%,  $t_R$  15.03 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  10.15 (s, 1 H, CONH), 9.20 (s, 1 H, NH), 8.46 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.42 (d,  $J = 9.0$  Hz, 1 H, Ar-H), 7.87 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.63 (s, 1 H, Ar-H), 7.56 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.44-7.26 (m, 5 H, Ar-H), 7.23 (s, 1 H, Ar-H), 7.02 (s, 1 H, Ar-H), 6.96 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.27 (bs, 1 H, OH), 4.47 (s, 2 H,  $\text{CH}_2$ ), 4.00 (bs, 1 H, NH), 3.94 (s, 2 H,  $\text{CH}_2$ ), 3.14 (s, 2 H,  $\text{CH}_2$ ); TOFMS  $m/z$  446.5 ( $\text{M}^+$ ).

**2-(4-Chloro-benzylamino)-N-[3-(7-chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-acetamide (17).** Compound 17 was prepared from chloroacetic acid (48 mg, 0.5 mmol, 1 eq.) and 4-chlorobenzylamine (243  $\mu$ L, 2 mmol, 4 eq.) by method A and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 85:15) as a yellow solid (70 mg, 29% yield);  $R_f$  0.70 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8.5:1.5); HPLC (C18V)  $P_{\text{HPLC}}$  100%,  $t_R$  14.40 min; HPLC (C18N)  $P_{\text{HPLC}}$  100%,  $t_R$  16.16 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.95 (s, 1 H, CONH), 9.32 (s, 1 H, NH), 8.47 (d,  $J = 5.2$  Hz, 1 H, Ar-H), 8.45 (d,  $J = 9.2$  Hz, 1 H, Ar-H), 7.89 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.67 (s, 1 H, Ar-H), 7.56 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.50-7.39 (m, 4 H, Ar-H), 7.29 (s, 1 H, Ar-H), 7.03 (s, 1 H, Ar-H), 6.97 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.23 (bs, 1 H, OH), 4.48 (s, 2 H,  $\text{CH}_2$ ), 4.06 (s, 2 H,  $\text{CH}_2$ ), 4.00 (s, 2 H,  $\text{CH}_2$ ), 3.75 (bs, 1 H, NH); TOFMS  $m/z$  482 ( $\text{M}^+$ ).

**N-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-2-(1,2,3,4-tetrahydro-isoquinolin-2-yl)-acetamide (18).** Compound 18 was prepared from chloroacetic acid (48 mg, 0.5 mmol, 1 eq.) and 1,2,3,4-tetrahydroisoquinoline (250  $\mu$ L, 2 mmol, 4 eq.) by method A and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 85:15) as a yellow solid (150 mg, 63% yield);  $R_f$  0.80 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8.5:1.5); mp 84°C (hydrochloride);

HPLC (C18V)  $P_{\text{HPLC}}$  98%,  $t_R$  13.63 min; HPLC (C18N)  $P_{\text{HPLC}}$  99%,  $t_R$  15.40 min;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  10.09 (s, 1 H, CONH), 8.91 (s, 1 H, NH), 8.52 (d,  $J = 9.0$  Hz, 1 H, Ar-H), 8.48 (d,  $J = 6.3$  Hz, 1 H, Ar-H), 7.09 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.67-7.65 (m, 2 H, Ar-H), 7.38 (s, 1 H, Ar-H), 7.34-7.11 (m, 4 H, Ar-H), 7.04 (s, 1 H, Ar-H), 6.90 (d,  $J = 6.1$  Hz, 1 H, Ar-H), 5.29 (t,  $J = 4.6$  Hz, 1 H, OH), 4.47 (d,  $J = 4.6$  Hz, 2 H, CH<sub>2</sub>), 4.23 (s, 2 H, CH<sub>2</sub>), 3.01-2.91 (m, 4 H, CH<sub>2</sub>), 2.68 (s, 2 H, CH<sub>2</sub>); TOFMS  $m/z$  472.5 ( $M^+$ ).

**2-(3-Amino-pyrazol-1-yl)-N-[3-(7-chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-acetamide (19).**

Compound **19** was prepared from chloroacetic acid (48 mg, 0.5 mmol, 1 eq.) and 3-aminopyrrazole (166 mg, 2 mmol, 4 eq.) by method A and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 85:15) as a yellow solid (85 mg, 40% yield);  $R_f$  0.55 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 173°C (hydrochloride); HPLC (C18V)  $P_{\text{HPLC}}$  95%,  $t_R$  11.74 min; HPLC (C18N)  $P_{\text{HPLC}}$  96%,  $t_R$  13.90 min;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  10.44 (bs, 1 H, NH), 10.10 (s, 1 H, CONH), 9.80 (s, 1 H, NH), 8.69 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 8.47 (d,  $J = 5.2$  Hz, 1 H, Ar-H), 8.04 (s, 1 H, Ar-H), 7.71 (d,  $J = 9.0$  Hz, 2 H, Ar-H), 7.67 (s, 1 H, Ar-H), 7.66 (s, 1 H, Ar-H), 7.41 (s, 1 H, Ar-H), 7.03 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.30 (bs, 1 H, OH), 4.47 (s, 2 H, CH<sub>2</sub>), 3.79 (bs, 1 H, NH), 3.12 (s, 2 H, CH<sub>2</sub>); TOFMS  $m/z$  422.5 ( $M^+$ ).

**2-Chloro-N-[3-(7-chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-acetamide (20).** To a solution of compound **1** (150 mg, 0.5 mmol, 1 eq.) in 10 mL of DMF were added chloroacetic acid (47 mg, 0.5 mmol, 1 eq.), PyBroP (235 mg, 0.5 mmol, 1 eq.) and DIEA (88  $\mu\text{L}$ , 1 mmol, 2 eq.). After stirring the mixture at room temperature for 18 h, the solvent was evaporated, the mixture taken up in 15 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed with aqueous NaHCO<sub>3</sub> 1 M and brine. The organic layer was separated, dried over MgSO<sub>4</sub>, the solvent evaporated and the residue purified by TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 85:15) to yield compound **20** as a yellow solid (120 mg, 64% yield);  $R_f$  0.65 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 135°C (hydrochloride); HPLC (C18V)  $P_{\text{HPLC}}$  98%,  $t_R$  13.56 min; HPLC (C18N)  $P_{\text{HPLC}}$  100%,  $t_R$  16.04 min;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  11.06 (s, 1 H, CONH), 9.20 (s, 1 H, NH), 8.50 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.46 (d,  $J = 9.0$  Hz, 1 H, Ar-H), 7.91 (d,  $J = 1.9$  Hz, 1 H, Ar-H), 7.61 (s, 1 H,

Ar-H), 7.59 (dd,  $J = 9.1, 1.9$  Hz, 1 H, Ar-H), 7.29 (s, 1 H, Ar-H), 7.07 (s, 1 H, Ar-H), 7.00 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.30 (t,  $J = 5.3$  Hz, 1 H, OH), 4.51 (d,  $J = 5.3$  Hz, 2 H, CH<sub>2</sub>), 4.27 (s, 2 H, CH<sub>2</sub>); TOFMS  $m/z$  376 (M<sup>+</sup>).

**1-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenylcarbamoylmethyl]-pyridinium chloride (21).**

A solution of compound **20** (80 mg, 0.21 mmol, 1 eq) in 10 mL of pyridine was stirred at room temperature for 24 h. Then the solvent was evaporated to yield compound **21** as a yellow solid (90 mg, 93% yield); mp 81°C; HPLC (C18V) P<sub>HPLC</sub> 92%,  $t_R$  11.60 min; HPLC (C18N) P<sub>HPLC</sub> 93%,  $t_R$  13.58 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  11.01 (s, 1 H, CONH), 9.31 (s, 1 H, NH), 9.03 (d,  $J = 5.8$  Hz, 2 H, Ar-H), 8.64 (t,  $J = 7.9$  Hz, 1 H, Ar-H), 8.45 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.43 (d,  $J = 9.0$  Hz, 1 H, Ar-H), 8.17-8.15 (m, 2 H, Ar-H), 7.87 (d,  $J = 2.1$  Hz, 1 H, Ar-H), 7.57 (s, 1 H, Ar-H), 7.54 (dd,  $J = 9.0, 2.1$  Hz, 1 H, Ar-H), 7.31 (s, 1 H, Ar-H), 7.03 (s, 1 H, Ar-H), 6.90 (d,  $J = 5.5$  Hz, 1 H, Ar-H), 5.66 (s, 2 H, CH<sub>2</sub>), 5.30 (t,  $J = 5.3$  Hz, 1 H, OH), 4.47 (d,  $J = 5.0$  Hz, 2 H, CH<sub>2</sub>); TOFMS  $m/z$  419.5 (M<sup>+</sup>-Cl).

