5. Experimental section

5.1 Chemical work

5.1.1 General methods

All the reagents and solvents required for synthesis were purified by general laboratory techniques before use. Compounds were purified through chromatographic separations using silica gel (100-200 mesh) as well as neutral alumina as stationary phases. Melting points of all the synthesized compounds were determined in open glass capillaries using a Veego make silicon oil bath-type melting point apparatus and are uncorrected. The IR spectra were recorded using KBr disc method on a Bruker FT-IR, Model ALPHA-T. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions on a Bruker Avance II 400 NMR spectrometer with TMS (tetramethylsilane) as the internal standard. Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS and multiplicities are given as s (singlet), d (doublet), t (triplet), m (multiplet) and bs (broad singlet). Mass spectra were recorded using a Thermo Fisher mass spectrometer with EI as ion source or an Advion mass spectrometer with ESI as ion source. Completion of reactions was monitored by thin layer chromatography (TLC) on silica gel G plates, visualizing with ultraviolet light or iodine vapors. Microwave reactions were performed in Catalyst, microwave reactor. Purity was determined by HPLC analysis and was found above 98% for all the compounds.

5.1.2 Synthesis of starting materials and intermediates

- **Synthesis of 2-amino-4,5-dimethoxybenzonitrile** (**132**)

Veratraldehyde (**128**)

Vanillin (**127**) (5.0 g, 33.00 mM) was taken in a three neck Rb flask equipped with two dropping funnels, and fused at 100 °C. Addition of an aqueous solution of potassium hydroxide (2.75 g, 49.10 mM in 6.0 mL of water) was started at a rate of 1-2 drops per second while the external heating was continued. Dimethyl sulfate (DMS) (4 mL, 43.05 mM) was added after addition of one-fourth part of potassium hydroxide solution and at the same rate as that of potassium hydroxide solution. The *p*H of the solution was always maintained basic by adjusting the rate of addition of the two reagents. The external heating was switched off after 5 min of the start of the addition and the solution was

allowed to reflux by the heat of the reaction. Yellow colored oil was separated out in the reaction mixture at the end of the addition. The solution was stirred for another 30 min after the addition of both of the reagents was completed. The reaction mixture was kept aside at 10-12 °C for 12-18 h. The solid mass so obtained was triturated with ice-cold water, filtered, washed with water and dried under vacuum to give white colored veratraldehyde (**128**) (4.5 g, 82.1 %) m. p. 41-43 °C (lit.[129,130] 43-44.5 °C).

Anal.:

TLC:	R_f 0.41 (*n*-Hexane: ethyl acetate, 19:1)
IR (KBr, cm^{-1}):	3018, 1688, 1590, 1513, 1274, 1137 and 1019.

3,4-Dimethoxybenzaldoxime (**129**)

Method A: Veratraldehyde (**128**) (5.0 g, 30.12 mM) was dissolved in warm methanol (12 mL) in an Rb flask (100 mL). Hydroxylamine hydrochloride (10.1 g, 144.57 mM) and sodium acetate trihydrate (20.5 g, 150.6 mM) were added in the above solution and the mixture was refluxed for 1-2 hours. After completion of the reaction, the reaction mixture was poured into ice cold water and acidified upto *p*H 3-4 by adding concentrated hydrochloric acid (drop-wise). The precipitate so obtained was subjected to filtration, washed with water and dried through vacuum to give 3,4-dimethoxybenzaldoxime (**129**) (4.5 g, 82%), m. p. 88-90 °C.

Anal.:

TLC:	R_f 0.43 (*n*-Hexane: ethyl acetate, 12:8)
IR (KBr, cm^{-1}):	3451, 3130, 3015, 1514, 1269 and 1020.

3,4-Dimethoxybenzonitrile (**130**)

Method B: 3,4-Dimethoxybenzaldoxime (**129)** (5 g, 27.6 mM) was dissolved in dry benzene in an Rb flask (100 mL). Thionyl chloride (4.03 mL, 55.2 mM) was added with constant stirring into the above solution through dropping funnel. The hydrogen chloride gas produced during the reaction was trapped through sodium hydroxide trap. The reaction mixture was allowed to stir for 2 hours. After completion, the reaction mixture was washed successively with cold water and the final wash was given with saturated solution of sodium bicarbonate. The mixture was extracted with chloroform, dried and

evaporated the organic solvent under reduced pressure to afford a light yellow solid mass of compound (**130**) (3.9 g, 86.6 %), m. p. 65-67 °C (lit.[131]67 °C).

Anal.:

TLC:	R_f 0.51 (*n*-Hexane: ethyl acetate, 16:4)
IR (KBr, cm^{-1}):	3012, 2935, 2223, 1597, 1515, 1270 and 1017.

4,5-Dimethoxy-2-nitrobenzonitrile (**131**)

Method C: In an Rb flask, concentrated nitric acid (23 mL) was cooled to 5 °C and 3,4-dimethoxybenzonitrile (**130**) (10 g, 61.30 mM) was added to it portion-wise over a period of 10 min, keeping the temperature of the reaction mixture between 5-10 °C. The reaction mixture was stirred at room temperature for another 2 hours and quenched into crushed ice to give yellow precipitate which was filtered, thoroughly washed with cold water and dried under vacuum to obtain compound (**131**) (11 g, 94.6%), m. p. 165-167 °C (lit.[132] 164-166 °C). As the product is light sensitive, enough care was taken to prevent the product from exposure to light.

Anal.:

TLC:	R_f 0.41 (*n*-Hexane: ethyl acetate, 16:4)
IR (KBr, cm^{-1}):	3130, 2926, 2229, 1525, 1386, 1293 and 1061.

2-Amino-4,5-dimethoxybenzonitrile (**132**)

Method D: 4,5-Dimethoxy-2-nitrobenzonitrile (**131**) (5 g, 24.00 mM) was taken in a two neck Rb flask (250 mL), concentrated hydrochloric acid (10 mL) and granulated tin (4.3 g, 36.02 mM) were added into the above solution and allowed to reflux for 2 hours on water bath. After completion of the reaction, the mixture was poured into ice-cold water and basified with sodium hydroxide until the precipitated tin oxide got dissolved, filtered the precipitate and it was washed with cold water to remove remaining tin oxide. The solid so obtained was dried under vacuum to obtain the desired compound **(132)** (3.5 g, 81.8%), m. p. 97-99 °C (lit.[133] 96-101 °C).

Anal.:

TLC:	R_f 0.24 (*n*-Hexane: ethyl acetate, 16:4)
IR (KBr, cm^{-1}):	3131, 3205, 3025, 2994, 2213, 1512, 1400, 1270, 1135, 1004 and 840.

- **Synthesis of 2-amino-4,5-methylenedioxybenzonitrile (138)**

Piperonal (**134**)

Piperonyl alcohol (**133**) (5.0 g, 33.31 mM) and Dess-Martin periodinane (DMP) (15.2 g, 40.20 mM) were dissolved in acetonitrile (ACN) (100 mL) in a single neck Rb flask (250 mL). Acetic acid (2.5 mL) was added into the above solution and the reaction mixture was stirred at room temperature for 1-2 hours. The solvent was evaporated under reduced pressure and the residue so obtained was directly separated through column chromatography using *n*-hexane and ethyl acetate as solvents (*n*-hexane: ethyl acetate, 9:1) to afford the desired compound (**134**) (4.4 g, 89%) m. p. 33-35 °C (lit.[134] 35-37 °C).

Anal.:

TLC: R_f 0.51 (*n*-Hexane: ethyl acetate, 15:5)

IR (KBr, cm^{-1}): 2919, 2852, 1675, 1450, 1260 and 1038.

3,4-Methylenedioxybenzaldoxime (**135**)

Reaction of piperonal (**134**) (5.0 g, 3.33 mM), sodium acetate trihydrate (2.27 g, 16.67 mM) and hydroxylamine hydrochloride (1.11 g, 15.98 mM) in methanol (5 mL) under a set of conditions described in **Method A**, afforded compound (**135**) (4.5 g, 88.3%) m. p. 85-86 °C.

Anal.:

TLC: R_f 0.55 (*n*-Hexane: ethyl acetate, 15:5)

IR (KBr, cm^{-1}): 3225, 3152, 3000, 1605, 1498, 1450, 1254, 1037 and 735.

3,4-Methylenedioxybenzonitrile (**136**)

Reaction of 3,4-methylenedioxybenzaldoxime (**135**) (5.0 g, 30.30 mM) and thionyl chloride (11.06 mL, 151.51 mM) in dry benzene (25 mL) under a set of conditions described in **Method B**, afforded compound (**136**) (3.5 g, 77.5%) m. p. 66-68 °C.

Anal.:

TLC: R_f 0.49 (*n*-Hexane: ethyl acetate, 15:5)

IR (KBr, cm^{-1}): 2921, 2222, 1604, 1490, 1442, 1259, 1033 and 812.

4,5-Methylenedioxy-2-nitrobenzonitrile (**137**)

Nitration of 3,4-methylenedioxybenzonitrile (**136**) (5.0 g, 33.50 mM) with concentrated nitric acid (10.40 mL, 234.50 mM) under a set of conditions described in **Method C**, gave a light yellow solid of compound (**137**) (3.2 g, 52.3%) m. p. 168-70 °C.

Anal.:

TLC: R_f 0.51 (*n*-Hexane: ethyl acetate, 16:4)

IR (KBr, cm^{-1}): 2925, 2231, 1602, 1530, 1338, 1289, 1035 and 885.

2-Amino-4,5-methylenedioxybenzonitrile (**138**)

4,5-Methylenedioxy-2-nitrobenzonitrile (**137**) (5.0 g, 26.0 mM) was refluxed with granulated tin (4.32 g, 36.40 mM) in concentrated hydrochloric acid (27.06 mL, 1053.0 mM) under a set of conditions described in **Method D**, to obtain a brown solid of compound (**138**) (3.2 g, 77.4%) m. p. 101-02 °C.

Anal.:

TLC: R_f 0.49 (*n*-Hexane: ethyl acetate, 15:5)

IR (KBr, cm^{-1}): 3457, 3363, 3247, 2917, 2203, 1642, 1612, 1483, 1269, 1037 and 928.

- **Synthesis of 2-amino-3,4-dimethoxybenzonitrile (145)**

4-Acetoxy-3-methoxybenzaldehyde (139)

Vanillin (**127**) (5.0 g, 32.90 mM) was taken in a single neck Rb flask and suspended in dichloromethane (DCM) (50 mL). Acetic anhydride (3.76 mL, 39.5 mM) and pyridine (3.28 mL, 39.5 mM) were added into the above solution and the reaction mixture was stirred for 8-10 hours at room temperature. After completion of the reaction, the excess solvent was evaporated under reduced pressure and the residue poured into ice-cold water to give a white precipitate. Filtered the precipitate, washed with 1N hydrochloric acid, subsequently washed with saturated solution of sodium bicarbonate, then with saturated brine solution and dried under vacuum to afford compound (**139**) (4.8 g, 90.1%) m. p. 76-78 °C (lit. 74-78 ^{0}C).

Anal.:

TLC: R_f 0.29 (*n*-Hexane: ethyl acetate, 15:5)

IR (KBr, cm^{-1}): 3017, 2968, 2847, 2805, 1756, 1690, 1598 and 1208.

4-Acetoxy-3-methoxy-2-nitrobenzaldehyde (140)

Fuming nitric acid (26.75 mL, 643.75 mM) was child at -10 ^{0}C in a single neck Rb flask and 4-acetoxy-3-methoxybenzaldehyde (**139**) (5.0 g, 25.75 mM) was added portionwise with vigorous and continuous stirring. After the complete addition, the reaction mixture was stirred for another 1 hour at -10 to -5 ^{0}C. The reaction mixture was quenched into excess of crushed ice to obtain a yellow precipitate which was filtered, washed with cold water until the filtrate was neutralized. The residue was dried under vacuum to obtain compound (**140**) (3.9 g, 63.4%) m. p. 83-85 °C.

Anal.:

TLC:	R_f 0.53 (*n*-Hexane: ethyl acetate, 15:5)
IR (KBr, cm^{-1}):	3017, 2918, 1755, 1703, 1690, 1547, 1342 and 1200.

4-Hydroxy-3-methoxy-2-nitrobenzaldehyde (141)

4-Acetoxy-3-methoxy-2-nitrobenzaldehyde (**140**) (5.0 g, 21.25 mM) was taken in one neck Rb flask. Then aqueous solution (15 mL) of potassium hydroxide (4.20 g, 74.37 mM) was added and refluxed for 1-2 hours. The reaction mixture was poured in ice, and acidified with drop-wise addition of concentrated hydrochloric acid to give a brown precipitate which was filtered, washed with cold water and dried under vacuum to afford compound (**141**) (2.9 g, 68.4%) m. p. 137-38 °C.

