## Development of Quinoline Analogous as Anti-Alzheimer's Agents

7.1 Development of quinolines as inhibitors of acetylcholinesterase (AChE) and β-site APP cleaving enzyme 1 (BACE1)

Quinoline analogs were found to be active against verity of diseases *viz.* anticancer, antimycobacterial, antimicrobial, anticonvulsant, antiinflamatory and cardiovascular activities(418-421). These have been commonly synthesized by Combes, Conrad-Limpach, Doebner, Doebner-Miller, Gould-Jacobs and Skraup methods. Quinoline-4-carboxylic acid containing intermediate have been frequently used for the synthesis of bioactive molecules in Doebner's reaction. Substituted anilines on reaction with aldehyde and pyruvic acid form quinoline-4-carboxylic acids (**Figure 7.1**)(422).

Figure 7.1 Doebner's reaction for the synthesis of quinoline-4-carboxylic acids
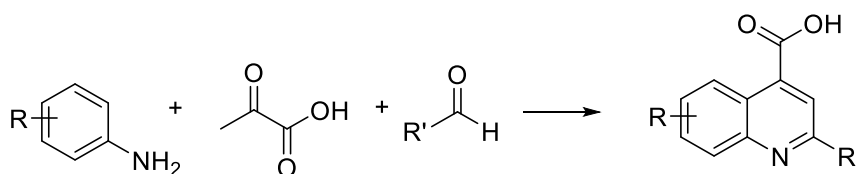
Skraup method of synthesis has also been used to develop novel quinoline analogous. Reaction takes place by heating mixture of aromatic amine, glycerol, concentrated sulphuric acid and suitable oxidizing reagent (**Figure 7.2**). The overall sequence of reaction involves conversion of glycerol into acrolein by action of sulphuric acid, 1,4-addition of aniline to acrolein yields 3-phenylaminopropanal, followed by an acid catalyzed cyclization and dehydration to yield 1,2-dihydroquinoline, which is finally oxidized to quinoline(423).

Figure 7.2 Skraup method of synthesis for quinoline
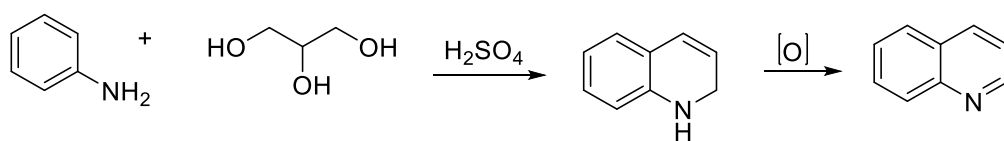
Drug design strategy for the development of AChE and BACE inhibitor

Fragments from different bioactive reported molecules *viz* donepezil, LY2811376, MK-8631 were assembled and docked against AChE, BACE1 and were further developed by fragment based approach. Quinolines were found to be active against AChE and Aβ_{1-42} fragments in our earlier study, piperazines constituted many CNS active drugs and also increased the water solubility of small synthetic molecules without altering its BBB permeability. Further linkers were used in the present study to increase the approach of tail group like substituted cyclohexan-1-amine or substitutedbenzyl-1-amine towards different amino acid residues. Increasing the length of linker by more than two carbons caused unfavorable rotation in the molecules which hampered the interaction (**Figure 7.3**).

Figure 7.3 Drug design strategy for the development of AChE and BACE inhibitor.
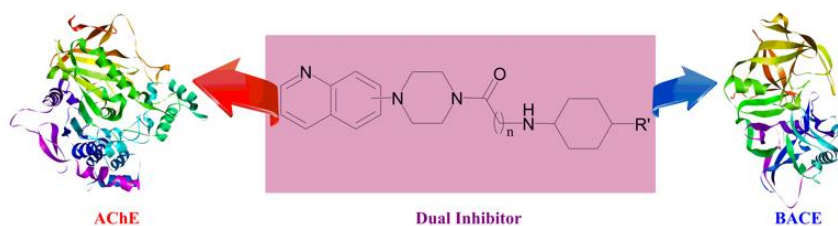
7.2 Experimental work
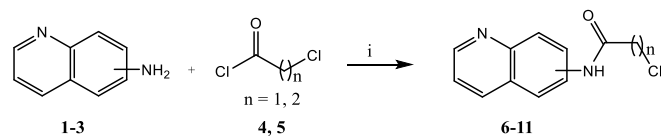
7.2.1 Docking study

Docking was performed by Autodock 4.0 in Lamarckian Genetic Algorithm (LGA), using algorithm with 10 runs, 150 population size, 2,500,000 maximum number of energy evaluations and 27,000 maximum number of generations. Free binding energy of ligand-receptor complex for scoring various conformations was estimated, that used 'semiempirical free energy force field' to evaluate conformations obtained by molecular docking. The docked conformers were visualized by Discovery Studio 2017R2. The detail procedure is mentioned in the section 6.1.4.
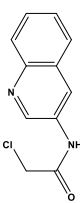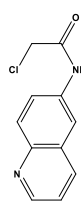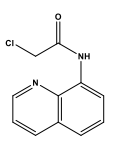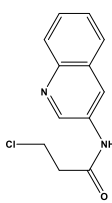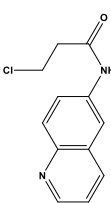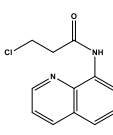
7.2.2 Synthesis and characterization

All the reagents were purchased from the Sigma-Aldrich, Avera, Spectrochem and Alfa Aesar. The progress of the reactions was monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 plates (Merck KGaA) and ultraviolet light (254 nm) or iodine vapors were used for visualization of spots. Silica gel (60-120 mesh size) was used as adsorbent in column chromatography, for the purification of compounds. Melting points were determined on automated melting point apparatus (Bamstead Electrothermal, UK). The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Advance spectrometer in DMSO-d_6 and CDCl$_3$. Chemical shift was measured in ppm (δ) and coupling constant (J) was measured in Hz. Mass analysis was performed on LC-MS Spectrometer Model Q-ToF Micro Waters Mass spectra with EI ion source and FTIR spectra was recorded in Bruker ALPHA-T (Germany) ATR /FT-IR instrument.

7.2.2.1 Scheme I: Synthesis of quinolinyl alkyl piperazine derivatives.

Step I Synthesis of quinolinyl alkyl chloride.

S.N	1	2	3	6	7	8	9	10	11
Amino quinoline (AQ)	$3\text{-}NH_2$	$6\text{-}NH_2$	$8\text{-}NH_2$						

Reagents and conditions: (i) TEA, CH_2Cl_2, 0ºC, stirring at rt, 4 h.

Step II Synthesis of quinolinyl piprazine.
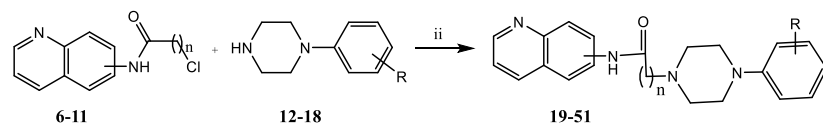
Reagents and conditions: (ii) K_2CO_3, KI, DMF, heat 180 ºC, 6-8 h.

Comp	12	13	14	15	16	17	18
R	$4\text{-}NO_2$	4-F	4-Cl	4-OH	$4\text{-}CH_3$	3-Cl	3-OH

Comp	AQ	n	R	Comp	AQ	n	R
19		1	4-NO$_2$	36		2	3-Cl
20		1	4-F	37		2	3-OH
21		1	4-Cl	38		1	4-NO$_2$
22		1	4-OH	39		1	4-F
23		1	4-CH$_3$	40		1	4-Cl
24		1	4-NO$_2$	41		1	4-OH
25		1	4-F	42		1	4-CH$_3$
26		1	4-Cl	43		2	4-NO$_2$
27		1	4-OH	44		2	4-F
28		1	4-CH$_3$	45		2	4-Cl
29		2	4-NO$_2$	46		2	4-OH
30		2	4-F	47		2	4-CH$_3$
31		2	4-Cl	48		1	3-Cl
32		2	4-OH	49		1	3-OH
33		2	4-CH$_3$	50		2	3-Cl
34		1	3-Cl	51		2	3-OH
35		1	3-OH				

7.2.2.2 Scheme II: Synthesis of quinolinyl piperazine alkyl derivatives

Step I Synthesis of 3/6/8-(piperazin-1-yl)quinoline.
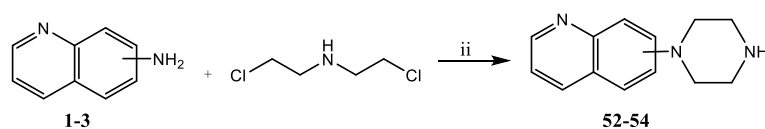
Comp	52	53	54
AQ			

Reagents and conditions: (ii) diethylene glycol monomethyl ether, 150 ºC, 6-12 h.

Step II Synthesis of quinolinyl piperazine alkyl chloride.
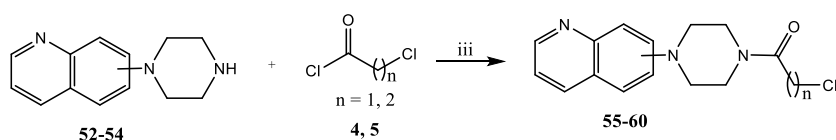
Comp	55	56	57	58	59	60
AQ						

Reagents and conditions: (iii) TEA, CH_2Cl_2, 0 ºC, stirring at rt, 8 h.

Step III Synthesis of aromatic quinolinyl piperazine derivatives.
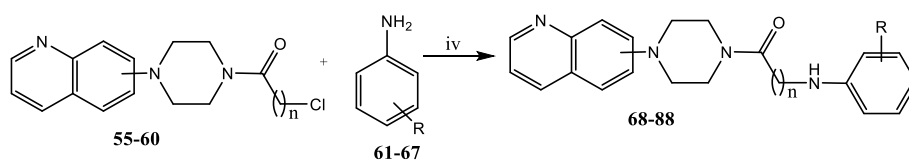
Comp	61	62	63	64	65	66	67
R	4-Cl	4-OH	4-F	4-CH$_3$	3-Cl	3-CH$_3$	3-OH
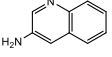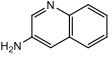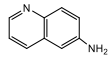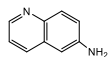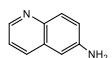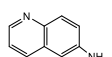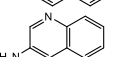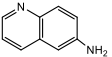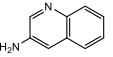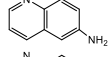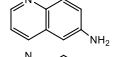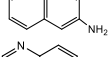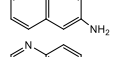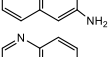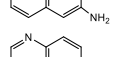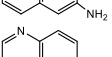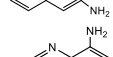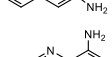
Reagents and conditions: (iv) K_2CO_3, KI, DMF, heat 180 ºC, 9-10 h.

Step IV Synthesis of aliphatic quinolinyl piperazine derivatives.
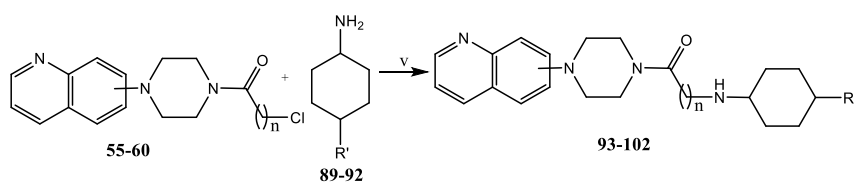
Comp	89	90	91	92
R'	4-CH$_3$	4-OH	4- CH$_2$-OH	4-H

Reagents and conditions: (v) K_2CO_3, KI, DMF, heat 180 ºC, 9-10 h.

Comp	AQ	n	R	Comp	AQ	n	R/R'
68	(3-aminoquinoline)	1	4-Cl	84	(8-amino, 3-amino quinoline)	2	4-CH$_3$
69	(3-aminoquinoline)	1	4-OH	85		2	4-OH
70	(6-aminoquinoline)	1	4-F	86		2	3-Cl
71	(6-aminoquinoline)	1	4-Cl	87		2	3-CH$_3$
72	(6-aminoquinoline)	1	4-CH$_3$	88		2	3-OH
73	(6-aminoquinoline)	1	4-OH	93		2	4-CH$_3$
74	(6-aminoquinoline)	2	4-Cl	94		2	4-OH
75	(6-aminoquinoline)	2	4-CH$_3$	95		2	4-OH
76	(6-aminoquinoline)	2	4-OH	96		2	4-CH$_3$
77	(6-aminoquinoline)	2	3-Cl	97		2	4-CH$_2$-OH
78	(6-aminoquinoline)	2	3-CH$_3$	98		2	4-H
79	(6-aminoquinoline)	2	3-OH	99		2	4-OH
80	(8-aminoquinoline)	1	4-Cl	100		2	4-CH$_3$
81	(8-aminoquinoline)	1	4-CH$_3$	101		2	4-CH$_2$-OH
82	(8-aminoquinoline)	1	4-OH	102		2	4-H
83	(8-aminoquinoline)	2	4-Cl				

7.2.2.3 Scheme I. General procedure for the synthesis of quinolinyl alkyl chloride from 3, 6 and 8 amino quinolines (6-11)

Appropriate aminoquinolines (3 or 6 or 8 derivatives, 500 mg, 3.5 mmol) and TEA (2.4 ml, 17.5 mmol) were taken in dichloromethane (5 ml) to the cold solution, solution of 2-chloroacetyl chloride/ 3-chloropropionyl chloride (1.3 ml, 17.5 mmol)in dichloromethane (5 ml) was added dropwise with stirring over 40 min. Brown-yellow colour solid was obtained after 4 h of stirring removing the solvent under reduced pressure. The crude product was purified over silica gel column chromatography in dichloromethane/ethyl acetate (1:1, v/v) eluent to afford the product(424).

7.2.2.4 General procedure for the synthesis of quinolinyl piperazine (19-51)

Appropriate quinolinyl alkyl chloride (0.0909 mmol, 1 equivalent) was dissolved in dry DMF containing 1-(*o/m*-substitutedphenyl)piperazines (0.0909 mmol, 1 equivalent). Dry potassium carbonate (23.63 mg, 0.1818 mmol, 2 equivalent) and potassium iodide (36.36 mg, 0.2272 mmol, 2.5 equivalent) were added to the reaction mixture. The reaction mixture was refluxed in nitrogen atmosphere for 6-8 h. The crude product was isolated from aqueous phase by using acetate and purified through silica gel column chromatography with hexane/ethyl acetate (1:1, v/v) as eluant to afford the product.

7.2.2.5 Scheme II. General procedure for the synthesis of 3/6/8-(piperazin-1-yl) quinoline by using 3, 6 and 8 amino quinolines (52-54)

Quinolines (3, 6 or 8 amino) (250 mg, 1.73 mmol, 1 equivalent), bis(2-chloroethyl)amine hydrochloride (300 mg, 1.73 mmol, 1 equivalent) and diethylene glycol monomethyl ether (0.75 mL) were heated at 150 ℃ for 6-12 h. in nitrogen atmosphere. The mixture was cooled down to room temperature and dissolved in MeOH (~4 mL), followed by addition of Et_2O(~150 mL). The precipitate was filtered and washed with Et_2O to obtain HCl salt. The HCl salt was further converted to free amine by treatment with Na_2CO_3 solution and extracted with EtOAc (2·). The organic layers were dried with anhydrous Na_2SO_4 and evaporated in vacuum to obtain pure free amine product. The product were purified by column chromatography and obtained in pure form(425).

7.2.2.6 General procedure for the synthesis of quinolinyl piperazine alkyl chloride (55-60)

3/6/8-(piperazin-1-yl)quinoline (3.5 mmol) and TEA (2.4 ml, 17.5 mmol) were taken in dichloromethane (5 ml). The solution was cooled, stirred and added with dichloromethane (5 ml) solution of 2-chloroacetyl chloride/ 3-chloropropionyl chloride

(1.3 ml, 17.5 mmol) dropwise over 40 min. The solvent was removed under reduced pressure after 4 h of stirring to obtain the crude brown-yellow solid product was purified by silica gel column chromatography using dichloromethane/ethyl acetate (1:1, v/v) as eluent.

7.2.2.7 General procedure for the synthesis of aromatic quinolinyl piperazine derivatives (68-88)

3/6/8-(piperazin-1-yl)quinolinyl alkyl chlorides (0.0909 mmol, 1 equivalent) were dissolved in dry DMF containing o/m-substitutedphenyl amine (0.0909 mmol, 1 equivalent). Dry potassium carbonate (23.63 mg, 0.1818 mmol, 2 equivalent) and potassium iodide (36.36 mg, 0.2272 mmol, 2.5 equivalent) were added to the reaction mixture. The reaction was refluxed in nitrogen atmosphere for 6-8 h. The crude products were isolated from aqueous phase by using ethyl acetate and purified by silica gel column chromatography and hexane/ethyl acetate (1:1, v/v) as eluant to afford the products.

7.2.2.8 General procedure for the synthesis of aliphatic quinolinyl piperazine derivatives (93-102)

3/6/8-(piperazin-1-yl)quinolinyl alkyl chlorides (0.0909 mmol, 1 equivalent) were dissolved in dry DMF containing *o/m*-substituted cyclohexan-1-amine (0.0909 mmol, 1 equivalent). Dry potassium carbonate (23.63 mg, 0.1818 mmol, 2 equivalent) and potassium iodide (36.36 mg, 0.2272 mmol, 2.5 equivalent) were added to the reaction mixture. The reaction mixture was refluxed in nitrogen atmosphere for 6-8 h. The crude products were isolated from aqueous phase using ethyl acetate and purified by silica gel column chromatography using hexane/ethyl acetate (1:1, v/v) as eluant to afford the products.

2-(4-(4-nitrophenyl)piperazin-1-yl)-N-(quinolin-3-yl)acetamide (**19**): It was synthesized as per general procedure described earlier in section 7.1.5.4 using 2-chloro-N-(quinolin-3-yl)acetamide (**6**) (20 mg) and 1-(4-nitrophenyl)piperazine (**12**) (18.82 mg) to get compound **19**, yield 65%; mp 278-280 °C; FTIR (KBr) cm^{-1}: 3364 (-NH), 3241 (Ar-str.), 1718 (C=O-str.);^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.84-8.79 (m, 2H, phenyl-C$_3$ -C$_5$), 8.20 (s, 1H, quinolin-C$_2$), 7.62-7.56 (m, 2H, phenyl-C$_2$ -C$_6$), 7.50 (s, 1H, quinolin-C$_4$), 7.21 (d, 1H, J = 10 Hz, quinolin-C$_8$), 7.10-7.05 (m, 2H, quinolin-C$_6$, -C$_7$), 6.91 (d, J = 5 Hz, 1H, quinolin-C$_5$), 3.84 (s, 1H, -NH), 3.51 (s, 2H, -CH$_2$), 3.31 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_3$, -C$_5$), 2.72 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_2$, -C$_6$);^{13}C NMR (125 MHz, DMSO-d$_6$) δ 171.14 (-CO), 159.81 (phenyl-C$_4$), 152.84 (quinolin-C$_3$), 147.64 (quinolin-C$_2$, -C$_9$), 144.34 (phenyl-C$_3$, -C$_5$), 140.84 (quinolin-C$_4$, phenyl-C$_1$), 138.25 (quinolin-C$_{10}$), 137.58 (quinolin-C$_6$, -C$_7$), 128.85 (phenyl-C$_2$, -C$_6$), 127.64 (quinolin-C$_8$), 124.54 (quinolin-C$_5$), 65.45 (-CH$_2$), 56.58 (piperazin-C$_3$, -C$_5$), 54.56 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 392.8 [M$^+$]; calculated for C$_{21}$H$_{21}$N$_5$O$_3$ 391.1.

2-(4-(4-fluorophenyl)piperazin-1-yl)-N-(quinolin-3-yl)acetamide (**20**): It was synthesized as per general procedure described earlier in section 7.1.5.4 using 2-chloro-N-(quinolin-3-yl)acetamide (**6**) (20 mg) and 1-(4-fluorophenyl)piperazine (**13**) (16.37 mg) to get compound **20**, yield 63%; mp 252-254 °C; FTIR (KBr) cm^{-1}: 3354 (-NH), 3274 (Ar-str.), 1710 (C=O-str.);^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.86-8.81 (m, 2H, phenyl-C$_3$-C$_5$), 8.25 (s, 1H, quinolin-C$_2$), 7.60-7.54 (m, 2H, phenyl-C$_2$-C$_6$), 7.51 (s, 1H, quinolin-C$_4$), 7.25 (d, 1H, J = 10 Hz, quinolin-C$_8$), 7.04-7.00 (m, 2H, quinolin-C$_6$, -C$_7$), 6.97 (d, 1H, J = 5 Hz, quinolin-C$_5$), 3.87 (s, 1H, -NH), 3.52 (s, 2H, -CH$_2$), 3.27 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_3$, -C$_5$), 2.81 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_2$, -C$_6$);^{13}C NMR (125 MHz, DMSO-d$_6$) δ 168.84 (-CO), 160.51 (phenyl-C$_4$), 157.94 (quinolin-

C_3), 149.85 (quinolin-C_2, -C_9), 147.64 (phenyl-C_3, -C_5), 142.64 (quinolin-C_4, phenyl-C_1), 139.64 (quinolin-C_{10}), 138.94 (quinolin-C_6, -C_7), 127.64 (phenyl-C_2, -C_6), 127.25 (quinolin-C_8), 125.94 (quinolin-C_5), 66.14 (-CH_2), 56.58 (piperazin-C_3, -C_5), 53.68 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 365.1 [M^+]; calculated for $C_{21}H_{21}FN_4O$ 364.1.