**N-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-2-hydroxy-acetamide (22).** To a solution of compound **20** (280 mg, 0.74 mmol, 1 eq.) in 15 mL of DMF was added potassium acetate (110 mg, 1.1 mmol, 1.5 eq.). Following reflux of the mixture for 3 h, the solvent was evaporated, the mixture taken up in 15 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed with aqueous NaHCO<sub>3</sub> 1 M and brine. The organic layer was separated, dried over MgSO<sub>4</sub> and the solvent evaporated. The solid was taken up in a solution of Na<sub>2</sub>CO<sub>3</sub> (120 mg, 1.1 mmol, 1.5 eq.) in 15 mL of MeOH. After stirring the mixture at room temperature for 3 h, the solvent was evaporated and the residue purified by TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 80:20) to yield compound **22** as a yellow solid (20 mg, 8% yield); R<sub>f</sub> 0.80 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 118°C (hydrochloride); HPLC (C18V) P<sub>HPLC</sub> 100%,  $t_R$  14.34 min; HPLC (C18N) P<sub>HPLC</sub> 98%,  $t_R$  14.32 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  9.73 (s, 1 H, CONH), 9.13 (s, 1 H, NH), 8.46 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.45 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 7.88 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.70 (s, 1 H, Ar-H), 7.55 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.39 (s, 1 H, Ar-H), 7.03 (s, 1 H, Ar-H), 6.98 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.70 (bs, 1 H, OH), 5.25 (bs, 1 H, OH), 4.47 (s, 2 H, CH<sub>2</sub>), 3.98 (s, 2 H, CH<sub>2</sub>); TOFMS  $m/z$  357.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-benzamide (23).** To a solution of compound 1 (300 mg, 1.0 mmol, 1 eq.) in 15 mL of DMF were added benzoic acid (122 mg, 1.0 mmol, 1 eq.), PyBroP (466 mg, 1.0 mmol, 1 eq.) and DIEA (260  $\mu$ L, 1.5 mmol, 1.5 eq.). After stirring the mixture at room temperature for 18 h, the solvent was evaporated, the residue taken up in 15 mL of  $\text{CH}_2\text{Cl}_2$  and washed with aqueous  $\text{NaHCO}_3$  1 M and brine. The organic layer was separated, dried over  $\text{MgSO}_4$ , the solvent evaporated and the residue purified by TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 90:10) to yield compound 23 as a yellow oil (320 mg, 69% yield);  $R_f$  0.60 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 9:1); HPLC (C18V)  $P_{\text{HPLC}}$  95%,  $t_R$  15.80 min; HPLC (C18N)  $P_{\text{HPLC}}$  96%,  $t_R$  16.02 min;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  10.30 (s, 1 H, CONH), 9.15 (s, 1 H, NH), 8.47 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.45 (d,  $J = 9.0$  Hz, 1 H, Ar-H), 7.90 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.70 (s, 1 H, Ar-H), 7.58-7.44 (m, 7 H, Ar-H), 7.05 (s, 1 H, Ar-H), 6.97 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 5.30 (bs, 1 H, OH), 4.51 (s, 2 H,  $\text{CH}_2$ ); TOFMS  $m/z$  403.5 ( $\text{M}^+$ ).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-hydroxymethyl-phenyl]-formamide (24).** To a solution of compound 1 (300 mg, 1.0 mmol, 1 eq.) in 15 mL of DMF were added PyBroP (466 mg, 1.0 mmol, 1 eq.) and DIEA (260  $\mu$ L, 1.5 mmol, 1.5 eq.). After stirring the mixture at room temperature for 18 h and at reflux for 4 h, the solvent was evaporated, the residue taken up in 15 mL of  $\text{CH}_2\text{Cl}_2$  and washed with aqueous  $\text{NaHCO}_3$  1 M and brine. The organic layer was separated, dried over  $\text{MgSO}_4$ , the solvent evaporated and the residue purified by TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 80:20) to yield compound 24 as a yellow solid (165 mg, 50% yield);  $R_f$  0.60 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8:2); mp  $> 250^\circ\text{C}$ ; HPLC (C18V)  $P_{\text{HPLC}}$  96%,  $t_R$  10.53 min; HPLC (C18N)  $P_{\text{HPLC}}$  96%,  $t_R$  12.49 min;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  10.29 (s, 1 H, CONH), 9.18 (s, 1 H, NH), 8.54 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.49 (d,  $J = 9.0$  Hz, 1 H, Ar-H), 8.33 (s, 1 H, COH), 7.95 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.66 (s, 1 H, Ar-H), 7.62 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.33 (s, 1 H, Ar-H), 7.11 (s, 1 H, Ar-H), 7.04 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 5.32 (bs, 1 H, OH), 4.55 (s, 2 H,  $\text{CH}_2$ ); TOFMS  $m/z$  327.5 ( $\text{M}^+$ ).

**(Piperidin-1-ylmethyl)-1-carboxylic acid 3-(7-chloro-quinolin-4-ylamino)-5-(2-piperidin-1-yl-acetylamino)-benzyl ester (25).** Compound **25** was prepared from chloroacetic acid (35 mg, 0.37 mmol, 1.05 eq.) and piperidine (350  $\mu$ L, 3.55 mmol, 10 eq.) by method B and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 85:15) as a yellow solid (135 mg, 70% yield);  $R_f$  0.60 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8.5:1.5); mp 87°C; HPLC (C18V)  $P_{\text{HPLC}}$  98%,  $t_R$  14.33 min; HPLC (C18N)  $P_{\text{HPLC}}$  97%,  $t_R$  13.91 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.84 (s, 1 H, CONH), 9.15 (s, 1 H, NH), 8.46 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.42 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 7.89 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.63 (s, 1 H, Ar-H), 7.54 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.25 (s, 1 H, Ar-H), 7.03 (s, 1 H, Ar-H), 6.94 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.07 (s, 2 H,  $\text{CH}_2$ ), 4.43 (s, 2 H,  $\text{CH}_2$ ), 3.20 (s, 2 H,  $\text{CH}_2$ ), 2.62-2.57 (m, 8 H, piperidine), 1.57-1.53 (m, 8 H, piperidine), 1.36-1.32 (m, 4 H, piperidine); TOFMS  $m/z$  549.5 ( $\text{M}^+$ ).

**(2-Piperidin-1-ylethyl)-1-carboxylic acid 3-(7-chloro-quinolin-4-ylamino)-5-(2-piperidin-1-yl-acetylamino)-benzyl ester (26).** Compound **26** was prepared from 3-bromopropanoic acid (55 mg, 0.36 mmol, 1 eq.) and piperidine (350  $\mu$ L, 3.55 mmol, 10 eq.) by method B and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 85:15) as a yellow solid (60 mg, 30% yield);  $R_f$  0.55 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8:2); mp 58°C; HPLC (C18V)  $P_{\text{HPLC}}$  98%,  $t_R$  14.72 min; HPLC (C18N)  $P_{\text{HPLC}}$  100%,  $t_R$  13.98 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.82 (s, 1 H, CONH), 9.13 (s, 1 H, NH), 8.43 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.41 (d,  $J = 8.8$  Hz, 1 H, Ar-H), 7.85 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.63 (s, 1 H, Ar-H), 7.52 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.26 (s, 1 H, Ar-H), 6.99 (s, 1 H, Ar-H), 6.93 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.03 (s, 2 H,  $\text{CH}_2$ ), 4.45 (s, 2 H,  $\text{CH}_2$ ), 3.20 (s, 2 H,  $\text{CH}_2$ ), 3.13-3.12 (m, 4 H,  $\text{CH}_2$ ), 2.63-2.59 (m, 4 H, piperidine), 2.51-2.49 (m, 4 H, piperidine), 1.47-1.45 (m, 8 H, piperidine), 1.37-1.35 (m, 4 H, piperidine); TOFMS  $m/z$  563.5 ( $\text{M}^+$ ).

**(4-Piperidin-1-ylbutyl)-1-carboxylic acid 3-(7-chloro-quinolin-4-ylamino)-5-(2-piperidin-1-yl-acetylamino)-benzyl ester (27).** Compound **27** was prepared from 5-bromovaleric acid (65 mg, 0.36 mmol, 1 eq.) and piperidine (350  $\mu$ L, 3.55 mmol, 10 eq.) by method B and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 95:5) as a yellow solid (110 mg, 53% yield);  $R_f$  0.35 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8.5:1.5); mp 38°C; HPLC (C18V)  $P_{\text{HPLC}}$

95%,  $t_R$  15.31 min; HPLC (C18N)  $P_{HPLC}$  96%,  $t_R$  14.82 min;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$  9.82 (s, 1 H, CONH), 9.13 (s, 1 H, NH), 8.46 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.42 (d,  $J = 9.0$  Hz, 1 H, Ar-H), 7.85 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.63 (s, 1 H, Ar-H), 7.54 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.26 (s, 1 H, Ar-H), 7.04 (s, 1 H, Ar-H), 6.93 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.00 (s, 2 H, CH<sub>2</sub>), 2.99 (s, 2 H, CH<sub>2</sub>), 2.41-2.20 (m, 12 H, piperidine and CH<sub>2</sub>), 1.48-1.34 (m, 16 H, piperidine and CH<sub>2</sub>);  $^{13}C$  NMR (DMSO- $d_6$ )  $\delta$  152.75, 128.53, 125.88, 125.42, 117.19, 114.95, 113.29, 103.18, 65.93, 63.53, 58.40, 54.89, 54.43, 34.14, 26.31, 25.91, 25.79, 25.57, 24.40, 23.20; TOFMS  $m/z$  591.5 ( $M^+$ ).

**(5-Piperidin-1-ylpentyl)-1-carboxylic acid 3-(7-chloro-quinolin-4-ylamino)-5-(2-piperidin-1-yl-acetylamino)-benzyl ester (28)**. Compound **28** was prepared from 6-bromohexanoic acid (70 mg, 0.36 mmol, 1 eq.) and piperidine (350  $\mu$ L, 3.55 mmol, 10 eq.) by method B and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95:5) as a yellow solid (110 mg, 51% yield);  $R_f$  0.30 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); HPLC (C18V)  $P_{HPLC}$  98%,  $t_R$  15.54 min; HPLC (C18N)  $P_{HPLC}$  97%,  $t_R$  15.48 min;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$  9.85 (s, 1 H, CONH), 9.17 (s, 1 H, NH), 8.46 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.42 (d,  $J = 9.0$  Hz, 1 H, Ar-H), 7.85 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.64 (s, 1 H, Ar-H), 7.54 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.28 (s, 1 H, Ar-H), 7.01 (s, 1 H, Ar-H), 6.95 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 5.02 (s, 2 H, CH<sub>2</sub>), 3.06 (s, 2 H, CH<sub>2</sub>), 2.48-2.25 (m, 12 H, piperidine and CH<sub>2</sub>), 1.51-1.22 (m, 18 H, piperidine and CH<sub>2</sub>); TOFMS  $m/z$  605.5 ( $M^+$ ).

**(7-Piperidin-1-ylheptyl)-1-carboxylic acid 3-(7-chloro-quinolin-4-ylamino)-5-(2-piperidin-1-yl-acetylamino)-benzyl ester (29)**. Compound **29** was prepared from 8-bromooctanoic acid (80 mg, 0.36 mmol, 1 eq.) and piperidine (350  $\mu$ L, 3.55 mmol, 10 eq.) by method B and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 90:10) as a yellow oil (100 mg, 45% yield);  $R_f$  0.20 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); HPLC (C18V)  $P_{HPLC}$  96%,  $t_R$  16.71 min; HPLC (C18N)  $P_{HPLC}$  96%,  $t_R$  16.53 min;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$  9.72 (s, 1 H, CONH), 9.20 (s, 1 H, NH), 8.41 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.35 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 7.82 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.67 (s, 1 H, Ar-H), 7.50 (dd,  $J = 9.0, 2.3$  Hz, 1 H, Ar-H), 7.28 (s, 1 H, Ar-H), 6.96 (s, 1 H, Ar-H), 6.91 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 5.00 (s, 2 H, CH<sub>2</sub>), 3.06 (s, 2 H, CH<sub>2</sub>), 2.48-2.25 (m, 12 H, piperidine and CH<sub>2</sub>), 1.51-1.22 (m, 18 H, piperidine and CH<sub>2</sub>); TOFMS  $m/z$  619.5 ( $M^+$ ).