Anal.:

TLC:	R_f 0.48 (*n*-Hexane: ethyl acetate, 12:8)
IR (KBr, cm^{-1}):	3285, 2957, 1672, 1583, 1533, and 1369.

3,4-Dimethoxy-2-nitrobenzaldehyde (142)

Dissolved 4-hydroxy-3-methoxy-2-nitrobenzaldehyde (**141**) (5.0 g, 25.50 mM) into ethyl alcohol (13.0 mL) and dimethyl sulphate (DMS) (10.35 mL, 109.25 mM) was added. The flask was immersed in ice-brine bath and stirred the mixture continuously. An aqueous solution (12 mL) of sodium hydroxide (4.50 g, 109.25 mM) was added drop-wise at a constant rate to give a yellow viscous mass. The reaction mixture was removed from ice-brine bath and kept at 45-50 ^{0}C for 1-2 hours with continuous stirring. The reaction mixture was then cooled to room temperature, diluted with small portion of cold water and adjusted to *p*H 7. Extracted the aqueous residue with diethyl ether, dried over

sodium sulphate and the solvent evaporated under vacuum to afford a thick oil (which solidified on storage at -20 ^{0}C) of compound 3,4-dimethoxy-2-nitrobenzaldehyde (**142**) (4.0 g, 76.2%) m. p. 62-64 °C.

Anal.:

TLC:	R_f 0.36 (*n*-Hexane: ethyl acetate, 12:8)
IR (KBr, cm^{-1}):	2997, 2847, 1690, 1598, 1540 and 1374.

3,4-Dimethoxy-2-nitrobenzaldoxime (**143**)

Reaction of 3,4-dimethoxy-2-nitrobenzaldehyde (**142**) (5.0 g, 23.67 mM), sodium acetate trihydrate (2.27 g, 16.67 mM) and hydroxylamine hydrochloride (1.11 g, 15.98 mM) in methanol (30 mL) under a set of conditions described in **Method A**, afforded compound (**143**) (5.0 g, 93.4%) m. p. 138-39 °C.

Anal.:

TLC:	R_f 0.48 (*n*-Hexane: ethyl acetate, 12:8)
IR (KBr, cm^{-1}):	3288, 3157, 2945, 1601, 1533 and 1366.

3,4-Dimethoxy-2-nitrobenzonitrile (**144**)

Reaction of 3,4-dimethoxy-2-nitrobenzaldoxime (**143**) (5 g, 22.10 mM) and thionyl chloride (5.65 mL, 77.37 mM) in dry benzene (20 mL) under a set of conditions described in **Method B**, afforded compound (**144**) (4.3 g, 92.4%) m. p. 67-69 °C.

Anal.:

TLC:	R_f 0.39 (*n*-Hexane: ethyl acetate, 12:8)
IR (KBr, cm^{-1}):	3089, 2988, 2234, 1601, 1535 and 1365.

2-Amino-3,4-dimethoxybenzonitrile (**145**)

Refluxed a solution of 3,4-dimethoxy-2-nitrobenzonitrile (**144**) (5.0 g, 24.02 mM), granulated tin (4.28 g, 36.02 mM) and concentrated hydrochloric acid (24.70 mL, 960.8 mM) under a set of conditions described in **Method D** to afford a brown viscous mass of compound (**145**) (2.75 g, 64.7%).

Anal.:

TLC:	R_f 0.68 (*n*-Hexane: ethyl acetate, 12:8)
IR (KBr, cm^{-1}):	3476, 3377, 2930, 2209, 1622 and 1098.
MS (ESI) (m/z):	178.5 $(M + 1)^+$.

- **Synthesis of substituted piperazines**

Synthesis of phenyl(piperazin-1-yl)methanone

Method E: Benzoic acid (2 g, 16.40 mM) was taken in a single neck Rb flask (100 mL) and thionyl chloride (3.60 mL, 49.14 mM) was added. The mixture was refluxed for half an hour. The excess of thionyl chloride was evaporated under vacuum to yield benzoyl chloride. Piperazine anhydrous (5.64 g, 65.52 mM) was suspended in dry dioxane (10 mL) separately. Benzoyl chloride was added dropwise in this suspension with continuous string at the temperature range of 2-10 ^{0}C. After complete addition, the reaction mixture was stirred for 2 hours. The solvent was evaporated under reduced pressure, residue was poured into ice-cold water and the precipitated 1,4-disubstituted piperazine biproduct was filtered off. The filtrate was extracted with dichloromethane, dried over sodium sulphate and the solvent was evaporated to obtain phenyl(piperazin-1-yl)methanone as a semisolid mass (1.2 g, 38.7%).

Anal.:

TLC: R_f 0.31 (*n*-Hexane: ethyl acetate, 6:14)

Synthesis of (2-fluorophenyl)(piperazin-1-yl)methanone

Reaction of 2-fluorobenzoic acid (2 g, 14.27 mM), thionyl chloride (3.1 mL, 42.82 mM) and piperazine anhydrous (4.9 g, 57.08 mM) under a set of conditions described in **Method E** afforded (2-fluorophenyl)(piperazin-1-yl)methanone (0.9 g, 30.3%).

Anal.:

TLC: R_f 0.39 (*n*-Hexane: ethyl acetate, 6:14)

IR (KBr, cm^{-1}): 3401, 2913, 1671 and 726.

Synthesis of (2-methoxyphenyl)(piperazin-1-yl)methanone

Reaction of 2-methoxybenzoic acid (2 g, 13.14 mM), thionyl chloride (2.9 mL, 39.43 mM) and piperazine anhydrous (4.5 g, 52.56 mM) under a set of conditions described in **Method E** afforded (2-methoxyphenyl)(piperazin-1-yl)methanone (1.1 g, 37.9%).

Anal.:

TLC: R_f 0.35 (*n*-Hexane: ethyl acetate, 6:14)

Synthesis of (3-methoxyphenyl)(piperazin-1-yl)methanone

Reaction of 3-methoxybenzoic acid (2 g, 13.14 mM), thionyl chloride (2.9 mL, 39.43 mM) and piperazine anhydrous (4.5 g, 52.56 mM) under a set of conditions described in **Method E** afforded (3-methoxyphenyl)(piperazin-1-yl)methanone (1.2 g, 41.4%).

Anal.:

TLC: R_f 0.34 (*n*-Hexane: ethyl acetate, 6:14)

Synthesis of (3-chlorophenyl)(piperazin-1-yl)methanone

Reaction of 2-chlorobenzoic acid (2 g, 12.78 mM), thionyl chloride (2.8 mL, 38.32 mM) and piperazine anhydrous (4.4 g, 51.12 mM) under a set of conditions described in **Method E** afforded (3-chlorophenyl)(piperazin-1-yl)methanone (0.8 g, 27.6%).

Anal:

TLC: R_f 0.38 (*n*-Hexane: ethyl acetate, 6:14)

Synthesis of (2,3-dichlorophenyl)(piperazin-1-yl)methanone

Reaction of 2,3-dichlorobenzoic acid (2 g, 10.47 mM), thionyl chloride (2.3 mL, 31.41 mM) and piperazine anhydrous (3.6 g, 41.88 mM) under a set of conditions described in **Method E** afforded (2,3-dichlorophenyl)(piperazin-1-yl)methanone (0.7 g, 25.9%).

Anal.:

TLC: R_f 0.41 (*n*-Hexane: ethyl acetate, 6:14)

Synthesis of (2,3-dimethoxyphenyl)(piperazin-1-yl)methanone

Reaction of 2,3-dimethoxybenzoic acid (2 g, 10.98 mM), thionyl chloride (2.4 mL, 32.94 mM) and piperazine anhydrous (3.8 g, 43.92 mM) under a set of conditions described in **Method E** afforded (2,3-dimethoxyphenyl)(piperazin-1-yl)methanone (0.8 g, 29.1%).

Anal.:

TLC: R_f 0.36 (*n*-Hexane: ethyl acetate, 6:14)

IR (KBr, cm^{-1}): 3441, 2927, 2855, 1673 and 774.

Synthesis of 3-methylphenylpiperazin-1-ylmethanone

Reaction of 3-methylbenzoic acid (2 g, 14.69 mM), thionyl chloride (3.2 mL, 44.07 mM) and piperazine anhydrous (5.1 g, 58.76 mM) under a set of conditions described in **Method E** afforded (3-methylphenyl)(piperazin-1-yl)methanone (1.2 g, 40.0%).

Anal.:

TLC: R_f 0.34 (*n*-Hexane: ethyl acetate, 6:14)

IR (KBr, cm^{-1}): 3339, 2929, 1670 and 766.

Synthesis of 4-fluorophenylpiperazin-1-ylmethanone

Reaction of 4-fluorobenzoic acid (2 g, 14.27 mM), thionyl chloride (3.1 mL, 42.82 mM) and piperazine anhydrous (4.9 g, 57.08 mM) under a set of conditions described in **Method E** afforded (4-fluorophenyl)(piperazin-1-yl)methanone (1.3 g, 43.8%).

Anal.:

TLC: R_f 0.37 (*n*-Hexane: ethyl acetate, 6:14)

IR (KBr, cm^{-1}): 3401, 2913, 1671 and 726.

Synthesis of 4-cyanophenylpiperazin-1-ylmethanone

Reaction of 4-cyanobenzoic acid (2 g, 13.59 mM), thionyl chloride (3.0 mL, 40.78 mM) and piperazine anhydrous (4.7 g, 54.36 mM) under a set of conditions described in **Method E** afforded (4-cyanophenyl)(piperazin-1-yl)methanone (1.0 g, 34.5%).

Anal.:

TLC: R_f 0.38 (*n*-Hexane: ethyl acetate, 6:14)

IR (KBr, cm^{-1}): 3325, 2942, 2223, 1668 and 761.

Synthesis of 2-phenyl-1-(piperazin-1-yl)ethanone

Reaction of 2-phenylacetic acid (2 g, 14.69 mM), thionyl chloride (3.2 mL, 44.07 mM) and piperazine anhydrous (5.1 g, 58.76 mM) under a set of conditions described in **Method E** afforded 2-phenyl-1-(piperazin-1-yl)ethanone (0.9 g, 30%).

Anal.:

TLC: R_f 0.30 (*n*-Hexane: ethyl acetate, 6:14)

Synthesis of 2-(3-chlorophenyl)-1-(piperazin-1-yl)ethanone

Reaction of 2-(3-chlorophenyl)acetic acid (2 g, 11.72 mM), thionyl chloride (2.5 mL, 35.17 mM) and piperazine anhydrous (4 g, 46.88 mM) under a set of conditions described in **Method E** afforded 2-(3-chlorophenyl)-1-(piperazin-1-yl)ethanone (0.9 g, 32.1%).

Anal.:

TLC: R_f 0.34 (*n*-Hexane: ethyl acetate, 6:14)

IR (KBr, cm^{-1}): 3409, 2971 and 1665.

Synthesis of 2-(4-methoxyphenyl)-1-(piperazin-1-yl)ethanone

Reaction of 2-(4-methoxyphenyl)acetic acid (2 g, 12.04 mM), thionyl chloride (2.6 mL, 36.11 mM) and piperazine anhydrous (4.1 g, 48.16 mM) under a set of conditions described in **Method E** afforded 2-(4-methoxyphenyl)-1-(piperazin-1-yl)ethanone (0.8 g, 28.6%).

Anal.:

TLC: R_f 0.32 (*n*-Hexane: ethyl acetate, 6:14)

IR (KBr, cm^{-1}): 3387, 2933 and 1669.

Synthesis of 1-benzylpiperazine

Method F: Piperazine anhydrous (4 g, 44.78 mM) was suspended in dry dioxane (10 mL) in a single neck Rb flask. The solution of benzyl bromide (2 g, 11.69 mM) in dry dioxane (5 mL) was added drop-wise into the above suspension with continuous stirring at the temperature range of 2-10 ^{0}C. The reaction mixture was allowed to stir for 4-6 hours at room temperature. After completion of reaction the mixture was poured into ice-cold water and the precipitated disubstituted byproduct was filtered off. The filtrate was extracted with dichloromethane, dried over sodium sulphate and evaporated at reduced pressure to afford desired compound 1-benzylpiperazine as a semisolid mass (0.9 g, 43.7%).