2-(4-(4-chlorophenyl)piperazin-1-yl)-N-(quinolin-3-yl)acetamide (**21**): This was synthesized as per general procedure described earlier in section 7.1.5.4 using 2-chloro-N-(quinolin-3-yl)acetamide (**6**) (20 mg) and 1-(4-chlorophenyl)piperazine (**14**) (17.82 mg) to get compound **21**, yield 66%; mp 282-284 °C; FTIR (KBr) cm^{-1}: 3364 (-NH), 3246 (Ar-str.), 1651 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79-8.74 (m, 2H, phenyl-C_3-C_5), 8.18 (s, 1H, quinolin-C_2), 7.59-7.53 (m, 2H, phenyl-C_2-C_6), 7.42 (s, 1H, quinolin-C_4), 7.19 (d, 1H, J_1 = 10 Hz, quinolin-C_8), 7.08-7.03 (m, 2H, quinolin-C_6, -C_7), 6.85 (d, 1H, J = 5 Hz, quinolin-C_5), 3.91 (s, 1H, -NH), 3.46 (s, 2H, -CH_2), 3.25 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_3, -C_5), 2.65 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_2, -C_6); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.88 (-CO), 160.84 (phenyl-C_4), 155.94 (quinolin-C_3), 148.84 (quinolin-C_2, -C_9), 145.91 (phenyl-C_3, -C_5), 138.87 (quinolin-C_4, phenyl-C_1), 137.95 (quinolin-C_{10}), 136.94 (quinolin-C_6, -C_7), 126.91 (phenyl-C_2, -C_6), 125.67 (quinolin-C_8), 125.67 (quinolin-C_5), 66.44 (-CH_2), 57.95 (piperazin-C_3, -C_5), 53.58 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 381.2 [M^+]; calculated for $C_{21}H_{21}ClN_4O$ 380.1.

2-(4-(4-hydroxyphenyl)piperazin-1-yl)-N-(quinolin-3-yl)acetamide (**22**): The compound **22** was synthesized as per general procedure described earlier in section (7.1.5.4) using 2-chloro-N-(quinolin-3-yl)acetamide (**6**) (20 mg) and 4-(piperazin-1-yl)phenol (**15**) (16.19 mg), yield 67%; mp 241-243 °C; FTIR (KBr) cm^{-1}: 3451 (-OH), 3284 (-NH), 3224 (Ar-str.), 1649 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15 (s, 1H, quinolin-C_2), 8.05-8.00 (m, 2H, phenyl-C_3-C_5), 7.46-7.41 (m, 2H, phenyl-C_2-C_6), 7.32

(s, 1H, quinolin-C_4), 7.11 (d, 1H, J = 10 Hz, quinolin-C_8), 7.00-6.96 (m, 2H, quinolin-C_6, -C_7), 6.71 (d, 1H, J = 5 Hz, quinolin-C_5), 3.84 (s, 1H, -NH), 3.55 (s, 1H, -OH), 3.24 (s, 2H, -CH_2), 3.14 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_3, -C_5), 2.52 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_2, -C_6);^{13}C NMR (125 MHz, DMSO-d_6) δ 168.64 (-CO), 160.94 (phenyl-C_4), 155.91 (quinolin-C_3), 148.62 (quinolin-C_2, -C_9), 145.67 (phenyl-C_3, -C_5), 138.93 (quinolin-C_4, phenyl-C_1), 137.37 (quinolin-C_{10}), 136.62 (quinolin-C_6, -C_7), 126.27 (phenyl-C_2, -C_6), 125.18 (quinolin-C_8), 125.01 (quinolin-C_5), 66.57 (-CH_2), 57.17 (piperazin-C_3, -C_5), 55.71 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 363.1 [M^+]; calculated for $C_{21}H_{22}N_4O_2$ 362.1.

N-(quinolin-3-yl)-2-(4-(p-tolyl)piperazin-1-yl)acetamide (**23**): It was synthesized as per general procedure described earlier in (section 7.1.5.4) using 2-chloro-N-(quinolin-3-yl)acetamide (**6**) (20 mg) and 1-(p-tolyl)piperazine (**15**) (16.01 mg) to get compound **23**, yield 68%; mp 233-235 ºC; FTIR (KBr) cm^{-1}: 3257 (-NH), 3247 (Ar-str.), 1685 (C=O-str.);^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (s, 1H, quinolin-C_2), 7.31 (s, 1H, quinolin-C_4), 7.24 (d, 1H, J = 10 Hz, quinolin-C_8), 7.20-7.17 (m, 2H, phenyl-C_2-C_6), 7.10-7.07 (m, 2H, phenyl-C_3-C_5), 6.98-6.95 (m, 2H, quinolin-C_6, -C_7), 6.64 (d, 1H, J = 5Hz, quinolin-C_5), 3.74 (s, 1H, -NH), 3.67 (s, 1H, -CH_3), 3.57 (s, 2H, -CH_2), 3.24 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_3, -C_5), 2.47 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_2, -C_6);^{13}C NMR (125 MHz, DMSO-d_6) δ 171.85 (-CO), 162.64 (phenyl-C_4), 156.94 (quinolin-C_3), 149.64 (quinolin-C_2, -C_9), 147.97 (phenyl-C_3, -C_5), 137.68 (quinolin-C_4, phenyl-C_1), 136.94 (quinolin-C_{10}), 135.94 (quinolin-C_6, -C_7), 128.94 (phenyl-C_2, -C_6), 126.85 (quinolin-C_8), 126.24 (quinolin-C_5), 64.93 (-2CH_2), 55.49 (piperazin-C_3, -C_5), 54.92 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 361.2 [M^+]; calculated for $C_{22}H_{24}N_4O$ 360.2.

2-(4-(4-nitrophenyl)piperazin-1-yl)-N-(quinolin-6-yl)acetamide (**24**): It was synthesized as per general procedure described in section 7.1.5.4 using quinolin-6-ylcarbamoyl chloride (**7**) (20 mg) and 1-(4-nitrophenyl)piperazine (**12**) (18.82 mg) to get compound **24**, yield 67%; mp 283-285 ºC; FTIR (KBr) cm^{-1}: 3328 (-NH), 3237 (Ar-str.), 1684 (C=O-str.);^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.86-8.81 (m, 2H, phenyl-C$_3$-C$_5$), 8.19 (s, 1H, quinolin-C$_2$), 7.60-7.54 (m, 2H, phenyl-C$_2$-C$_6$), 7.52 (d, 1H, J_1 = 10 Hz, quinolin-C$_7$), 7.34 (s, 1H, quinolin-C$_5$), 7.6-7.02 (m, 2H, quinolin-C$_3$, -C$_8$), 6.87 (d, 1H, J = 10 Hz, quinolin-C$_4$), 3.84 (s, 1H, -NH), 3.51 (s, 2H, -CH$_2$), 3.31 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_3$, -C$_5$), 2.72 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_2$, -C$_6$);^{13}C NMR (125 MHz, DMSO-d$_6$) δ 168.94 (-CO), 159.78 (phenyl-C$_4$), 158.67 (quinolin-C$_6$), 148.84 (quinolin-C$_2$, -C$_9$), 145.49 (phenyl-C$_3$, -C$_5$), 142.57 (quinolin-C$_5$, -C$_7$), 141.46 (quinolin-C$_8$), 138.84 (quinolin-C$_3$), 132.57 (phenyl-C$_2$, -C$_6$), 128.94 (quinolin-C$_{10}$), 125.67 (quinolin-C$_4$, phenyl-C$_1$), 66.57 (-CH$_2$), 57.94 (piperazin-C$_3$, -C$_5$), 55.27 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 392.4 [M$^+$]; calculated for C$_{21}$H$_{21}$N$_5$O$_3$ 391.1.

2-(4-(4-fluorophenyl)piperazin-1-yl)-N-(quinolin-6-yl)acetamide (**25**): This was synthesized as per general procedure described earlier in section 7.1.5.4 using quinolin-6-ylcarbamoyl chloride (**7**) (20 mg) and 1-(4-fluorophenyl)piperazine (**13**) (16.37 mg) to get compound **25**, yield 65%; mp 262-264 ºC; FTIR (KBr) cm^{-1}: 3346 (-NH), 3274 (Ar-str.), 1694 (C=O-str.);^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.88-8.83 (m, 2H, phenyl-C$_3$-C$_5$), 8.21 (s, 1H, quinolin-C$_2$), 7.62-7.56 (m, 2H, phenyl-C$_2$-C$_6$), 7.54 (d, 1H, J_1 = 10 Hz, quinolin-C$_7$), 7.41 (s, 1H, quinolin-C$_5$), 7.08-7.03 (m, 2H, quinolin-C$_3$, -C$_8$), 6.76 (d, 1H, J = 10 Hz, quinolin-C$_4$), 3.72 (s, 1H, -NH), 3.43 (s, 2H, -CH$_2$), 3.40 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_3$, -C$_5$), 2.78 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_2$, -C$_6$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 170.27 (-CO), 161.92 (phenyl-C$_4$), 164.67 (quinolin-C$_6$), 151.37 (quinolin-C$_2$, -C$_9$), 150.37 (phenyl-C$_3$, -C$_5$), 148.37 (quinolin-C$_5$, -C$_7$), 145.34

(quinolin-C_8), 138.75 (quinolin-C_3), 132.27 (phenyl-C_2, -C_6), 129.37 (quinolin-C_{10}), 126.84 (quinolin-C_4, phenyl-C_1), 67.37 (-CH_2), 58.94 (piperazin-C_3, -C_5), 56.71 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 365.1 [M^+]; calculated for $C_{21}H_{21}FN_4O$ 364.1.

2-(4-(4-chlorophenyl)piperazin-1-yl)-N-(quinolin-6-yl)acetamide (**26**): The compound **26** was synthesized as per general procedure described earlier in section (7.1.5.4) using quinolin-6-ylcarbamoyl chloride (**7**) (20 mg) and 1-(4-chlorophenyl)piperazine (**14**) (17.82 mg), yield 66%; mp 278-280 ℃; FTIR (KBr) cm^{-1}: 3425 (-NH), 3228 (Ar-str.), 1715 (C=O-str.);^{1}H NMR (500 MHz, DMSO-d_6) δ 8.84-8.79 (m, 2H, phenyl-C_3-C_5), 8.18 (s, 1H, quinolin-C_2), 7.59-7.53 (m, 2H, phenyl-C_2-C_6), 7.49 (d, 1H, J_1 = 10 Hz, quinolin-C_7), 7.38 (s, 1H, quinolin-C_5), 7.00-6.95 (m, 2H, quinolin-C_3, -C_8), 6.64 (d, 1H, J = 10 Hz, quinolin-C_4), 3.64 (s, 1H, -NH), 3.41 (s, 2H, -CH_2), 3.21 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_3, -C_5), 2.67 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_2, -C_6);^{13}C NMR (125 MHz, DMSO-d_6) δ 164.37 (-CO), 162.27 (phenyl-C_4), 160.71 (quinolin-C_6), 150.18 (quinolin-C_2, -C_9), 149.74 (phenyl-C_3, -C_5), 146.84 (quinolin-C_5, -C_7), 144.34 (quinolin-C_8), 137.81 (quinolin-C_3), 131.81 (phenyl-C_2, -C_6), 128.57 (quinolin-C_{10}), 127.64 (quinolin-C_4, phenyl-C_1), 68.37 (-CH_2), 57.69 (piperazin-C_3, -C_5), 55.91 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 381.2 [M^+]; calculated for $C_{21}H_{21}ClN_4O$ 380.1.

2-(4-(4-hydroxyphenyl)piperazin-1-yl)-N-(quinolin-6-yl)acetamide (**27**): It was synthesized as per general procedure described earlier in section 7.1.5.4 using quinolin-6-ylcarbamoyl chloride (**7**) (20 mg) and 4-(piperazin-1-yl)phenol (**15**) (16.19 mg) to get compound **27**, yield 67%; mp 262-266 ℃; FTIR (KBr) cm^{-1}: 3445 (-NH), 3294 (Ar-str.), 1712 (C=O-str.);^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62-8.58 (m, 2H, phenyl-C_3-C_5), 8.11 (s, 1H, quinolin-C_2), 7.57-7.52 (m, 2H, phenyl-C_2, -C_6), 7.41 (d, 1H, J = 10 Hz, quinolin-C_7), 7.24 (s, 1H, quinolin-C_5), 6.82-6.78 (m, 2H, quinolin-C_3, -C_8), 6.57

(d, 1H, J_1 = 10 Hz, quinolin-C$_4$), 3.32 (s, 1H, -NH), 3.25 (s, 2H, -CH$_2$), 3.14 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_3$, -C$_5$), 2.47 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_2$, -C$_6$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 171.07 (-CO), 163.94 (phenyl-C$_4$), 161.94 (quinolin-C$_6$), 153.94 (quinolin-C$_2$, -C$_9$), 149.67 (phenyl-C$_3$, -C$_5$), 145.64 (quinolin-C$_5$, -C$_7$), 142.84 (quinolin-C$_8$), 138.38 (quinolin-C$_3$), 138.06 (phenyl-C$_2$, -C$_6$), 127.94 (quinolin-C$_{10}$), 126.37 (quinolin-C$_4$, phenyl-C$_1$), 69.85 (-CH$_2$), 58.67 (piperazin-C$_3$, -C$_5$), 56.84 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 363.1 [M$^+$]; calculated for C$_{21}$H$_{22}$N$_4$O$_2$ 362.1.

N-(quinolin-6-yl)-2-(4-(p-tolyl)piperazin-1-yl)acetamide (**28**): It was synthesized as per general procedure described earlier (section 7.1.5.4) with quinolin-6-ylcarbamoyl chloride (**7**) (20 mg) and 1-(p-tolyl)piperazine (**15**) (16.01 mg) to get compound **28**, yield 64%; mp 254-258 ºC; FTIR (KBr) cm^{-1}: 3446 (-NH), 3294 (Ar-str.), 1716 (C=O-str.);^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.02 (s, 1H, quinolin-C$_2$), 7.52-7.48 (m, 2H, phenyl-C$_2$, -C$_6$), 7.32-7.28 (m, 2H, phenyl-C$_3$, -C$_5$), 7.15 (d, 1H, J = 10 Hz, quinolin-C$_7$), 7.08 (s, 1H, quinolin-C$_5$), 6.75-6.70 (m, 2H, quinolin-C$_3$, -C$_8$), 6.45 (d, 1H, J_1 = 10 Hz, quinolin-C$_4$), 3.84 (s, 1H, -NH), 3.32 (s, 2H, -CH$_2$), 3.22 (s, 3H, -CH$_3$), 3.12 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_3$, -C$_5$), 2.58 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_2$, -C$_6$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 169.64 (-CO), 160.84 (quinolin-C$_6$), 152.94 (quinolin-C$_2$, -C$_9$), 150.61 (phenyl-C$_3$, -C$_5$), 146.64 (quinolin-C$_5$, -C$_7$), 141.84 (quinolin-C$_8$), 137.94 (phenyl-C$_2$, -C$_6$), 136.27 (quinolin-C$_3$), 135.84 (phenyl-C$_4$), 132.82 (quinolin-C$_{10}$), 130.84 (quinolin-C$_4$, phenyl-C$_1$), 67.27 (-CH$_2$), 57.52 (piperazin-C$_3$, -C$_5$), 55.74 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 361.1 [M$^+$]; calculated for C$_{22}$H$_{24}$N$_4$O 360.2.

3-(4-(4-nitrophenyl)piperazin-1-yl)-N-(quinolin-6-yl)propanamide (**29**): It was synthesized as per general procedure described earlier in section 7.1.5.4 using quinolin-6-ylcarbamoyl chloride (**7**) (20 mg) and 1-(4-nitrophenyl)piperazine (**12**) (18.82 mg) to get compound **29**, yield 64%; mp 285-287 ºC; FTIR (KBr) cm^{-1}: 3317 (-NH), 3247 (Ar-

str.), 1674 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.82-8.77 (m, 2H, phenyl-C$_3$-C$_5$), 8.22 (s, 1H, quinolin-C$_2$), 7.64-7.58 (m, 2H, phenyl-C$_2$-C$_6$), 7.54 (s, 1H, quinolin-C$_4$), 7.30 (d, 1H, J = 10 Hz, quinolin-C$_8$), 7.5-7.01 (m, 2H, quinolin-C$_6$, -C$_7$), 6.94 (d, 1H, quinolin-C$_5$), 4.07 (s, 1H, -NH), 3.41-3.38 (m, 2H, -CH$_2$), 3.37 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_3$, -C$_5$), 3.12-3.08 (m, 2H, -CH$_2$), 2.72 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_2$, -C$_6$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 168.64 (-CO), 162.84 (phenyl-C$_4$), 158.62 (quinolin-C$_3$), 148.84 (quinolin-C$_2$, -C$_9$), 143.45 (phenyl-C$_3$, -C$_5$), 139.91 (quinolin-C$_4$, phenyl-C$_1$), 137.85 (quinolin-C$_{10}$), 136.72 (quinolin-C$_6$, -C$_7$), 135.47 (phenyl-C$_2$, -C$_6$), 128.75 (quinolin-C$_8$), 126.67 (quinolin-C$_5$), 68.62 (-CH$_2$), 58.57 (piperazin-C$_3$, -C$_5$), 55.37 (piperazin-C$_2$, -C$_6$), 53.48 (-CH$_2$); MS (ESI): *m/z* found 406.5 [M$^+$]; calculated for C$_{22}$H$_{23}$N$_5$O$_3$ 405.1.

3-(4-(4-fluorophenyl)piperazin-1-yl)-N-(quinolin-6-yl)propanamide (**30**): This was synthesized as per general procedure described earlier in section (7.1.5.4) using quinolin-6-ylcarbamoyl chloride (**7**) (20 mg) and 1-(4-fluorophenyl)piperazine (**13**) (16.37 mg) to get compound **30**, yield 67%; mp 291-293 ºC; FTIR (KBr) cm^{-1}: 3384 (-NH), 3262 (Ar-str.), 1728 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.84-8.79 (m, 2H, phenyl-C$_3$-C$_5$), 8.74 (s, 1H, quinolin-C$_2$), 7.62-7.56 (m, 2H, phenyl-C$_2$-C$_6$), 7.49 (s, 1H, quinolin-C$_4$), 7.28 (d, 1H, J = 10 Hz, quinolin-C$_8$), 7.07-7.03 (m, 2H, quinolin-C$_6$, -C$_7$), 6.85 (d, 1H, quinolin-C$_5$), 4.12 (s, 1H, -NH), 3.51-3.49 (m, 2H, -CH$_2$), 3.42 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_3$, -C$_5$), 3.09-3.05 (m, 2H, -CH$_2$), 2.68 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_2$, -C$_6$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 168.94 (-CO), 163.82 (phenyl-C$_4$), 158.64 (quinolin-C$_3$), 149.34 (quinolin-C$_2$, -C$_9$), 144.94 (phenyl-C$_3$, -C$_5$), 140.57 (quinolin-C$_4$, phenyl-C$_1$), 138.28 (quinolin-C$_{10}$), 137.67 (quinolin-C$_6$, -C$_7$), 136.94 (phenyl-C$_2$, -C$_6$), 130.55 (quinolin-C$_8$), 128.64 (quinolin-C$_5$), 70.67 (-CH$_2$), 60.94

(piperazin-C_3, -C_5), 56.46 (piperazin-C_2, -C_6), 55.49 (-CH_2); MS (ESI): *m/z* found 379.5 [M^+]; calculated for $C_{22}H_{23}FN_4O$ 378.1.

3-(4-(4-chlorophenyl)piperazin-1-yl)-N-(quinolin-6-yl)propanamide (**31**): The compound **31** was synthesized as per general procedure described earlier in section (7.1.5.4) using quinolin-6-ylcarbamoyl chloride (**7**) (20 mg) and 1-(4-chlorophenyl)piperazine (**14**) (17.82 mg), yield 65%; mp 275-277 ℃; FTIR (KBr) cm^{-1}: 3337 (-NH), 3267 (Ar-str.), 1684 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79-8.74 (m, 2H, phenyl-C_3-C_5), 8.70 (s, 1H, quinolin-C_2), 7.59-7.52 (m, 2H, phenyl-C_2-C_6), 7.38 (s, 1H, quinolin-C_4), 7.21 (d, 1H, J_1 = 10 Hz, quinolin-C_8), 7.02-6.98 (m, 2H, quinolin-C_6, -C_7), 6.75 (d, 1H, quinolin-C_5), 4.32 (s, 1H, -NH), 3.45-3.42 (m, 2H, -CH_2), 3.27 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_3, -C_5), 3.07-3.03 (m, 2H, -CH_2), 2.54 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_2, -C_6); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.94 (-CO), 167.46 (phenyl-C_4), 164.81 (quinolin-C_3), 159.16 (quinolin-C_2, -C_9), 151.64 (phenyl-C_3, -C_5), 145.64 (quinolin-C_4, phenyl-C_1), 141.67 (quinolin-C_{10}), 138.84 (quinolin-C_6, -C_7), 137.51 (phenyl-C_2, -C_6), 132.47 (quinolin-C_8), 129.49 (quinolin-C_5), 71.37 (-CH_2), 62.49 (piperazin-C_3, -C_5), 57.67 (piperazin-C_2, -C_6), 56.94 (-CH_2); MS (ESI): *m/z* found 395.1 [M^+]; calculated for $C_{22}H_{23}ClN_4O$ 394.1.