H, Ar-H), 5.00 (s, 2 H, CH<sub>2</sub>), 3.00 (s, 2 H, CH<sub>2</sub>), 2.42-2.11 (m, 12 H, piperidine and CH<sub>2</sub>), 1.47-1.14 (m, 22 H, piperidine and CH<sub>2</sub>); TOFMS m/z 633.5 (M<sup>+</sup>).

**(4-Pyrrolidin-1-ylbutyl)-1-carboxylic acid 3-(7-chloro-quinolin-4-ylamino)-5-(2-piperidin-1-yl-acetylamino)-benzyl ester (30).** Compound **30** was prepared from 5-bromovaleric acid (65 mg, 0.36 mmol, 1 eq.) and pyrrolidine (290 μL, 3.55 mmol, 10 eq.) by method B and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 85:15) as a yellow oil (75 mg, 37% yield); R<sub>f</sub> 0.30 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); HPLC (C18V) P<sub>HPLC</sub> 94%, t<sub>R</sub> 15.08 min; HPLC (C18N) P<sub>HPLC</sub> 95%, t<sub>R</sub> 14.54 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.83 (s, 1 H, CONH), 9.17 (s, 1 H, NH), 8.48 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.42 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.89 (d, *J* = 2.1 Hz, 1 H, Ar-H), 7.74 (s, 1 H, Ar-H), 7.56 (dd, *J* = 9.0, 2.1 Hz, 1 H, Ar-H), 7.35 (s, 1 H, Ar-H), 7.04 (s, 1 H, Ar-H), 6.98 (d, *J* = 5.3 Hz, 1 H, Ar-H), 5.07 (s, 2 H, CH<sub>2</sub>), 3.06 (s, 2 H, CH<sub>2</sub>), 2.51-2.49 (m, 2 H, CH<sub>2</sub>), 2.47-2.44 (m, 4 H, piperidine), 2.39-2.37 (m, 2 H, CH<sub>2</sub>), 2.32-2.29 (m, 4 H, pyrrolidine), 1.61-1.54 (m, 12 H, pyrrolidine, piperidine and CH<sub>2</sub>), 1.40-1.38 (m, 2 H, piperidine); TOFMS m/z 577.5 (M<sup>+</sup>).

**(4-Morpholin-4-ylbutyl)-1-carboxylic acid 3-(7-chloro-quinolin-4-ylamino)-5-(2-piperidin-1-yl-acetylamino)-benzyl ester (31).** Compound **31** was prepared from 5-bromovaleric acid (65 mg, 0.36 mmol, 1 eq.) and morpholine (314 μL, 3.55 mmol, 10 eq.) by method B and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 85:15) as a yellow solid (50 mg, 24% yield); R<sub>f</sub> 0.35 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 33°C; HPLC (C18V) P<sub>HPLC</sub> 100%, t<sub>R</sub> 12.34 min; HPLC (C18N) P<sub>HPLC</sub> 98%, t<sub>R</sub> 14.21 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.83 (s, 1 H, CONH), 9.17 (s, 1 H, NH), 8.48 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.42 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.89 (d, *J* = 2.1 Hz, 1 H, Ar-H), 7.74 (s, 1 H, Ar-H), 7.56 (dd, *J* = 9.0, 2.1 Hz, 1 H, Ar-H), 7.35 (s, 1 H, Ar-H), 7.04 (s, 1 H, Ar-H), 6.98 (d, *J* = 5.3 Hz, 1 H, Ar-H), 5.05 (s, 2 H, CH<sub>2</sub>), 3.50 (m, 4 H, morpholine), 3.10 (s, 2 H, CH<sub>2</sub>), 2.37 (t, *J* = 7.2 Hz, 2 H, CH<sub>2</sub>), 2.28-2.20 (m, 10 H, piperidine, morpholine and CH<sub>2</sub>), 1.74-1.63 (m, 4 H, CH<sub>2</sub>), 1.55-1.38 (m, 4 H, piperidine), 1.25-1.22 (m, 2 H, piperidine); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 152.79, 128.56, 125.89, 125.41, 117.21,

114.95, 113.25, 103.18, 67.01, 65.91, 63.53, 54.89, 54.12, 46.69, 34.21, 26.31, 26.05, 24.40, 23.25; TOFMS  $m/z$  593.5 ( $M^+$ ).

**(4-(4-Methyl-piperazin-1-yl)-butyl)-1-carboxylic acid 3-(7-chloro-quinolin-4-ylamino)-5-(2-piperidin-1-yl-acetylamino)-benzyl ester (32).** Compound 32 was prepared from 5-bromovaleric acid (65 mg, 0.36 mmol, 1 eq.) and 4-methylpiperazine (290  $\mu$ L, 3.55 mmol, 10 eq.) by method B and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 85:15) as a yellow oil (60 mg, 28% yield);  $R_f$  0.15 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8.5:1.5); HPLC (C18V)  $P_{\text{HPLC}}$  97%,  $t_R$  14.95 min; HPLC (C18N)  $P_{\text{HPLC}}$  97%,  $t_R$  14.23 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.97 (s, 1 H, CONH), 9.15 (s, 1 H, NH), 8.48 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.45 (d,  $J = 9.0$  Hz, 1 H, Ar-H), 7.90 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.73 (s, 1 H, Ar-H), 7.56 (dd,  $J = 9.0, 2.1$  Hz, 1 H, Ar-H), 7.36 (s, 1 H, Ar-H), 7.05 (s, 1 H, Ar-H), 6.98 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 5.07 (s, 2 H,  $\text{CH}_2$ ), 3.14 (s, 2 H,  $\text{CH}_2$ ), 2.72-2.55 (m, 10 H, piperazine and  $\text{CH}_2$ ), 2.43-2.36 (m, 6 H, piperidine and  $\text{CH}_2$ ), 2.07 (s, 3 H,  $\text{NCH}_3$ ), 1.75-1.25 (m, 10 H, piperidine and  $\text{CH}_2$ ); TOFMS  $m/z$  606.5 ( $M^+$ ).

**(4-Diethylaminobutyl)-1-carboxylic acid 3-(7-chloro-quinolin-4-ylamino)-5-(2-piperidin-1-yl-acetylamino)-benzyl ester (33).** Compound 33 was prepared from 5-bromovaleric acid (65 mg, 0.36 mmol, 1 eq.) and diethylamine (365  $\mu$ L, 3.55 mmol, 10 eq.) by method B and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 85:15) as a yellow oil (70 mg, 34% yield);  $R_f$  0.30 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8.5:1.5); HPLC (C18V)  $P_{\text{HPLC}}$  95%,  $t_R$  22.02 min; HPLC (C18N)  $P_{\text{HPLC}}$  94%,  $t_R$  22.26 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.91 (s, 1 H, CONH), 9.13 (s, 1 H, NH), 8.46 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.41 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 7.89 (d,  $J = 2.1$  Hz, 1 H, Ar-H), 7.74 (s, 1 H, Ar-H), 7.56 (dd,  $J = 9.0, 2.1$  Hz, 1 H, Ar-H), 7.31 (s, 1 H, Ar-H), 7.04 (s, 1 H, Ar-H), 6.98 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 5.08 (s, 2 H,  $\text{CH}_2$ ), 3.08 (s, 2 H,  $\text{CH}_2$ ), 2.98-2.96 (m, 4 H,  $\text{N}(\text{CH}_2\text{CH}_3)_2$ ), 2.50-2.35 (m, 8 H, piperidine and  $\text{CH}_2$ ), 1.75-1.00 (m, 14 H, piperidine,  $\text{CH}_2$  and  $\text{N}(\text{CH}_2\text{CH}_3)_2$ ); TOFMS  $m/z$  579.5 ( $M^+$ ).

**(4-Bromobutyl)-1-carboxylic acid 3-(7-chloro-quinolin-4-ylamino)-5-(2-piperidin-1-yl-acetylamino)-benzyl ester (34).** Compound **34** was prepared from 5-bromovaleric acid (65 mg, 0.36 mmol, 1 eq.) by method C and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 85:15) as a yellow solid (75 mg, 36% yield); R<sub>f</sub> 0.80 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 42°C; HPLC (C18V) P<sub>HPLC</sub> 99%, t<sub>R</sub> 20.07 min; HPLC (C18N) P<sub>HPLC</sub> 100%, t<sub>R</sub> 18.79 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.80 (s, 1 H, CONH), 9.15 (s, 1 H, NH), 8.48 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.42 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.89 (d, *J* = 2.1 Hz, 1 H, Ar-H), 7.74 (s, 1 H, Ar-H), 7.56 (dd, *J* = 9.0, 2.1 Hz, 1 H, Ar-H), 7.35 (s, 1 H, Ar-H), 7.04 (s, 1 H, Ar-H), 6.98 (d, *J* = 5.3 Hz, 1 H, Ar-H), 5.09 (s, 2 H, CH<sub>2</sub>), 3.57 (s, 2 H, CH<sub>2</sub>), 2.74-2.72 (m, 2 H, CH<sub>2</sub>), 2.45-2.35 (m, 6 H, piperidine and CH<sub>2</sub>), 1.80-1.25 (m, 10 H, piperidine, CH<sub>2</sub> and CH<sub>3</sub>); TOFMS m/z 587.5 (M<sup>+</sup>).

**Benzyl-1-carboxylic acid 3-(7-chloro-quinolin-4-ylamino)-5-(2-piperidin-1-yl-acetylamino)-benzyl ester (35).** Compound **35** was prepared from benzoic acid (45 mg, 0.36 mmol, 1 eq.) by method C and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 85:15) as a yellow solid (85 mg, 47% yield); R<sub>f</sub> 0.85 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8:2); mp 86°C; HPLC (C18V) P<sub>HPLC</sub> 95%, t<sub>R</sub> 19.57 min; HPLC (C18N) P<sub>HPLC</sub> 94%, t<sub>R</sub> 19.31 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.76 (s, 1 H, CONH), 9.12 (s, 1 H, NH), 8.39 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.35 (d, *J* = 8.9 Hz, 1 H, Ar-H), 7.95 (dd, *J* = 6.1, 2.1 Hz, 2 H, Ar-H), 7.82 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.73 (s, 1 H, Ar-H), 7.59 (td, *J* = 6.1, 2.3 Hz, 1 H, Ar-H), 7.52-7.45 (m, 3 H, Ar-H), 7.37 (s, 1 H, Ar-H), 7.08 (s, 1 H, Ar-H), 6.95 (d, *J* = 5.3 Hz, 1 H, Ar-H), 5.28 (s, 2 H, CH<sub>2</sub>), 3.00 (s, 2 H, CH<sub>2</sub>), 2.39-2.36 (m, 4 H, piperidine), 1.48-1.43 (m, 4 H, piperidine), 1.32-1.30 (m, 2 H, piperidine); TOFMS m/z 528.5 (M<sup>+</sup>).