Anal.:

TLC: R_f 0.29 (*n*-Hexane: ethyl acetate, 6:14)

IR (KBr, cm^{-1}): 3408, 2976, 1621 and 1467.

Synthesis of 1-(2-trifluoromethylbenzyl)piperazine

Reaction of 2-trifluoromethylbenzyl bromide (2 g, 8.37 mM) and piperazine anhydrous (2.9 g, 33.47 mM) under a set of conditions described in **Method F** afforded 1-(2-trifluoromethylbenzyl)piperazine (0.7 g, 34.3%).

Anal.:

TLC: R_f 0.37 (*n*-Hexane: ethyl acetate, 6:14)

Synthesis of 1-(2-methylbenzyl)piperazine

Reaction of 2-methylbenzyl bromide (2 g, 10.80 mM) and piperazine anhydrous (3.7 g, 43.23 mM) under a set of conditions described in **Method F** afforded 1-(2-methylbenzyl)piperazine (0.8 g, 39%).

Anal.:

TLC: R_f 0.32 (*n*-Hexane: ethyl acetate, 6:14)

IR (KBr, cm^{-1}): 3417, 2977, 1600 and 1470.

Synthesis of 1-(2-bromobenzyl)piperazine

Reaction of 2-bromobenzyl bromide (2 g, 8.0 mM) and piperazine anhydrous (2.8 g, 32.0 mM) under a set of conditions described in **Method F** afforded 1-(2-bromobenzyl)piperazine (0.7 g, 34.3%).

Anal.:

TLC: R_f 0.38 (*n*-Hexane: ethyl acetate, 6:14)

IR (KBr, cm^{-1}): 3458, 2938, 1576 and 1462.

Synthesis of 1-(2-cyanobenzyl)piperazine

Reaction of 2-cyanobenzyl bromide (2 g, 10.2 mM) and piperazine anhydrous (3.5 g, 40.8 mM) under a set of conditions described in **Method F** afforded 1-(2-cyanobenzyl)piperazine (0.9 g, 43.9%).

Anal.:

TLC: R_f 0.39 (*n*-Hexane: ethyl acetate, 6:14)

IR (KBr, cm^{-1}): 3429, 2956, 2225, 1627 and 1476.

Synthesis of 1-(4-bromobenzyl)piperazine

Reaction of 4-bromobenzyl bromide (2 g, 8.0 mM) and piperazine anhydrous (2.8 g, 32.0 mM) under a set of conditions described in **Method F** afforded 1-(4-bromobenzyl)piperazine (0.8 g, 39.2%).

Anal.:

TLC: R_f 0.37 (*n*-Hexane: ethyl acetate, 6:14)

Synthesis of 1-(4-methylbenzyl)piperazine

Reaction of 4-methylbenzyl bromide (2 g, 10.8 mM) and piperazine anhydrous (3.7 g, 43.23 mM) under a set of conditions described in **Method F** afforded 1-(4-methylbenzyl)piperazine (1 g, 48.8%).

Anal.:

TLC: R_f 0.31 (*n*-Hexane: ethyl acetate, 6:14)

Synthesis of 1-(4-methoxybenzyl)piperazine

Reaction of 4-methoxybenzyl bromide (2 g, 9.95 mM) and piperazine anhydrous (3.4 g, 39.79 mM) under a set of conditions described in **Method F** afforded 1-(4-methoxybenzyl)piperazine (0.7 g, 34.1%).

Anal.:

TLC: R_f 0.35 (*n*-Hexane: ethyl acetate, 6:14)

Synthesis of 1-(4-*t*.butylbenzyl)piperazine

Reaction of 4-*t*.butylbenzyl bromide (2 g, 8.8 mM) and piperazine anhydrous (3.0 g, 35.2 mM) under a set of conditions described in **Method F** afforded 1-(4-*t*.butylbenzylbenzyl)piperazine (0.6 g, 29.4%).

Anal.:

TLC: R_f 0.33 (*n*-Hexane: ethyl acetate, 6:14)

IR (KBr, cm^{-1}): 3270, 2956, 1648 and 1459.

Synthesis of 1-[4-(2'cyanophenyl)benzyl]piperazine

Reaction of 4-(2'-cyanophenyl)benzyl bromide (2 g, 7.35 mM) and piperazine anhydrous (2.5 g, 29.4 mM) under a set of conditions described in **Method F** afforded 1-[4-(2'cyanophenyl)benzyl]piperazine (0.7 g, 34.3%).

Anal.:

TLC: R_f 0.32 (*n*-Hexane: ethyl acetate, 6:14)

IR (KBr, cm^{-1}): 3129, 2928, 2813, 2226, 1400 and 777.

Synthesis of 1-(2-methoxyphenyl)piperazine hydrochloride

Method G: 2-Methoxyaniline (0.5 g, 4.06 mM) and bis(2-chloroethyl)amine hydrochloride (0.7 g, 4.06 mM) were mixed with diethylene glycol monomethyl ether (2 mL) in an Rb flask (50 mL). The mixture was subjected to microwave irradiation at 340 W for 6-8 min. After completion of reaction the mixture was cooled to room temperature and a few drops of methanol were added. The reaction mixture was poured into ice-cold diethyl ether to give a white precipitate which was filtered and washed with diethyl ether to afford 1-(2-Methoxyphenyl)piperazine hydrochloride (0.4 g, 42.4%), m. p. 38-40 °C (lit. 35-40 °C).

Anal.:

TLC: R_f 0.38 (Chloroform: methanol, 19:1)

Synthesis of 1-(3,4,5-trimethoxyphenyl)piperazine hydrochloride

Reaction of 3,4,5-trimethoxyaniline (0.5 g, 2.73 mM) and bis(2-chloroethyl)amine hydrochloride (0.5 g, 2.73 mM) under a set of conditions described in **Method G** afforded 1-(3,4,5-trimethoxyphenyl)piperazine hydrochloride (0.3 g, 38.0%).

Anal.:

TLC: R_f 0.41 (Chloroform: methanol, 19:1)

Synthesis of 2'/4'-substituted *N*-benzylpiperidine-4-carboxamides (146-151)

Synthesis of *N*-benzylpiperidine-4-carboxamide (146)

Method H: Piperidine-4-carboxamide (1.0 g, 7.80 mM) was suspended in ethyl alcohol (5 mL) in a single neck Rb flask (50 mL). Benzyl chloride (0.45 mL, 3.90 mM) and potassium carbonate (1.08 g, 7.80 mM) were added in the above suspension and the mixture stirred continuously at 60-80 ^{0}C for 12-14 hours. The solvent was evaporated under reduced pressure and the residue was poured into ice-cold water to give a white precipitate which was filtered, washed and dried under vacuum to afford compound (**146**) (1.2 g, 70.6%), m. p. 113-15 °C.

Anal.:

TLC: R_f 0.67 (Chloroform: methanol, 18:2)

IR (KBr, cm^{-1}): 3329, 3156, 2951, 1667 and 1268.

Synthesis of *N*-(2-bromobenzyl)piperidine-4-carboxamide (147)

Following **Method H**, but using 2-bromobenzyl bromide (0.85 mL, 3.9 mM), the desired compound (**147**) was obtained as white solid (1.3 g, 56.3%) m. p. 117-18 °C.

Anal.:

TLC: R_f 0.72 (Chloroform: methanol, 18:2)

IR (KBr, cm^{-1}): 3338, 3144, 2925, 1663 and 1219.

Synthesis of *N*-(2-cyanobenzyl)piperidine-4-carboxamide (148)

Following **Method H**, but using 2-cyanobenzyl bromide (0.74 mL, 3.9 mM), the desired compound (**148**) was obtained as white solid (1.2 g, 63.2%) m. p. 123-25 °C.

Anal.:

TLC: R_f 0.65 (Chloroform: methanol, 18:2)

IR (KBr, cm^{-1}): 3318, 3156, 2913, 2222, 1663 and 1256.

Synthesis of *N*-(2-methylbenzyl)piperidine-4-carboxamide (149)

Following **Method H**, but using 2-methylbenzyl bromide (0.68 mL, 3.9 mM), the desired compound (**149**) was obtained as a white solid (1.1 g, 61.1%) m. p. 118-20 °C.

Anal.:

TLC: R_f 0.58 (Chloroform: methanol, 18:2)

IR (KBr, cm^{-1}): 3372, 3188, 2940, 1652 and 1301.

Synthesis of *N*-(3-methoxybenzyl)piperidine-4-carboxamide (150)

Following **Method H**, but using 3-methoxybenzyl bromide (0.75 mL, 3.9 mM), the desired compound (**150**) was obtained as a white solid (0.9 g, 47.5%) m. p. 126-27 °C.

Anal.:

TLC: R_f 0.61 (Chloroform: methanol, 18:2)

IR (KBr, cm^{-1}): 3336, 3166, 2946, 1653 and 1266.

Synthesis of *N*-(4-methylbenzyl)piperidine-4-carboxamide (151)

Following **Method H**, but using 4-methylbenzyl bromide (0.68 mL, 3.9 mM), the desired compound (**151**) was obtained as a white solid (1.3 g, 72.2%) m. p. 127-28 °C.

Anal.:

TLC: R_f 0.55 (Chloroform: methanol, 18:2)

IR (KBr, cm^{-1}): 3251, 3147, 2952, 1659 and 1253.

- **Synthesis of 2'/4'-substituted *N*-benzylpiperidin-4-amines (152-157)**

Synthesis of *N*-benzylpiperidin-4-amine (152)

Method I: *N*-Benzylpiperidine-4-carboxamide (**146**) (0.5 g, 2.30 mM) was dissolved in acetonitrile (5 mL) and water (3.75 mL). Bis(trifluoroacetoxy)iodobenzene (1.2 g, 2.75 mM) was added into the above solution and stirred continuously at 65 ^{0}C for 12-14 hours. After complete rearrangement of *N*-benzylpiperidine-4-carboxamide into *N*-benzylpiperidin-4-amine, the reaction mixture was cooled to room temperature, diluted with small portion of water and acidified with concentrated hydrochloric acid. Washed the acidic solution with diethyl ether three times then basified with potassium carbonate (5 g, 0.024 mM) and extracted with DCM. The extract was dried over sodium sulphate and evaporated under reduced pressure to give a viscous mass of compound (**152**) (0.35 g, 80.1%).

Anal.:

TLC: R_f 0.57 (Chloroform: methanol, 18:2)

IR (KBr, cm^{-1}): 3413, 3130, 2949 and 1619.

Synthesis of *N*-(2-bromobenzyl)piperidin-4-amine (153)

Reaction of *N*-(2-bromobenzyl)piperidine-4-carboxamide (**147**) (0.5 g, 1.70 mM) and bis(trifluoroacetoxy)iodobenzene (0.88 g, 2.04 mM) under a set of conditions described in **Method I** afforded compound (**153**) (0.3 g, 77.3%).

Anal.:

TLC: R_f 0.60 (Chloroform: methanol, 18:2)

IR (KBr, cm^{-1}): 3341, 3058, 2936, 1559 and 750.

Synthesis of *N*-(2-cyanobenzyl)piperidin-4-amine (154)

Reaction of *N*-(2-cyanobenzyl)piperidine-4-carboxamide (**148**) (0.5 g, 2.06 mM) and bis(trifluoroacetoxy)iodobenzene (1.06 g, 2.47 mM) under a set of conditions described in **Method I** afforded compound (**154**) (0.3 g, 75%).

Anal.:

TLC: R_f 0.53 (Chloroform: methanol, 18:2)

IR (KBr, cm^{-1}): 3337, 3143, 2934, 2223, 1626 and 762.

Synthesis of *N*-(2-methylbenzyl)piperidin-4-amine (155)

Reaction of *N*-(2-methylbenzyl)piperidine-4-carboxamide (**149**) (0.5 g, 2.15 mM) and bis(trifluoroacetoxy)iodobenzene (1.11 g, 2.58 mM) under a set of conditions described in **Method I** afforded compound (**155**) (0.3 g, 68.2%).

Anal.:

TLC: R_f 0.48 (Chloroform: methanol, 18:2)

IR (KBr, cm^{-1}): 3328, 3138, 2913, 1604 and 757.

Synthesis of *N*-(3-methoxybenzyl)piperidin-4-amine (156)

Reaction of *N*-(3-methoxybenzyl)piperidine-4-carboxamide (**150**) (0.5 g, 2.01 mM) and bis(trifluoroacetoxy)iodobenzene (1.04 g, 2.42 mM) under a set of conditions described in **Method I** afforded compound (**156**) (0.3 g, 63.6%).