3-(4-(4-hydroxyphenyl)piperazin-1-yl)-N-(quinolin-6-yl)propanamide (**32**): It was synthesized as per general procedure described earlier in section 7.1.5.4 using quinolin-6-ylcarbamoyl chloride (**7**) (20 mg) and 4-(piperazin-1-yl)phenol (**15**) (16.19 mg) to get compound **32**, yield 65%; mp 231-233 ℃; FTIR (KBr) cm^{-1}: 3464 (-NH), 3254 (Ar-str.), 1657 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63-8.59 (m, 2H, phenyl-C_3-C_5), 8.12 (s, 1H, quinolin-C_2), 7.58-7.54 (m, 2H, phenyl-C_2, -C_6), 7.50 (d, 1H, J_1 = 10 Hz, quinolin-C_7), 7.31 (s, 1H, quinolin-C_5), 6.84-6.80 (m, 2H, quinolin-C_3, -C_8), 6.59 (d, 1H, J_1 = 10 Hz, quinolin-C_4), 3.40 (s, 1H, -NH), 3.34-3.31 (m, 2H, -CH_2), 3.21 (t,

4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_3$, -C$_5$), 3.02-2.97 (m, 2H, -CH$_2$), 2.52 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_2$, -C$_6$), ; ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 168.48 (-CO), 164.48 (phenyl-C$_4$), 162.15 (quinolin-C$_6$), 157.57 (quinolin-C$_2$, -C$_9$), 150.48 (phenyl-C$_3$, -C$_5$), 148.67 (quinolin-C$_5$, -C$_7$), 147.54 (quinolin-C$_8$), 142.48 (quinolin-C$_3$), 137.46 (phenyl-C$_2$, -C$_6$), 126.49 (quinolin-C$_{10}$), 125.68 (quinolin-C$_4$, phenyl-C$_1$), 68.94 (-CH$_2$), 59.48 (piperazin-C$_3$, -C$_5$), 57.66 (piperazin-C$_2$, -C$_6$), 54.49 (-CH$_2$); MS (ESI): *m/z* found 377.1 [M$^+$]; calculated for C$_{22}$H$_{24}$N$_4$O$_2$ 376.1.

N-(quinolin-6-yl)-3-(4-(p-tolyl)piperazin-1-yl)propanamide (**33**): It was also synthesized as per general procedure described earlier in section 7.1.5.4 using quinolin-6-ylcarbamoyl chloride (**7**) (20 mg) and 1-(p-tolyl)piperazine (**15**) (16.01 mg) to get compound **33**, yield 65%; mp 233-235 ºC; FTIR (KBr) cm^{-1}: 3364 (-NH), 3254 (Ar-str.), 1694 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 7.90 (s, 1H, quinolin-C$_2$), 7.40 (s, 1H, quinolin-C$_4$), 7.21 (d, 1H, $J_1 = 10$ Hz, quinolin-C$_8$), 7.19-7.15 (m, 2H, phenyl-C$_2$, -C$_6$), 7.12-7.09 (m, 2H, phenyl-C$_3$-C$_5$), 6.95-6.89 (m, 2H, quinolin-C$_6$, -C$_7$), 6.71 (d, $J = 10$ Hz, 1H, quinolin-C$_5$), 3.65 (s, 1H, -NH), 3.67 (s, 3H, -CH$_3$), 3.34-3.32 (m, 2H, -CH$_2$), 3.18 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_3$, -C$_5$), 2.98-2.95 (m, 2H, -CH$_2$), 2.38 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_2$, -C$_6$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 169.49 (-CO), 168.13 (phenyl-C$_4$), 157.46 (quinolin-C$_3$), 150.92 (quinolin-C$_2$, -C$_9$), 146.47 (phenyl-C$_3$, -C$_5$), 139.67 (quinolin-C$_4$, phenyl-C$_1$), 137.38 (quinolin-C$_{10}$), 136.95 (quinolin-C$_6$, -C$_7$), 127.46 (phenyl-C$_2$, -C$_6$), 125.46 (quinolin-C$_8$), 125.13 (quinolin-C$_5$), 63.49 (-2CH$_2$), 59.65 (CH$_3$) 56.94 (piperazin-C$_3$, -C$_5$), 53.61 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 375.2 [M$^+$]; calculated for C$_{23}$H$_{26}$N$_4$O 374.2.

2-(4-(3-chlorophenyl)piperazin-1-yl)-N-(quinolin-6-yl)acetamide (**34**): It was synthesized as per general procedure described earlier in (section 7.1.5.4) using quinolin-6-ylcarbamoyl chloride (**7**) (20 mg) and 1-(3-chlorophenyl)pipera-zine (**14**)

(17.82 mg) to get compound **34** yield 65 %; mp 238-241 ºC; FTIR (KBr) cm^{-1}: 3345 (-NH), 3267 (Ar-str.), 1684 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 7.90 (s, 1H, quinolin-C$_2$), 7.40 (s, 1H, quinolin-C$_4$), 7.21 (d, 1H, J = 10 Hz, quinolin-C$_8$),7.19-7.15 (m, 2H, phenyl-C$_2$, -C$_4$), 7.12-7.09 (m, 2H, phenyl-C$_5$-C$_6$), 6.95-6.89 (m, 2H, quinolin-C$_3$, -C$_7$), 6.71 (d, 1H, J = 10 Hz, quinolin-C$_5$), 3.65 (s, 1H, -NH), 3.34-3.31 (m, 2H, -CH$_2$), 3.18 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_3$, -C$_5$), 2.98-2.95 (m, 2H, -CH$_2$), 2.38 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_2$, -C$_6$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 169.49 (-CO), 168.13 (phenyl-C$_4$), 157.46 (quinolin-C$_3$), 150.92 (quinolin-C$_2$, -C$_9$), 146.47 (phenyl-C$_3$, -C$_5$), 139.67 (quinolin-C$_4$, phenyl-C$_1$), 137.38 (quinolin-C$_{10}$), 136.95 (quinolin-C$_6$, -C$_7$), 127.46 (phenyl-C$_2$, -C$_6$), 125.46 (quinolin-C$_8$), 125.13 (quinolin-C$_5$), 63.49 (-CH$_2$), 56.94 (piperazin-C$_3$, -C$_5$), 53.61 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 375.2 [M$^+$]; calculated for C$_{23}$H$_{26}$N$_4$O 374.2.

2-(4-(3-hydroxyphenyl)piperazin-1-yl)-N-(quinolin-6-yl)acetamide   (**35**):   It   was synthesized as per general procedure described earlier in (section 7.1.5.4) using quinolin-6-ylcarbamoyl chloride (**7**) (20 mg) and 1-(3-hydroxyphenyl)pipera-zine (**18**) (17.18 mg) to get compound **35** yield 63 %; mp 251-253 ºC; FTIR (KBr) cm^{-1}: 3364 (-NH), 3216 (Ar-str.), 1694 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 7.86 (s, 1H, quinolin-C$_2$), 7.41 (s, 1H, quinolin-C$_4$), 7.34 (d, 1H, J = 10 Hz, quinolin-C$_8$),7.20-7.16 (m, 2H, phenyl-C$_2$, -C$_4$), 7.14-7.11 (m, 2H, phenyl-C$_5$-C$_6$), 6.96-6.90 (m, 2H, quinolin-C$_3$, -C$_7$), 6.64 (d, 1H, J = 10 Hz, quinolin-C$_5$), 3.49 (s, 1H, -NH), 3.41 (s, 1H, -OH), 3.32-3.30 (m, 2H, -CH$_2$), 3.15 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_3$, -C$_5$), 2.99-2.97 (m, 2H, -CH$_2$), 2.15 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_2$, -C$_6$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 169.64 (-CO), 169.18 (phenyl-C$_4$), 158.84 (quinolin-C$_3$), 150.34 (quinolin-C$_2$, -C$_9$), 146.94 (phenyl-C$_3$, -C$_5$), 139.31 (quinolin-C$_4$, phenyl-C$_1$), 137.64 (quinolin-C$_{10}$), 136.12 (quinolin-C$_6$, -C$_7$), 127.74 (phenyl-C$_2$, -C$_6$), 125.84 (quinolin-

C$_8$), 125.74 (quinolin-C$_5$), 64.31 (-CH$_2$), 57.92 (piperazin-C$_3$, -C$_5$), 54.31 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 363.1 [M$^+$]; calculated for C$_{21}$H$_{22}$N$_4$O$_2$ 362.1.

3-(4-(3-chlorophenyl)piperazin-1-yl)-N-(quinolin-6-yl)propanamide (**36**): It was synthesized as per general procedure described earlier in (section 7.1.5.4) using 3-chloro-N-(quinolin-6-yl)propanamide (**10**) (20 mg) and 1-(3-chlorophenyl)pipera-zine (**14**) (17.82 mg) to get compound **36** yield 65 %; mp 262-264 ºC; FTIR (KBr) cm^{-1}: 3384 (-NH), 3267 (Ar-str.), 1634 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 7.64 (s, 1H, quinolin-C$_2$), 7.34 (s, 1H, quinolin-C$_4$), 7.64 (d, 1H, *J* = 10 Hz, quinolin-C$_8$),7.21-7.17 (m, 2H, phenyl-C$_2$, -C$_4$), 7.14-7.11 (m, 2H, phenyl-C$_5$-C$_6$), 6.96-6.90 (m, 2H, quinolin-C$_3$, -C$_7$), 6.73 (d, 1H, *J* = 10 Hz, quinolin-C$_5$), 3.67 (s, 1H, -NH), 3.36-3.33 (m, 2H, -CH$_2$), 3.12 (t, 4H, *J$_1$* = *J$_2$* = 5 Hz, piperazin-C$_3$, -C$_5$), 2.99-2.94 (m, 4H, -CH$_2$), 2.48 (t, 4H, *J$_1$* = *J$_2$* = 5 Hz, piperazin-C$_2$, -C$_6$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 170.68 (-CO), 168.46 (phenyl-C$_4$), 158.34 (quinolin-C$_3$), 151.46 (quinolin-C$_2$, -C$_9$), 146.74 (phenyl-C$_3$, -C$_5$), 139.13 (quinolin-C$_4$, phenyl-C$_1$), 138.48 (quinolin-C$_{10}$), 136.84 (quinolin-C$_6$, -C$_7$), 128.46 (phenyl-C$_2$, -C$_6$), 125.15 (quinolin-C$_8$), 126.42 (quinolin-C$_5$), 63.17 (-2CH$_2$), 56.94 (piperazin-C$_3$, -C$_5$), 53.37 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 395.1 [M$^+$]; calculated for C$_{22}$H$_{23}$ClN$_4$O 394.1.

3-(4-(3-hydroxyphenyl)piperazin-1-yl)-N-(quinolin-6-yl)propanamide (**37**): It was synthesized as per general procedure described earlier in (section 7.1.5.4) using 3-chloro-N-(quinolin-6-yl)propanamide (**10**) (20 mg) and 1-(3-hydroxyphenyl)pipera-zine (**18**) (17.18 mg) to get compound **37** yield 66 %; mp 261-263 ºC; FTIR (KBr) cm^{-1}: 3348 (-NH), 3284 (Ar-str.), 1674 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 7.88 (s, 1H, quinolin-C$_2$), 7.51 (s, 1H, quinolin-C$_4$), 7.40 (d, 1H, *J* = 10 Hz, quinolin-C$_8$),7.19-7.15 (m, 2H, phenyl-C$_2$, -C$_4$), 7.15-7.12 (m, 2H, phenyl-C$_5$-C$_6$), 6.97-6.91 (m, 2H, quinolin-C$_3$, -C$_7$), 6.65 (d, 1H, *J* = 10 Hz, quinolin-C$_5$), 3.47 (s, 1H, -NH), 3.41 (s,

1H, -OH), 3.33-3.29 (m, 4H, -CH$_2$), 3.13 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_3$, -C$_5$), 2.97-2.95 (m, 2H, -CH$_2$), 2.16 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_2$, -C$_6$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 170.84 (-CO), 169.24 (phenyl-C$_4$), 158.21 (quinolin-C$_3$), 150.13 (quinolin-C$_2$, -C$_9$), 146.64 (phenyl-C$_3$, -C$_5$), 138.34 (quinolin-C$_4$, phenyl-C$_1$), 137.35 (quinolin-C$_{10}$), 136.63 (quinolin-C$_6$, -C$_7$), 127.76 (phenyl-C$_2$, -C$_6$), 125.22 (quinolin-C$_8$), 125.84 (quinolin-C$_5$), 64.25 (-2CH$_2$), 56.96 (piperazin-C$_3$, -C$_5$), 55.24 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 377.1 [M$^+$]; calculated for C$_{22}$H$_{24}$N$_4$O$_2$ 376.1.

2-(4-(4-nitrophenyl)piperazin-1-yl)-N-(quinolin-8-yl)acetamide (**38**): This was synthesized as per general procedure described earlier in section 7.1.5.4 using 2-chloro-N-(quinolin-8-yl)acetamide (**8**) (20 mg) and 1-(4-nitrophenyl)piperazine (**12**) (18.82 mg) to get compound **38**, yield 67%; mp 281-283 ℃; FTIR (KBr) cm^{-1}: 3314 (-NH), 3125 (Ar-str.), 1715 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 11.49 (s, 1H, -CONH), 8.83-8.80 (m, 2H, phenyl-C$_3$-C$_5$), 8.19 (d, 1H, $J = 10$ Hz, quinolin-C$_2$), 7.59-7.54 (m, 2H, phenyl-C$_2$-C$_6$), 7.47 (dd, 1H, $J_1 = J_2 = 5$ Hz, quinolin-C$_7$), 7.45-7.44 (m, 2H, quinolin-C$_3$, -C$_6$), 6.97-6.49 (m, 2H, quinolin-C$_4$, -C$_5$), 3.42 (s, 2H, -CH$_2$), 3.35 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_3$, -C$_5$), 2.90 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_2$, -C$_6$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 168.18 (-CO), 158.28 (phenyl-C$_4$), 149.98 (quinolin-C$_8$), 147.53 (quinolin-C$_2$, -C$_9$), 139.71 (phenyl-C$_3$, -C$_5$), 138.21 (quinolin-C$_7$), 136.86 (quinolin-C$_3$, -C$_6$), 127.42 (phenyl-C$_2$, -C$_6$), 125.06 (phenyl-C$_6$), 120.65 (quinolin-C$_4$, C$_5$), 119.56 (, phenyl-C$_1$), 118.59 (quinolin-C$_{10}$), 60.23 (-CH$_2$), 51.54 (piperazin-C$_3$, -C$_5$), 50.36 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 392.4 [M$^+$]; calculated for C$_{21}$H$_{21}$N$_5$O$_3$ 391.1.

2-(4-(4-fluorophenyl)piperazin-1-yl)-N-(quinolin-8-yl)acetamide (**39**): It was synthesized as per general procedure described earlier in section 7.1.5.4 using 2-chloro-N-(quinolin-8-yl)acetamide (**8**) (20 mg) and 1-(4-fluorophenyl)piperazine (**13**) (16.37

mg) to get compound **39**, yield 64%; mp 251-254 ºC; FTIR (KBr) cm^{-1}: 3250 (-NH), 3024 (Ar-str.), 1681 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.84-8.80 (m, 2H, phenyl-C$_3$-C$_5$), 8.19 (d, 1H, J = 10 Hz, quinolin-C$_2$), 7.60-7.54 (m, 2H, phenyl-C$_2$-C$_6$), 7.47 (dd, 1H, J_1 = J_2= 5 Hz, quinolin-C$_7$), 7.05-7.01 (m, 2H, quinolin-C$_3$, -C$_6$), 6.98-6.95 (m, 2H, quinolin-C$_4$, -C$_5$), 3.51 (s, 1H, -NH), 3.39 (s, 2H, -CH$_2$), 3.35 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_3$, -C$_5$), 2.90 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_2$, -C$_6$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 170.14 (-CO), 159.14 (phenyl-C$_4$), 148.28 (quinolin-C$_8$), 147.84 (quinolin-C$_2$, -C$_9$), 140.58 (phenyl-C$_3$, -C$_5$), 139.41 (quinolin-C$_7$), 137.54 (quinolin-C$_3$, -C$_6$), 129.28 (phenyl-C$_2$, -C$_6$), 128.28 (quinolin-C$_4$, C$_5$, phenyl-C$_1$), 127.16 (quinolin-C$_{10}$), 63.17 (-CH$_2$), 54.14 (piperazin-C$_3$, -C$_5$), 52.14 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 364.9 [M$^+$]; calculated for C$_{21}$H$_{21}$FN$_4$O 364.1.

2-(4-(4-chlorophenyl)piperazin-1-yl)-N-(quinolin-8-yl)acetamide (**40**): The compound **40** was synthesized as per general procedure described earlier in section 7.1.5.4 using 2-chloro-N-(quinolin-8-yl)acetamide (**8**) (20 mg) and 1-(4-chlorophenyl)piperazine (**14**) (17.82 mg), yield 66%; mp 262-264 ºC; FTIR (KBr) cm^{-1}: 3298 (-NH), 3152 (Ar-str.), 1714 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.82-8.78 (m, 2H, phenyl-C$_3$-C$_5$), 8.17 (d, 1H, J = 10 Hz, quinolin-C$_2$), 7.57-7.51 (m, 2H, phenyl-C$_2$-C$_6$), 7.45 (dd, 1H, J_1= J_2 = 5 Hz, quinolin-C$_7$), 7.03-7.00 (m, 2H, quinolin-C$_3$, -C$_6$), 6.95-6.92 (m, 2H, quinolin-C$_4$, -C$_5$), 3.49 (s, 1H, -NH), 3.37 (s, 2H, -CH$_2$), 3.34 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_3$, -C$_5$), 2.87 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_2$, -C$_6$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 169.28 (-CO), 156.14 (phenyl-C$_4$), 146.85 (quinolin-C$_8$), 145.17 (quinolin-C$_2$, -C$_9$), 140.15 (phenyl-C$_3$, -C$_5$), 138.58 (quinolin-C$_7$), 136.17 (quinolin-C$_3$, -C$_6$), 129.47 (phenyl-C$_2$, -C$_6$), 128.84 (quinolin-C$_4$, C$_5$, phenyl-C$_1$), 128.01 (quinolin-C$_{10}$), 64.17 (-CH$_2$), 54.47 (piperazin-C$_3$, -C$_5$), 52.85 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 381.6 [M$^+$]; calculated for C$_{21}$H$_{21}$ClN$_4$O 380.1.

2-(4-(4-hydroxyphenyl)piperazin-1-yl)-N-(quinolin-8-yl)acetamide (**41**): It was synthesized as per general procedure described earlier in section 7.1.5.4 using 2-chloro-N-(quinolin-8-yl)acetamide (**8**) (20 mg) and 4-(piperazin-1-yl)phenol (**15**) (16.19 mg) to get compound **41**, yield 63%; mp 241-243 ºC; FTIR (KBr) cm^{-1}: 3458 (-OH), 3217 (-NH), 3148 (Ar-str.), 1684 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.88 (d, 1H, J = 10 Hz, quinolin-C$_2$), 8.68 (d, 1H, J = 10 Hz, quinolin-C$_7$), 8.41 (d, 1H, J = 10 Hz, quinolin-C$_4$), 7.68 (d, 1H, J = 10 Hz, quinolin-C$_5$), 7.62-7.58 (m, 2H, quinolin-C$_3$, -C$_6$), 6.96 (d, 2H, J = 10 Hz, phenyl-C$_3$, -C$_5$), 6.86 (d, 2H, J = 10 Hz, phenyl-C$_2$, -C$_6$), 3.70 (s, 2H, -CH$_2$), 3.51 (s, 1H, -NH), 3.33 (s, 1H, -OH), 3.19 (s, 4H, piperazin-C$_3$, -C$_5$), 2.76 (s, 4H, piperazin-C$_2$, -C$_6$);^{13}C NMR (125 MHz, DMSO-d$_6$) δ 166.15 (-CO), 144.85 (quinolin-C$_8$), 143.57 (quinolin-C$_2$, -C$_9$), 141.28 (phenyl-C$_4$), 140.14 (phenyl-C$_3$, -C$_5$), 137.48 (quinolin-C$_7$), 135.74 (phenyl-C$_1$), 134.84 (quinolin-C$_3$, -C$_6$), 127.57 (phenyl-C$_2$, -C$_6$), 125.84 (quinolin-C$_4$, -C$_5$), 124.42 (quinolin-C$_{10}$), 58.41 (-CH$_2$), 51.58 (piperazin-C$_3$, -C$_5$), 50.28 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 363.2 [M$^+$]; calculated for C$_{21}$H$_{22}$N$_4$O$_2$ 362.1.

N-(quinolin-8-yl)-2-(4-(p-tolyl)piperazin-1-yl)acetamide (**42**): It was synthesized as per general procedure described earlier in section 7.1.5.4 using 2-chloro-N-(quinolin-8-yl)acetamide (**8**) (20 mg) and 1-(p-tolyl)piperazine (**15**) (16.01 mg) to get compound **42**, yield 60%; mp 271-273 ºC; FTIR (KBr) cm^{-1}: 3328 (-NH), 3251 (Ar-str.), 1695 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.52 (d, 1H, J = 10 Hz, quinolin-C$_2$), 8.41 (d, 1H, J = 10 Hz, quinolin-C$_7$), 8.32 (d, 1H, J = 10 Hz, quinolin-C$_4$), 7.60 (d, 1H, J = 10 Hz, quinolin-C$_5$), 7.59-7.55 (m, 2H, quinolin-C$_3$, -C$_6$), 6.81 (d, 2H, J = 10 Hz, phenyl-C$_2$, -C$_6$), 6.77 (d, 2H, J = 10 Hz, phenyl-C$_3$, -C$_5$), 3.64 (s, 2H, -CH$_2$), 3.10 (s, 4H, piperazin-C$_3$, -C$_5$), 2.68 (s, 4H, piperazin-C$_2$, -C$_6$), 2.47 (s, 3H, - CH$_3$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 168.19 (-CO), 146.84 (quinolin-C$_8$), 144.24 (quinolin-C$_2$, -C$_9$),

143.42 (phenyl-C_1), 142.91 (phenyl-C_3, -C_5), 138.65 (quinolin-C_7), 135.64 (quinolin-C_3, -C_6), 125.82 (phenyl-C_2, -C_6), 125.61 (quinolin-C_4, -C_5), 124.34 (quinolin-C_{10}), 122.95 (phenyl-C_4), 57.54 (-CH_2), 50.45 (piperazin-C_3, -C_5), 48.64 (piperazin-C_2, -C_6), 31.07 (-CH_3); MS (ESI): *m/z* found 361.0 [M^+]; calculated for $C_{22}H_{24}N_4O$ 360.2.