**Quinolin-4-yl-1-carboxylic acid 3-(7-chloro-quinolin-4-ylamino)-5-(2-piperidin-1-yl-acetylamino)-benzyl ester (36).** Compound **36** was prepared from 4-quinolinic acid (60 mg, 0.36 mmol, 1 eq.) by method C and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 90:10) as a yellow solid (75 mg, 37% yield); R<sub>f</sub> 0.80 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 96°C; HPLC (C18V) P<sub>HPLC</sub> 97%, t<sub>R</sub> 16.03 min; HPLC (C18N) P<sub>HPLC</sub> 96%, t<sub>R</sub> 18.51 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.77 (s, 1 H, CONH), 9.13 (s, 1 H, NH), 9.02 (d, *J* = 4.4 Hz, 1 H, Ar-H), 8.58 (d, *J* = 8.3 Hz, 1 H,

Ar-H), 8.39 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.35 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 8.08 (d,  $J = 8.4$  Hz, 1 H, Ar-H), 7.93 (d,  $J = 4.4$  Hz, 1 H, Ar-H), 7.83 (d,  $J = 2.3$  Hz, 1 H, Ar-H), 7.80-7.77 (m, 1 H, Ar-H), 7.74 (s, 1 H, Ar-H), 7.68-7.65 (m, 1 H, Ar-H), 7.50 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.45 (s, 1 H, Ar-H), 7.15 (s, 1 H, Ar-H), 6.97 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 5.42 (s, 2 H, CH<sub>2</sub>), 3.00 (s, 2 H, CH<sub>2</sub>), 2.39-2.36 (m, 4 H, piperidine), 1.50-1.43 (m, 4 H, piperidine), 1.32-1.30 (m, 2 H, piperidine); TOFMS  $m/z$  579.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-formyl-phenyl]-2-piperidin-1-yl-acetamide (37).** To a solution of compound **8** (500 mg, 1.18 mmol, 1 eq.) in 50 mL of CH<sub>2</sub>Cl<sub>2</sub> was added MnO<sub>2</sub> (1.54 g, 11.8 mmol, 10 eq.). After stirring at room temperature for 18 h, the mixture was filtrated on celite, the celite washed by MeOH and the filtrate concentrated. The residue was then purified by TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 90:10) to yield compound **37** as a yellow solid (260 mg, 52% yield); R<sub>f</sub> 0.90 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 119°C; HPLC (C18V) P<sub>HPLC</sub> 100%,  $t_R$  12.66 min; HPLC (C18N) P<sub>HPLC</sub> 98%,  $t_R$  14.62 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 10.88 (s, 1 H, CHO), 10.00 (bs, 2 H, NH and CONH), 8.58 (d,  $J = 6.1$  Hz, 1 H, Ar-H), 8.53 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 7.98 (d,  $J = 2.1$  Hz, 1 H, Ar-H), 7.97 (s, 1 H, Ar-H), 7.92 (s, 1 H, Ar-H), 7.76 (dd,  $J = 9.1, 2.2$  Hz, 1 H, Ar-H), 7.70 (s, 1 H, Ar-H), 7.07 (d,  $J = 6.1$  Hz, 1 H, Ar-H), 3.14 (s, 2 H, CH<sub>2</sub>), 2.50-2.45 (m, 4 H, piperidine), 1.76-1.73 (m, 4 H, piperidine), 1.54-1.52 (m, 2 H, piperidine); TOFMS  $m/z$  422.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-(2-dimethylaminoethylamino)methyl-phenyl]-2-piperidin-1-yl-acetamide (38).** Compound **38** was prepared from *N,N*-dimethylethylenediamine (21 mg, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH, 85:15:1) as a yellow solid (70 mg, 60% yield); R<sub>f</sub> 0.15 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8:2); mp 106°C; HPLC (C18V) P<sub>HPLC</sub> 99%,  $t_R$  10.47 min; HPLC (C18N) P<sub>HPLC</sub> 99%,  $t_R$  11.76 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.69 (s, 1 H, CONH), 9.10 (s, 1 H, NH), 8.46-8.41 (m, 2 H, Ar-H), 7.88 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.67 (s, 1 H, Ar-H), 7.54 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.28 (s, 1 H, Ar-H), 7.04 (s, 1 H, Ar-H), 6.95 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 3.69 (s, 2 H, CH<sub>2</sub>), 3.05 (s, 2 H, CH<sub>2</sub>), 2.58 (t,  $J = 6.4$  Hz, 2 H,

CH<sub>2</sub>), 2.46-2.42 (m, 4 H, piperidine), 2.33 (t, *J* = 6.3 Hz, 2 H, CH<sub>2</sub>), 2.11 (s, 6 H, N(CH<sub>3</sub>)<sub>2</sub>), 1.58-1.51 (m, 4 H, piperidine), 1.39-1.37 (m, 2 H, piperidine); TOFMS *m/z* 494.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-(3-dimethylaminopropylamino)methyl-phenyl]-2-piperidin-1-yl-acetamide (39).** Compound **39** was prepared from 2-(dimethylamino)propylamine (30 μL, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH, 80:20:1) as a yellow solid (75 mg, 42% yield); *R<sub>f</sub>* 0.35 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH, 8:2:0.1); mp 76°C; HPLC (C18V) *P*<sub>HPLC</sub> 96%, *t<sub>R</sub>* 10.70 min; HPLC (C18N) *P*<sub>HPLC</sub> 96%, *t<sub>R</sub>* 11.73 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.71 (s, 1 H, CONH), 9.13 (s, 1 H, NH), 8.46 (d, *J* = 5.4 Hz, 1 H, Ar-H), 8.42 (d, *J* = 9.0 Hz, 1 H, Ar-H), 7.87 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.67 (s, 1 H, Ar-H), 7.54 (dd, *J* = 9.0, 2.3 Hz, 1 H, Ar-H), 7.32 (s, 1 H, Ar-H), 7.08 (s, 1 H, Ar-H), 6.97 (d, *J* = 5.3 Hz, 1 H, Ar-H), 3.75 (s, 2 H, CH<sub>2</sub>), 3.05 (s, 2 H, CH<sub>2</sub>), 2.61 (t, *J* = 7.0 Hz, 2 H, CH<sub>2</sub>), 2.47-2.42 (m, 4 H, piperidine), 2.33 (t, *J* = 7.0 Hz, 2 H, CH<sub>2</sub>), 2.05 (s, 6 H, N(CH<sub>3</sub>)<sub>2</sub>), 1.64-1.54 (m, 6 H, piperidine and CH<sub>2</sub>), 1.38-1.37 (m, 2 H, piperidine); TOFMS *m/z* 508.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-{*N*-(2-dimethylaminoethyl)-*N*-methylaminomethyl}-phenyl]-2-piperidin-1-yl-acetamide (40).** Compound **40** was prepared from *N,N,N'*-trimethylethylenediamine (30 μL, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH, 90:10:1) as a yellow oil (60 mg, 50% yield); *R<sub>f</sub>* 0.15 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8:2); HPLC (C18V) *P*<sub>HPLC</sub> 100%, *t<sub>R</sub>* 10.75 min; HPLC (C18N) *P*<sub>HPLC</sub> 100%, *t<sub>R</sub>* 11.84 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.73 (s, 1 H, CONH), 9.12 (s, 1 H, NH), 8.48-8.43 (m, 2 H, Ar-H), 7.89 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.71 (s, 1 H, Ar-H), 7.56 (dd, *J* = 9.0, 2.2 Hz, 1 H, Ar-H), 7.29 (s, 1 H, Ar-H), 7.01 (s, 1 H, Ar-H), 6.96 (d, *J* = 5.3 Hz, 1 H, Ar-H), 3.46 (s, 2 H, CH<sub>2</sub>), 3.07 (s, 2 H, CH<sub>2</sub>), 2.47-2.40 (m, 8 H, piperidine and CH<sub>2</sub>), 2.16 (s, 9 H, CH<sub>3</sub>), 2.05 (s, 6 H, CH<sub>3</sub>), 1.59-1.52 (m, 4 H, piperidine), 1.40-1.39 (m, 2 H, piperidine); TOFMS *m/z* 508.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-{*N*-(2-pyrrolidin-1-ylethyl)-aminomethyl}-phenyl]-2-piperidin-1-yl-acetamide (41).** Compound 41 was prepared from *N*-(2-aminoethyl)pyrrolidine (30  $\mu$ L, 0.24 mmol, 1 eq.) by method E and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ , 85:15:1) as a yellow solid (60 mg, 49% yield);  $R_f$  0.10 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8:2); mp 62°C; HPLC (C18V)  $P_{\text{HPLC}}$  97%,  $t_R$  10.80 min; HPLC (C18N)  $P_{\text{HPLC}}$  98%,  $t_R$  11.92 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.70 (s, 1 H, CONH), 9.11 (s, 1 H, NH), 8.46 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.44 (d,  $J = 9.3$  Hz, 1 H, Ar-H), 7.89 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.69 (s, 1 H, Ar-H), 7.56 (dd,  $J = 9.1, 2.2$  Hz, 1 H, Ar-H), 7.29 (s, 1 H, Ar-H), 7.05 (s, 1 H, Ar-H), 6.96 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 3.69 (s, 2 H,  $\text{CH}_2$ ), 3.06 (s, 2 H,  $\text{CH}_2$ ), 2.61 (t,  $J = 6.2$  Hz, 2 H,  $\text{CH}_2$ ), 2.62-2.41 (m, 6 H, piperidine and  $\text{CH}_2$ ), 2.40-2.37 (m, 4 H, pyrrolidine), 1.66-1.60 (m, 4 H, pyrrolidine), 1.58-1.52 (m, 4 H, piperidine), 1.41-1.39 (m, 2 H, piperidine); TOFMS  $m/z$  520.5 ( $\text{M}^+$ ).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-{*N*-(2-piperidin-1-ylethyl)-aminomethyl}-phenyl]-2-piperidin-1-yl-acetamide (42).** Compound 42 was prepared from *N*-(2-aminoethyl)pyrrolidine (34  $\mu$ L, 0.24 mmol, 1 eq.) by method E and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ , 85:15:1) as a yellow solid (70 mg, 55% yield);  $R_f$  0.15 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 7:3); mp 59°C; HPLC (C18V)  $P_{\text{HPLC}}$  94%,  $t_R$  12.00 min; HPLC (C18N)  $P_{\text{HPLC}}$  95%,  $t_R$  12.16 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.70 (s, 1 H, CONH), 9.10 (s, 1 H, NH), 8.45 (d,  $J = 5.5$  Hz, 1 H, Ar-H), 8.43 (d,  $J = 9.3$  Hz, 1 H, Ar-H), 7.88 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.67 (s, 1 H, Ar-H), 7.55 (dd,  $J = 9.0, 2.3$  Hz, 1 H, Ar-H), 7.27 (s, 1 H, Ar-H), 7.03 (s, 1 H, Ar-H), 6.95 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 3.67 (s, 2 H,  $\text{CH}_2$ ), 3.05 (s, 2 H,  $\text{CH}_2$ ), 2.57 (t,  $J = 6.5$  Hz, 2 H,  $\text{CH}_2$ ), 2.46-2.43 (m, 4 H, piperidine), 2.33 (t,  $J = 6.5$  Hz, 2 H,  $\text{CH}_2$ ), 2.27-2.25 (m, 4 H, piperidine), 1.56-1.53 (m, 4 H, piperidine), 1.45-1.33 (m, 8 H, piperidine); TOFMS  $m/z$  534.5 ( $\text{M}^+$ ).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-{*N*-(2-morpholin-4-ylethyl)-aminomethyl}-phenyl]-2-piperidin-1-yl-acetamide (43).** Compound 43 was prepared from *N*-(2-aminoethyl)morpholine (32  $\mu$ L, 0.24 mmol, 1 eq.) by method E and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ , 90:10:1) as a yellow solid (60 mg, 47% yield);  $R_f$  0.55 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 7:3); mp 53°C; HPLC (C18V)  $P_{\text{HPLC}}$  95%,  $t_R$  10.93 min; HPLC (C18N)  $P_{\text{HPLC}}$