Anal:

TLC: R_f 0.51 (Chloroform: methanol, 18:2)

IR (KBr, cm^{-1}): 3353, 3142, 2937, 1595, 1047 and 746.

Synthesis of *N*-(4-methylbenzyl)piperidin-4-amine (157)

Reaction of *N*-(4-methylbenzyl)piperidine-4-carboxamide (**151**) (0.5 g, 2.15 mM) and bis(trifluoroacetoxy)iodobenzene (1.11 g, 2.58 mM) under a set of conditions described in **Method I** afforded compound (**157**) (0.35 g, 79.5%).

Anal:

TLC: R_f 0.54 (Chloroform: methanol, 18:2)

IR (KBr, cm^{-1}): 3327, 3108, 2923, 1611 and 745.

- **Synthesis of substituted 4-amino-1,1'-biphenyls (158-163)**

4-Amino-1,1'-biphenyl (158)

Method J: Dissolved the palladium acetate (1 mol%) and triphenylphosphine (TPP) (10-20 mg) in DMA (2 mL) in a pressure vessel and stirred for 10 minutes. 4-Bromoaniline (0.2 g, 1.2 mM) and aqueous solution of sodium carbonate (0.25 g, 2.4 mM) were added into it. After 10 min of stirring, phenylboronic acid (0.35 g, 2.9 mM) was added to the above solution. The reaction mixture was continuously stirred at 120 °C for 6-8 hours, poured into ice-cold water and extracted with ethyl acetate, dried over sodium sulphate and evaporated the solvent under vacuum to afford compound (**158**) (0.15 g, 75%), m. p. 54-55 °C.

Anal.:

TLC: R_f 0.35 (*n*-Hexane: ethyl acetate, 18:2)

MS (EI) (m/z): 169.2 (M^+).

4-Amino-2'-chloro-1,1'-biphenyl (159)

Following **Method J**, but using 2-chlorophenylboronic acid (0.45 g, 2.9 mM), compound (**65**) was obtained (0.17 g, 70.8%) m. p. 58-60 °C.

Anal:

TLC: R_f 0.30 (*n*-Hexane: ethyl acetate, 18:2)

MS (EI) (m/z): 231.1 (M^+).

4-Amino-2'-methyl-1,1'-biphenyl (160)

Following **Method J**, but using 2-methylphenylboronic acid (0.39 g, 2.9 mM), the desired compound (**160**) was obtained as a solid mass (0.18 g, 81.8%) m. p. 63-65 °C.

Anal:

TLC: R_f 0.32 (*n*-Hexane: ethyl acetate, 18:2)

MS (EI) (m/z): 183.3 (M^+).

4-Amino-4'-cyano-1,1'-biphenyl (161)

Following **Method J**, but using 4-cyanophenylboronic acid (0.42 g, 2.9 mM), the desired compound (**161**) was obtained as a solid mass (0.16 g, 69.6%) m. p. 60-62 °C.

Anal:

TLC: R_f 0.30 (*n*-Hexane: ethyl acetate, 18:2)

IR (KBr, cm^{-1}): 3129, 2928, 2813, 2226, 1400 and 777.

MS (EI) (m/z): 194.2 (M^+).

4-Amino-4'-thiomethyl-1,1'-biphenyl (162)

Following **Method J**, but using 4-thiomethylphenylboronic acid (0.49 g, 2.9 mM), the desired compound (**162**) was obtained as a solid mass (0.18 g, 69.2%) m. p. 65-67 °C.

Anal:

TLC: R_f 0.36 (*n*-Hexane: ethyl acetate, 18:2)

IR (KBr, cm^{-1}): 3426, 3016, 2939, 2810, 2483, 1457 and 745.

MS (EI) (m/z): 215.4 (M^+).

4-Amino-4'-*t*.butyl-1,1'-biphenyl (163)

Following **Method J**, but using 4-*t*.butylphenylboronic acid (0.52 g, 2.9 mM), the desired compound (**163**) was obtained as a solid mass (0.20 g, 74.1%) m. p. 69-71 °C.

Anal:

TLC: R_f 0.33 (*n*-Hexane: ethyl acetate, 18:2)

MS (EI) (m/z): 225.3 (M^+).

5.1.3 Synthesis of 4-amino-2-chloromethyl-6,7-dimethoxyquinazoline (164) and 4-amino-6,7-dimethoxy-2-vinylquinazoline (166)

4-Amino-2-choloromethyl-6,7-dimethoxyquinazoline (**164**)

Method K: Chloroacetonitrile (0.71 mL, 11.24 mM) was taken in an Rb flask (100 mL). Saturated solution of dry HCl gas (1.23 g, 33.72 mM) in dry dioxane (10 mL) was added into the above and allowed to stir for half an hour. 2-Amino-4,5-dimethoxybenzonitrile (**132**) (1 g, 5.62 mM) was added to the above solution. The reaction mixture was allowed to stir at room temperature for 24 hours. The reaction mixture was quenched into ice-cold water (50 mL). The suspension so formed was filtered and the precipitate was rejected. The filtrate was basified with ammonia solution to give a precipitate which was filtered, dried under vacuum and purified through column chromatography using chloroform and methanol ($CHCl_3$: methanol, 99.5:0.5) as eluent to afford compound (**164**) (0.8 g, 56.3%) m. p. 250-52 °C (lit.[89] 250-52 °C).

Anal.:

TLC: R_f 0.21 (*n*-Hexane: ethyl acetate, 6:14).

IR (KBr, cm^{-1}): 3380, 3328, 3132, 2834, 1657, 1618, 1509, 1485 and 1032.

MS (EI) (m/z): 253.0 (M^+), 255.0 $(M + 2)^+$.

4-Amino-6,7-dimethoxy-2-vinylquinazoline (**166**)

3-Bromopropionitrile (0.94 mL, 11.24 mM), and 2-amino-4,5-dimethoxybenzonitrile (**132**) (1 g, 5.62 mM)) were reacted under a set of conditions mentioned in **Method K** but using a pressure vessel in place of Rb flask and the temperature was raised upto 110 ^{0}C for 12-14 hours. The reaction mixture was poured into ice-cold water (25 mL) to give a brown precipitate which was filtered, washed and dried. The dried mass was purified through column chromatography using chloroform and methanol as eluent (chloroform: methanol, 99.5:0.5) to obtain compound (**166**) (0.9 g, 69.2%) m. p. >275 °C.

Anal.:

TLC: R_f 0.29 (*n*-Hexane: ethyl acetate, 8:12)

IR (KBr, cm^{-1}): 3415, 3320, 3106, 2970, 1654, 1577 and 857.

^{1}H-NMR (DMSO-d_6): δ 7.57 (s, 1H), 7.33 (bs, 2H), 7.07 (s, 1H), 6.66-6.59 (m, 1H), 6.43-6.39 (d, 1H, *J* = 17.3) and 5.54-5.51 (d, 1H, *J* = 10.4).

MS (EI) (m/z): 231.1 (M^+).

5.1.4 Synthesis of 4-amino-2-(4-substituted piperazin-1-yl)methyl-6,7-dimethoxyquina zolines (167-192) (Series I)

4-Amino-2-[4-(benzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (167)

Method L: 4-Amino-2-chloromethyl-6,7-dimethoxyquinazoline (0.20 g, 0.79 mM), 1-benzoylpiperazine (0.45 g, 2.37 mM), flame dried potassium carbonate (0.22 g, 1.58 mM) and dried DMF (2 mL) were taken in an Rb flask (50 mL). The reaction mixture was stirred overnight at 60 ^{0}C and poured into ice-cold water (20 ml) to give a precipitate which was filtered under vacuum and dried. The solid thus obtained was crystallized from DCM-methanol to afford compound (**167**) (0.25 g, 78.1%) m. p. 207-09 °C.

Anal.:

TLC: R_f 0.59 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3309, 3146, 2998, 1666, 1633, 1577, 1418 and 1249.

^{1}H-NMR ($CDCl_3$): δ 7.41-7.39 (m, 5H), 7.23 (s, 1H), 6.97 (s, 1H), 5.60 (bs, 2H), 4.00 (s, 3H), 3.97 (s, 3H), 3.87 (bs, 2H), 3.71 (s, 2H), 3.50 (bs, 2H), 2.69 (bs, 2H) and 2.54 (bs, 2H).

MS (ESI) (m/z): 408.6 $(M + 1)^+$.

4-Amino-2-[4-(2-fluorobenzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (168)

Following **Method L**, but using 1-(2-fluorobenzoyl)piperazine (0.50 g, 2.37 mM), the desired compound (**168**) was obtained as white solid (0.22 g, 64.7%) m. p. 206-08 °C.

Anal.:

TLC: R_f 0.47 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3385, 3341, 3197, 2997, 1665, 1617, 1580, 1437, 1244 and 1018.

^{1}H-NMR ($CDCl_3$): δ 7.39-7.34 (m, 2H), 7.22 (s, 1H), 7.20-7.16 (m, 1H), 7.09 (s, 1H), 7.07-7.05 (d, 1H, *J* = 8.7 Hz), 5.92 (bs, 2H), 3.99 (s, 3H), 3.94 (s, 3H), 3.88-3.87 (t, 2H, *J* = 4.5 Hz), 3.70 (s, 2H), 3.41 (bs, 2H), 2.70-2.68 (t, 2H, *J* = 4.5 Hz) and 2.50-2.48 (bs, 2H).

MS (ESI) (m/z): 426.7 $(M + 1)^+$.

4-Amino-2-[4-(2-methoxybenzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (169)

Following **Method L**, but using 1-(2-methoxybenzoyl)piperazine (0.52 g, 2.37 mM), the desired compound (**169**) was obtained as white solid (0.24 g, 68.6%) m. p. 159-61 °C.

Anal.:

TLC: R_f 0.48 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3378, 3335, 3130, 2925, 2854, 1664, 1619, 1577, 1510, 1476, 1441, 1244, 1021 and 755.

^{1}H-NMR ($CDCl_3$): δ 7.34-7.22 (m, 2H) 7.21 (s, 1H), 7.10 (s, 1H), 6.97-6.94 (m, 1H), 6.88-6.86 (d, 1H, *J* = 7.8 Hz), 5.99 (bs, 2H), 3.99

(s, 3H), 3.95 (s, 3H), 3.89 (bs, 2H), 3.79 (s, 3H), 3.70 (s, 2H), 3.34 (bs, 2H), 2.65 (bs, 2H) and 2.48 (bs, 2H).

MS (ESI) (m/z): 438.7 $(M + 1)^+$.

4-Amino-2-[4-(3-methoxybenzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (170)

Following **Method L**, but using 1-(3-methoxybenzoyl)piperazine (0.52 g, 2.37 mM), the desired compound (**170**) was obtained as white solid (0.29 g, 82.9%) m. p. 212-14 °C.

Anal.:

TLC: R_f 0.63 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3323, 3154, 3018, 2984, 2831, 1663, 1636, 1579, 1513, 1487, 1418, 1284, 1252, 987 and 792.

^{1}H-NMR ($CDCl_3$): δ 7.22-7.19 (m, 1H), 7.14 (s, 1H), 7.00 (s, 1H), 6.87-6.84 (m, 2H), 6.83 (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.78 (bs, 2H), 3.72 (s, 3H), 3.63 (s, 2H), 3.42 (bs, 2H), 2.61 (bs, 2H) and 2.46 (bs, 2H).

MS (ESI) (m/z): 437.8 $(M + 1)^+$.

4-Amino-2-[4-(3-chlorobenzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (171)

Following **Method L**, but using 1-(3-chlorobenzoyl)piperazine (0.53 g, 2.37 mM), the desired compound (**171**) was obtained as white solid (0.25 g, 72%) m. p. 225-27 °C.

Anal.:

TLC: R_f 0.60 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3320, 3150, 2954, 2831, 1663, 1638, 1578, 1512, 1488, 1402, 1238, 1212, 1008 and 796.

^{1}H-NMR ($CDCl_3$): δ 7.31 (s, 1H), 7.30-7.24 (m, 3H), 7.20 (s, 1H), 7.17 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.79 (bs, 2H), 3.65 (s, 2H), 3.42 (bs, 2H), 2.62 (bs, 2H) and 2.49 (bs, 2H).

MS (ESI) (m/z): 442.8 $(M + 1)^+$, 444.9 $(M + 3)^+$.

4-Amino-2-[4-(2,3-dichlorobenzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (172)

Following **Method L**, but using 1-(2,3-dichlorobenzoyl)piperazine (0.60 g, 2.37 mM), the desired compound (**172**) was obtained as white solid (0.23 g, 67.3%) m. p. 259-61 °C.