3-(4-(4-nitrophenyl)piperazin-1-yl)-N-(quinolin-8-yl)propanamide (**43**): This was synthesized as per general procedure described earlier in section 7.1.5.4 using 3-chloro-N-(quinolin-8-yl)propanamide (**11**) (21.27 mg) and 1-(4-nitrophenyl)piperazine (**12**) (18.82 mg) to get compound **43**, yield 69%; mp 277-279 ℃; FTIR (KBr) cm^{-1}: 3374 (-NH), 3254 (Ar-str.), 1645 (C=O-str.);^{1}H NMR (500 MHz, DMSO-d_6) δ 8.84-8.79 (m, 2H, phenyl-C_3-C_5), 8.21 (d, 1H, *J* = 10 Hz, quinolin-C_2), 7.57-7.52 (m, 2H, phenyl-C_2-C_6), 7.47 (dd, 1H, *J* = 10 Hz, quinolin-C_7), 7.04-7.00 (m, 2H, quinolin-C_3, -C_6), 6.89-6.85 (m, 2H, quinolin-C_4, -C_5), 3.43-3.41 (m, 2H, -CH_2), 3.25 (s, 1H, -NH), 3.15 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_3, -C_5), 3.00-2.96 (m, 2H, -CH_2), 2.72 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_2, -C_6);^{13}C NMR (125 MHz, DMSO-d_6) δ 169.84 (-CO), 159.45 (phenyl-C_4), 152.12 (quinolin-C_8), 147.54 (quinolin-C_2, -C_9), 145.94 (phenyl-C_3, -C_5), 140.54 (quinolin-C_7), 138.54 (quinolin-C_3, -C_6), 129.54 (phenyl-C_2, -C_6), 127.84 (quinolin-C_4, -C_5, phenyl-C_1), 126.61 (quinolin-C_{10}), 68.54 (-CH_2), 57.64 (piperazin-C_3, -C_5), 54.94 (piperazin-C_2, -C_6), 52.32 (-CH_2); MS (ESI): *m/z* found 406.2 [M^+]; calculated for $C_{22}H_{23}N_5O_3$ 405.1.

2-(4-(4-fluorophenyl)piperazin-1-yl)-N-(quinolin-8-yl)acetamide (**44**): The compound was synthesized as per general procedure described earlier in section 7.1.5.4 using 3-chloro-N-(quinolin-8-yl)propanamide (**11**) (21.27 mg) and 1-(4-fluorophenyl)pipera-zine (**13**) (16.37 mg) to get compound **44**, yield 63%; mp 285-287 ℃; FTIR (KBr) cm^{-1}: 3361 (-NH), 3164 (Ar-str.), 1687 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.84-8.79 (m, 2H, phenyl-C_3-C_5), 8.23 (d, 1H, *J* = 10 Hz, quinolin-C_2), 7.63-7.57 (m, 2H,

phenyl-C_2-C_6), 7.50 (dd, 1H, $J_1 = J_2 = 5$ Hz, quinolin-C_7), 7.00-6.96 (m, 2H, quinolin-C_3, -C_6), 6.93-6.90 (m, 2H, quinolin-C_4, -C_5), 3.60 (s, 1H, -NH), 3.41-3.38 (m, 2H, -CH_2), 3.25 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_3, -C_5), 2.94 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_2, -C_6), 2.41-2.37 (m, 2H, -CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.54 (-CO), 160.18 (phenyl-C_4), 151.15 (quinolin-C_8), 148.54 (quinolin-C_2, -C_9), 145.84 (phenyl-C_3, -C_5), 140.84 (quinolin-C_7), 137.94 (quinolin-C_3, -C_6), 131.84 (phenyl-C_2, -C_6), 128.51 (quinolin-C_4, -C_5), 128.02 (quinolin-C_{10}), 64.81 (-2CH_2), 52.41 (piperazin-C_3, -C_5), 53.45 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 379.2 [M$^+$]; calculated for $C_{22}H_{23}FN_4O$ 378.1.

3-(4-(4-chlorophenyl)piperazin-1-yl)-N-(quinolin-8-yl)propanamide (**45**): It was synthesized as per general procedure described earlier (section 7.1.5.4) using 3-chloro-N-(quinolin-8-yl)propanamide (**11**) (21.27 mg) and 1-(4-chlorophenyl)pipera-zine (**14**) (17.82 mg) to get compound **45**, yield 69%; mp 258-260 ℃; FTIR (KBr) cm^{-1}: 3358 (-NH), 3258 (Ar-str.), 1727 (C=O-str.); ^1H NMR (500 MHz, DMSO-d_6) δ 8.81-8.76 (m, 2H, phenyl-C_3-C_5), 8.18 (d, 1H, $J = 10$ Hz, quinolin-C_2), 7.60-7.53 (m, 2H, phenyl-C_2-C_6), 7.48 (dd, 1H, $J_1 = J_2 = 5$ Hz, quinolin-C_7), 7.03-6.98 (m, 2H, quinolin-C_3, -C_6), 6.90-6.88 (m, 2H, quinolin-C_4, -C_5), 3.57 (s, 1H, -NH), 3.38-3.35 (m, 2H, -CH_2), 3.23 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_3, -C_5), 2.84 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_2, -C_6), 2.37-2.33 (m, 2H, -CH_2) ; ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.08 (-CO), 158.81 (phenyl-C_4), 149.54 (quinolin-C_8), 146.81 (quinolin-C_2, -C_9), 144.81 (phenyl-C_3, -C_5), 139.41 (quinolin-C_7), 138.94 (quinolin-C_3, -C_6), 130.68(phenyl-C_2, -C_6), 127.64 (quinolin-C_4, -C_5, phenyl C_1), 127.11 (quinolin-C_{10}), 63.74 (-2CH_2), 51.81 (piperazin-C_3, -C_5), 50.71 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 395.2 [M$^+$]; calculated for $C_{22}H_{23}ClN_4O$ 394.1.

3-(4-(4-hydroxyphenyl)piperazin-1-yl)-N-(quinolin-8-yl)propanamide (**46**): It was synthesized as per general procedure described earlier (section 7.1.5.4) using 3-chloro-N-(quinolin-8-yl)propanamide (**11**) (21.27 mg) and 4-(piperazin-1-yl)phenol (**15**) (16.19 mg) to get compound **46**, yield 62%; mp 239-241 ºC; FTIR (KBr) cm^{-1}: 3481 (-OH), 3197 (-NH), 3128 (Ar-str.), 1661 (C=O-str.);^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.78 (d, 1H, J = 10 Hz, quinolin-C$_2$), 8.65 (d, 1H, J = 10 Hz, quinolin-C$_7$), 8.37 (d, 1H, J = 10 Hz, quinolin-C$_4$), 7.65 (d, 1H, J = 10 Hz, quinolin-C$_5$), 7.60-7.57 (m, 2H, quinolin-C$_3$, -C$_6$), 6.87 (d, 2H, J = 10 Hz, phenyl-C$_3$, -C$_5$), 6.82 (d, 2H, J = 10 Hz, phenyl-C$_2$, -C$_6$), 3.66 (s, 2H, -CH$_2$), 3.52 (s, 1H, -NH), 3.24 (s, 1H, -OH), 3.04 (s, 4H, piperazin-C$_3$, -C$_5$), 2.64 (s, 4H, piperazin-C$_2$, -C$_6$), 2.35-2.31 (m, 2H, -CH$_2$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 168.61 (-CO), 147.64 (quinolin-C$_8$), 145.64 (quinolin-C$_2$, -C$_9$), 142.52 (phenyl-C$_4$), 139.74 (phenyl-C$_3$, -C$_5$), 136.27 (quinolin-C$_7$), 134.91 (phenyl-C$_1$), 133.45 (quinolin-C$_3$, -C$_6$), 128.64 (phenyl-C$_2$, -C$_6$), 126.31 (quinolin-C$_4$, -C$_5$), 123.94 (quinolin-C$_{10}$), 57.54 (-CH$_2$), 52.84 (piperazin-C$_3$, -C$_5$), 51.84 (piperazin-C$_2$, -C$_6$) 47.07(-CH$_2$); MS (ESI): *m/z* found 377.2 [M$^+$]; calculated for C$_{22}$H$_{24}$N$_4$O$_2$ 376.1.

N-(quinolin-8-yl)-3-(4-(p-tolyl)piperazin-1-yl)propanamide (**47**): This was synthesized as per general procedure described earlier in section 7.1.5.4 using 3-chloro-N-(quinolin-8-yl)propanamide (**11**) (21.27 mg) and 1-(p-tolyl)piperazine (**15**) (16.01 mg) to get compound **47**, yield 63%; mp 262-264 ºC; FTIR (KBr) cm^{-1}: 3354 (-NH), 3254 (Ar-str.), 1684 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.49 (d, 1H, J = 10 Hz, quinolin-C$_2$), 8.38 (d, 1H, J = 10 Hz, quinolin-C$_7$), 8.30 (d, 1H, J = 10 Hz, quinolin-C$_4$), 7.64 (d, 1H, J = 10 Hz, quinolin-C$_5$), 7.60-7.57 (m, 2H, quinolin-C$_3$, -C$_6$), 6.78 (d, 2H, J = 10 Hz, phenyl-C$_2$, -C$_6$), 6.75 (d, 2H, J = 10 Hz, phenyl-C$_3$, -C$_5$), 3.71 (s, 2H, -CH$_2$), 3.23 (s, 4H, piperazin-C$_3$, -C$_5$), 2.62 (s, 4H, piperazin-C$_2$, -C$_6$), 2.42 (s, 3H, - CH$_3$), 2.37-2.34 (m, 2H, -CH$_2$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 169.55 (-CO), 147.94

(quinolin-C_8), 145.84 (quinolin-C_2, -C_9), 144.84 (phenyl-C_1), 143.45 (phenyl-C_3, -C_5), 139.54 (quinolin-C_7), 136.57 (quinolin-C_3, -C_6), 126.74 (phenyl-C_2, -C_6), 124.84 (quinolin-C_4, -C_5), 123.84 (quinolin-C_{10}), 122.84 (phenyl-C_4), 59.57 (-CH_2), 48.84 (piperazin-C_3, -C_5), 47.84 (piperazin-C_2, -C_6), 46.94(-CH_2), 30.91 (-CH_3); MS (ESI): *m/z* found 375.1 [M^+]; calculated for $C_{23}H_{26}N_4O$ 374.2.

2-(4-(3-chlorophenyl)piperazin-1-yl)-N-(quinolin-8-yl)acetamide (**48**): It was synthesized as per general procedure described earlier in section 7.1.5.4 using 2-chloro-N-(quinolin-8-yl)acetamide (**8**) (20 mg) and 1-(3-chlorophenyl)piperazine (**14**) (17.82 mg) to get compound **48**, yield 59 %; mp 238-240 ºC; FTIR (KBr) cm^{-1}: 3364 (-NH), 3127 (Ar-str.), 1717 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (s, 1H, phenyl-C_2), 8.65 (d, 1H, *J* = 5 Hz, phenyl-C_4), 8.25 (d, 1H, *J* = 10 Hz, quinolin-C_2), 7.86 (d, 1H, *J* = 5 Hz, phenyl-C_6), 7.55-7.49 (m, 1H, phenyl-C_5), 7.38 (dd, 1H, $J_1 = J_2 = 10$ Hz, quinolin-C_7), 7.10-7.06 (m, 2H, quinolin-C_3, -C_6), 6.94-6.89 (m, 2H, quinolin-C_4, -C_5), 3.55 (s, 1H, -NH), 3.45 (s, 2H, -CH_2), 3.40 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_3, -C_5), 3.04 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_2, -C_6); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.57 (-CO), 160.54 (phenyl-C_3), 151.74 (quinolin-C_8), 149.74 (quinolin-C_2, -C_9), 141.62 (phenyl-C_4,), 138.41 (quinolin-C_7), 137.24 (quinolin-C_3), 130.84 (phenyl-C_5), 129.24 (phenyl- C_1,-C_2,-C_6), 128.47 (quinolin-C_4, -C_5), 126.74 (quinolin-C_6, -C_{10}), 64.84 (-CH_2), 55.75 (piperazin-C_3, -C_5), 53.88 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 381.2 [M^+]; calculated for $C_{21}H_{21}ClN_4O$ 380.1.

2-(4-(3-hydroxyphenyl)piperazin-1-yl)-N-(quinolin-8-yl)acetamide (**49**): It was synthesized as per general procedure described earlier (section 7.1.5.4) using 2-chloro-N-(quinolin-8-yl)acetamide (**8**) (20 mg) and 1-(3-hydroxphenyl)piperazine (**18**) (16.19 mg) to get compound **49**, yield 58 %; mp 244-246 ºC; FTIR (KBr) cm^{-1}: 3384 (-NH), 3218 (Ar-str.), 1684 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H, phenyl-

C_2), 8.51 (d, 1H, $J = 5$ Hz, phenyl-C_4), 8.30 (d, 1H, $J = 10$ Hz, quinolin-C_2), 7.87 (d, 1H, $J = 5$ Hz, phenyl-C_6), 7.54-7.48 (m, 1H, phenyl-C_5), 7.29 (dd, 1H, $J_1 = J_2 = 10$ Hz, quinolin-C_7), 7.08-7.04 (m, 2H, quinolin-C_3, -C_6), 6.92-6.87 (m, 2H, quinolin-C_4, -C_5), 3.47 (s, 1H, -NH), 3.42 (s, 2H, -CH_2), 3.38 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_3, -C_5), 3.10 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_2, -C_6); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.85 (-CO), 161.41 (phenyl-C_3), 154.74 (quinolin-C_8), 150.84 (quinolin-C_2, -C_9), 144.54 (phenyl-C_4,), 140.54 (quinolin-C_7), 138.74 (quinolin-C_3), 135.56 (phenyl-C_5), 130.74 (phenyl- C_1,-C_2,-C_6), 129.51 (quinolin-C_4, -C_5), 127.54 (quinolin-C_6, -C_{10}), 63.74 (-CH_2), 57.44 (piperazin-C_3, -C_5), 55.54 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 363.2 [M^+]; calculated for $C_{21}H_{22}N_4O_2$ 362.1.

3-(4-(3-chlorophenyl)piperazin-1-yl)-N-(quinolin-8-yl)propanamide (**50**): This compound was synthesized as per general procedure described earlier in section 7.1.5.4 using 3-chloro-N-(quinolin-8-yl)propanamide (**11**) (21.27 mg) and 1-(3-chlorophenyl)pipera-zine (**14**) (17.82 mg) to get compound **50** yield 62 %; mp 275-278 ºC; FTIR (KBr) cm^{-1}: 3348 (-NH), 3154 (Ar-str.), 1647 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (s, 1H, phenyl-C_2), 8.62 (d, 1H, $J = 5$ Hz, phenyl-C_4), 8.26 (d, 1H, $J = 10$ Hz, quinolin-C_2), 7.88 (d, 1H, $J = 5$ Hz, phenyl-C_6), 7.53-7.47 (m, 1H, phenyl-C_5), 7.35 (dd, 1H, $J_1 = J_2 = 10$ Hz, quinolin-C_7), 7.12-7.09 (m, 2H, quinolin-C_3, -C_6), 6.96-6.90 (m, 2H, quinolin-C_4, -C_5), 3.67 (s, 1H, -NH), 3.42-3.40 (m, 2H, -CH_2), 3.37 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_3, -C_5), 3.00 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_2, -C_6), 2.35-2.31 (m, 2H, -CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.84 (-CO), 160.54 (phenyl-C_3), 151.73 (quinolin-C_8), 149.54 (quinolin-C_2, -C_9), 141.99 (phenyl-C_4,), 138.54 (quinolin-C_7), 137.54 (quinolin-C_3), 130.85 (phenyl-C_5), 129.28 (phenyl-C_1,-C_2,-C_6), 128.44 (quinolin-C_4, -C_5), 126.76 (quinolin-C_6, -C_{10}), 64.88 (-CH_2), 55.72

(piperazin-C_3, -C_5), 53.84 (piperazin-C_2, -C_6), 30.84 (-CH_3); MS (ESI): *m/z* found 395.2 [M^+]; calculated for $C_{22}H_{23}ClN_4O$ 394.1.

3-(4-(3-hydroxyphenyl)piperazin-1-yl)-N-(quinolin-8-yl)propanamide (**51**): It was synthesized as per general procedure described earlier in section 7.1.5.4 using 3-chloro-N-(quinolin-8-yl)propanamide (**11**) (21.27 mg) and 1-(3-hydroxphenyl)pipera-zine (**18**) (16.19 mg) to get compound **51**, yield 57 %; mp 262-264 ºC; FTIR (KBr) cm^{-1}: 3457 (-OH), 3289 (-NH), 3264 (Ar-str.), 1712 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.64 (s, 1H, phenyl-C_2), 8.55 (d, 1H, *J* = 5 Hz, phenyl-C_4), 8.27 (d, 1H, *J* = 10 Hz, quinolin-C_2), 7.77 (d, 1H, *J* = 5 Hz, phenyl-C_6), 7.53-7.46 (m, 1H, phenyl-C_5), 7.34 (dd, 1H, *J* = 10 Hz, quinolin-C_7), 7.03-6.98 (m, 2H, quinolin-C_3, -C_6), 6.90-6.85 (m, 2H, quinolin-C_4, -C_5), 4.52 (s, 1H, -NH), 3.88 (s, 1H, -OH), 3.46 (s, 2H, -CH_2), 3.37 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_3, -C_5), 3.15 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_2, -C_6), 2.33-2.29 (m, 2H, -CH_2); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 169.28 (-CO), 161.54 (phenyl-C_3), 154.54 (quinolin-C_8), 150.64 (quinolin-C_2, -C_9), 144.94 (phenyl-C_4,), 140.64 (quinolin-C_7), 138.94 (quinolin-C_3), 135.66 (phenyl-C_5), 130.84 (phenyl- C_1,-C_2,-C_6), 129.94 (quinolin-C_4, -C_5), 127.67 (quinolin-C_6, -C_{10}), 63.84 (-CH_2), 57.24 (piperazin-C_3, -C_5), 55.66 (piperazin-C_2, -C_6), 30.54 (-CH_3); MS (ESI): *m/z* found 377.2 [M^+]; calculated for $C_{22}H_{24}N_4O_2$ 376.1.

2-((4-chlorophenyl)amino)-1-(4-(quinolin-3-yl)piperazin-1-yl)ethan-1-one (**68**): It was synthesized as per general procedure described earlier (section 7.1.5.7) using 2-chloro-1-(4-(quinolin-3-yl)piperazin-1-yl)ethan-1-one (**55**) (26.27 mg) and 4-chloroaniline (**61**) (11.59 mg) to get compound **68**, yield 57 %; mp 187-189 ºC; FTIR (KBr) cm^{-1}: 3341 (-NH), 3174 (Ar-str.), 1685 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.76 (s, 1H, quinolin-C_2), 7.88 (d, 1H, *J* = 10 Hz, quinolin-C_8), 7.58 (s, 1H, quinolin-C_4), 7.37-7.33 (m, 2H, quinolin-C_5, -C_7), 7.19-7.14 (m, 3H, phenyl-C_3, -C_5, quinolin-C_6), 6.98 (d,

2H, $J = 5$ Hz, phenyl-C_2, -C_6,), 4.21 (s, 2H, -CH_2), 3.60 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_3, -C_5), 3.32 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_2, -C_6), 2.87 (s, 1H, -NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.14 (-CO), 149.71 (quinolin-C_3), 148.12 (quinolin-C_2, -C_9), 146.64 (quinolin-C_4), 140.17 (phenyl-C_4), 137.28 (phenyl-C_3, -C_5), 135.98 (phenyl-C_1), 130.85 (phenyl-C_2, -C_6), 128.17 (quinolin-C_{10}), 126.17 (quinolin-C_5, -C_8), 125.58 (quinolin-C_6, -C_7), 70.94 (-CH_2), 60.94 (piperazin-C_3, -C_5), 57.63 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 381.2 [M$^+$]; calculated for $C_{21}H_{21}ClN_4O$ 380.1.