94%,  $t_R$  11.92 min;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  9.68 (s, 1 H, CONH), 9.10 (s, 1 H, NH), 8.45 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.43 (d,  $J = 9.2$  Hz, 1 H, Ar-H), 7.88 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.66 (s, 1 H, Ar-H), 7.55 (dd,  $J = 9.0$ , 2.2 Hz, 1 H, Ar-H), 7.28 (s, 1 H, Ar-H), 7.03 (s, 1 H, Ar-H), 6.94 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 3.68 (s, 2 H,  $\text{CH}_2$ ), 3.51 (t,  $J = 4.6$  Hz, 4 H, morpholine), 3.05 (s, 2 H,  $\text{CH}_2$ ), 2.59 (t,  $J = 6.4$  Hz, 2 H,  $\text{CH}_2$ ), 2.46-2.42 (m, 4 H, piperidine), 2.37 (t,  $J = 6.4$  Hz, 2 H,  $\text{CH}_2$ ), 2.32 (t,  $J = 4.5$  Hz, 4 H, morpholine), 1.58-1.51 (m, 4 H, piperidine), 1.40-1.38 (m, 2 H, piperidine); TOFMS  $m/z$  536.5 ( $\text{M}^+$ ).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-diethylaminomethyl-phenyl]-2-piperidin-1-yl-acetamide (44).**

Compound **44** was prepared from diethylamine (25  $\mu\text{L}$ , 0.24 mmol, 1 eq.) by method E and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 85:15) as a yellow solid (40 mg, 39% yield);  $R_f$  0.70 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8:2); mp 81°C; HPLC (C18V)  $P_{\text{HPLC}}$  97%,  $t_R$  10.84 min; HPLC (C18N)  $P_{\text{HPLC}}$  98%,  $t_R$  11.92 min;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  9.74 (s, 1 H, CONH), 9.12 (s, 1 H, NH), 8.47 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.44 (d,  $J = 9.1$  Hz, 1H, Ar-H), 7.89 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.70 (s, 1 H, Ar-H), 7.56 (dd,  $J = 9.0$ , 2.2 Hz, 1 H, Ar-H), 7.30 (s, 1 H, Ar-H), 7.04 (s, 1 H, Ar-H), 6.96 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 3.54 (s, 2 H,  $\text{CH}_2$ ), 3.07 (s, 2 H,  $\text{CH}_2$ ), 2.53-2.45 (m, 8 H, piperidine and  $\text{N}(\text{CH}_2\text{CH}_3)_2$ ), 1.57-1.52 (m, 4 H, piperidine), 1.40-1.39 (m, 2 H, piperidine), 1.00 (t,  $J = 7.0$  Hz, 6 H,  $\text{N}(\text{CH}_2\text{CH}_3)_2$ ); TOFMS  $m/z$  479.5 ( $\text{M}^+$ ).

***N*-{3-*Tert*-butylaminomethyl-5-(7-Chloro-quinolin-4-ylamino)-phenyl]-2-piperidin-1-yl-acetamide (45).**

Compound **45** was prepared from *tert*-butylamine (26  $\mu\text{L}$ , 0.24 mmol, 1 eq.) by method E and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 85:15) as a yellow solid (75 mg, 53% yield);  $R_f$  0.35 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8.5:1.5); mp 89°C; HPLC (C18V)  $P_{\text{HPLC}}$  92%,  $t_R$  11.49 min; HPLC (C18N)  $P_{\text{HPLC}}$  93%,  $t_R$  12.95 min;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  9.69 (s, 1 H, CONH), 9.10 (s, 1 H, NH), 8.46 (d,  $J = 5.5$  Hz, 1 H, Ar-H), 8.45 (d,  $J = 9.0$  Hz, 1 H, Ar-H), 7.88 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.68 (s, 1 H, Ar-H), 7.59 (dd,  $J = 9.0$ , 2.3 Hz, 1 H, Ar-H), 7.30 (s, 1 H, Ar-H), 7.07 (s, 1 H, Ar-H), 6.95 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 3.65 (s, 2 H,  $\text{CH}_2$ ), 3.05 (s, 2 H,  $\text{CH}_2$ ), 2.46-2.43 (m, 4 H,

piperidine), 1.56-1.51 (m, 4 H, piperidine), 1.39-1.38 (m, 2 H, piperidine), 1.09 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>); TOFMS m/z 479.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-piperidin-1-ylmethyl-phenyl]-2-piperidin-1-yl-acetamide (46).**

Compound **46** was prepared from piperidine (23  $\mu$ L, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 85:15) as a yellow solid (90 mg, 51% yield); R<sub>f</sub> 0.35 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8:2); mp 100°C; HPLC (C18V) P<sub>HPLC</sub> 100%, t<sub>R</sub> 11.49 min; HPLC (C18N) P<sub>HPLC</sub> 100%, t<sub>R</sub> 13.03 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  9.82 (s, 1 H, CONH), 9.15 (s, 1 H, NH), 8.46 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.42 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.88 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.70 (s, 1 H, Ar-H), 7.55 (dd, *J* = 9.0, 2.2 Hz, 1 H, Ar-H), 7.30 (s, 1 H, Ar-H), 7.04 (s, 1 H, Ar-H), 6.97 (d, *J* = 5.2 Hz, 1 H, Ar-H), 3.35 (s, 2 H, CH<sub>2</sub>), 3.12 (s, 2 H, CH<sub>2</sub>), 2.55-2.53 (m, 8 H, piperidine), 1.57-1.53 (m, 8 H, piperidine), 1.41-1.38 (m, 4 H, piperidine); TOFMS m/z 491.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-pyrrolidin-1-ylmethyl-phenyl]-2-piperidin-1-yl-acetamide (47).**

Compound **47** was prepared from pyrrolidine (20  $\mu$ L, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 85:15) as a yellow solid (40 mg, 30% yield); R<sub>f</sub> 0.50 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8:2); mp 96°C; HPLC (C18V) P<sub>HPLC</sub> 100%, t<sub>R</sub> 11.32 min; HPLC (C18N) P<sub>HPLC</sub> 100%, t<sub>R</sub> 12.77 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  9.71 (s, 1 H, CONH), 9.09 (s, 1 H, NH), 8.46 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.42 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.87 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.68 (s, 1 H, Ar-H), 7.54 (dd, *J* = 9.0, 2.2 Hz, 1 H, Ar-H), 7.29 (s, 1 H, Ar-H), 6.99 (s, 1 H, Ar-H), 6.95 (d, *J* = 5.4 Hz, 1 H, Ar-H), 3.54 (s, 2 H, CH<sub>2</sub>), 3.04 (s, 2 H, CH<sub>2</sub>), 2.50-2.43 (m, 8 H, piperidine and pyrrolidine), 1.68-1.67 (m, 4 H, pyrrolidine), 1.55-1.52 (m, 4 H, piperidine), 1.34-1.30 (m, 2 H, piperidine); TOFMS m/z 477.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-(4-methyl-piperazin-1-ylmethyl)-phenyl]-2-piperidin-1-yl-**

**acetamide (48).** Compound **48** was prepared from *N*-methylpiperazine (38  $\mu$ L, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH, 85:15:1) as a yellow solid (45 mg, 39% yield); R<sub>f</sub> 0.20

(CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8:2); mp 87°C; HPLC (C18V) P<sub>HPLC</sub> 98%, *t<sub>R</sub>* 10.86 min; HPLC (C18N) P<sub>HPLC</sub> 100%, *t<sub>R</sub>* 12.49 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.66 (s, 1 H, CONH), 9.05 (s, 1 H, NH), 8.41 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.37 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.83 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.64 (s, 1 H, Ar-H), 7.49 (dd, *J* = 9.0, 2.2 Hz, 1 H, Ar-H), 7.21 (s, 1 H, Ar-H), 6.94 (s, 1 H, Ar-H), 6.90 (d, *J* = 5.3 Hz, 1 H, Ar-H), 3.36 (s, 2 H, CH<sub>2</sub>), 2.99 (s, 2 H, CH<sub>2</sub>), 2.39-2.31 (m, 12 H, piperidine and piperazine), 2.08 (s, 3 H, NCH<sub>3</sub>), 1.53-1.45 (m, 4 H, piperidine), 1.34-1.32 (m, 2 H, piperidine); TOFMS *m/z* 506.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-morpholin-4-ylmethyl-phenyl]-2-piperidin-1-yl-acetamide (49).**