Anal.:

TLC: R_f 0.54 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3347, 3140, 3002, 2958, 2830, 2803, 1675, 1620, 1578, 1513, 1488, 1438, 1243, 1211, 1008 and 854.

^{1}H-NMR ($CDCl_3$): δ 7.48-7.46 (d, 1H, *J* = 7.5 Hz), 7.25-7.23 (m, 2H), 7.20-7.18 (d, 1H, *J* = 7.5 Hz), 6.96 (s, 1H), 5.70 (bs, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.93 (bs, 2H), 3.72 (s, 2H), 3.32 (bs, 2H), 2. 68 (bs, 2H) and 2.51 (bs, 2H).

^{13}C-NMR (DMSO-d_6): 164.73, 160.83, 160.69, 153.84, 147.96, 137.78, 134.26, 132.35, 130.49, 127.59, 125.93, 115.32, 106.54, 102.65, 55.85, 55.47, 52.85, 52.37 and 46.15.

MS (ESI) (m/z): 477.7 $(M + 1)^+$, 479.7 $(M + 3)^+$.

4-Amino-2-[4-(2,3-dimethoxybenzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (173)

Following **Method L**, but using 1-(2,3-dimethoxybenzoyl)piperazine (0.59 g, 2.37 mM), the desired compound (**173**) was obtained as white solid (0.25 g, 67.6%) m. p. 145-47 °C.

Anal.:

TLC: R_f 0.54 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3344, 3212, 3001, 2936, 2835, 1621, 1581, 1510, 1480, 1437, 1267, 1000, 865 and 783.

^{1}H-NMR ($CDCl_3$): δ 7.21 (s, 1H), δ 7.09-7.05 (m, 1H), 7.02 (s, 1H), 6.92-6.90 (d, 1H, *J* = 7.7 Hz), 6.83-6.81 (d, 1H, *J* = 7.7 Hz), 5.75 (bs, 2H), 3.99 (s, 3H), 3.95 (s, 3H) 3.89 (s, 3H), 3.87 (s, 3H), 3.84 (s, 2H), 3.37 (bs, 2H), 3.28 (bs, 2H), 2.60 (bs, 2H) and 2.48 (bs, 2H).

^{13}C-NMR ($CDCl_3$): 167.46, 161.17, 160.22, 154.95, 152.56, 149.03, 147.47, 144.96, 131.06, 124.73, 119.18, 116.47, 112.88, 107.44, 106.79, 100.41, 65.50, 61.51, 56.26, 56.20, 55.80, 53.81, 53.08, 46.82 and 41.50.

MS (ESI) (m/z): 468.8 $(M + 1)^+$.

4-Amino-2-[4-(3-methylbenzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (174)

Following **Method L**, but using 1-(3-methylbenzoyl)piperazine (0.48 g, 2.37 mM), the desired compound (**174**) was obtained as white solid (0.22 g, 66.7%) m. p. 216-18 °C.

Anal.:

TLC: R_f 0.63 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3316, 3147, 3009, 2950, 2876, 2831, 1667, 1628, 1579, 1512, 1488, 1212, 1009 and 868.

^{1}H-NMR ($CDCl_3$): δ 7.24 (s, 1H), 7.21 (s, 1H), 7.19-7.06 (m, 3H), 6.91 (s, 1H), 5.62 (bs, 2H), 4.00 (s, 3H), 3.97 (s, 3H), 3.87 (bs, 2H), 3.71 (s, 2H), 3.50 (bs, 2H), 2.69 (bs, 2H), 2.62 (bs, 2H) and 2.36 (s, 3H).

MS (ESI) (m/z): 422.9 $(M + 1)^+$.

4-Amino-2-[4-(4-fluorobenzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (175)

Following **Method L**, but using 1-(4-fluorobenzoyl)piperazine (0.49 g, 2.37 mM), the desired compound (**175**) was obtained as white solid (0.25 g, 73.5%) m. p. 200-02 °C.

Anal.:

TLC: R_f 0.60 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3324, 3154, 2954, 2832, 1662, 1636, 1577, 1511, 1490, 1402, 1233, 1007 and 846.

^{1}H-NMR ($CDCl_3$): δ 7.43-7.40 (d, 2H, J = 8.5 Hz), 7.25 (s, 1H), 7.13-7.08 (d, 2H, J = 8.5), 7.06 (s, 1H), 6.30 (bs, 2H), 4.01 (s, 6H), 3.89 (bs, 2H), 3.74 (s, 2H), 3.55 (bs, 2H), 2.69 (bs, 2H) and 2.59 (bs, 2H).

MS (ESI) (m/z): 426.7 $(M + 1)^+$.

4-Amino-2-[4-(4-cyanobenzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (176)

Following **Method L**, but using 1-(4-cyanobenzoyl)piperazine (0.51 g, 2.37 mM), the desired compound (**176**) was obtained as white solid (0.23 g, 67.3%) m. p. 221-23 °C. Anal.:

TLC: R_f 0.51 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3225, 3164, 3006, 2924, 2875, 2830, 2230, 1661, 1642, 1576, 1509, 1483, 1434, 1279, 1006 and 848.

^{1}H-NMR ($CDCl_3$): δ 7.71-7.69 (d, 2H, *J* = 7.5 Hz), 7.51-7.49 (d, 2H, *J* = 7.5 Hz), 7.22 (s, 1H), 6.99 (s, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 3.87 (bs, 2H), 3.72 (s, 2H), 3.43 (bs, 2H), 2.71 (bs, 2H) and 2.56 (bs, 2H).

MS (ESI) (m/z): 433.8 $(M + 1)^+$.

4-Amino-2-(4-benzylpiperazin-1-yl)methyl-6,7-dimethoxyquinazoline (177)

Following **Method L**, but using *N*-benzylpiperazine (0.42 g, 2.37 mM), the desired compound (**177**) was obtained as white solid (0.23 g, 74.2%) m. p. 205-07 °C. Anal.:

TLC: R_f 0.51 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3429, 3133, 2812, 2830, 1629, 1589, 1514, 1400, 1139, 1012 and 855.

^{1}H-NMR (DMSO-d_6): δ 7.76 (bs, 2H), 7.66 (s, 1H), 7.32-7.23 (m, 5H), 7.15 (s, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.81 (bs, 4H), 3.73 (s, 2H), 3.58 (s, 2H), 2.81 (bs, 2H) and 2.54 (bs, 2H).

MS (ESI) (m/z): 394.9 $(M + 1)^+$.

4-Amino-2-[4-(2-trifluoromethylbenzyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (178)

Following **Method L**, but using 2-trifluoromethylbenzylpiperazine (0.58 g, 2.37 mM), the desired compound (**178**) was obtained as white solid (0.24 g, 66.7%) m. p. 221-22 °C.

Anal.:

TLC: R_f 0.50 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3497, 3430, 3290, 3063, 3028, 2943, 2877, 2805, 2766, 1641, 1577, 1510, 1476, 1274, 1060, 840 and 774.

^{1}H-NMR (DMSO-d_6): δ 7.79-7.77 (d, 1H, *J* = 7.7 Hz), 7.64-7.59 (m, 2H), 7.57 (s, 1H), 7.42-7.38 (d, 1H, *J* = 7.7 Hz), 7.37 (bs, 2H), 7.09 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.61 (s, 2H), 3.51 (s, 2H), 2.58 (bs, 4H) and 2.46 (bs, 4H).

^{13}C-NMR (DMSO-d_6): 161.29, 160.67, 153.82, 147.85, 146.72, 137.39, 131.96, 130.14, 127.46, 126.83, 125.64, 125.29, 122.91, 106.58, 102.53, 65.17, 57.65, 55.82, 55.45, 52.96 and 52.72.

MS (ESI) (m/z): 462.8 $(M + 1)^+$.

4-Amino-2-[4-(2-methylbenzyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (179)

Following **Method L**, but using 2-methylbenzylpiperazine (0.45 g, 2.37 mM), the desired compound (**179**) was obtained as white solid (0.23 g, 71.9%) m. p. 223-25 °C.

Anal.:

TLC: R_f 0.52 (Chloroform: methanol: methanolic ammonia, 17:2:1).

IR (KBr, cm^{-1}): 3491, 3071, 3002, 2958, 2933, 2801, 2759, 1634, 1563, 1506, 1479, 1435, 1246, 1009, 847 and 755.

^{1}H-NMR ($CDCl_3$): δ 7.26-7.24 (m, 4H), 7.14 (s, 1H), 6.88 (s, 1H), 5.44 (bs, 2H), 4.00 (s, 3H), 3.99 (s, 3H), 3.68 (s, 2H), 3.47 (s, 2H), 2.62 (bs, 4H), 2.56 (bs, 4H) and 2.35 (s, 3H).

^{13}C-NMR ($CDCl_3$): 161.94, 160.13, 154.88, 148.94, 147.66, 137.48, 136.56, 130.18, 129.75, 126.90, 125.43, 107.66, 106.75, 100.04, 65.80, 60.76, 56.28, 56.18, 53.67, 52.99 and 19.29.

4-Amino-2-[4-(2-bromobenzyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (180)

Following **Method L**, but using 2-bromobenzylpiperazine (0.48 g, 2.37 mM), the desired compound (**180**) was obtained as white solid (0.29 g, 78.4%) m. p. 225-26 °C.

Anal.:

TLC: R_f 0.59 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3493, 3277, 3068, 3004, 2936, 2871, 2802, 2760, 1634, 1566, 1506, 1476, 1436, 1222, 1000 and 756.

^{1}H-NMR ($CDCl_3$): δ 7.53-7.51 (d, 1H, *J* = 7.8 Hz), 7.49-7.46 (d, 1H, *J* = 7.8 Hz), 7.28-7.26 (m, 1H), 7.24 (s, 1H), 7.11-7.06 (m, 1H), 6.91 (s, 1H), 5.69 (bs, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.70 (s, 2H), 3.62 (s, 2H) and 2.64 (bs, 8H).

MS (ESI) (m/z): 472.8 $(M + 1)^+$, 474.8 $(M + 3)^+$.

4-Amino-2-[4-(2-cyanobenzyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (181)

Following **Method L**, but using 2-cyanobenzylpiperazine (0.48 g, 2.37 mM), the desired compound (**181**) was obtained as white solid (0.30 g, 90.9%) m. p. 206-08 °C.

Anal.:

TLC: R_f 0.55 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3494, 3443, 3281, 3066, 2938, 2878, 2809, 2225, 1642, 1576, 1509, 1477, 1435, 1270, 1010, 866 and 765.

^{1}H-NMR ($CDCl_3$): δ 7.64-7.62 (d, 1H, *J* = 7.6 Hz), 7.56-7.53 (m, 2H), 7.35-7.31 (m, 1H), 7.27 (s, 1H), 7.24 (s, 1H), 5.58 (bs, 2H), 4.00 (s, 3H), 3.99 (s, 3H), 3.73 (s, 2H), 3.70 (s, 2H) and 2.64 (bs, 8H).

^{13}C-NMR ($CDCl_3$): 161.74, 160.12, 154.91, 148.98, 147.62, 142.40, 132.88, 132.52, 130.05, 127.47, 117.89, 112.92, 107.62, 106.75, 100.09, 65.64, 60.37, 56.28, 56.22, 53.42 and 52.68.

MS (ESI) (m/z): 418.9 $(M + 1)^+$.

4-Amino-2-[4-(4-bromobenzyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (182)

Following **Method L**, but using 4-bromobenzylpiperazine (0.60 g, 2.37 mM), the desired compound (**182**) was obtained as white solid (0.23 g, 62.2%) m. p. >275 °C.

Anal.:

TLC: R_f 0.49 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3324, 3158, 3003, 2931, 2818, 1663, 1622, 1579, 1511, 1483, 1249, 1215, 1012, 867 and 841.

^{1}H-NMR ($CDCl_3$): δ 7.42-7.40 (d, 2H, *J* = 8.3 Hz), 7.23 (s, 1H), 7.19-7.17 (d, 2H, *J* = 8.3 Hz), 6.95 (s, 1H), 5.85 (bs, 2H), 3.98 (s, 3H), 3.94 (s, 3H), 3.68 (s, 2H), 3.44 (s, 2H), 2.63 (bs, 4H) and 2.52 (bs, 4H).

MS (ESI) (m/z): 473.7 $(M + 1)^+$, 474.7 $(M + 2)^+$.

4-Amino-2-[4-(4-methylbenzyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (183)

Following **Method L**, but using 4-methylbenzylpiperazine (0.45 g, 2.37 mM), the desired compound (**183**) was obtained as white solid (0.22 g, 68.8%) m. p. 229-31 °C. Anal.:

TLC: R_f 0.47 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3313, 3148, 3007, 2933, 2825, 1663, 1619, 1578, 1512, 1486, 1014 and 795.