2-((4-hydroxyphenyl)amino)-1-(4-(quinolin-3-yl)piperazin-1-yl)ethan-1-one (**69**): This was synthesized as per general procedure described earlier in section 7.1.5.7 using 2-chloro-1-(4-(quinolin-3-yl)piperazin-1-yl)ethan-1-one (**55**) (26.27 mg)   and 4-aminophenol (**62**) (10 mg) to get compound **69**, yield 67 %; mp 152-154 ºC; FTIR (KBr) cm^{-1}: 3421 (-OH), 3321 (-NH), 3157 (Ar-str.), 1704 (C=O-str.); ^1H NMR (500 MHz, DMSO-d_6) δ 8.64 (s, 1H, quinolin-C_2), 7.75 (d, 1H, $J = 10$ Hz, quinolin-C_8), 7.51 (s, 1H, quinolin-C_4), 7.35-7.31 (m, 2H, quinolin-C_5, -C_7), 7.10-7.04 (m, 3H, phenyl-C_3, -C_5, quinolin-C_6), 6.76 (d, 2H, $J = 5$ Hz, phenyl-C_2, -C_6,), 3.99 (s, 2H, -CH_2), 3.51 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_3, -C_5), 3.36 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_2, -C_6), 3.12 (s, 1H, -OH), 2.75 (s, 1H, -NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.48 (-CO), 150.94 (quinolin-C_3), 147.45 (quinolin-C_2, -C_9), 147.24 (quinolin-C_4), 139.49 (phenyl-C_4), 138.54 (phenyl-C_3, -C_5), 136.27 (phenyl-C_1), 129.48 (phenyl-C_2, -C_6), 127.94 (quinolin-C_{10}), 125.94 (quinolin-C_5, -C_8), 124.67 (quinolin-C_6, -C_7), 67.67 (-CH_2), 61.82 (piperazin-C_3, -C_5), 56.48 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 363.1 [M$^+$]; calculated for $C_{21}H_{22}ClN_4O_2$ 362.1.

2-((4-fluorophenyl)amino)-1-(4-(quinolin-6-yl)piperazin-1-yl)ethan-1-one (**70**): It was synthesized as per general procedure described earlier in section 7.1.5.7 using 2-chloro-

1-(4-(quinolin-6-yl)piperazin-1-yl)ethan-1-one (**56**) (26.27 mg)   and 4-fluoroaniline (**63**) (10 mg) to get compound **70**, yield 67 %; mp 166-168 ºC; FTIR (KBr) cm^{-1}: 3341 (-NH), 3137 (Ar-str.), 1694 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.52 (d, 1H, J = 10 Hz, quinolin-C$_2$), 7.66 (d, 1H, J = 10 Hz, quinolin-C$_7$), 7.41 (s, 1H, quinolin-C$_5$), 7.31 (d, 1H, J = 10 Hz, quinolin-C$_8$), 7.24-7.20 (m, 2H, quinolin-C$_3$, -C$_4$), 7.18 (s, 2H, J = 5 Hz, phenyl-C$_3$, -C$_5$), 7.10 (d, 2H, J = 5 Hz, phenyl-C$_2$, -C$_6$,), 4.09 (s, 2H, -CH$_2$), 3.74 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_3$, -C$_5$), 3.47 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_2$, -C$_6$), 2.88 (s, 1H, -NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 170.94 (-CO), 149.84 (quinolin-C$_6$), 148.74 (quinolin-C$_2$, -C$_9$), 147.84 (quinolin-C$_7$, -C$_5$), 143.41 (phenyl-C$_4$), 140.21 (phenyl-C$_3$, -C$_5$), 138.85 (penyl-C$_1$), 130.87 (phenyl-C$_2$, -C$_6$), 128.28 (quinolin-C$_{10}$), 126.85 (quinolin-C$_8$), 125.27 (quinolin-C$_3$, -C$_4$), 68.54 (-CH$_2$), 63.17 (piperazin-C$_3$, -C$_5$), 59.43 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 365.2 [M$^+$]; calculated for C$_{21}$H$_{21}$FN$_4$O 364.1.

2-((4-chlorophenyl)amino)-1-(4-(quinolin-6-yl)piperazin-1-yl)ethan-1-one (**71**): It was synthesized as per general procedure described earlier (section 7.1.5.7) using 2-chloro-1-(4-(quinolin-6-yl)piperazin-1-yl)ethan-1-one (**56**) (26.27 mg)   and 4-fluoroaniline (**61**) (11.54 mg) to get compound **71**, yield 64 %; mp 141-143 ºC; FTIR (KBr) cm^{-1}: 3364 (-NH), 3194 (Ar-str.), 1684 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.56 (d, 1H, J = 10 Hz, quinolin-C$_2$), 7.57 (d, 1H, J = 10 Hz, quinolin-C$_7$), 7.47 (s, 1H, quinolin-C$_5$), 7.42 (d, 1H, J = 10 Hz, quinolin-C$_8$), 7.22-7.18 (m, 2H, quinolin-C$_3$, -C$_4$), 7.14 (s, 2H, J = 5 Hz, phenyl-C$_3$, -C$_5$), 7.08 (d, 2H, J = 5 Hz, phenyl-C$_2$, -C$_6$,), 3.81 (s, 2H, -CH$_2$), 3.78 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_3$, -C$_5$), 3.54 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C$_2$, -C$_6$), 3.41 (s, 1H, -NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 167.84 (-CO), 150.48 (quinolin-C$_6$), 149.94 (quinolin-C$_2$, -C$_9$), 146.37 (quinolin-C$_7$, -C$_5$), 142.84 (phenyl-C$_4$), 141.92 (phenyl-C$_3$, -C$_5$), 139.48 (penyl-C$_1$), 131.37 (phenyl-C$_2$, -C$_6$),

130.67 (quinolin-C_{10}), 127.37 (quinolin-C_8), 126.81 (quinolin-C_3, -C_4), 70.81 (-CH_2), 64.38 (piperazin-C_3, -C_5), 60.84 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 381.4 [M^+]; calculated for $C_{21}H_{21}ClN_4O$ 380.1.

1-(4-(quinolin-6-yl)piperazin-1-yl)-2-(p-tolylamino)ethan-1-one (**72**): The compound was synthesized as per general procedure described earlier in section 7.1.5.7 using 2-chloro-1-(4-(quinolin-6-yl)piperazin-1-yl)ethan-1-one (**56**) (26.27 mg) and *p*-toluidine (**64**) (10 mg) to get compound **72**, yield 63 %; mp 149-152 ºC; FTIR (KBr) cm^{-1}: 3345 (-NH), 3186 (Ar-str.), 1688 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.38 (d, 1H, *J* = 10 Hz, quinolin-C_2), 7.67 (d, 1H, *J* = 10 Hz, quinolin-C_7), 7.31 (s, 1H, quinolin-C_5), 7.35 (d, 1H, *J* = 10 Hz, quinolin-C_8), 7.20-7.16 (m, 2H, quinolin-C_3, -C_4), 7.05 (d, 2H, *J* = 5 Hz, phenyl-C_2, -C_6,), 7.00 (s, 2H, *J* = 5 Hz, phenyl-C_3, -C_5), 3.71 (s, 2H, -CH_2), 3.63 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_3, -C_5), 3.52 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_2, -C_6), 3.71 (s, 1H, -NH), 3.07 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.93 (-CO), 150.42 (quinolin-C_6), 148.18 (quinolin-C_2, -C_9), 145.92 (quinolin-C_7, -C_5), 140.54 (phenyl-C_2, -C_6), 137.64 (penyl-C_1), 131.54 (quinolin-C_{10}), 128.27 (quinolin-C_8), 127.94 (phenyl-C_3, -C_5), 125.74 (quinolin-C_3, -C_4), 125.32 (phenyl-C_4), 70.47 (-CH_2), 63.57 (piperazin-C_3, -C_5), 62.27 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 361.1 [M^+]; calculated for $C_{22}H_{24}ClN_4O$ 360.2.

2-((4-hydroxyphenyl)amino)-1-(4-(quinolin-6-yl)piperazin-1-yl)ethan-1-one (**73**): It was synthesized as per general procedure described earlier in section 7.1.5.7 using 2-chloro-1-(4-(quinolin-6-yl)piperazin-1-yl)ethan-1-one (**56**) (26.27 mg) and 4-aminophenol (**62**) (10 mg) to get compound **73**, yield 66 %; mp 166-168 ºC; FTIR (KBr) cm^{-1}: 3419 (-OH), 3348 (-NH), 3174 (Ar-str.), 1688 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 (d, 1H, *J* = 10 Hz, quinolin-C_2), 7.49 (d, 1H, *J* = 10 Hz, quinolin-C_7), 7.38 (s, 1H, quinolin-C_5), 7.36 (d, 1H, *J* = 10 Hz, quinolin-C_8), 7.18-7.13

(m, 2H, quinolin-C_3, -C_4), 7.10 (s, 2H, J = 5 Hz, phenyl-C_3, -C_5), 7.03 (d, 2H, J = 5 Hz, phenyl-C_2, -C_6,), 3.83 (s, 2H, -CH_2), 3.67 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_3, -C_5), 3.50 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_2, -C_6), 3.22 (s, 1H, -OH), 3.17 (s, 1H, -NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.45 (-CO), 147.25 (quinolin-C_6), 145.72 (quinolin-C_2, -C_9), 144.75(quinolin-C_7, -C_5), 142.28 (phenyl-C_4), 140.74 (phenyl-C_3, -C_5), 138.82 (penyl-C_1), 133.85 (phenyl- C_1, -C_2, -C_6), 131.77 (quinolin-C_{10}), 128.32 (quinolin-C_8), 125.82 (quinolin-C_3, -C_4), 71.74 (-CH_2), 65.58 (piperazin-C_3, -C_5), 61.72 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 362.8 [M^+]; calculated for $C_{21}H_{22}N_4O_2$ 362.1.

3-((4-chlorophenyl)amino)-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**74**): It was synthesized as per general procedure described earlier in (section 7.1.5.7) using 3-chloro-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**59**) (27.54 mg) and 4-chloroaniline (**61**) (11.54 mg) to get compound **74**, yield 62 %; mp 129-131 ºC; FTIR (KBr) cm^{-1}: 3347 (-NH), 3155 (Ar-str.), 1714 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 (d, 1H, J = 10 Hz, quinolin-C_2), 7.74 (d, 1H, J = 10 Hz, quinolin-C_7), 7.47 (s, 1H, quinolin-C_5), 7.43 (d, 1H, J = 10 Hz, quinolin-C_8), 7.25-7.21 (m, 2H, quinolin-C_3, -C_4), 7.16 (s, 2H, J = 5 Hz, phenyl-C_3, -C_5), 7.12 (d, 2H, J = 5 Hz, phenyl-C_2, -C_6,), 3.79-3.76 (m, 2H, -CH_2), 3.65 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_3, -C_5), 3.55 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_2, -C_6), 3.41 (s, 1H, -NH), 2.85-2.80 (m, 2H, -CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.10 (-CO), 148.93 (quinolin-C_6), 145.84 (quinolin-C_2, -C_9), 145.11 (quinolin-C_7, -C_5), 143.54 (phenyl-C_4), 140.28 (phenyl-C_3, -C_5), 137.54 (penyl-C_1), 130.87 (phenyl-C_2, -C_6), 129.58 (quinolin-C_{10}), 128.74 (quinolin-C_8), 127.28 (quinolin-C_3, -C_4), 71.27 (-2CH_2), 65.32 (piperazin-C_3, -C_5), 62.57 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 395.2 [M^+]; calculated for $C_{22}H_{23}ClN_4O$ 394.1.

1-(4-(quinolin-6-yl)piperazin-1-yl)-3-(p-tolylamino)propan-1-one (**75**): It was synthesized as per general procedure described earlier in section 7.1.5.7 using 3-chloro-

1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**59**) (27.54 mg) and p-toluidine (**64**) (10 mg) to get compound **75**, yield 61 %; mp 126-128 ℃; FTIR (KBr) cm^{-1}: 3347 (-NH), 3185 (Ar-str.), 1674 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.34 (d, 1H, J = 10 Hz, quinolin-C$_2$), 7.64 (d, 1H, J = 10 Hz, quinolin-C$_7$), 7.32 (s, 1H, quinolin-C$_5$), 7.31 (d, 1H, J = 10 Hz, quinolin-C$_8$), 7.21-7.17 (m, 2H, quinolin-C$_3$, -C$_4$), 7.03 (d, 2H, J = 5 Hz, phenyl-C$_2$, -C$_6$,), 7.01 (s, 2H, J = 5 Hz, phenyl-C$_3$, -C$_5$), 3.75-3.73 (m, 2H, -CH$_2$), 3.56 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_3$, -C$_5$), 3.47 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_2$, -C$_6$), 3.20 (s, 1H, -NH), 3.07 (s, 1H, -CH$_3$), 2.81-2.77 (m, 2H, -CH$_2$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 165.85 (-CO), 150.42 (quinolin-C$_6$), 148.47 (quinolin-C$_2$, -C$_9$), 145.74 (quinolin-C$_7$, -C$_5$), 140.25 (phenyl-C$_2$, -C$_6$), 137.74 (penyl-C$_1$), 131.14 (quinolin-C$_{10}$), 127.63 (quinolin-C$_8$), 126.37 (phenyl-C$_3$, -C$_5$), 124.83 (quinolin-C$_3$, -C$_4$), 123.48 (phenyl-C$_4$), 72.83 (-2CH$_2$), 64.77 (piperazin-C$_3$, -C$_5$), 63.82 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 375.4 [M$^+$]; calculated for C$_{23}$H$_{26}$N$_4$O 374.2.

3-((4-hydroxyphenyl)amino)-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**76**): It was synthesized as per general procedure described earlier in section 7.1.5.7 using 3-chloro-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**59**) (27.54 mg) (26.27 mg) and 4-aminophenol (**62**) (10 mg) to get compound **76**, yield 65 %; mp 157-159 ℃; FTIR (KBr) cm^{-1}: 3445 (-OH), 3348 (-NH), 3184 (Ar-str.), 1625 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.64 (d, 1H, J = 10 Hz, quinolin-C$_2$), 7.51 (d, 1H, J = 10 Hz, quinolin-C$_7$), 7.40 (s, 1H, quinolin-C$_5$), 7.37 (d, 1H, J = 10 Hz, quinolin-C$_8$), 7.15-7.10 (m, 2H, quinolin-C$_3$, -C$_4$), 7.07 (s, 2H, J = 5 Hz, phenyl-C$_3$, -C$_5$), 7.00 (d, 2H, J = 5 Hz, phenyl-C$_2$, -C$_6$,), 3.84-3.82 (m, 2H, -CH$_2$), 3.69 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_3$, -C$_5$), 3.48 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_2$, -C$_6$), 3.20 (s, 1H, -NH), 2.80-2.76 (m, 2H, -CH$_2$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 169.75 (-CO), 147.25 (quinolin-C$_6$), 145.95 (quinolin-C$_2$, -C$_9$), 144.85(quinolin-C$_7$, -C$_5$), 142.48 (phenyl-C$_4$), 141.74

(phenyl-C_3, -C_5), 138.25 (penyl-C_1), 133.28 (phenyl-C_2, -C_6), 131.45 (quinolin-C_{10}), 128.45 (quinolin-C_8), 125.62 (quinolin-C_3, -C_4), 71.53 (-2CH_2), 65.72 (piperazin-C_3, -C_5), 61.53 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 377.2 [M^+]; calculated for $C_{22}H_{24}N_4O_2$ 376.1.

3-((3-chlorophenyl)amino)-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**77**): The was synthesized as per general procedure described earlier in section 7.1.5.7 using 3-chloro-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**59**) (27.54 mg) and 3-chloroaniline (**65**) (11.54 mg) to get compound **77**, yield 63 %; mp 132-134 ºC; FTIR (KBr) cm^{-1}: 3365 (-NH), 3138 (Ar-str.), 1684 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.65 (d, 1H, *J* = 10 Hz, quinolin-C_2), 7.68 (d, 1H, *J* = 10 Hz, quinolin-C_7), 7.46 (s, 1H, quinolin-C_5), 7.38 (d, 1H, *J* = 10 Hz, quinolin-C_8), 7.36 (s, 1H, phenyl-C_2), 7.34 (d, 1H, *J* = 5 Hz, phenyl-C_4), 7.32-7.25 (m, 4H, quinolin-C_3, -C_4, phenyl-C_5, -C_6), 3.82-3.79 (m, 2H, -CH_2), 3.71 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_3, -C_5), 3.61 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_2, -C_6), 2.96 (s, 1H, -NH), 2.83-2.78 (m, 2H, -CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.54 (-CO), 147.65 (quinolin-C_6), 146.67 (quinolin-C_2, -C_9), 144.93 (quinolin-C_7, -C_5), 142.44 (phenyl-C_4), 141.38 (phenyl-C_3, -C_5), 138.67 (penyl-C_1), 134.67 (phenyl-C_2, -C_6), 130.67 (quinolin-C_{10}), 129.68 (quinolin-C_8), 126.74 (quinolin-C_3, -C_4), 73.78 (-2CH_2), 66.38 (piperazin-C_3, -C_5), 64.77 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 395.2 [M^+]; calculated for $C_{22}H_{23}ClN_4O$ 394.1.

1-(4-(quinolin-6-yl)piperazin-1-yl)-3-(m-tolylamino)propan-1-one (**78**): It was synthesized as per general procedure described earlier in section 7.1.5.7 using 3-chloro-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**59**) (27.54 mg) and m-toluidine (**66**) (10 mg) to get compound **78**, yield 62 %; mp 126-128 ºC; FTIR (KBr) cm^{-1}: 3316 (-NH), 3147 (Ar-str.), 1688 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.47 (d, 1H, *J* = 10 Hz, quinolin-C_2), 7.62 (d, 1H, *J* = 10 Hz, quinolin-C_7), 7.38 (s, 1H, quinolin-C_5),

7.37 (d, 1H, J = 10 Hz, quinolin-C_8), 7.30-7.23 (m, 4H, quinolin-C_3, -C_4, phenyl-C_5, -C_6), 7.20 (s, 1H, phenyl-C_2), 7.18 (d, 1H, J = 5 Hz, phenyl-C_4), 3.71-3.69 (3, 2H, -CH_2), 3.68 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_3, -C_5), 3.57 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_2, -C_6), 2.96 (s, 1H, -NH), 2.80-2.77 (m, 2H, -CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.47 (-CO), 146.58 (quinolin-C_6), 145.78 (quinolin-C_2, -C_9), 143.77 (quinolin-C_7, -C_5), 140.75 (phenyl-C_1), 138.27 (phenyl-C_6), 137.77 (penyl-C_2), 133.07 (phenyl-C_5), 128.47 (quinolin-C_{10}), 128.27 (quinolin-C_8), 127.17 (quinolin-C_3, -C_4), 126.58 (phenyl-C_4), 125.44 (phenyl-C_3), 70.82 (-2CH_2), 65.17 (piperazin-C_3, -C_5), 63.28 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 375.3 [M^+]; calculated for $C_{23}H_{26}N_4O$ 374.2.

3-((3-hydroxyphenyl)amino)-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**79**): The compound was synthesized as per general procedure described earlier (section 7.1.5.7) using 3-chloro-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**59**) (27.54 mg) and 3-aminophenol (**67**) (10 mg) to get compound **79**, yield 62 %; mp 159-162 ºC; FTIR (KBr) cm^{-1}: 3459 (-OH), 3379 (-NH), 3147 (Ar-str.), 1710 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (d, 1H, J = 10 Hz, quinolin-C_2), 7.72 (d, 1H, J = 10 Hz, quinolin-C_7), 7.62 (s, 1H, quinolin-C_5), 7.42 (d, 1H, J = 10 Hz, quinolin-C_8), 7.20 (s, 1H, phenyl-C_2), 7.18 (d, 1H, J = 5 Hz, phenyl-C_4), 7.15-7.08 (m, 4H, quinolin-C_3, -C_4, phenyl-C_5, -C_6), 3.75 (s, 2H, -CH_2), 3.70 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_3, -C_5), 3.57 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_2, -C_6), 3.21 (s, 1H, -OH), 2.87 (s, 1H, -NH), 2.80-2.75 (m, 2H, -CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.84 (-CO), 148.67 (quinolin-C_6), 147.67 (quinolin-C_2, -C_9), 145.51 (quinolin-C_7, -C_5), 141.64 (phenyl-C_4), 139.54 (phenyl-C_3, -C_5), 137.96 (penyl-C_1), 135.15 (phenyl-C_2, -C_6), 130.67 (quinolin-C_{10}), 129.27 (quinolin-C_8), 126.73 (quinolin-C_3, -C_4), 73.93 (-2CH_2), 67.81 (piperazin-

C$_3$, -C$_5$), 65.92 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 377.2 [M$^+$]; calculated for C$_{22}$H$_{24}$N$_4$O$_2$ 376.1.

2-((4-chlorophenyl)amino)-1-(4-(quinolin-8-yl)piperazin-1-yl)ethan-1-one (**80**): It was synthesized as per general procedure described earlier in section 7.1.5.7 using 2-chloro-1-(4-(quinolin-8-yl)piperazin-1-yl)ethan-1-one (**57**) (27.54 mg) and 4-chloroaniline (**61**) (11.54 mg) to get compound **80**, yield 63 %; mp 174-176 ºC; FTIR (KBr) cm^{-1}: 3385 (-NH), 3144 (Ar-str.), 1685 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.72 (d, 1H, *J* = 10 Hz, quinolin-C$_2$), 8.20 (d, 1H, *J* = 10 Hz, quinolin-C$_7$), 8.11 (d, 1H, *J* = 10 Hz, quinolin-C$_4$), 7.70 (d, 1H, *J* = 10 Hz, quinolin-C$_5$), 7.60-7.56 (m, 2H, quinolin-C$_3$, -C$_6$), 7.27 (s, 2H, *J* = 5 Hz, phenyl-C$_3$, -C$_5$), 7.20 (d, 2H, *J* = 5 Hz, phenyl-C$_2$, -C$_6$,), 3.82 (s, 2H, -CH$_2$), 3.52 (t, 4H, *J$_1$* = *J$_2$* = 5 Hz, piperazin-C$_3$, -C$_5$), 3.41 (t, 4H, *J$_1$* = *J$_2$* = 5 Hz, piperazin-C$_2$, -C$_6$), 3.20 (s, 1H, -NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 169.27 (-CO), 147.52 (quinolin-C$_8$), 144.57 (quinolin-C$_2$, -C$_9$), 143.02 (quinolin-C$_7$, -C$_5$), 142.84 (phenyl-C$_4$), 141.22 (phenyl-C$_3$, -C$_5$), 138.84 (penyl-C$_1$), 133.77 (phenyl-C$_2$, -C$_6$), 130.85 (quinolin-C$_{10}$), 129.18 (quinolin-C$_4$), 128.27 (quinolin-C$_3$, -C$_6$), 71.55 (-CH$_2$), 68.52 (piperazin-C$_3$, -C$_5$), 65.22 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 381.3 [M$^+$]; calculated for C$_{22}$H$_{23}$ClN$_4$O 380.1.