Compound **49** was prepared from morpholine (21 μL, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 85:15) as a yellow solid (55 mg, 47% yield); R<sub>f</sub> 0.90 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 84°C; HPLC (C18V) P<sub>HPLC</sub> 96%, *t<sub>R</sub>* 11.11 min; HPLC (C18N) P<sub>HPLC</sub> 97%, *t<sub>R</sub>* 12.49 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.74 (s, 1 H, CONH), 9.12 (s, 1 H, NH), 8.48 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.43 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.89 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.71 (s, 1 H, Ar-H), 7.56 (dd, *J* = 9.0, 2.3 Hz, 1 H, Ar-H), 7.30 (s, 1 H, Ar-H), 7.02 (s, 1 H, Ar-H), 6.97 (d, *J* = 5.3 Hz, 1 H, Ar-H), 3.58 (t, *J* = 4.3 Hz, 4 H, morpholine), 3.42 (s, 2 H, CH<sub>2</sub>), 3.06 (s, 2 H, CH<sub>2</sub>), 2.46-2.43 (m, 4 H, piperidine), 2.39-2.38 (m, 4 H, morpholine), 1.59-1.51 (m, 4 H, piperidine), 1.42-1.38 (m, 2 H, piperidine); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 152.79, 128.53, 125.81, 125.42, 118.53, 116.21, 112.69, 103.03, 67.07, 63.50, 63.26, 54.91, 54.09, 26.29, 24.37; TOFMS *m/z* 493.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-(4-hydroxypiperidin-1-ylmethyl)-phenyl]-2-piperidin-1-yl-acetamide (50).** Compound **50** was prepared from 4-hydroxypiperidine (24 mg, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH, 90:10:1) as a yellow solid (95 mg, 79% yield); R<sub>f</sub> 0.60 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8:2); mp 84°C; HPLC (C18V) P<sub>HPLC</sub> 96%, *t<sub>R</sub>* 10.65 min; HPLC (C18N) P<sub>HPLC</sub> 96%, *t<sub>R</sub>* 12.33 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.75 (s, 1 H, CONH), 9.14 (s, 1 H, NH), 8.49 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.45 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.91 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.73 (s, 1 H, Ar-H), 7.58 (dd, *J* = 9.0, 2.2 Hz, 1 H, Ar-H), 7.29 (s, 1 H, Ar-H), 7.02 (s, 1 H, Ar-H), 6.99 (d, *J* = 5.4 Hz, 1 H, Ar-H), 4.59 (d, *J* = 4.1 Hz, 1 H, OH), 3.43 (s,

2 H, CH<sub>2</sub>), 3.08 (s, 2 H, CH<sub>2</sub>), 2.49-2.46 (m, 4 H, piperidine), 2.08-2.06 (m, 3 H, piperidine), 2.73-2.70 (m, 4 H, piperidine), 1.74-1.71 (m, 4 H, piperidine), 1.59-1.56 (m, 4 H, piperidine), 1.42-1.39 (m, 4 H, piperidine); TOFMS *m/z* 507.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-{*N*-(2-hydroxyethyl)-piperazin-1-ylmethyl}phenyl]-2-piperidin-1-yl-acetamide (51).** Compound 51 was prepared from *N*-(2-hydroxyethyl)piperazine (29 μL, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>4</sub>OH, 90:10:1) as a yellow solid (50 mg, 39% yield); R<sub>f</sub> 0.30 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8:2); mp 96°C; HPLC (C18V) P<sub>HPLC</sub> 100%, *t<sub>R</sub>* 10.06 min; HPLC (C18N) P<sub>HPLC</sub> 100%, *t<sub>R</sub>* 12.33 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.70 (s, 1 H, CONH), 9.09 (s, 1 H, NH), 8.45 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.40 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.87 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.68 (s, 1 H, Ar-H), 7.53 (dd, *J* = 9.0, 2.2 Hz, 1 H, Ar-H), 7.25 (s, 1 H, Ar-H), 6.98 (s, 1 H, Ar-H), 6.94 (d, *J* = 5.4 Hz, 1 H, Ar-H), 4.36 (d, *J* = 5.3 Hz, 1 H, OH), 3.47-3.43 (m, 2 H, CH<sub>2</sub>), 3.40 (s, 2 H, CH<sub>2</sub>), 3.03 (s, 2 H, CH<sub>2</sub>), 2.44-2.31 (m, 14 H, piperidine, piperazine and CH<sub>2</sub>), 1.56-1.49 (m, 4 H, piperidine), 1.37-1.36 (m, 2 H, piperidine); TOFMS *m/z* 536.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-(*N*-phenyl-piperazin-1-ylmethyl)-phenyl]-2-piperidin-1-yl-acetamide (52).** Compound 52 was prepared from *N*-phenylpiperazine (36 μL, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 85:15) as a yellow solid (65 mg, 48% yield); R<sub>f</sub> 0.75 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 93°C; HPLC (C18V) P<sub>HPLC</sub> 99%, *t<sub>R</sub>* 14.28 min; HPLC (C18N) P<sub>HPLC</sub> 99%, *t<sub>R</sub>* 15.49 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.74 (s, 1 H, CONH), 9.12 (s, 1 H, NH), 8.47 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.42 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.88 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.72 (s, 1 H, Ar-H), 7.55 (dd, *J* = 9.0, 2.2 Hz, 1 H, Ar-H), 7.31 (s, 1 H, Ar-H), 7.04 (s, 1 H, Ar-H), 6.98 (d, *J* = 5.3 Hz, 1 H, Ar-H), 6.89 (d, *J* = 7.9 Hz, 2 H, Ar-H), 6.75 (t, *J* = 7.2 Hz, 2 H, Ar-H), 3.52 (s, 2 H, CH<sub>2</sub>), 3.14-3.10 (m, 4 H, piperazine), 3.05 (s, 2 H, CH<sub>2</sub>), 2.55-2.51 (m, 4 H, piperazine), 2.48-2.43 (m, 4 H, piperidine), 1.57-1.50 (m, 4 H, piperidine), 1.38-1.37 (m, 2 H, piperidine); TOFMS *m/z* 568.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-(*N*-benzyl-piperazin-1-ylmethyl)phenyl]-2-piperidin-1-yl-acetamide (53).** Compound 53 was prepared from *N*-benzylpiperazine (41  $\mu$ L, 0.24 mmol, 1 eq.) by method E and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 90:10) as a yellow solid (85 mg, 62% yield);  $R_f$  0.65 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8.5:1.5); mp 78°C; HPLC (C18V)  $P_{\text{HPLC}}$  95%,  $t_R$  13.12 min; HPLC (C18N)  $P_{\text{HPLC}}$  94%,  $t_R$  14.45 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.70 (s, 1 H, CONH), 9.09 (s, 1 H, NH), 8.45 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.41 (d,  $J = 9.2$  Hz, 1 H, Ar-H), 7.87 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.69 (s, 1 H, Ar-H), 7.54 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.31 (s, 1 H, Ar-H), 6.98 (s, 1 H, Ar-H), 6.95 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 6.89 (d,  $J = 7.9$  Hz, 2 H, Ar-H), 6.75 (t,  $J = 7.2$  Hz, 2 H, Ar-H), 3.44 (s, 2 H,  $\text{CH}_2$ ), 3.42 (s, 2 H,  $\text{CH}_2$ ), 3.04 (s, 2 H,  $\text{CH}_2$ ), 2.49-2.37 (m, 12 H, piperidine and piperazine), 1.60-1.51 (m, 4 H, piperidine), 1.38-1.36 (m, 2 H, piperidine); TOFMS  $m/z$  582.5 ( $\text{M}^+$ ).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-(*N*-diphenylmethyl-piperazin-1-ylmethyl)phenyl]-2-piperidin-1-yl-acetamide (54).** Compound 54 was prepared from *N*-(diphenylmethyl)piperazine (60 mg, 0.24 mmol, 1 eq.) by method E and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 90:10) as a yellow solid (90 mg, 70% yield);  $R_f$  0.60 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 9:1); mp 115°C; HPLC (C18V)  $P_{\text{HPLC}}$  100%,  $t_R$  17.34 min; HPLC (C18N)  $P_{\text{HPLC}}$  98%,  $t_R$  18.56 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.73 (s, 1 H, CONH), 9.12 (s, 1 H, NH), 8.47 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.44 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 7.88 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.72 (s, 1 H, Ar-H), 7.57 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.43-7.41 (m, 6 H, Ar-H), 7.32-7.27 (m, 4 H, Ar-H), 7.20 (s, 1 H, Ar-H), 7.01 (s, 1 H, Ar-H), 6.97 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 4.29 (s, 1 H, CH), 3.47 (s, 2 H,  $\text{CH}_2$ ), 3.07 (s, 2 H,  $\text{CH}_2$ ), 2.48-2.45 (m, 8 H, piperazine), 2.36-2.30 (m, 4 H, piperidine), 1.58-1.53 (m, 4 H, piperidine), 1.42-1.40 (m, 2 H, piperidine); TOFMS  $m/z$  658.5 ( $\text{M}^+$ ).

***N*-[3-{*N*-(4-Chloro-benzyl)-piperazin-1-ylmethyl}-5-(7-chloro-quinolin-4-ylamino)-phenyl]-2-piperidin-1-yl-acetamide (55).** *N*-(4-Chlorobenzyl)piperazine was prepared from 4-chlorobenzaldehyde (200 mg, 1.4 mmol, 1 eq.) by method D and was obtained as a yellow oil (130 mg, 43% yield);  $R_f$  0.30 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 9:1);