^{1}H-NMR ($CDCl_3$): δ 7.23 (s, 1H), 7.19-7.17 (d, 2H, *J* = 7.9 Hz), 7.11-7.09 (d, 2H, *J* = 7.9 Hz), 6.97 (s, 1H), 6.07 (bs, 2H), 3.98 (s, 3H), 3.93 (s, 3H), 3.68 (s, 2H), 3.47 (s, 2H), 2.63 (bs, 4H), 2.53 (bs, 4H) and 2.32 (s, 3H).

^{13}C-NMR ($CDCl_3$): 161.85, 160.32, 154.83, 148.88, 147.59, 136.59, 134.89, 129.04, 128.85, 107.58, 106.78, 100.26, 65.73, 62.87, 56.24, 56.13, 53.47, 52.86 and 21.10.

MS (ESI) m/z: 408.6 $(M + 1)^+$.

4-Amino-2-[4-(4-methoxybenzyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (184)

Following **Method L**, but using 4-methoxybenzylpiperazine (0.49 g, 2.37 mM), the desired compound (**184**) was obtained as white solid (0.24 g, 72.7%) m. p. 216-17 °C. Anal.:

TLC: R_f 0.53 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3311, 3143, 3009, 2931, 2827, 1662, 1616, 1579, 1512, 1485, 1250, 1011 and 844.

^{1}H-NMR ($CDCl_3$): δ 7.24 (s, 1H), 7.23-7.21 (d, 2H, *J* = 9.0 Hz), 6.90 (s, 1H), 6.85-6.83 (d, 2H, *J* = 9.0 Hz), 5.63 (bs, 2H), 4.00 (s, 3H),

3.98 (s, 3H), 3.79 (s, 3H), 3.69 (s, 2H), 3.46 (s, 2H), 2.63 (bs, 4H) and 2.54 (bs, 4H).

MS (ESI) m/z: 424.8 $(M + 1)^+$.

4-Amino-2-[4-(4-*t*.butylbenzyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (185)

Following **Method L**, but using 4-*t*.butylbenzylpiperazine (0.48 g, 2.37 mM), the desired compound (**185**) was obtained as white solid (0.28 g, 77.8%) m. p. 232-34 °C.

Anal.:

TLC: R_f 0.58 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3315, 3151, 3002, 2958, 2929, 2870, 2820, 1664, 1623, 1579, 1511, 1484, 1227, 1017 and 848.

^{1}H-NMR ($CDCl_3$): δ 7.32-7.30 (d, 2H, *J* = 8.2 Hz), 7.23 (s, 1H), 7.23-7.21 (d, 2H, *J* = 8.2 Hz), 6.93 (s, 1H), 5.85 (bs, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 3.69 (s, 2H), 3.50 (s, 2H), 2.64 (bs, 4H), 2.55 (bs, 4H) and 1.30 (s, 9H).

^{13}C-NMR ($CDCl_3$): 161.86, 160.10, 154.88, 149.90, 148.94, 147.66, 134.76, 129.09, 125.05, 107.67, 106.73, 100.02, 65.73, 62.71, 56.27, 56.19, 53.46, 52.74, 34.46 and 31.40.

4-Amino-2-{4-[4-(2-cyanophenyl)benzyl]piperazin-1-yl}methyl-6,7-dimethoxyquinazoline (186)

Following **Method L**, but using [1-(2-cyanophenyl)benzyl]piperazine (0.66 g, 2.37 mM), the desired compound (**186**) was obtained as white solid (0.30 g, 76.9%) m. p. 230-32 °C.

Anal.:

TLC: R_f 0.48 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3301, 3133, 3004, 2929, 2829, 2807, 2224, 1663, 1619, 1578, 1557, 1512, 1489, 1142, 1012, 869 and 764.

^{1}H-NMR (DMSO-d_6):δ 7.84-7.82 (d, 1H, *J* = 7.8 Hz), 7.75-7.71 (m, 1H), 7.57 (s, 1H), 7.55-7.54 (m, 2H), 7.52-7.50 (d, 2H, *J* = 8.2 Hz), 7.45-7.43 (d, 2H, *J* = 8.2 Hz), 7.25 (bs, 2H), 7.09 (s, 1H), 3.91 (s, 6H), 3.56 (s, 2H), 3.53 (s, 2H), 2.59 (bs, 4H) and 2.49 (bs, 4H).

MS (ESI) m/z: 495.9 $(M + 1)^+$.

4-Amino-2-[4-(1-naphthylmethyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (187)

Following **Method L**, but using 1-(1-naphthylmethyl)piperazine (0.54 g, 2.37 mM), the desired compound (**187**) was obtained as white solid (0.24 g, 68.6%) m. p. 217-19 °C.

Anal.:

TLC: R_f 0.45 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3431, 3306, 3156, 3006, 2935, 2873, 2809, 2767, 1633, 1582, 1512, 1478, 1137, 1012, 843 and 784.

^{1}H-NMR (DMSO-d_6): δ 8.26-8.24 (d, 1H, *J* = 7.5 Hz), 7.87-7.85 (d, 1H, *J* = 7.5 Hz), 7.80-7.78 (m, 1H), 7.56 (s, 1H), 7.53-7.50 (m, 2H), 7.48-7.46 (d, 2H), 7.42 (bs, 2H), 7.09 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.88 (s, 2H), 3.55 (s, 2H), 2.60 (bs, 4H) and 2.53 (bs, 4H).

^{13}C-NMR (DMSO-d_6): 160.69, 153.92, 147.94, 133.65, 133.33, 132.00, 128.00, 127.54, 127.14, 125.51, 125.39, 124.92, 124.58, 106.51, 106.31, 102.60, 99.49, 60.45, 55.87, 55.49, 52.91 and 52.54.

MS (ESI) m/z: 444.7 $(M + 1)^+$.

4-Amino-2-[(4-benzhydryl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (188)

Following **Method L**, but using 1-benzhydrylpiperazine (0.60 g, 2.37 mM), the desired compound (**188**) was obtained as white solid (0.29 g, 78.4%) m. p. 236-38 °C.

Anal.:

TLC: R_f 0.52 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3492, 3270, 3026, 2972, 2943, 2872, 2759, 1647, 1578, 1564, 1509, 1481, 1250, 1007, 851 and 706.

^{1}H-NMR ($CDCl_3$): δ 7.41-7.39 (d, 4H, *J* = 7.4 Hz), 7.26 (s, 1H), 7.24-7.21 (m, 4H), 7.16-7.13 (m, 2H), 6.92 (s, 1H), 5.70 (bs, 2H), 4.23 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.70 (s, 2H), 2.65 (bs, 4H) and 2.49 (bs, 4H).

^{13}C-NMR ($CDCl_3$): 161.71, 160.13, 154.88, 148.93, 147.58, 142.80, 128.41, 127.95, 126.85, 107.59, 106.73, 100.14, 65.63, 56.26, 56.19, 53.79 and 51.61.

4-Amino-2-[4-(cyclohexylmethyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (189)

Following **Method L**, but using 1-(cyclohexylmethyl)piperazine (0.43 g, 2.37 mM), the desired compound (**189**) was obtained as white solid (0.21 g, 65.6%) m. p. 207-08 °C.

Anal.:

TLC: R_f 0.54 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3338, 3156, 3001, 2924, 2846, 1660, 1623, 1580, 1512, 1489, 1255, 1227, 1019 and 868.

^{1}H-NMR ($CDCl_3$): δ 7.24 (s, 1H), 6.92 (s, 1H), 5.72 (bs, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.69 (s, 2H), 2.65 (bs, 4H), 2.51 (bs, 4H), 2.13 (s, 2H), 1.77-1.64 (m, 4H), 1.50-1.45 (m, 1H), 1.26-1.13 (m, 4H) and 0.90-0.81 (m, 2H).

1-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylpiperazin-1-yl]-2-phenylethanone (190)

Following **Method L**, but using 2-phenyl-1-(piperazin-1-yl)ethanone (0.49 g, 2.37 mM), the desired compound (**190**) was obtained as white solid (0.27 g, 81.8%) m. p. 219-21 °C.

Anal.:

TLC: R_f 0.67 (Chloroform: methanol, 19:1).

IR (KBr, cm^{-1}): 3336, 3164, 2965, 2832, 1657, 1618, 1577, 1553, 1511, 1400, 1255, 1227, 988 and 868.

^{1}H-NMR ($CDCl_3$): δ 7.25 (bs, 2H), 7.23 (s, 1H), 7.21-7.20 (d, 2H), 7.15-7.14 (m, 3H), 6.88 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.66 (bs, 2H, 2H), 3.57 (s, 2H), 3.47-3.45 (t, 2H, J = 4.5 Hz), 2.50-2.48 (t, 2H, J = 4.5 Hz) and 2.34 (t, 2H).

MS (ESI) m/z: 422.9 $(M + 1)^+$.

1-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylpiperazin-1-yl]-2-(3-chlorophenyl)ethanone (191)

Following **Method L**, but using 2-(3-chlorophenyl)-1-(piperazin-1-yl)ethanone (0.56 g, 2.37 mM), the desired compound (**191**) was obtained as white solid (0.31 g, 86.1%) m. p. 220-22 °C.

Anal.:

TLC:	R_f 0.69 (Chloroform: methanol, 19:1).
IR (KBr, cm^{-1}):	3332, 3146, 3004, 2962, 2829, 1657, 1618, 1577, 1554, 1511, 1488, 1254, 1227, 987, 866 and 764.
^{1}H-NMR ($CDCl_3$):	δ 7.24 (s, 1H), 7.23 (s, 1H), 7.22-7.21 (d, 2H), 7.13-7.11 (m, 1H), 6.92 (s, 1H), 4.01 (s, 3H), 4.00 (s, 3H), 3.75-3.73 (t, 2H, *J* = 5.0 Hz), 3.69 (s, 2H), 3.67 (s, 2H), 3.54-3.51 (t, 2H, *J* = 5.0 Hz), 2.59-2.56 (t, 2H, *J* = 5.0 Hz) and 2.48-2.45 (t, 2H, *J* = 5.0 Hz).
MS (ESI) m/z:	456.7 $(M + 1)^+$, 457.7 $(M + 2)^+$.

1-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylpiperazin-1-yl]-2-(4-methoxyphenyl)ethanone (192)

Following **Method L**, but using 2-(4-methoxyphenyl)-1-(piperazin-1-yl)ethanone (0.55 g, 2.37 mM), the desired compound (**192**) was obtained as white solid (0.26 g, 72.2%) m. p. 212-14 °C.

Anal.:

TLC:	R_f 0.67 (Chloroform: methanol, 19:1).
IR (KBr, cm^{-1}):	3333, 3161, 3009, 2960, 2833, 1657, 1616, 1578, 1512, 1490, 1252, 1226, 988, 865 and 788.
^{1}H-NMR ($CDCl_3$):	δ 7.23 (s, 1H), 7.15-7.13 (d, 2H, *J* = 8.9 Hz), 6.96 (s, 1H), 6.86-6.82 (d, 2H, *J* = 8.9 Hz), 4.01 (s, 3H), 4.00 (s, 3H), 3.79 (s, 3H), 3.75-3.72 (t, 2H, *J* = 4.9 Hz), 3.66 (s, 2H), 3.65 (s, 2H), 3.55-3.53 (t, 2H, *J* = 4.9 Hz), 2.57-2.55 (t, 2H, *J* = 4.9 Hz) and 2.44-2.41 (t, 2H, *J* = 4.9 Hz).
MS (ESI) m/z:	452.9 $(M + 1)^+$.

5.1.5 Synthesis of 4-amino-2-(1-substituted piperidin-4-ylamino)methyl-6,7-dimethoxyquinazolines (193-198) (Series II)

4-Amino-2-[(1-benzylpiperidin-4-yl)amino]methyl-6,7-dimethoxyquinazoline (193)

Method M: 4-Amino-2-chloromethyl-6,7-dimethoxyquinazoline (0.2 g, 0.79 mM), 4-amino-1-benzylpiperidine (0.13 g, 0.66 mM), flame dried potassium carbonate (0.22 gm, 1.58 mM), potassium iodide (0.02 g, 0.13 mM) and dried DMF (2 mL) were taken in an Rb flask (50 ml). The reaction mixture was stirred overnight at 60^0 C and poured into ice-cold water (20 ml) to give a precipitate. It was filtered through vacuum filtration, dried, and purified through column chromatography using chloroform and methanol as eluents (chloroform: methanol, 98:2) to obtain compound (**193**) as white solid (0.18 g, 56.3%) m. p. 273-75 °C.