1-(4-(quinolin-8-yl)piperazin-1-yl)-2-(p-tolylamino)ethan-1-one (**81**): It was synthesized as per general procedure described earlier in section 7.1.5.7 using 2-chloro-1-(4-(quinolin-8-yl)piperazin-1-yl)ethan-1-one (**57**) (27.54 mg) and p-toluidine (**64**) (10 mg) to get compound **81**, yield 62 %; mp 138-140 ºC; FTIR (KBr) cm^{-1}: 3374 (-NH), 3182 (Ar-str.), 1682 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.61 (d, 1H, *J* = 10 Hz, quinolin-C$_2$), 8.18 (d, 1H, *J* = 10 Hz, quinolin-C$_7$), 8.09 (d, 1H, *J* = 10 Hz, quinolin-C$_4$), 7.68 (d, 1H, *J* = 10 Hz, quinolin-C$_5$), 7.54-7.50 (m, 2H, quinolin-C$_3$, -C$_6$), 7.16 (d, 2H, *J* = 5 Hz, phenyl-C$_2$, -C$_6$,), 7.12 (s, 2H, *J* = 5 Hz, phenyl-C$_3$, -C$_5$), 3.58 (s,

2H, -CH$_2$), 3.47 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_3$, -C$_5$), 3.34 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_2$, -C$_6$), 3.18 (s, 1H, -NH), 2.52 (-CH$_3$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 170.62 (-CO), 146.92 (quinolin-C$_8$), 145.58 (quinolin-C$_2$, -C$_9$), 142.97 (quinolin-C$_7$, -C$_5$), 141.77 (phenyl-C$_1$), 140.61 (phenyl-C$_2$, -C$_6$), 139.62 (penyl-C$_4$), 136.82 (phenyl-C$_3$, -C$_5$), 132.67 (quinolin-C$_{10}$), 128.97 (quinolin-C$_4$), 127.17 (quinolin-C$_3$, -C$_6$), 78.28 (-CH$_2$), 68.82 (piperazin-C$_3$, -C$_5$), 64.52 (piperazin-C$_2$, -C$_6$), 58.27 (-CH$_3$); MS (ESI): *m/z* found 361.4 [M$^+$]; calculated for C$_{22}$H$_{23}$ClN$_4$O 360.2.

2-((4-hydroxyphenyl)amino)-1-(4-(quinolin-8-yl)piperazin-1-yl)ethan-1-one (**82**): It was synthesized as per general procedure described earlier (section 7.1.5.7) using 2-chloro-1-(4-(quinolin-8-yl)piperazin-1-yl)ethan-1-one (**57**) (27.54 mg) and 4-aminophenol (**62**) (10 mg) to get compound **82**, yield 61 %; mp 141-143 ºC; FTIR (KBr) cm^{-1}: 3482 (-OH), 3316 (-NH), 3151 (Ar-str.), 1676 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.64 (d, 1H, $J = 10$ Hz, quinolin-C$_2$), 8.31 (d, 1H, $J = 10$ Hz, quinolin-C$_7$), 8.09 (d, 1H, $J = 10$ Hz, quinolin-C$_4$), 7.64 (d, 1H, $J = 10$ Hz, quinolin-C$_5$), 7.56-7.52 (m, 2H, quinolin-C$_3$, -C$_6$), 7.14 (s, 2H, $J = 5$ Hz, phenyl-C$_3$, -C$_5$), 7.07 (d, 2H, $J = 5$ Hz, phenyl-C$_2$, -C$_6$,), 4.08 (-OH), 3.41 (s, 2H, -CH$_2$), 3.32 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_3$, -C$_5$), 3.24 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C$_2$, -C$_6$), 3.18 (s, 1H, -NH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 168.92 (-CO), 148.67 (quinolin-C$_8$), 145.81 (quinolin-C$_2$, -C$_9$), 145.13 (quinolin-C$_7$, -C$_5$), 141.24 (phenyl-C$_4$), 140.37 (phenyl-C$_3$, -C$_5$), 139.61 (penyl-C$_1$), 134.22 (phenyl-C$_2$, -C$_6$), 131.67 (quinolin-C$_{10}$), 128.61 (quinolin-C$_4$), 127.46 (quinolin-C$_3$, -C$_6$), 70.44 (-CH$_2$), 69.66 (piperazin-C$_3$, -C$_5$), 66.97 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 363.1 [M$^+$]; calculated for C$_{21}$H$_{22}$N$_4$O$_2$ 362.1.

3-((4-chlorophenyl)amino)-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**83**): It was synthesized as per general procedure described earlier in section 7.1.5.7 using 3-chloro-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**60**) (27.55 mg) and 4-

chloroaniline (**61**) (11.54 mg) to get compound **83**, yield 63 %; mp 178-181 ºC; FTIR (KBr) cm^{-1}: 3355 (-NH), 3217 (Ar-str.), 1720 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.62 (d, 1H, *J* = 10 Hz, quinolin-C$_2$), 8.17 (d, 1H, *J* = 10 Hz, quinolin-C$_7$), 8.07 (d, 1H, *J* = 10 Hz, quinolin-C$_4$), 7.64 (d, 1H, *J* = 10 Hz, quinolin-C$_5$), 7.58-7.53 (m, 2H, quinolin-C$_3$, -C$_6$), 7.21 (s, 2H, *J* = 5 Hz, phenyl-C$_3$, -C$_5$), 7.18 (d, 2H, *J* = 5 Hz, phenyl-C$_2$, -C$_6$,), 3.57 (s, 2H, -CH$_2$), 3.50 (t, 4H, *J$_1$* = *J$_2$* = 5 Hz, piperazin-C$_3$, -C$_5$), 3.44 (t, 4H, *J$_1$* = *J$_2$* = 5 Hz, piperazin-C$_2$, -C$_6$), 3.34 (s, 1H, -NH), 2.53-2.47 (m, 2H, -CH$_2$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 169.84 (-CO), 146.87 (quinolin-C$_8$), 145.21 (quinolin-C$_2$, -C$_9$), 144.37 (quinolin-C$_7$, -C$_5$), 143.74 (phenyl-C$_4$), 140.21 (phenyl-C$_3$, -C$_5$), 139.71 (penyl-C$_1$), 134.58 (phenyl-C$_2$, -C$_6$), 132.57 (quinolin-C$_{10}$), 130.88 (quinolin-C$_4$), 128.37 (quinolin-C$_3$, -C$_6$), 71.07 (-CH$_2$), 67.67 (piperazin-C$_3$, -C$_5$), 66.51 (piperazin-C$_2$, -C$_6$); MS (ESI): *m/z* found 395.5 [M$^+$]; calculated for C$_{22}$H$_{23}$ClN$_4$O 394.1.

1-(4-(quinolin-8-yl)piperazin-1-yl)-3-(p-tolylamino)propan-1-one　(**84**):　It　was synthesized as per general procedure described earlier section 7.1.5.7 using 3-chloro-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**60**) (27.55 mg) and p-toluidine (**64**) (10 mg) to get compound **84**, yield 65 %; mp 146-150 ºC; FTIR (KBr) cm^{-1}: 3318 (-NH), 3174 (Ar-str.), 1691 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.52 (d, 1H, *J* = 10 Hz, quinolin-C$_2$), 8.20 (d, 1H, *J* = 10 Hz, quinolin-C$_7$), 8.16 (d, 1H, *J* = 10 Hz, quinolin-C$_4$), 7.52 (d, 1H, *J* = 10 Hz, quinolin-C$_5$), 7.50-7.44 (m, 2H, quinolin-C$_3$, -C$_6$), 7.20 (d, 2H, *J* = 5 Hz, phenyl-C$_2$, -C$_6$,), 7.15 (s, 2H, *J* = 5 Hz, phenyl-C$_3$, -C$_5$), 3.60-3.59 (m, 2H, -CH$_2$), 3.50 (t, 4H, *J$_1$* = *J$_2$* = 5 Hz, piperazin-C$_3$, -C$_5$), 3.41 (t, 4H, *J$_1$* = *J$_2$* = 5 Hz, piperazin-C$_2$, -C$_6$), 3.20 (s, 1H, -NH), 2.54-2.48 (m, 5H, -CH$_2$, -CH$_3$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 169.57 (-CO), 147.67 (quinolin-C$_8$), 146.47 (quinolin-C$_2$, -C$_9$), 143.87 (quinolin-C$_7$, -C$_5$), 142.84 (phenyl-C$_1$), 141.47 (phenyl-C$_2$, -C$_6$), 138.62 (penyl-

C_4), 136.57 (phenyl-C_3, -C_5), 133.44 (quinolin-C_{10}), 129.30 (quinolin-C_4), 129.15 (quinolin-C_3, -C_6), 79.67 (-2CH_2), 69.67 (piperazin-C_3, -C_5), 65.27 (piperazin-C_2, -C_6), 59.66 (-CH_3); MS (ESI): *m/z* found 375.3 [M^+]; calculated for $C_{23}H_{26}N_4O$ 374.2.

3-((4-hydroxyphenyl)amino)-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**85**): This was synthesized as per general procedure described earlier in section 7.1.5.7 using 3-chloro-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**60**) (27.55 mg) and 4-aminophenol (**62**) (10 mg) to get compound **85**, yield 63 %; mp 145-147 ºC; FTIR (KBr) cm^{-1}: 3482 (-OH), 3316 (-NH), 3151 (Ar-str.), 1676 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, 1H, *J* = 10 Hz, quinolin-C_2), 8.34 (d, 1H, *J* = 10 Hz, quinolin-C_7), 8.10 (d, 1H, *J* = 10 Hz, quinolin-C_4), 7.67 (d, 1H, *J* = 10 Hz, quinolin-C_5), 7.54-7.50 (m, 2H, quinolin-C_3, -C_6), 7.12 (s, 2H, *J* = 5 Hz, phenyl-C_3, -C_5), 7.05 (d, 2H, *J* = 5 Hz, phenyl-C_2, -C_6,), 4.09 (-OH), 3.38-3.36 (m, 2H, -CH_2), 3.34 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_3, -C_5), 3.28 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_2, -C_6), 3.20 (s, 1H, -NH), 2.51-2.45 (m, 2H, -CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.38 (-CO), 148.77 (quinolin-C_8), 145.47 (quinolin-C_2, -C_9), 145.24 (quinolin-C_7, -C_5), 141.17 (phenyl-C_4), 140.22 (phenyl-C_3, -C_5), 139.74 (penyl-C_1), 134.31 (phenyl-C_2, -C_6), 131.74 (quinolin-C_{10}), 128.17 (quinolin-C_4), 127.74 (quinolin-C_3, -C_6), 70.41 (-2CH_2), 69.71(piperazin-C_3, -C_5), 65.74 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 377.2 [M^+]; calculated for $C_{22}H_{24}N_4O_2$ 376.1.

3-((3-chlorophenyl)amino)-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**86**): It was synthesized as per general procedure described earlier in section 7.1.5.7 using 3-chloro-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**60**) (27.55 mg) and 3-chloroaniline (**61**) (11.54 mg) to get compound **86**, yield 65 %; mp 182-184 ºC; FTIR (KBr) cm^{-1}: 3355 (-NH), 3185 (Ar-str.), 1692 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, 1H, *J* = 10 Hz, quinolin-C_2), 8.31(d, 1H, *J* = 10 Hz, quinolin-C_7), 8.10 (d,

1H, J = 10 Hz, quinolin-C_4), 7.74 (d, 1H, J = 10 Hz, quinolin-C_5), 7.62-7.59 (m, 2H, quinolin-C_3, -C_6), 7.40 (s, 1H, phenyl-C_2), 7.38 (d, 1H, J = 5 Hz, phenyl-C_4), 7.28-7.24 (m, 2H, phenyl-C_5, -C_6), 3.76-3.74 (m, 2H, -CH_2), 3.56 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_3, -C_5), 3.39 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_2, -C_6), 3.19 (s, 1H, -NH), 2.48-2.45 (m, 2H, -CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.17 (-CO), 148.44 (quinolin-C_8), 145.88 (quinolin-C_2, -C_9), 143.02 (quinolin-C_7, -C_5, phenyl-C_3), 142.47 (phenyl-C_4, -C_5), 139.17 (penyl-C_1), 133.88 (phenyl-C_2, -C_6), 131.47 (quinolin-C_{10}), 130.17 (quinolin-C_4), 129.47 (quinolin-C_3, -C_6), 72.81 (-CH_2), 69.71 (piperazin-C_3, -C_5), 66.37 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 395.2 [M$^+$]; calculated for $C_{22}H_{23}ClN_4O$ 394.1.

1-(4-(quinolin-8-yl)piperazin-1-yl)-3-(m-tolylamino)propan-1-one (**87**): It was synthesized as per general procedure described earlier (section 7.1.5.7) using 3-chloro-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**60**) (27.55 mg) and 3-chloroaniline (**65**) (11.54 mg) to get compound **87**, yield 64 %; mp 186-188 ºC; FTIR (KBr) cm^{-1}: 3347 (-NH), 3127 (Ar-str.), 1674 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, 1H, J = 10 Hz, quinolin-C_2), 8.27(d, 1H, J = 10 Hz, quinolin-C_7), 8.08 (d, 1H, J = 10 Hz, quinolin-C_4), 7.69 (d, 1H, J = 10 Hz, quinolin-C_5), 7.59-7.56 (m, 2H, quinolin-C_3, -C_6), 7.31-7.27 (m, 2H, phenyl-C_5, -C_6), 7.24 (s, 1H, phenyl-C_2), 7.18 (d, 1H, J = 5 Hz, phenyl-C_4), 3.41-3.40 (m, 2H, -CH_2), 3.39 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_3, -C_5), 3.35 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_2, -C_6), 3.28 (s, 1H, -NH), 2.50-2.45 (m, 5H, -CH_2, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.28 (-CO), 149.28 (quinolin-C_8), 146.74 (quinolin-C_2, -C_9), 142.72 (quinolin-C_7, -C_5), 140.22 (phenyl-C_1), 136.71 (phenyl-C_2, -C_6), 131.47 (quinolin-C_{10}), 130.17 (quinolin-C_4), 129.47 (quinolin-C_3, -C_6), 128.47 (phenyl-C_4, -C_5), 126.12 (phenyl-C_3), 71.44 (-CH_2), 68.46 (piperazin-C_3, -

C_5), 67.57 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 375.1 [M$^+$]; calculated for $C_{23}H_{26}N_4O$ 374.2.

3-((3-hydroxyphenyl)amino)-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**88**): It was synthesized as per general procedure described earlier in section 7.1.5.7 using 3-chloro-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**60**) (27.55 mg) and 3-aminophenol (**67**) (10 mg) to get compound **88**, yield 61 %; mp 163-167 ºC; FTIR (KBr) cm^{-1}: 3485 (-OH), 3384 (-NH), 3154 (Ar-str.), 1685 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 (d, 1H, *J* = 10 Hz, quinolin-C_2), 8.29 (d, 1H, *J* = 10 Hz, quinolin-C_7), 8.08 (d, 1H, *J* = 10 Hz, quinolin-C_4), 7.63 (d, 1H, *J* = 10 Hz, quinolin-C_5), 7.59-7.56 (m, 2H, quinolin-C_3, -C_6), 7.37 (s, 1H, phenyl-C_2), 7.30 (d, 1H, *J* = 5 Hz, phenyl-C_4), 7.23-7.18 (m, 2H, phenyl-C_5, -C_6), 3.68 (s, 2H, -CH_2), 3.51 (t, 4H, $J_1 = J_2 = $ 5 Hz, piperazin-C_3, -C_5), 3.41 (t, 4H, $J_1 = J_2 = $ 5 Hz, piperazin-C_2, -C_6), 3.24 (s, 1H, -NH), 3.17 (s, 1H, -OH), 2.46-2.43 (m, 2H, -CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.24 (-CO), 147.27 (quinolin-C_8), 144.74 (quinolin-C_2, -C_9), 142.37 (quinolin-C_7, -C_5, phenyl-C_3), 141.77 (phenyl-C_4, -C_5), 138.25 (penyl-C_1), 134.38 (phenyl-C_2, -C_6), 129.58 (quinolin-C_{10}), 128.44 (quinolin-C_4), 127.24 (quinolin-C_3, -C_6), 73.74 (-2CH_2), 69.47 (piperazin-C_3, -C_5), 67.54 (piperazin-C_2, -C_6); MS (ESI): *m/z* found 377.2 [M$^+$]; calculated for $C_{22}H_{24}N_4O_2$ 376.1.

3-((4-methylcyclohexyl)amino)-1-(4-(quinolin-3-yl)piperazin-1-yl)propan-1-one (**93**): This compound was synthesized as per general procedure described earlier in section 7.1.5.8 using 3-chloro-1-(4-(quinolin-3-yl)piperazin-1-yl)propan-1-one (**58**) (27.55 mg) and 4-methylcyclohexan-1-amine (**89**) (10 .28 mg) to get compound **93**, yield 56 %; mp 278-280 ºC; FTIR (KBr) cm^{-1}: 3347 (-NH), 3256 (Ar-str.), 1716 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H, quinolin-C_2), 7.69 (d, 1H, *J* = 10 Hz, quinolin-C_8), 7.56 (s, 1H, quinolin-C_4), 7.28-7.23 (m, 2H, quinolin-C_5, -C_7), 7.15 (t, 1H, $J_1 = J_2 = 10$

Hz, quinolin-C_6), 3.72-3.70 (m, 1H, cyclohexyl-C_1), 3.57-3.54 (m, 2H, -CH_2), 3.52-3.51 (m, 1H, cyclohexyl-C_4), 3.49 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_3, -C_5), 3.42 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_2, -C_6), 3.37 (s, 1H, -NH), 2.52-2.46 (m, 5H, -CH_2, -CH_3), 2.15-2.09 (m, 4H, cyclohexyl-C_2, -C_6), 1.84-1.79 (m, 4H, cyclohexyl-C_3, -C_5); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.61 (-CO), 152.37 (quinolin-C_3), 148.61 (quinolin-C_2, -C_9), 146.82 (quinolin-C_4), 130.27 (quinolin-C_{10}), 126.81 (quinolin-C_5, -C_8), 125.85 (quinolin-C_6, -C_7), 80.27 (-CH_2), 68.54 (piperazin-C_3, -C_5), 67.28 (piperazin-C_2, -C_6), 60.27 (cyclohexyl-C_1), 59.66 (-CH_2), 54.47 (cyclohexyl-C_2, -C_6), 50.12 (cyclohexyl-C_3, -C_5), 48.24 (cyclohexyl-C_4), 47.51 (-CH_3); MS (ESI): *m/z* found 381.2 [M^+]; calculated for $C_{23}H_{32}N_4O$ 380.2.

3-((4-hydroxycyclohexyl)amino)-1-(4-(quinolin-3-yl)piperazin-1-yl)propan-1-one (**94**): It was synthesized as per general procedure described earlier in section 7.1.5.8 using 3-chloro-1-(4-(quinolin-3-yl)piperazin-1-yl)propan-1-one (**58**) (27.55 mg) and 4-aminocyclohexan-1-ol (**90**) (10 .46 mg) to get compound **94**, yield 57 %; mp 291-293 ºC; FTIR (KBr) cm^{-1}: 3485 (-OH), 3346 (-NH), 3256 (Ar-str.), 1687 (C=O-str.); ^1H NMR (500 MHz, DMSO-d_6) δ 8.61 (s, 1H, quinolin-C_2), 7.71 (d, 1H, $J = 10$ Hz, quinolin-C_8), 7.62 (s, 1H, quinolin-C_4), 7.30-7.25 (m, 2H, quinolin-C_5, -C_7), 7.20 (t, 1H, $J_1 = J_2 = 10$ Hz, quinolin-C_6), 3.71-3.70 (m, 1H, cyclohexyl-C_1), 3.60 (s, 2H, -CH_2), 3.55-3.54 (m, 1H, cyclohexyl-C_4), 3.51 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_3, -C_5), 3.46 (t, 4H, $J_1 = J_2 = 5$ Hz, piperazin-C_2, -C_6), 3.40 (s, 1H, -NH), 3.12 (s, 1H, -OH), 2.35-2.33 (m, 2H, -CH_2), 2.17-2.11 (m, 4H, cyclohexyl-C_3, -C_5), 1.86-1.81 (m, 4H, cyclohexyl-C_2, -C_6); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.27 (-CO), 152.37 (quinolin-C_3), 148.74 (quinolin-C_2, -C_9), 146.17 (quinolin-C_4), 131.74 (quinolin-C_{10}), 127.58 (quinolin-C_5, -C_8), 126.85 (quinolin-C_6, -C_7), 81.74 (-CH_2), 69.28 (piperazin-C_3, -C_5), 68.47 (piperazin-C_2, -C_6), 61.38 (cyclohexyl-C_1), 60.27 (cyclohexyl-C_4), 59.37 (-

CH$_2$), 55.47 (cyclohexyl-C$_3$, -C$_5$), 52.14 (cyclohexyl-C$_2$, -C$_6$), 48.22 (-CH$_2$); MS (ESI): *m/z* found 383.3 [M$^+$]; calculated for C$_{23}$H$_{32}$N$_4$O 382.2.