HPLC (C18V)  $P_{\text{HPLC}}$  100%,  $t_R$  9.64 min;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  7.41 (d,  $J$  = 8.6 Hz, 2 H, Ar-H), 7.35 (d,  $J$  = 8.7 Hz, 2 H, Ar-H), 4.24 (bs, 1 H, NH), 3.47 (s, 2 H, CH<sub>2</sub>), 2.82-2.78 (m, 4 H, piperazine), 2.39-2.36 (m, 4 H, piperazine); TOFMS  $m/z$  210.5 ( $M^+$ ). Compound **55** was prepared from *N*-(4-chlorobenzyl)piperazine (50 mg, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 93:7) as a yellow solid (80 mg, 55% yield);  $R_f$  0.70 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 86°C; HPLC (C18V)  $P_{\text{HPLC}}$  100%,  $t_R$  14.14 min; HPLC (C18N)  $P_{\text{HPLC}}$  100%,  $t_R$  15.92 min;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  9.70 (s, 1 H, CONH), 9.09 (s, 1 H, NH), 8.44 (d,  $J$  = 5.3 Hz, 1 H, Ar-H), 8.40 (d,  $J$  = 9.1 Hz, 1 H, Ar-H), 7.87 (d,  $J$  = 2.2 Hz, 1 H, Ar-H), 7.69 (s, 1 H, Ar-H), 7.53 (dd,  $J$  = 9.0, 2.2 Hz, 1 H, Ar-H), 7.34 (d,  $J$  = 8.5 Hz, 2 H, Ar-H), 7.28 (d,  $J$  = 8.5 Hz, 2 H, Ar-H), 7.25 (s, 1 H, Ar-H), 6.98 (s, 1 H, Ar-H), 6.94 (d,  $J$  = 5.4 Hz, 1 H, Ar-H), 3.42 (s, 2 H, CH<sub>2</sub>), 3.41 (s, 2 H, CH<sub>2</sub>), 3.03 (s, 2 H, CH<sub>2</sub>), 2.44-2.34 (m, 12 H, piperidine and piperazine), 1.54-1.49 (m, 4 H, piperidine), 1.38-1.36 (m, 2 H, piperidine); TOFMS  $m/z$  617 ( $M^+$ ).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-{*N*-(4-methoxy-benzyl)-piperazin-1-ylmethyl}-phenyl]-2-piperidin-1-yl-acetamide (56).** *N*-(4-Methoxybenzyl)piperazine was prepared from 4-methoxybenzaldehyde (170 mg, 1.4 mmol, 1 eq.) by method D and was obtained as a yellow oil (140 mg, 49% yield);  $R_f$  0.35 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1); HPLC (C18V)  $P_{\text{HPLC}}$  100%,  $t_R$  7.99 min;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  7.41 (d,  $J$  = 8.6 Hz, 2 H, Ar-H), 6.91 (d,  $J$  = 8.7 Hz, 2 H, Ar-H), 4.04 (bs, 1 H, NH), 3.76 (s, 3 H, OCH<sub>3</sub>), 3.39 (s, 2 H, CH<sub>2</sub>), 2.79-2.76 (m, 4 H, piperazine), 2.35-2.33 (m, 4 H, piperazine); TOFMS  $m/z$  206 ( $M^+$ ). Compound **56** was prepared from *N*-(4-methoxybenzyl)piperazine (50 mg, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 93:7) as a yellow solid (65 mg, 45% yield);  $R_f$  0.60 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 91°C; HPLC (C18V)  $P_{\text{HPLC}}$  96%,  $t_R$  12.95 min; HPLC (C18N)  $P_{\text{HPLC}}$  95%,  $t_R$  14.70 min;  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  9.70 (s, 1 H, CONH), 9.09 (s, 1 H, NH), 8.45 (d,  $J$  = 5.3 Hz, 1 H, Ar-H), 8.40 (d,  $J$  = 9.1 Hz, 1 H, Ar-H), 7.87 (d,  $J$  = 2.2 Hz, 1 H, Ar-H), 7.68 (s, 1 H, Ar-H), 7.53 (dd,  $J$  = 9.0, 2.2 Hz, 1 H, Ar-H), 7.25 (s, 1 H, Ar-H), 7.16 (d,  $J$  = 8.6 Hz, 2 H, Ar-H), 6.97 (s, 1 H, Ar-H), 6.94 (d,  $J$  = 5.3 Hz, 1 H, Ar-H), 6.84 (d,  $J$  = 8.7 Hz, 2 H, Ar-H), 3.70 (s, 3 H,

OCH<sub>3</sub>), 3.40 (s, 2 H, CH<sub>2</sub>), 3.36 (s, 2 H, CH<sub>2</sub>), 3.03 (s, 2 H, CH<sub>2</sub>), 2.44-2.35 (m, 12 H, piperidine and piperazine), 1.54-1.49 (m, 4 H, piperidine), 1.38-1.36 (m, 2 H, piperidine); TOFMS m/z 612.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-{*N*-(4-nitro-benzyl)-piperazin-1-ylmethyl}-phenyl]-2-piperidin-1-yl-acetamide (57).** *N*-(4-Nitrobenzyl)piperazine was prepared from 4-nitrobenzaldehyde (210 mg, 1.4 mmol, 1 eq.) by method D and was obtained as a yellow solid (95 mg, 31% yield); R<sub>f</sub> 0.10 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1); mp 34°C; HPLC (C18V) P<sub>HPLC</sub> 100%, t<sub>R</sub> 8.96 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.24 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.63 (d, *J* = 8.8 Hz, 2 H, Ar-H), 4.06 (bs, 1 H, NH), 3.66 (s, 2 H, CH<sub>2</sub>), 3.47-3.37 (m, 4 H, piperazine), 2.95-2.90 (m, 4 H, piperazine); TOFMS m/z 221 (M<sup>+</sup>). Compound **57** was prepared from *N*-(4-nitrobenzyl)piperazine (53 mg, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 93:7) as a yellow solid (40 mg, 27% yield); R<sub>f</sub> 0.75 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 81°C; HPLC (C18V) P<sub>HPLC</sub> 98%, t<sub>R</sub> 13.69 min; HPLC (C18N) P<sub>HPLC</sub> 100%, t<sub>R</sub> 15.51 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.76 (s, 1 H, CONH), 9.15 (s, 1 H, NH), 8.51 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.47 (d, *J* = 9.1 Hz, 1 H, Ar-H), 8.23 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.93 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.74 (s, 1 H, Ar-H), 7.62 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.60 (dd, *J* = 8.9, 2.2 Hz, 1 H, Ar-H), 7.32 (s, 1 H, Ar-H), 7.04 (s, 1 H, Ar-H), 7.00 (d, *J* = 5.3 Hz, 1 H, Ar-H), 3.64 (s, 2 H, CH<sub>2</sub>), 3.49 (s, 2 H, CH<sub>2</sub>), 3.09 (s, 2 H, CH<sub>2</sub>), 2.50-2.47 (m, 12 H, piperidine and piperazine), 1.63-1.55 (m, 4 H, piperidine), 1.44-1.42 (m, 2 H, piperidine); TOFMS m/z 627.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-{*N*-(4-diethylamino-benzyl)-piperazin-1-ylmethyl}-phenyl]-2-piperidin-1-yl-acetamide (58).** *N*-(4-Diethylaminobenzyl)piperazine was prepared from 4-diethylaminobenzaldehyde (250 mg, 1.4 mmol, 1 eq.) by method D and was obtained as a yellow oil (155 mg, 45% yield); R<sub>f</sub> 0.35 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1); HPLC (C18V) P<sub>HPLC</sub> 100%, t<sub>R</sub> 7.05 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.04 (d, *J* = 8.7 Hz, 2 H, Ar-H), 6.59 (d, *J* = 8.8 Hz, 2 H, Ar-H), 4.01 (bs, 1 H, NH), 3.33-3.26 (m, 4 H, N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 2.77-2.74 (m, 4 H, piperazine), 2.33-2.30 (m, 4 H, piperazine), 1.07 (t, *J* = 6.9 Hz, 6 H, N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>); TOFMS m/z 247 (M<sup>+</sup>). Compound **58** was prepared from *N*-(4-diethylaminobenzyl)piperazine

(59 mg, 0.24 mmol, 1 eq.) by method E and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 93:7) as a yellow solid (80 mg, 52% yield);  $R_f$  0.75 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8.5:1.5); mp 85°C; HPLC (C18V)  $P_{\text{HPLC}}$  100%,  $t_R$  11.62 min; HPLC (C18N)  $P_{\text{HPLC}}$  98%,  $t_R$  13.80 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.76 (s, 1 H, CONH), 9.15 (s, 1 H, NH), 8.51 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.46 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 7.93 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.75 (s, 1 H, Ar-H), 7.59 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.30 (s, 1 H, Ar-H), 7.07 (d,  $J = 8.7$  Hz, 2 H, Ar-H), 7.04 (s, 1 H, Ar-H), 7.00 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 6.61 (d,  $J = 8.8$  Hz, 2 H, Ar-H), 3.35-3.32 (m, 4 H,  $\text{N}(\text{CH}_2\text{CH}_3)_2$ ), 3.46 (s, 2 H,  $\text{CH}_2$ ), 3.29 (s, 2 H,  $\text{CH}_2$ ), 3.09 (s, 2 H,  $\text{CH}_2$ ), 2.53-2.47 (m, 12 H, piperidine and piperazine), 1.60-1.55 (m, 4 H, piperidine), 1.44-1.42 (m, 2 H, piperidine), 1.09 (t,  $J = 6.9$  Hz, 6 H,  $\text{N}(\text{CH}_2\text{CH}_3)_2$ ); TOFMS  $m/z$  653.5 ( $\text{M}^+$ ).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-{*N*-(4-cyano-benzyl)-piperazin-1-ylmethyl}-phenyl]-2-piperidin-1-yl-acetamide (59).** *N*-(4-Cyanobenzyl)piperazine was prepared from 4-cyanobenzaldehyde (185 mg, 1.4 mmol, 1 eq.) by method D and was obtained as a yellow oil (50 mg, 18% yield);  $R_f$  0.10 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 9:1); HPLC (C18V)  $P_{\text{HPLC}}$  100%,  $t_R$  8.03 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  7.79 (d,  $J = 8.3$  Hz, 2 H, Ar-H), 7.51 (d,  $J = 8.4$  Hz, 2 H, Ar-H), 3.52 (s, 2 H,  $\text{CH}_2$ ), 2.75-2.71 (m, 4 H, piperazine), 2.33-2.30 (m, 4 H, piperazine); TOFMS  $m/z$  201 ( $\text{M}^+$ ). Compound **59** was prepared from *N*-(4-cyanobenzyl)piperazine (48 mg, 0.24 mmol, 1 eq.) by method E and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 93:7) as a yellow solid (90 mg, 63% yield);  $R_f$  0.70 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8.5:1.5); mp 58°C; HPLC (C18V)  $P_{\text{HPLC}}$  100%,  $t_R$  13.10 min; HPLC (C18N)  $P_{\text{HPLC}}$  100%,  $t_R$  14.80 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.73 (s, 1 H, CONH), 9.12 (s, 1 H, NH), 8.48 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 8.44 (d,  $J = 9.1$  Hz, 1 H, Ar-H), 7.90 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.78 (d,  $J = 8.4$  Hz, 2 H, Ar-H), 7.71 (s, 1 H, Ar-H), 7.56 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.50 (d,  $J = 8.4$  Hz, 2 H, Ar-H), 7.28 (s, 1 H, Ar-H), 7.01 (s, 1 H, Ar-H), 6.97 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 3.55 (s, 2 H,  $\text{CH}_2$ ), 3.34 (s, 2 H,  $\text{CH}_2$ ), 3.06 (s, 2 H,  $\text{CH}_2$ ), 2.47-2.41 (m, 12 H, piperidine and piperazine), 1.59-1.52 (m, 4 H, piperidine), 1.42-1.39 (m, 2 H, piperidine); TOFMS  $m/z$  607.5 ( $\text{M}^+$ ).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-(4-piperonyl-piperazin-1-ylmethyl)-phenyl]-2-piperidin-1-yl-acetamide (60).** Compound **60** was prepared from *N*-piperonylpiperazine (58 mg, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 90:10) as a yellow solid (90 mg, 80% yield); R<sub>f</sub> 0.50 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1); mp 104°C; HPLC (C18V) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 13.11 min; HPLC (C18N) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 14.67 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.75 (s, 1 H, CONH), 9.13 (s, 1 H, NH), 8.49 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.45 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.91 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.73 (s, 1 H, Ar-H), 7.58 (dd, *J* = 9.0, 2.3 Hz, 1 H, Ar-H), 7.29 (s, 1 H, Ar-H), 7.02 (s, 1 H, Ar-H), 6.99 (d, *J* = 5.3 Hz, 1 H, Ar-H), 6.85-6.73 (m, 3 H, Ar-H), 3.55 (s, 2 H, CH<sub>2</sub>), 6.00 (s, 2 H, OCH<sub>2</sub>O), 3.38 (s, 2 H, CH<sub>2</sub>), 3.08 (s, 2 H, CH<sub>2</sub>), 2.47-2.40 (m, 12 H, piperidine and piperazine), 1.60-1.54 (m, 4 H, piperidine), 1.42-1.41 (m, 2 H, piperidine); TOFMS *m/z* 626.5 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-phenylaminomethyl-phenyl]-2-piperidin-1-yl-acetamide (61).**