Anal.:

TLC: R_f 0.56 (Chloroform: methanol: methanolic ammonia, 17:2:1).

IR (KBr, cm^{-1}): 3346, 3196, 2935, 2804, 1648, 1583, 1512, 1488, 1282, 1111 and 1001.

^{1}H-NMR (DMSO-d_6): δ 7.61 (s, 1H), 7.50 (bs, 2H), 7.33-7.22 (m, 5H), 7.05 (s, 1H), 3.90 (s, 6H), 3.88 (s, 2H), 3.46 (s, 2H), 2.84-2.76 (m, 4H), 2.00-1.91 (m, 4H) and 1.55-1.49 (m, 1H).

MS (ESI) (m/z): 408.4 $(M + 1)^+$.

4-Amino-2-[1-(2-bromobenzyl)piperidin-4-ylamino]methyl-6,7-dimethoxyquinazoline (194)

Following **Method M**, but using 4-amino-1-(2-bromobenzyl)piperidine (0.18 g, 0.66 mM), the desired compound (**194**) was obtained as white solid (0.17 g, 44.7%) m. p. 208-09 °C.

Anal.:

TLC: R_f 0.62 (Chloroform: methanol: methanolic ammonia, 17:2:1).

IR (KBr, cm^{-1}): 3272, 3102, 2931, 2802, 2758, 1668, 1624, 1578, 1509, 1479, 1432, 1248 and 749.

^{1}H-NMR (DMSO-d_6): δ 7.52-7.50 (d, 1H, J = 7.6 Hz), 7.49-7.47 (d, 1H, J = 7.6 Hz), 7.29-7.25 (m, 1H), 7.15 (s, 1H), 7.11-7.06 (m, 1H),

6.93 (s, 1H), 5.71 (bs, 2H), 3.99 (s, 3H), 3.96 (s, 3H), 3.95 (s, 2H), 3.58 (s, 2H), 2.91-2.88 (m, 2H), 2.64-2.59 (m, 1H), 2.18-2.12 (t, 2H), 1.96-1.93 (m, 2H) and 1.60-1.51 (m, 2H).

MS (ESI) m/z: 486.4 $(M + 1)^+$.

4-Amino-2-[1-(2-cyanobenzyl)piperidin-4-ylamino]methyl-6,7-dimethoxyquinazoline (195)

Following **Method M**, but using 4-amino-1-(2-cyanobenzyl)piperidine (0.14 g, 0.66 mM), the desired compound (**195**) was obtained as white solid (0.25 g, 66.5%) m. p. 261-63 °C.

Anal.:

TLC: R_f 0.57 (Chloroform: methanol: methanolic ammonia, 17:2:1).

IR (KBr, cm^{-1}): 3338, 3147, 2940, 2633, 2537, 2225, 1670, 1623, 1590, 1519, 1402, 993 and 767.

^{1}H-NMR (DMSO-d_6): δ 7.75-7.73 (d, 1H, J = 7.5 Hz), 7.71 (s, 1H), 7.67-7.63 (m, 1H), 7.56-7.54 (d, 1H, J = 7.5 Hz), 7.46-7.42 (m, 1H), 7.05 (s, 1H), 4.12 (s, 2H), 3.90 (s, 6H), 3.65 (s, 2H), 3.20-3.14 (m, 2H), 2.91-2.89 (bs, 2H), 2.15-2.08 (m, 4H) and 1.78-1.70 (m, 2H).

MS (ESI) m/z: 433.2 $(M + 1)^+$.

4-Amino-2-[1-(2-methylbenzyl)piperidin-4-ylamino]methyl-6,7-dimethoxyquinazoline (196)

Following **Method M**, but using 4-amino-1-(2-methylbenzyl)piperidine (0.13 g, 0.66 mM), the desired compound (**196**) was obtained as white solid (0.10 g, 30.3%) m. p. 255-56 °C.

Anal.:

TLC: R_f 0.70 (Chloroform: methanol: methanolic ammonia, 17:2:1).

IR (KBr, cm^{-1}): 3270, 3216, 3102, 2932, 2805, 1669, 1581, 1510, 1481, 1430, 1248, 1212 and 745.

^{1}H-NMR (DMSO-d_6): δ 7.55 (s, 1H), 7.25 (bs, 2H), 7.20-7.18 (m, 1H), 7.12-7.08 (m, 3H), 7.04 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.73 (s,

2H), 3.39 (s, 2H), 3.30 (bs, 2H), 2.79-2.76 (m, 2H), 2.32 (s, 3H), 2.05-1.99 (m, 2H), 1.86-1.83 (m, 2H) and 1.42-1.33 (m, 2H).

4-Amino-2-[1-(3-methoxybenzyl)piperidin-4-ylamino]methyl-6,7-dimethoxyquinazoline (197)

Following **Method M**, but using 4-amino-1-(3-methoxybenzyl)piperidine (0.15 g, 0.66 mM), the desired compound (**197**) was obtained as white solid (0.16 g, 47.2%) m. p. 242-44 °C.

Anal.:

TLC: R_f 0.65 (Chloroform: methanol: methanolic ammonia, 17:2:1).

IR (KBr, cm^{-1}): 3349, 3209, 2937, 2835, 1639, 1581, 1510, 1481, 1257, 864, and 798.

^{1}H-NMR ($CDCl_3$): δ 7.18-7.14 (m, 1H), 7.10 (bs, 2H, 1H), 7.05 (s, 1H), 6.81 (s, 1H), 6.81-6.79 (d, 1H), 6.75-6.73 (d, 1H), 3.93 (s, 2H), 3.82 (s, 6H), 3.75 (s, 3H), 3.34 (s, 2H), 2.85-2.83 (m, 2H), 2.62 (bs, 1H), 1.91 (bs, 2H) and 1.82-1.67 (m, 4H).

^{13}C-NMR ($CDCl_3$): 163.17, 160.55, 159.50, 154.56, 148.52, 146.90, 140.11, 129.05, 126.71, 121.46, 114.63, 112.27, 107.11, 101.23, 65.90, 62.97, 58.95, 58.25, 56.04, 55.16, 53.50 and 27.44.

4-Amino-2-[1-(4-methylbenzyl)piperidin-4-ylamino]methyl-6,7-dimethoxyquinazoline (198)

Following **Method M**, but using 4-amino-1-(4-methylbenzyl)piperidine (0.13 g, 0.66 mM), the desired compound (**198**) was obtained as white solid (0.18 g, 54.5%) m. p. 269-71 °C.

Anal.:

TLC: R_f 0.54 (Chloroform: methanol: methanolic ammonia, 17:2:1).

IR (KBr, cm^{-1}): 3125, 2958, 2795, 1672, 1622, 1582, 1510, 1481, 1401 and 1244.

^{1}H-NMR (DMSO-d_6): δ 7.55 (s, 1H), 7.33 (bs, 2H), 7.16-7.14 (d, 2H, J = 7.9 Hz), 7.10-7.08 (d, 2H, J = 7.9 Hz), 7.03 (s, 1H), 3.90 (s, 3H),

3.88 (s, 3H), 3.70 (s, 2H), 3.38 (s, 2H), 3.33 (s, 1H), 2.77-2.74 (m, 2H), 2.49-2.48 (m, 1H), 2.29 (s, 3H), 1.99-1.91 (m, 2H), 1.83-1.81 (m, 2H) and 1.39-1.34 (m, 2H).

5.1.6 Synthesis of 4-amino-2-(2'/4'-substitued 1,1'-biphenyl-4-ylamino)methyl-6,7-dimethoxyquinazolines (199-204) (Series III)

4-Amino-2-(1,1'-biphenyl-4-amino)methyl-6,7-dimethoxyquinazoline (199)

Following **Method M**, but using 4-amino-1,1'-biphenyl (0.11 g, 0.66 mM), the desired compound (**199**) was obtained as white solid (0.14 g, 45.2%) m. p. 228-30 °C.

Anal.:

TLC: R_f 0.59 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3389, 3132, 2927, 1664, 1619, 1579, 1512, 1482, 1416, 1255, 1216 and 866.

^{1}H-NMR (DMSO-d_6): δ 7.59 (s,1H), 7.52-7.50 (d, 2H, *J* = 8.3 Hz), 7.42-7.39 (d, 2H, *J* = 8.3 Hz), 7.39 (bs, 2H) 7.37-7.33 (m, 2H), 7.21-7.18 (m, 1H), 7.11 (s, 1H), 6.78-6.76 (d, 2H, *J* = 8.3 Hz), 5.94-5.92 (t, 1H, *J* = 4.9), 4.27-4.26 (d, 2H, *J* = 4.9), 3.94 (s, 3H) and 3.91 (s, 3H).

MS (EI) m/z: 387.1 (M^+).

4-Amino-2-(2'-chloro-1,1'-biphenyl-4-amino)methyl-6,7-dimethoxyquinazoline (200)

Following **Method M**, but using 4-amino-2'-chloro-1,1'-biphenyl (0.13 g, 0.66 mM), the desired compound (**200**) was obtained as white solid (0.13 g, 40.4%) m. p. 184-85 °C.

Anal.:

TLC: R_f 0.62 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3430, 3379, 3146, 2925, 1668, 1614, 1579, 1512, 1482, 1435, 1256, 1209, 1032 and 754.

^{1}H-NMR ($CDCl_3$): δ 7.59 (s, 1H), 7.44-7.42 (d, 1H), 7.41 (bs, 2H), 7.33-7.28 (m, 2H), 7.26-7.21 (m, 3H), 7.12 (s, 1H), 6.76-6.74 (d, 2H), 6.03-6.00 (t, 1H, *J* = 4.8), 4.27-4.26 (d, 2H, *J* = 4.8), 3.94 (s, 3H) and 3.91 (s, 3H).

MS (EI) m/z: 421.4 (M^+), 423.4 $(M + 2)^+$.

4-Amino-2-(2'-methyl-1,1'-biphenyl-4-amino)methyl-6,7-dimethoxyquinazoline (201)

Following **Method M**, but using 4-amino-2'-methyl-1,1'-biphenyl (0.12 g, 0.66 mM), the desired compound (**201**) was obtained as white solid (0.14 g, 43.8%) m. p. 215-17 °C.

Anal.:

TLC: R_f 0.55 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3390, 3132, 2926, 1664, 1619, 1579, 1512, 1483, 1416, 1255, 1217, 1126 and 805.

^{1}H-NMR ($CDCl_3$): δ 7.25 (s, 1H), 7.24-7.17 (m, 6H), 6.89 (s, 1H), 6.83-6.81 (d, 2H, *J* = 8.4 Hz), 5.54 (bs, 2H), 5.32 (bs, 1H), 4.46 (s, 2H), 4.04 (s, 3H), 3.98 (s, 3H) and 2.31 (s, 3H).

MS (EI) m/z: 400.8 (M^+).

4-Amino-2-(4'-cyano-1,1'-biphenyl-4-amino)methyl-6,7-dimethoxyquinazoline (202)

Following **Method M**, but using 4-amino-4'-cyano-1,1'-biphenyl (0.13 g, 0.66 mM), the desired compound (**202**) was obtained as white solid (0.12 g, 37.5%) m. p. 264-66 °C.

Anal.:

TLC: R_f 0.49 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3404, 3208, 2923, 2833, 2223, 1654, 1592, 1498, 1239, 1127, 854 and 815.

^{1}H-NMR (DMSO-d_6): δ 7.71 (bs, 4H), 7.58 (s, 1H) ,7.51-7.49 (d, 2H, *J* = 8.7 Hz), 7.39 (bs, 2H), 7.09 (s, 1H), 6.80-6.78 (d, 2H, *J* = 8.7 Hz), 6.28-6.24 (t, 1H), 4.28-4.27 (d, 2H, *J* = 4.9 Hz), 3.93 (s, 3H) and 3.90 (s, 3H).

MS (EI) m/z: 411.6 (M^+).

4-Amino-2-(4'-methylthio-1,1'-biphenyl-4-amino)methyl-6,7-dimethoxyquinazoline (203)

Following **Method M**, but using 4-amino-4'-methylthio-1,1'-biphenyl (0.14 g, 0.66 mM), the desired compound (**203**) was obtained as white solid (0.11 g, 32.4%) m. p. 213-14 °C.

Anal.:

TLC: R_f 0.51 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3469, 3359, 3105, 2966, 2925, 1648, 1613, 1577, 1479, 1426, 1370, 1320, 1232, 1205, 987 and 808.