3-((4-hydroxycyclohexyl)amino)-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**95**):

It was synthesized as per general procedure described earlier in section 7.1.5.8 using 3-chloro-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**59**) (27.54 mg) and 4-aminocyclohexan-1-ol (**90**) (10 .46 mg) to get compound **95**, yield 57 %; mp 315-318 ºC; FTIR (KBr) cm^{-1}: 3472 (-OH), 3374 (-NH), 3128 (Ar-str.), 1717 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.58 (d, 1H, *J* = 10 Hz, quinolin-C$_2$), 7.62 (d, 1H, *J* = 10 Hz, quinolin-C$_7$), 7.39 (s, 1H, quinolin-C$_5$), 7.36 (d, 1H, *J* = 10 Hz, quinolin-C$_8$), 7.20-7.15 (m, 2H, quinolin-C$_3$, -C$_4$), 3.78 (s, 2H, -CH$_2$), 3.64-3.63 (m, 1H, cyclohexyl-C$_4$), 3.56 (t, 4H, *J$_1$* = *J$_2$* = 5 Hz, piperazin-C$_3$, -C$_5$), 3.51 (t, 4H, *J$_1$* = *J$_2$* = 5 Hz, piperazin-C$_2$, -C$_6$), 3.23 (s, 1H, -NH), 3.15 (s, 1H, -OH), 2.97-2.95 (m, 1H, cyclohexyl-C$_1$), 2.80-2.76 (m, 2H, -CH$_2$) 2.20-2.14 (m, 4H, cyclohexyl-C$_3$, -C$_5$), 1.90-1.85 (m, 4H, cyclohexyl-C$_2$, -C$_6$);^{13}C NMR (125 MHz, DMSO-d$_6$) δ 170.15 (-CO), 148.47 (quinolin-C$_6$), 146.27 (quinolin-C$_2$, -C$_9$), 145.34 (quinolin-C$_7$, -C$_5$), 138.44 (quinolin-C$_{10}$), 134.45 (quinolin-C$_8$), 127.62 (quinolin-C$_3$, -C$_4$), 72.62 (-CH$_2$), 64.91 (piperazin-C$_3$, -C$_5$), 62.84 (piperazin-C$_2$, -C$_6$), 60.17 (cyclohexyl-C$_1$), 59.37 (cyclohexyl-C$_4$), 58.23 (-CH$_2$), 56.81 (cyclohexyl-C$_3$, -C$_5$), 53.29 (cyclohexyl-C$_2$, -C$_6$), 47.57 (-CH$_2$); MS (ESI): *m/z* found 383.6 [M$^+$]; calculated for C$_{22}$H$_{30}$N$_4$O$_2$ 382.2.

3-((4-methylcyclohexyl)amino)-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**96**):

The compound was synthesized as per general procedure described earlier in section 7.1.5.8 using 3-chloro-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**59**) (27.54 mg) (26.27 mg) and 4-methylcyclohexan-1-amine (**89**) (10 .28 mg) to get compound **96**, yield 55 %; mp 258-260 ºC; FTIR (KBr) cm^{-1}: 3362 (-NH), 3154 (Ar-str.), 1682 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.53 (d, 1H, *J* = 10 Hz, quinolin-C$_2$), 7.59 (d,

1H, J = 10 Hz, quinolin-C_7), 7.40 (s, 1H, quinolin-C_5), 7.32 (d, 1H, J = 10 Hz, quinolin-C_8), 7.18-7.13 (m, 2H, quinolin-C_3, -C_4), 3.72-3.71 (m, 1H, cyclohexyl-C_4), 3.68-3.66 (m, 2H, -CH_2), 3.54 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_3, -C_5), 3.49 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_2, -C_6), 3.37 (s, 1H, -NH), 3.31-3.30 (m, 1H, cyclohexyl-C_1), 2.76-2.72 (m, 2H, -CH_2) 2.18-2.11 (m, 4H, cyclohexyl-C_2, -C_6), 1.88-1.75 (m, 7H, cyclohexyl-C_3, -C_5, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.95 (-CO), 149.27 (quinolin-C_6), 147.92 (quinolin-C_2, -C_9), 146.67 (quinolin-C_7, -C_5), 140.37 (quinolin-C_{10}), 138.37 (quinolin-C_8), 128.37 (quinolin-C_3, -C_4), 73.67 (-CH_2), 65.93 (piperazin-C_3, -C_5), 63.61 (piperazin-C_2, -C_6), 61.57 (cyclohexyl-C_1), 57.37 (-CH_2), 55.94 (cyclohexyl-C_2, -C_6), 52.57 (cyclohexyl-C_3, -C_5), 51.62 (cyclohexyl-C_4), 48.37 (-CH_2, -CH_3); MS (ESI): *m/z* found 381.3 [M^+]; calculated for $C_{23}H_{32}N_4O$ 380.2.

3-((4-(hydroxymethyl)cyclohexyl)amino)-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**97**): This was synthesized as per general procedure described earlier in section (7.1.5.8) using 3-chloro-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**59**) (27.54 mg) (26.27 mg) and (4-aminocyclohexyl)methanol (**91**) (11.73 mg) to get compound **97**, yield 50 %; mp 272-275 ºC; FTIR (KBr) cm^{-1}: 3412 (-OH), 3324 (-NH), 3174 (Ar-str.), 1692 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 (d, 1H, J = 10 Hz, quinolin-C_2), 7.60 (d, 1H, J = 10 Hz, quinolin-C_7), 7.43 (s, 1H, quinolin-C_5), 7.30 (d, 1H, J = 10 Hz, quinolin-C_8), 7.15-7.10 (m, 2H, quinolin-C_3, -C_4), 4.21 (s, 1H, -OH), 4.02 (s, 1H, -NH), 3.70 (s, 2H, -CH_2), 3.69-3.68 (m, 1H, cyclohexyl-C_4), 3.51 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_3, -C_5), 3.45 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_2, -C_6), 3.12-3.11 (m, 1H, cyclohexyl-C_1), 2.74-2.68 (m, 4H, -CH_2, -CH_2-OH) 2.20-2.13 (m, 4H, cyclohexyl-C_2, -C_6), 1.90-1.78 (m, 7H, cyclohexyl-C_3, -C_5, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.37 (-CO), 150.37 (quinolin-C_6), 148.31 (quinolin-C_2, -C_9), 147.27 (quinolin-C_7, -C_5), 141.85 (quinolin-C_{10}), 139.57 (quinolin-C_8), 129.27

(quinolin-C_3, -C_4), 74.57 (-CH_2), 66.74 (piperazin-C_3, -C_5), 64.84 (piperazin-C_2, -C_6), 62.37 (cyclohexyl-C_1), 59.37 (-CH_2), 56.68 (cyclohexyl-C_2, -C_6), 53.38 (cyclohexyl-C_3, -C_5), 52.28 (cyclohexyl-C_4), 49.63 (-CH_2); MS (ESI): *m/z* found 397.2 [M^+]; calculated for $C_{23}H_{32}N_4O_2$ 396.5.

3-(cyclohexylamino)-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**98**): It was synthesized as per general procedure described earlier in section 7.1.5.8 using 3-chloro-1-(4-(quinolin-6-yl)piperazin-1-yl)propan-1-one (**59**) (27.54 mg) and cyclohexanamine (**92**) (10 .46 mg) to get compound **98**, yield 58 %; mp 250-254 ºC; FTIR (KBr) cm^{-1}: 3327 (-NH), 3167 (Ar-str.), 1684 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 (d, 1H, *J* = 10 Hz, quinolin-C_2), 7.58 (d, 1H, *J* = 10 Hz, quinolin-C_7), 7.37 (s, 1H, quinolin-C_5), 7.35 (d, 1H, *J* = 10 Hz, quinolin-C_8), 7.17-7.12 (m, 2H, quinolin-C_3, -C_4), 3.80-3.79 (m, 2H, -CH_2), 3.54 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_3, -C_5), 3.49 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_2, -C_6), 3.21 (s, 1H, -NH), 2.79-2.75 (m, 2H, -CH_2) 2.00-1.91 (m, 11H, cyclohexyl- C_1 to -C_6); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.34 (-CO), 149.27 (quinolin-C_6), 147.47 (quinolin-C_2, -C_9), 146.58 (quinolin-C_7, -C_5), 139.68 (quinolin-C_{10}), 137.28 (quinolin-C_8), 128.55 (quinolin-C_3, -C_4), 65.28 (piperazin-C_3, -C_5), 63.55 (piperazin-C_2, -C_6), 59.28 (cyclohexyl-C_1), 58.75 (cyclohexyl-C_4), 56.33 (-CH_2), 55.27 (cyclohexyl-C_3, -C_5), 51.46 (cyclohexyl-C_2, -C_6), 48.38 (-CH_2); MS (ESI): *m/z* found 367.6 [M^+]; calculated for $C_{22}H_{30}N_4O$ 366.2.

3-((4-hydroxycyclohexyl)amino)-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**99**): This was synthesized as per general procedure described earlier in section (7.1.5.8) using 3-chloro-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**60**) (27.54 mg) and 4-aminocyclohexan-1-ol (**90**) (10 .46 mg) to get compound **99**, yield 57 %; mp 323-326 ºC; FTIR (KBr) cm^{-1}: 3432 (-OH), 3328 (-NH), 3161 (Ar-str.), 1674 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (d, 1H, *J* = 10 Hz, quinolin-C_2), 8.29 (d, 1H, *J* = 10

Hz, quinolin-C_7), 8.06 (d, 1H, J = 10 Hz, quinolin-C_4), 7.70 (d, 1H, J = 10 Hz, quinolin-C_5), 7.52-7.48 (m, 2H, quinolin-C_3, -C_6), 3.73-3.72 (m, 1H, cyclohexyl-C_4), 3.68-3.67 (m, 2H, -CH_2), 3.52 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_3, -C_5), 3.49 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_2, -C_6), 3.18 (s, 1H, -NH), 2.97-2.96 (m, 1H, cyclohexyl-C_1), 2.82-2.78 (m, 2H, -CH_2) 2.17-2.11 (m, 4H, cyclohexyl-C_3, -C_5), 1.89-1.84 (m, 4H, cyclohexyl-C_2, -C_6); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.47 (-CO), 149.02 (quinolin-C_8), 146.23 (quinolin-C_2, -C_9), 144.68 (quinolin-C_7, -C_5), 138.85 (quinolin-C_{10}), 130.85 (quinolin-C_4), 128.28 (quinolin-C_3, -C_6), 65.27 (piperazin-C_3, -C_5), 63.36 (piperazin-C_2, -C_6), 61.87 (cyclohexyl-C_4), 60.47 (cyclohexyl-C_1), 59.57 (-CH_2), 57.68 (cyclohexyl-C_3, -C_5), 54.58 (cyclohexyl-C_2, -C_6), 48.26 (-CH_2); MS (ESI): *m/z* found 383.3 [M^+]; calculated for $C_{22}H_{30}N_4O_2$ 382.2.

3-((4-methylcyclohexyl)amino)-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**100**): It was synthesized as per general procedure described earlier (section 7.1.5.8) using 3-chloro-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**60**) (27.54 mg) and 4-methylcyclohexan-1-amine (**89**) (10 .28 mg) to get compound **100**, yield 55 %; mp 305-308 ºC; FTIR (KBr) cm^{-1}: 3285(-NH), 3184 (Ar-str.), 1688 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (d, 1H, J = 10 Hz, quinolin-C_2), 8.25 (d, 1H, J = 10 Hz, quinolin-C_7), 8.05 (d, 1H, J = 10 Hz, quinolin-C_4), 7.68 (d, 1H, J = 10 Hz, quinolin-C_5), 7.49-7.45 (m, 2H, quinolin-C_3, -C_6), 3.70-3.68 (m, 3H, cyclohexyl-C_4, -CH_2), 3.54 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_3, -C_5), 3.51 (t, 4H, $J_1 = J_2$ = 5 Hz, piperazin-C_2, -C_6), 3.32 (s, 1H, -NH), 2.79-2.74 (m, 2H, -CH_2) 2.15-2.09 (m, 5H, cyclohexyl-C_1, -C_2, -C_6), 1.85-1.79 (m, 4H, cyclohexyl-C_3, -C_5), 1.65 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.08 (-CO), 150.17 (quinolin-C_8), 147.38 (quinolin-C_2, -C_9), 145.72 (quinolin-C_7, -C_5), 140.27 (quinolin-C_{10}), 129.74 (quinolin-C_4), 128.58 (quinolin-C_3, -C_6), 72.27 (-CH_2), 64.47 (cyclohexyl-C_1), 63.34 (piperazin-C_2, -C_6), 62.54 (piperazin-

C$_3$, -C$_5$), 60.62 (cyclohexyl-C$_4$), , 59.57 (-CH$_2$), 57.68 (cyclohexyl-C$_3$, -C$_5$), 54.58 (cyclohexyl-C$_2$, -C$_6$), 47.36 (-CH$_2$, -CH$_3$); MS (ESI): *m/z* found 381.4 [M$^+$]; calculated for C$_{23}$H$_{32}$N$_4$O 380.2.

3-((4-(hydroxymethyl)cyclohexyl)amino)-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**101**): It was synthesized as per general procedure described earlier in section (7.1.5.8) using 3-chloro-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**60**) (27.54 mg) and (4-aminocyclohexyl)methanol (**91**) (11.73 mg) to get compound **101**, yield 56 %; mp 283-285 ℃; FTIR (KBr) cm^{-1}: 3452 (-OH), 3238(-NH), 3114 (Ar-str.), 1673 (C=O-str.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.64 (d, 1H, *J* = 10 Hz, quinolin-C$_2$), 8.24 (d, 1H, *J* = 10 Hz, quinolin-C$_7$), 8.00 (d, 1H, *J* = 10 Hz, quinolin-C$_4$), 7.70 (d, 1H, *J* = 10 Hz, quinolin-C$_5$), 7.50-7.46 (m, 2H, quinolin-C$_3$, -C$_6$), 3.76-3.74 (m, 3H, cyclohexyl-C$_4$, -CH$_2$), 3.60 (t, 4H, *J$_1$* = *J$_2$* = 5 Hz, piperazin-C$_3$, -C$_5$), 3.55 (t, 4H, *J$_1$* = *J$_2$* = 5 Hz, piperazin-C$_2$, -C$_6$), 3.40 (s, 1H, -NH), 3.21-3.20 (m, 1H, cyclohexyl-C$_1$), 2.81-2.76 (m, 3H, -CH$_2$, -OH) 2.17-2.12 (m, 4H, cyclohexyl-C$_2$, -C$_6$), 1.87-1.81 (m, 4H, cyclohexyl-C$_3$, -C$_5$), 1.67 (s, 2H, -CH$_2$); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 170.15 (-CO), 150.27 (quinolin-C$_8$), 147.42 (quinolin-C$_2$, -C$_9$), 145.85 (quinolin-C$_7$, -C$_5$), 141.57 (quinolin-C$_{10}$), 129.55 (quinolin-C$_4$), 127.38 (quinolin-C$_3$, -C$_6$), 72.55 (-CH$_2$), 65.77 (cyclohexyl-C$_1$), 64.67 (piperazin-C$_2$, -C$_6$), 63.88 (piperazin-C$_3$, -C$_5$), 61.69 (cyclohexyl-C$_4$), , 59.77 (-CH$_2$), 58.73 (cyclohexyl-C$_3$, -C$_5$), 55.76 (cyclohexyl-C$_2$, -C$_6$), 48.85 (-CH$_2$); MS (ESI): *m/z* found 397.2 [M$^+$]; calculated for C$_{23}$H$_{32}$N$_4$O$_2$ 396.2.

3-(cyclohexylamino)-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**102**): The compound was synthesized as per general procedure described earlier in section 7.1.5.8 using 3-chloro-1-(4-(quinolin-8-yl)piperazin-1-yl)propan-1-one (**60**) (27.54 mg) and cyclohexanamine (**92**) (10 .46 mg) to get compound **102**, yield 58 %; mp 262-266 ℃; FTIR (KBr) cm^{-1}: 3227(-NH), 3169 (Ar-str.), 1716 (C=O-str.); ^{1}H NMR (500 MHz,

DMSO-d_6) δ 8.60 (d, 1H, J = 10 Hz, quinolin-C_2), 8.31 (d, 1H, J = 10 Hz, quinolin-C_7), 8.09 (d, 1H, J = 10 Hz, quinolin-C_4), 7.72 (d, 1H, J = 10 Hz, quinolin-C_5), 7.51-7.47 (m, 2H, quinolin-C_3, -C_6), 3.69 (s, 2H, -CH_2), 3.58 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_3, -C_5), 3.53 (t, 4H, J_1 = J_2 = 5 Hz, piperazin-C_2, -C_6), 3.38 (s, 1H, -NH), 2.82-2.77 (m, 2H, -CH_2) 1.98-1.89 (m, 11H, cyclohexyl- C_1 to –C_6); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.13 (-CO), 148.24 (quinolin-C_8), 146.85 (quinolin-C_2, -C_9), 145.27 (quinolin-C_7, -C_5), 142.38(quinolin-C_{10}), 130.24 (quinolin-C_4), 129.64 (quinolin-C_3, -C_6), 73.43 (-CH_2), 65.58 (cyclohexyl-C_1), 64.26 (piperazin-C_2, -C_6), 63.68 (piperazin-C_3, -C_5), 61.64 (cyclohexyl-C_4), , 58.27 (-CH_2), 56.28 (cyclohexyl-C_3, -C_5), 55.82 (cyclohexyl-C_2, -C_6), 48.24 (-CH_2); MS (ESI): *m/z* found 367.3 [M^+]; calculated for $C_{22}H_{30}N_4O$ 366.2.

7.2.3 *In-vitro* AChE, and BuChE inhibition assays

The procedure described in section 4.1.6.1 was used to performed the assays (358). Brifely, the different concentrations in range of 10 µM to 0.1 nM of test compounds were used to determine the IC_{50}.

7.2.4 *In- vitro* β-site APP cleaving enzyme 1 (BACE1) inhibition assay

The assay was performed by fluorimetric method in Synergy HTX multi-mode reader (BioTek, USA) in black 96-well plates. Different concentrations, in range of 10 µM to 0.1 nM of test compounds were used to determine the IC_{50}. The inhibitors were added in acetate buffer of, pH 4.5, and incubated at 37 °C with 20 µL of BACE-1 (0.33U/ml) solution for 60 min. 100 nM final concentration of substrate (MCA-SEVNLDAEFR-Ednp-KRR-NH_2·3TFA) was added to start reaction. Hydrolysis of substrate was followed kinetically for two hours at interval of fifteen minutes. Percentage inhibitions were calculated from expression: 100-(v_i/v_o X 100) where, v_i is rate calculated in

presence of inhibitor and v_o is enzyme activity. The IC_{50} values were calculated by GraphPad Prism 4.0 (GraphPad Software Inc., San Diego, CA, USA) (268, 426, 427).

7.2.5 PAMPA assay

The detail of assay protocol was mentioned in section 4.1.6.5. The concentration of drug in acceptor, donor and reference wells were determined by UV spectroscopy. Each sample was scanned to at least five different wavelengths and in three independent runs.

7.2.6 Pharmacokinetic studies

Male Wistar rats of 200-250g (n=3) were used for pharmacokinetic studies. Selected compound was suspended in 0.1% CMC and administered by i.p route at a dose of 25 mg/kg. After administration, the animals were anesthetized with ether and blood, CSF and brain samples were collected at five time points (0.5, 1, 2, 4 and 6 hr). 250 µL of blood was collected for plasma related experiments by cardiac puncture in heparin containing tubes. To each sample 25 µL of internal standard was added. Blood samples were centrifuged at 3500 rpm for 10 min (4 °C) to isolate plasma. 25 µL of plasma and 100 µL of mobile phase (methanol: acetonitrile, 0.5:0.5) were mixed and vortexed for one min followed by centrifugation at 12300 rpm for 5 min. 20 µL aliquot of the resulting solution was analysed by HPLC. Further, 25 µL of CSF was collected and dilution with 50 µL of mobile phase and vortex for one min. 20 µL of the filtered CSF mixture was injected in HPLC for analysis. Accumulation of drug within hippocampus was determined by isolating brain from the animals after collecting blood and CSF. Animals were sacrificed by cervical dislocation, following which their brain was isolated, rinsed by cold saline and stored at -80 °C for further use. On the day of assay frozen tissues were thawed at room temperature and hippocampus was isolated. Hippocampal tissue was homogenized with 0.5 ml of methanol for 1 min followed by

vortex for 1 min. 25 µL aliquot was transferred into an eppendorf tube. To each sample, 25 µL of methanol was added, and the samples were centrifuged at 11 000 g for 5 min. A 20 µL aliquot of the supernatants was diluted to 60 µL with the mobile phase and a 20 µL aliquot was injected into HPLC for analysis. Quantification of the drug concentration in each aliquot was achieved by standard curve method. Half-life of compounds was calculated by GraphPad software, fitting to a single-phase exponential decay equation.

7.2.7 Cell line based neuroprotection studies

The assay was performed according to the protocol mentioned in the section 4.1.6.6. Briefly, cells were incubated with +TC and –TC in CO_2 incubator. In the test group (70-1µM) TC was absent (TC-). The absorbance was immediately recorded at 570 nm and response was expressed in percentage cell viability relative to +TC as a control.