Compound **61** was prepared from aniline (22 μL, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 90:10) as a yellow solid (60 mg, 51% yield); R<sub>f</sub> 0.65 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 65°C; HPLC (C18V) P<sub>HPLC</sub> 98%, *t*<sub>R</sub> 14.83 min; HPLC (C18N) P<sub>HPLC</sub> 98%, *t*<sub>R</sub> 17.11 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.71 (s, 1 H, CONH), 9.10 (s, 1 H, NH), 8.40 (d, *J* = 9.1 Hz, 1 H, Ar-H), 8.36 (d, *J* = 5.4 Hz, 1 H, Ar-H), 7.86 (d, *J* = 2.2 Hz, 1 H, Ar-H), 7.66 (s, 1 H, Ar-H), 7.52 (dd, *J* = 9.1, 2.2 Hz, 1 H, Ar-H), 7.31 (s, 1 H, Ar-H), 7.07-7.01 (m, 3 H, Ar-H), 6.83 (d, *J* = 5.2 Hz, 1 H, Ar-H), 6.56-6.53 (m, 3 H, Ar-H), 6.27 (t, *J* = 6.0 Hz, 1 H, NH), 4.24 (d, *J* = 6.0 Hz, 2 H, CH<sub>2</sub>), 3.05 (s, 2 H, CH<sub>2</sub>), 2.49-2.43 (m, 4 H, piperidine), 1.57-1.52 (m, 4 H, piperidine), 1.38-1.35 (m, 2 H, piperidine); TOFMS *m/z* 499.5 (M<sup>+</sup>).

***N*-[3-Benzylaminomethyl-5-(7-chloro-quinolin-4-ylamino)-phenyl]-2-piperidin-1-yl-acetamide (62).**

Compound **62** was prepared from benzylamine (26 μL, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 90:10) as a yellow oil (35 mg, 45% yield); R<sub>f</sub> 0.25 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1); HPLC (C18V) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 12.47 min; HPLC (C18N) P<sub>HPLC</sub> 99%, *t*<sub>R</sub> 14.26 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 9.72 (s, 1 H, CONH), 9.13 (s, 1 H, NH), 8.48 (d, *J* = 5.3 Hz, 1 H, Ar-H), 8.46 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.91 (d, *J* = 2.3 Hz,

1 H, Ar-H), 7.72 (s, 1 H, Ar-H), 7.58 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.39-7.32 (m, 5 H, Ar-H), 7.26 (s, 1 H, Ar-H), 7.11 (s, 1 H, Ar-H), 7.00 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 3.73 (s, 2 H, CH<sub>2</sub>), 3.69 (s, 2 H, CH<sub>2</sub>), 3.08 (s, 2 H, CH<sub>2</sub>), 2.49-2.43 (m, 4 H, piperidine), 1.62-1.54 (m, 4 H, piperidine), 1.42-1.41 (m, 2 H, piperidine); TOFMS  $m/z$  513.5 (M<sup>+</sup>).

***N*-[3-Benzhydrylaminomethyl-5-(7-chloro-quinolin-4-ylamino)-phenyl]-2-piperidin-1-yl-acetamide (63).**

Compound **63** was prepared from benzhydrylamine (41  $\mu$ L, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 93:7) as a yellow solid (60 mg, 43% yield);  $R_f$  0.80 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1); mp 79°C; HPLC (C18V)  $P_{HPLC}$  97%,  $t_R$  15.06 min; HPLC (C18N)  $P_{HPLC}$  97%,  $t_R$  16.70 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  9.69 (s, 1 H, CONH), 9.11 (s, 1 H, NH), 8.43 (d,  $J = 5.1$  Hz, 1 H, Ar-H), 8.42 (d,  $J = 9.2$  Hz, 1 H, Ar-H), 7.87 (d,  $J = 2.3$  Hz, 1 H, Ar-H), 7.72 (s, 1 H, Ar-H), 7.54 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.43-7.32 (m, 4 H, Ar-H), 7.31-7.24 (m, 5 H, Ar-H), 7.22-7.18 (m, 2 H, Ar-H), 7.08 (s, 1 H, Ar-H), 6.97 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 4.83 (s, 1 H, CH), 4.81 (bs, 1 H, NH), 3.58 (s, 2 H, CH<sub>2</sub>), 3.04 (s, 2 H, CH<sub>2</sub>), 2.45-2.42 (m, 4 H, piperidine), 1.57-1.50 (m, 4 H, piperidine), 1.39-1.38 (m, 2 H, piperidine); TOFMS  $m/z$  589.5 (M<sup>+</sup>).

***N*-[3-{*N*-(4-Chloro-benzyl)-aminomethyl}-5-(7-chloro-quinolin-4-ylamino)-phenyl]-2-piperidin-1-yl-acetamide (64).** Compound **64** was prepared from 4-chlorobenzylamine (29  $\mu$ L, 0.24 mmol, 1 eq.) by method E and was obtained after TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 90:10) as a yellow solid (100 mg, 77% yield);  $R_f$  0.70 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8.5:1.5); mp 59°C; HPLC (C18V)  $P_{HPLC}$  96%,  $t_R$  13.80 min; HPLC (C18N)  $P_{HPLC}$  96%,  $t_R$  15.47 min; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  9.70 (s, 1 H, CONH), 9.11 (s, 1 H, NH), 8.46 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.44 (d,  $J = 9.2$  Hz, 1 H, Ar-H), 7.89 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.70 (s, 1 H, Ar-H), 7.56 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.40-7.34 (m, 4 H, Ar-H), 7.30 (s, 1 H, Ar-H), 7.27 (bs, 1 H, NH), 7.07 (s, 1 H, Ar-H), 6.97 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 3.70 (s, 2 H, CH<sub>2</sub>), 3.66 (s, 2 H, CH<sub>2</sub>), 3.06 (s, 2 H, CH<sub>2</sub>), 2.47-2.44 (m, 4 H, piperidine), 1.59-1.52 (m, 4 H, piperidine), 1.42-1.39 (m, 2 H, piperidine); TOFMS  $m/z$  548 (M<sup>+</sup>).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-{*N*-(4-methoxy-benzyl)-aminomethyl}-phenyl]-2-piperidin-1-yl-acetamide (65).** Compound **65** was prepared from 4-methoxybenzylamine (31  $\mu$ L, 0.24 mmol, 1 eq.) by method E and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 90:10) as a yellow solid (85 mg, 66% yield);  $R_f$  0.80 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8.5:1.5); mp 64°C; HPLC (C18V)  $P_{\text{HPLC}}$  96%,  $t_R$  12.95 min; HPLC (C18N)  $P_{\text{HPLC}}$  98%,  $t_R$  14.66 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.70 (s, 1 H, CONH), 9.11 (s, 1 H, NH), 8.46 (d,  $J = 5.6$  Hz, 1 H, Ar-H), 8.44 (d,  $J = 9.2$  Hz, 1 H, Ar-H), 7.89 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.70 (s, 1 H, Ar-H), 7.55 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.29 (s, 1 H, Ar-H), 7.26 (d,  $J = 8.6$  Hz, 1 H, Ar-H), 7.07 (s, 1 H, Ar-H), 6.97 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 6.86 (d,  $J = 8.6$  Hz, 1 H, Ar-H), 3.72 (s, 3 H,  $\text{OCH}_3$ ), 3.64 (s, 2 H,  $\text{CH}_2$ ), 3.63 (s, 2 H,  $\text{CH}_2$ ), 3.06 (s, 2 H,  $\text{CH}_2$ ), 2.47-2.44 (m, 4 H, piperidine), 1.57-1.52 (m, 4 H, piperidine), 1.40-1.39 (m, 2 H, piperidine); TOFMS  $m/z$  543.5 ( $\text{M}^+$ ).

***N*-[3-(7-Chloro-quinolin-4-ylamino)-5-{*N*-(4-trifluoromethyl-benzyl)-aminomethyl}-phenyl]-2-piperidin-1-yl-acetamide (66).** Compound **66** was prepared from 4-trifluoromethylbenzylamine (34  $\mu$ L, 0.24 mmol, 1 eq.) by method E and was obtained after TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 90:10) as a yellow solid (100 mg, 73% yield);  $R_f$  0.80 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 8.5:1.5); mp 60°C; HPLC (C18V)  $P_{\text{HPLC}}$  97%,  $t_R$  14.84 min; HPLC (C18N)  $P_{\text{HPLC}}$  99%,  $t_R$  16.37 min;  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$  9.70 (s, 1 H, CONH), 9.11 (s, 1 H, NH), 8.46 (d,  $J = 5.4$  Hz, 1 H, Ar-H), 8.44 (d,  $J = 9.2$  Hz, 1 H, Ar-H), 7.89 (d,  $J = 2.2$  Hz, 1 H, Ar-H), 7.70 (s, 1 H, Ar-H), 7.67 (d,  $J = 8.2$  Hz, 2 H, Ar-H), 7.62 (d,  $J = 8.2$  Hz, 2 H, Ar-H), 7.55 (dd,  $J = 9.0, 2.2$  Hz, 1 H, Ar-H), 7.30 (s, 1 H, Ar-H), 7.09 (s, 1 H, Ar-H), 6.97 (d,  $J = 5.3$  Hz, 1 H, Ar-H), 3.80 (s, 2 H,  $\text{CH}_2$ ), 3.67 (s, 2 H,  $\text{CH}_2$ ), 3.06 (s, 2 H,  $\text{CH}_2$ ), 2.47-2.44 (m, 4 H, piperidine), 1.59-1.52 (m, 4 H, piperidine), 1.42-1.39 (m, 2 H, piperidine); TOFMS  $m/z$  543.5 ( $\text{M}^+$ ).