7.3 Result & discussion

7.3.1 Docking study

Docking study was performed for selected set of compounds on three targets viz. AChE (PDB id 4EY7), BuChE (PDB id 4BDS), and BACE-1 (PDB id 6EQM). The results are summarized in **Table 7.1**

The docking poses of important interactions were observed. **Figure 7.4A** represent docking poses of compound **97** with AChE (PDB id 4EY7). The compound lies within the vicinity of active site and important interactions include H-bonding interactions with Tyr 103, Pro 119, Asn118, and Trp 117, π-π interactions with Phe 317, Phe 328, Phe 369 and Tyr368.
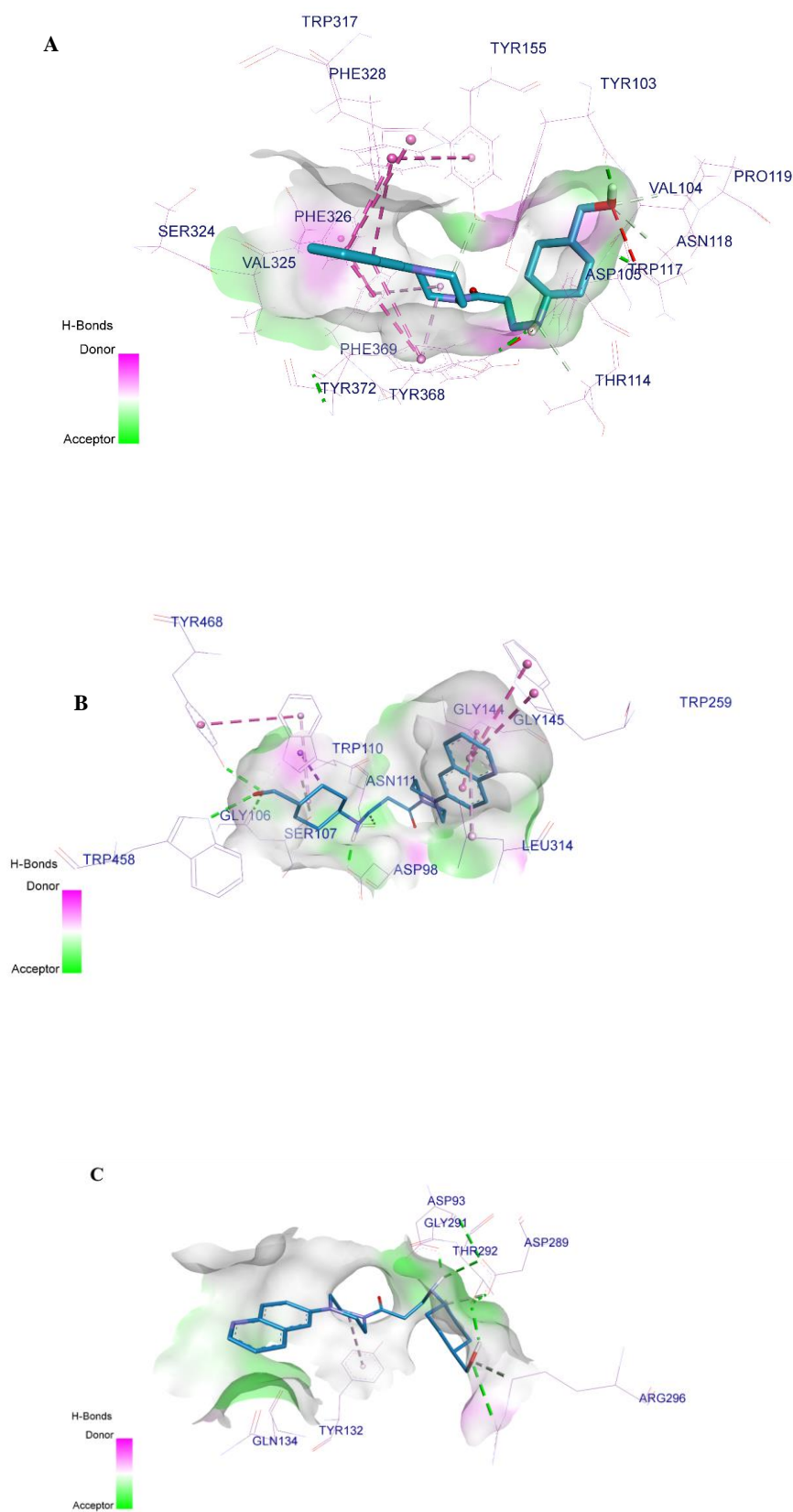
Figure 7.4B represents docking pose of compound **97** with BuChE (PDB id 4BDS). The compound lies in the region of active site. The important interactions include H-

bonding interaction with Gly 106, Trp 458, and Tyr 468, π-π interactions with Gly 144, Gly 145, and Leu 314.

Table 7.1 Binding energy of compound against AChE (PDB id 4EY7), BuChE (PDB id 4BDS), and BACE-1 (PDB id 6EQM).

Compound	Binding energy (Kcal/mol)		
	AChE	**BuChE**	**BACE1**
32	-11.529	-10.08	-8.32
46	-10.73	-9.75	-7.36
76	-10.33	-8.66	-7.7
83	-11.22	-9.07	-6.9
85	-11.09	-8.71	-7.61
93	-12.03	-10.8	-8.43
94	-11.77	-9.94	-8.56
95	-11.68	-9.83	-7.94
96	-12.1	-10.23	-8.65
97	-12.33	-10.95	-7.88
98	-11.71	-9.11	-7.64
99	-11.83	-9.63	-7.04

Figure 7.4 Doking pose of compound **97** with (**A**) AChE (PDB id 4EY7), (**B**) BuChE (PDB id 4BDS) and (**C**) BACE-1 (PDB id 6EQM).

The docking poses of compound **97** with BACE-1 (PDB id 6EQM) represented in **Figure 7.4C**. The compound lies within the region of active site and important interactions H-bonding interaction with Asp 289, Arg 296 and Tyr 468, π-alkyl interactions with Tyr 132 and π- π interactions with Gln 134.

7.3.2 *In-vitro* AChE, and BuChE inhibition assays

AChE and BuChE were found to be involved in the pathogenesis of the AD. *Para* and *meta* substituted phenyl piperazinyl-*N*-quinolin-3/6/8-yl-alkylamides (**19-51**) were obtained from different *in-silico* optimization. Three different series of compounds containing substitution at third, sixth and eighth positions of quinoline were synthesized. These quinolines were further attached with linkers containing one or two carbons and substituted phenyl piperazine. The *in-vivo* screening of the compounds showed that the substitution at sixth position of quinoline yielded better results followed by eighth and third position in both series (**Table 7.2**).

7.3.3 *In-vivo* β-site APP cleaving enzyme 1 (BACE1) inhibition assay

BACE1 produces toxic Aβ which plays major role in pathogenesis of AD. Although, BACE1 inhibitor drug development has been challenging, but several inhibitors have lately entered in clinical trials and efficacy of these inhibitors has been reported. The pharmacophore *p/m*-substituted phenyl piperazinyl-*N*-quinolin-3/6/8-yl-alkylamide (**19-51**) were designed as multitargeting molecules. Initially, the designed molecules (**19-23**) failed to hit the BACE1. Molecules have IC$_{50}$ >300 µM indicating that the pattern of arrangement of different fragments in are not suitable for the enzyme cavity. Though, docking study of these molecules displayed the descent binding score and desirable amino acid residue ligand interactions. The *in-vitro* results indicated that three amino quinolins containing compounds **19-23** were not active against BACE1. Six amino quinolins containing compounds **24-37** exhibited some *in-vitro* activity against

BACE1, followed by eight amino quinolins **38**-**51**. Compound **32** (IC$_{50}$ 85.623±0.1226 μM) containing two carbon linker and hydrogen bond donor (hydroxyl group) at para position of phenyl group displayed the maximum activity in the series, followed by compound **27** (IC$_{50}$ 90.109±0.1781 μM). The series of compounds (**19**-**51**) have certain BACE1 inhibition potential but it was not enough to consider these molecules as hits (**Table 7.2**).

The challenge in new design strategy was to maintain or improve AChE and BuChE inhibition potential along with decrease in BACE1 inhibition. Accordingly, we changed the position of piperazine and synthesized new series of molecules **68**-**88**. These molecules showed better with the targets and registered further lower IC$_{50}$'s against AChE and BuChE along with BACE1. As the earlier series of compounds, six amino quinolins containing molecules with two carbon linker and hydroxyl group at para position were active and similar observations were recorded in this series **68**-**88** also. Compound **76** (IC$_{50}$ 02.153±0.0890 μM) was found to be most active, followed by compound **73** (IC$_{50}$ 10.289±0.0078 μM). Compounds **75** (IC$_{50}$ 11.245±0.0024 μM)and **72** (IC$_{50}$ 13.582±0.1841 μM) also possessed good activity. Further, these compounds were tuned for ADME improvement and that lead to compounds **93**-**102**. ADME maintenance provided the compounds, which have highest activity among all compounds against AChE, BuChE and BACE1. These compounds have IC$_{50}$ in the range of 06.263 to 00.032 μM. Compound **95** (IC$_{50}$ 00.032±0.0012 μM) exhibited most potent activity among both series with IC$_{50}$ of 00.032±0.0012 μM, followed by compounds **98** (IC$_{50}$ 00.835±0.0013 μM) and **97** (IC$_{50}$ 01.036±0.0014 μM). Compound **99** containing eight amino quinolins and para hydroxyl group also showed remarkable inhibition potential (IC$_{50}$ 01.327±0.0027 μM) (**Table 7.3**).

Table 7.2 Quinolinyl alkyl piperazine (scheme I) analogues with inhibitory activities (IC$_{50}$) AChE, BuChE and BACE-1 assay ±SE.

Comp	AQ	R	n	AChE IC$_{50}$ ±SE (μM)	BuChE IC$_{50}$ ±SE (μM)	BACE-1 IC$_{50}$ ±SE (μM)
19	-3NH	4-NO$_2$	1	261.240±2.129	375.241±0.1071	>300
20	-3NH	4-F	1	243.060±1.630	338.549±0.1027	>300
21	-3NH	4-Cl	1	218.623±1.073	315.224±0.1140	>300
22	-3NH	4-OH	1	235.214±2.819	328.027±0.0377	286.345±0.08348
23	-3NH	4-CH$_3$	1	288.026±1.048	382.186±0.0433	>300
24	-6NH	4-NO$_2$	1	42.885±1.373	63.114±0.0773	163.917±0.1103
25	-6NH	4-F	1	30.951±0.1369	52.358±0.1124	155.262±0.0963
26	-6NH	4-Cl	1	21.052±0.0544	50.294±0.0471	138.182±0.1071
27	-6NH	4-OH	1	20.157±0.2982	42.185±0.0406	90.109±0.1781
28	-6NH	4-CH$_3$	1	62.853±0.0516	82.964±0.0391	120.131±0.1663
29	-6NH	4-NO$_2$	2	20.158±0.0878	60.281±0.0472	132.615±0.1126
30	-6NH	4-F	2	18.015±0.1158	43.284±0.0455	128.694±0.0979
31	-6NH	4-Cl	2	13.518±0.2132	31.632±0.0362	113.126±0.0900
32	-6NH	4-OH	2	15.362±0.0610	30.284±0.0371	85.623±0.1226
33	-6NH	4-CH$_3$	2	42.156±0.1766	61.714±0.0243	98.127±0.1176
34	-6NH	3-Cl	1	53.829±0.0678	123.354±0.0281	136.125±0.1725
35	-6NH	3-OH	1	31.284±0.1280	133.584±0.0437	128.251±0.1478
36	-6NH	3-Cl	2	40.385±0.1127	142.321±0.0294	145.247±0.1228
37	-6NH	3-OH	2	50.181±0.0503	134.284±0.0295	115.104±0.1433
38	-8NH	4-NO$_2$	1	106.358±0.133	185.439±0.0326	225.354±0.1379
39	-8NH	4-F	1	95.516±0.0831	146.851±0.0389	215.026±0.1147
40	-8NH	4-Cl	1	81.637±0.1153	132.584±0.0451	207.325±0.0964
41	-8NH	4-OH	1	95.432±0.1606	118.321±0.0336	118.864±0.1043
42	-8NH	4-CH$_3$	1	108.215±0.094	123.217±0.0391	134.187±0.1053
43	-8NH	4-NO$_2$	2	52.428±0.1295	83.614±0.0315	196.311±0.0661
44	-8NH	4-F	2	45.584±0.0281	62.284±0.0412	188.252±0.0903
45	-8NH	4-Cl	2	31.925±0.0326	48.369±0.0474	172.387±0.0958
46	-8NH	4-OH	2	35.246±0.0367	53.842±0.0986	100.925±0.0918
47	-8NH	4-CH$_3$	2	83.231±0.0603	238.647±0.0385	113.816±0.1824
48	-8NH	3-Cl	1	153.315±0.069	225.952±0.0322	153.272±0.1073
49	-8NH	3-OH	1	161.257±0.189	238.175±0.0327	135.422±0.1048
50	-8NH	3-Cl	2	148.315±0.072	218.954±0.0455	241.015±0.0823
51	-8NH	3-OH	2	136.129±0.039	229.358±0.1457	129.314±0.1002

Table 7.3 Quinolinyl piperazine alkyl (scheme II) analogues with inhibitory activities (IC$_{50}$) AChE, BuChE and BACE-1 assay ±SE.

Comp	AQ	R	n	AChE IC$_{50}$ ±SE (µM)	BuChE IC$_{50}$ ±SE (µM)	BACE-1 IC$_{50}$ ±SE (µM)
68	-3NH	4-Cl	1	85.321±0.0780	231.748±0.0692	181.624±0.0694
69	-3NH	4-OH	1	103.813±0.0185	253.110±0.0780	113.186±0.1280
70	-6NH	4-F	1	01.976±0.0130	09.115±0.0145	35.162±0.1077
71	-6NH	4-Cl	1	01.0296±0.0125	10.817±0.6541	30.265±0.1286
72	-6NH	4-CH$_3$	1	03.175±0.0220	53.249±0.2240	13.582±0.1841
73	-6NH	4-OH	1	00.641±0.0017	08.359±0.0749	10.289±0.0078
74	-6NH	4-Cl	2	00.0362±0.0025	03.354±0.0357	25.137±0.0153
75	-6NH	4-CH$_3$	2	01.816±0.0380	28.137±0.3576	11.245±0.0024
76	-6NH	4-OH	2	00.0471±0.0012	03.586±0.2722	02.153±0.0890
77	-6NH	3-Cl	2	03.618±0.0165	21.834±0.3854	30.247±0.0281
78	-6NH	3-CH$_3$	2	08.217±0.1358	68.640±0.1859	27.418±0.0026
79	-6NH	3-OH	2	07.316±0.0273	45.537±0.3462	24.316±0.0947
80	-8NH	4-Cl	1	08.953±0.0509	53.394±0.1723	100.026±0.5088
81	-8NH	4-CH$_3$	1	21.254±0.0822	108.582±0.2376	80.311±0.1893
82	-8NH	4-OH	1	10.284±0.1437	28.951±0.2540	60.241±0.0211
83	-8NH	4-Cl	2	02.018±0.0203	06.294±0.0152	75.274±0.0561
84	-8NH	4-CH$_3$	2	27.584±0.1744	72.110±0.2533	56.237±0.0162
85	-8NH	4-OH	2	02.957±0.0018	07.885±0.2044	50.271±0.0768
86	-8NH	3-Cl	2	30.982±0.0428	103.538±0.2605	76.542±0.0975
87	-8NH	3-CH$_3$	2	58.637±0.1271	158.437±0.0894	71.423±0.1538
88	-8NH	3-OH	2	40.286±0.0255	98.357±0.0278	65.126±0.0023
93	-3NH	4-CH$_3$	2	41.358±0.4793	206.382±0.1721	06.263±0.0407
94	-3NH	4-OH	2	23.591±0.1238	195.349±0.1470	05.327±0.0091
95	-6NH	4-OH	2	00.062±0.0010	02.681±0.0574	00.032±0.0012
96	-6NH	4-CH$_3$	2	05.183±0.0327	08.817±0.2971	02.631±0.0748
97	-6NH	4-CH$_2$-OH	2	07.315±0.0307	09.682±0.0174	01.036±0.0014
98	-6NH	4-H	2	03.826±0.0455	06.915±0.5271	00.835±0.0013
99	-8NH	4-OH	2	01.513±0.0325	08.354±0.0745	01.327±0.0027
100	-8NH	4-CH$_3$	2	11.617±0.0273	20.134±0.1852	04.385±0.0478
101	-8NH	4-CH$_2$-OH	2	13.258±0.0190	35.834±0.2473	03.624±0.0195
102	-8NH	4-H	2	08.926±0.0263	31.296±0.1247	02.392±0.0056
DNP	-----	-----	----	00.021±0.0013	01.267±0.0422	00.183±0.0150
Peptide	-----	-----	----	>500±	>1000	00.021±0.0020

7.3.4 PAMPA assay

The synthesized compounds were further assessed for their BBB permeability. Compounds **19**-**51** and **68**-**88** possess reasonable good BBB permeability. Improvement in BBB permeability of compounds **93-98** was observed due to the conversion of aromatic system into non-aromatic moiety. Compounds **26** and **27** showed BBB permeability of $4.58\pm0.84\times10^{-6}$ and $4.72\pm0.57\times 10^{-6}$ cm s^{-1}. Compounds **31**and **32** registered minor increase in the permeability (Pe $6.13\pm0.95\times10^{-6}$, $7.62\pm0.75\times10^{-6}$ cm s^{-1}) due to increase in the lipophilicity of compounds. Compound **97** had highest BBB permeability with Pe of $14.6.\pm0.57\times10^{-6}$ cm s^{-1} followed by compound **93** (Pe $11.57\pm0.85\times10^{-6}$ cm s^{-1}) (**Table 7.4**).

Table 7.4 Permeability, Pe (10-6 cm s1) determined by BBB-PAMPA study.

Comp.	Pe (10^{-6} cm s^{-1}) SE	Prediction[b]
26	4.58±0.84	CNS+
27	4.72±0.57	CNS+
31	6.13±0.95	CNS+
32	7.62±0.75	CNS+
76	7.29±0.21	CNS+
93	11.57±0.85	CNS+
95	9.85±0.26	CNS+
97	14.6.±0.57	CNS+
98	8.28±0.73	CNS+

Pe (exp) > 4.3926(10^{-6} cms^{-1})- high BBB permeable.
Pe (exp) in between 4.3926- 1.7766 (10^{-6} cms^{-1})- unpredictable.
Pe (exp) < 1.7766 (10^{-6} cms^{-1})- low BBB permeable.

7.3.5 ADME prediction

Pharmacokinetic studies were performed to learn the penetration and localization of compounds **76** and **95** in brain and hippocampus. Peak plasma concentration was attained after thirty min of dosing and half-life of compounds **76** and **95** were found to be 0.8 and 1.05 h, respectively. Hippocampus is center of memory and learning process

thus, localization of the compounds in this region was evaluated, which was 38 and 98 ng/mg in 100X30 mm dimension for compounds **76** and **95**, respectively. Presence of compounds in hippocampus in such concentrations established their suitability in management of neurodegenerative diseases. Log BB value is generally used for the determination of brain permeability of drugs. Log BB$\geq$ -1 are considered as acceptable for crossing the blood brain barrier (BBB). Compounds **76** and **95** showed log BB values of -0.54 and -0.44, which were appropriate for crossing BBB (**Table 7.5**).

Tables.7.5 Pharmacokinetic studies of compounds **76** and **95**; concentration of compound in plasma, brain and hippocampus after 30 min of dosing.

Comp	Sample	Plasma (ng/ml)	Brain (ng/gm)	Hippocampus[a] (ng/mg)	Log BB[b]	Half life[c] (h.)
76	n = 2	1124.25	321.37	38.00	-0.54	0.8
95	n =2	1586.48	570.28	98.00	-0.44	1.05

[a]150 mg of 100×30mm size of dissect pieces was used; [b]ratio of brain to plasma concentration.

7.3.6 Cell line based neuroprotection studies

Neuronal death was found to be associated with AD where, ROS was considered to be mainly responsible, among the other factors. The mutated neuronal cell line MC65 itself produces Aβ in the absence of tetracycline (TC-) leading to the generation of ROS. Compound **95** showed significant decrease in Aβ production, when compared with TC- cells at doses of 50 and 100 μM (**Figure 7.5**).

Figure 7.5 Neuroprotection assay of compound **95** on MC 65 cell line (One-way ANOVA followed by Newman-Keuls multiple comparison test compare all pair of column *** $p < 0.0001$).
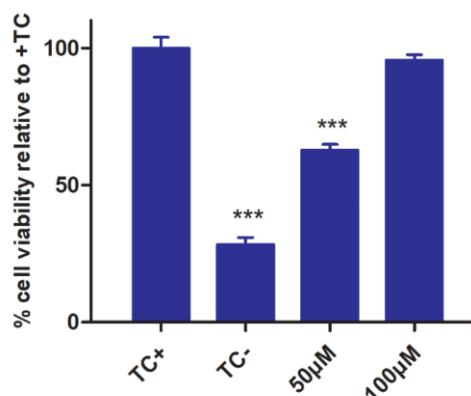
7.4 Conclusion

Compounds **19**-**23** produced mild activity against AChE, BuChE and were feebly active against BACE1. Compound **32**, of six amino quinoline series containing hydroxyl group at fourth position and two carbon linker, was found to be most active among quinolinyl alkyl piperazine (scheme I) series of compounds (**19**-**31**) followed by compound **27**. This series was further optimized to improve the potency against AChE, BuChE and BACE1. The activity of compounds were increased by 200 times due to shifting the position of piperazine. Compounds **72**, **73**, **75** and **76** were found to be more potent than their previous analogues. Compound **76**, of series of compounds **68**-**88** was found to be more active but its BBB permeability and pharmacokinetic properties were not much impressive. These results led to the synthesis of compounds **93**-**102**, which showed very good activity, BBB permeability and ADME properties. Compound **95** of the series can be considered as lead compound of the series with balanced potency and drugability.