^{1}H-NMR (DMSO-d_6): δ 7.58 (s, 1H), 7.48-7.46 (d, 2H, *J* = 8.4 Hz), 7.40-7.38 (d, 2H, *J* = 8.5 Hz), 7.26-7.23 (d, 2H, *J* = 8.4 Hz), 7.10 (s, 1H), 6.76-6.74 (d, 2H, *J* = 8.5 Hz), 5.98-5.95 (t, 1H, *J* = 5.1 Hz), 4.26-4.25 (d, 2H, *J* = 5.1 Hz), 3.93 (s, 3H), 3.90 (s, 3H) and 2.48 (s, 3H).

MS (EI) m/z: 432.6 (M^+).

4-Amino-2-(4'-*t*.butyl-1,1'-biphenyl-4-amino)methyl-6,7-dimethoxyquinazoline (204)

Following **Method M**, but using 4-amino-4'-*t*.butyl-1,1'-biphenyl (0.15 g, 0.66 mM), the desired compound (**204**) was obtained as white solid (0.16 g, 45.7%) m. p. 246-48 °C.

Anal.:

TLC: R_f 0.52 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3384, 3148, 2958, 2866, 1614, 1575, 1505, 1475, 1433, 1251, 1212 and 816.

^{1}H-NMR (DMSO-d_6): δ 7.58 (s, 1H), 7.45-7.43 (d, 2H, *J* = 7.7 Hz), 7.41 (bs, 2H), 7.41-7.39 (d, 2H, *J* = 7.7 Hz), 7.37-7.35 (d, 2H, *J* = 8.4 Hz), 7.10 (s, 1H), 6.76-6.74 (d, 2H, *J* = 8.4 Hz), 5.98-5.95 (t, 1H, *J* = 5.1 Hz), 4.25-4.24 (d, 2H, *J* = 5.1 Hz), 3.93 (s, 3H), 3.89 (s, 3H) and 1.31 (s, 9H).

MS (EI) m/z: 442.6 (M^+).

5.1.7 Synthesis of 4-amino-2-(4-substituted piperazin-1-yl)ethyl-6,7-dimethoxy-quinazolines (205-210) (Series IV)

4-Amino-2-[4-(2-chlorophenyl)piperazin-1-yl]ethyl-6,7-dimethoxyquinazoline (205)

Reaction of 4-amino-6,7-dimethoxy-2-vinylquinazoline (**166**) (0.2 g, 0.86 mM) and 1-(2-chlorophenyl)piperazine (0.51 g, 2.60 mM) under a set of conditions described in **Method M** afforded compound (**205**) (0.19 g, 51.4%) m. p. 248-50 °C.

Anal.:

TLC: R_f 0.31 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3323, 3095, 2960, 2826, 1677, 1626, 1586, 1485, 1443, 1375, 1254, 1217, 1120, 1038, 997, 854 and 763.

^{1}H-NMR (DMSO-d_6): δ 7.54 (s, 1H), 7.36-7.33 (d, 1H, *J* = 7.8), 7.27 (bs, 2H), 7.26-7.23 (m, 1H), 7.10-7.08 (d, 1H, *J* = 7.8), 7.03 (s, 1H), 7.01-6.97 (m, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.23-3.22 (t, 2H), 3.01 (bs, 4H), 2.88-2.84 (t, 2H) and 2.66 (bs, 4H).

MS (ESI) m/z: 427.9 $(M + 1)^+$.

4-Amino-2-[4-(2-cyanophenyl)piperazin-1-yl]ethyl-6,7-dimethoxyquinazoline (206)

Reaction of 4-amino-6,7-dimethoxy-2-vinylquinazoline (**166**) (0.2 g, 0.86 mM) and 1-(2-cyanophenyl)piperazine (0.48 g, 2.60 mM) under a set of conditions described in **Method M** afforded compound (**206**) (0.21 g, 58.3%) m. p. 218-19 °C.

Anal.:

TLC: R_f 0.33 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3336, 3137, 2948, 2832, 2219, 1641, 1584, 1510, 1486, 1445, 1375 and 764.

^{1}H-NMR ($CDCl_3$): δ 7.57-7.54 (d, 1H, *J* = 7.9 Hz), 7.50-7.45 (m, 1H), 7.17 (s, 1H), 7.02 (s, 1H), 7.01-6.99 (m, 2H), 6.17 (bs, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.27-3.25 (t, 4H), 3.09-2.99 (m, 4H) and 2.81-2.79 (m, 4H).

MS (ESI) m/z: 419.2 $(M + 1)^+$.

4-Amino-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl-6,7-dimethoxyquinazoline (207)

Reaction of 4-amino-6,7-dimethoxy-2-vinylquinazoline (**166**) (0.2 g, 0.86 mM) and 1-(2-methoxyphenyl)piperazine (0.50 g, 2.60 mM) under a set of conditions described in **Method M** afforded compound (**207**) (0.15 g, 41.7%) m. p. 182-84 °C.

Anal.:

TLC: R_f 0.38 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3342, 3125, 2941, 2827, 1627, 1581, 1504, 1374, 1249, 1124, 857 and 751.

^{1}H-NMR ($CDCl_3$): δ 7.19 (s, 1H), 7.03-6.99 (m, 2H), 6.97-6.92 (m, 2H), 6.87-6.86 (d, 1H, *J* = 7.9 Hz), 6.27 (bs, 2H), 4.00 (s, 3H), 3.97 (s, 3H), 3.86 (s, 3H), 3.14 (bs, 4H), 3.10-3.05 (m, 2H), 3.02-2.98 (m, 2H) and 2.81 (bs, 4H).

4-Amino-2-[4-(2-methylphenyl)piperazin-1-yl]ethyl-6,7-dimethoxyquinazoline (208)

Reaction of 4-amino-6,7-dimethoxy-2-vinylquinazoline (**166**) (0.2 g, 0.86 mM) and 1-(2-methylphenyl)piperazine (0.46 g, 2.60 mM) under a set of conditions described in **Method M** afforded compound (**208**) (0.19 g, 54.3%) m. p. 263-65 °C.

Anal.:

TLC: R_f 0.43 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3330, 3161, 2938, 2814, 1651, 1578, 1512, 1487, 1380, 1256 and 1222.

^{1}H-NMR ($CDCl_3$): δ 7.19 (s, 1H), 7.19-7.15 (m, 2H), 7.05-7.03 (d, 1H, *J* = 7.8 Hz), 7.00-6.96 (m, 2H), 5.84 (bs, 2H), 4.01 (s, 3H), 4.00 (s, 3H), 3.13-3.07 (m, 4H), 3.01-2.99 (t, 4H, *J* = 4.5 Hz), 2.80 (bs, 4H) and 2.30 (s, 3H).

MS (ESI) m/z: 408.2 $(M + 1)^+$.

4-Amino-2-[4-(2-pyridyl)piperazin-1-yl]ethyl-6,7-dimethoxyquinazoline (209)

Reaction of 4-amino-6,7-dimethoxy-2-vinylquinazoline (**166**) (0.2 g, 0.86 mM) and 1-(2-pyridyl)piperazine (0.42 g, 2.60 mM) under a set of conditions described in **Method M** afforded compound (**209**) (0.14 g, 41.2%) m. p. 242-43 °C.

Anal.:

TLC: R_f 0.41 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3374, 3118, 2831, 1626, 1592, 1508, 1485, 1441, 1375, 1257, 1036, 865 and 783.

^{1}H-NMR ($CDCl_3$): δ 8.20-8.18 (d, 1H, *J* = 6.2 Hz), 7.50-7.45 (m, 1H), 7.18 (s, 1H), 6.93 (s, 1H), 6.66-6.63 (m, 1H), 6.63-6.60 (d, 1H, *J* = 6.2 Hz), 5.75 (bs, 2H), 4.01 (s, 3H), 3.98 (s, 3H), 3.59-3.56 (t, 4H, *J* = 5.0 Hz), 3.09-3.04 (m, 2H), 3.01-2.96 (m, 2H) and 2.71-2.69 (t, 4H, *J* = 5.0 Hz).

MS (ESI) m/z: 395.3 $(M + 1)^+$.

4-Amino-2-[4-(benzhydryl)piperazin-1-yl]ethyl-6,7-dimethoxyquinazoline (210)

Reaction of 4-amino-6,7-dimethoxy-2-vinylquinazoline (**166**) (0.2 g, 0.86 mM) and 1-benzhydrylpiperazine (0.66 g, 2.60 mM) under a set of conditions described in **Method M** afforded compound (**210**) (0.22 g, 52.4%) m. p. 152-54 °C.

Anal.:

TLC: R_f 0.33 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3537, 3484, 3313, 3094, 2968, 2823, 1684, 1623, 1588, 1488, 1448, 1414, 1279, 1220, 1139, 1035, 1000, 859 and 708.

^{1}H-NMR (DMSO-d_6): δ 7.52 (s, 1H), 7.42-7.40 (d, 4H, *J* = 7.1 Hz), 7.28-7.26 (m, 4H), 7.25 (bs, 2H), 7.17-7.14 (m, 2H), 7.01 (s, 1H), 4.22 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.77 (bs, 4H), 2.49 (bs, 4H) and 2.33 (bs, 4H).

MS (ESI) m/z: 483.9 $(M + 1)^+$.

5.1.8 Synthesis of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (211) & 4-amino-2-(4-substituted piperazin-1-yl)methyl-6,7-methylenedioxyquinazolines (212-228) (Series V)

4-Amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**)

Reaction of 2-amino-4,5-methylenedioxybenzonitrile (**138**) (0.5 g, 3.09 mM) with chloroacetonitrile (0.5 mL, 6.18 mM) under a set of conditions described in **Method K** afforded compound (**211**) (0.52 g, 71.2%) m. p. 241-43 °C dec.

Anal.:

TLC: R_f 0.70 (*n*-Hexane: ethyl acetate, 7:13).

IR (KBr, cm^{-1}): 3490, 3315, 3102, 2913, 1657, 1565 and 1038.

^{1}H-NMR (DMSO-d_6): δ 7.61 (s, 1H), 7.48 (bs, 2H), 7.02 (s, 1H), 6.15 (s, 2H) and 4.49 (s, 2H).

4-Amino-2-(4-phenylpiperazin-1-yl)methyl-6,7-methylenedioxyquinazoline (212)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-phenylpiperazine (0.47 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**212**) (0.30 g, 85.7%) m. p. 273-75 °C dec.

Anal.:

TLC: R_f 0.70 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3323, 3146, 3037, 2940, 2901, 2825, 1660, 1604, 1560, 1505, 1469, 1333, 1261, 1231, 1145, 1037, 940 and 756.

^{1}H-NMR (DMSO-d_6): δ 7.59 (s, 1H), 7.30 (bs, 2H), 7.20-7.16 (m, 2H), 7.02 (s, 1H), 6.90-6.88 (d, 2H, J = 7.7 Hz), 6.77-6.75 (m, 1H), 6.14 (s, 2H), 3.52 (s, 2H), 3.15-3.13 (t, 4H, J = 4.9 Hz) and 2.68-2.66 (t, 4H, J = 4.9 Hz).

LC-MS/MS: t_R 11.07 min, 365.16 (M+H).

4-Amino-2-[4-(2-fluorophenyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (213)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(2-fluorophenyl)piperazine (0.52 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**213**) (0.30 g, 83.3%) m. p. 255-56 °C.

Anal.:

TLC: R_f 0.70 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3299, 3134, 2933, 2817, 1664, 1614, 1562, 1502, 1469, 1260, 1234, 1220, 1141, 1038, 939, 856 and 749.

^{1}H-NMR (DMSO-d_6): δ 7.58 (s, 1H), 7.29 (bs, 2H), 7.07-7.02 (m, 2H), 7.01 (s, 1H), 6.98-6.90 (m, 2H), 6.13 (s, 2H), 3.51 (s, 2H), 3.03-3.01 (t, 4H, *J* = 4.4 Hz) and 2.68-2.66 (t, 4H, *J* = 4.4 Hz).

MS (EI) m/z: 381.5 (M^+).

LC-MS/MS: t_R 11.61 min, 382.17 (M+H).

4-Amino-2-[4-(2-cyanophenyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (214)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(2-cyanophenyl)piperazine (0.50 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**214**) (0.30 g, 81.0%) m. p. 222-24 °C.

Anal.:

TLC: R_f 0.67 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3424, 3341, 3136, 2953, 2927, 2841, 2222, 1667, 1594, 1565, 1494, 1467, 1448, 1374, 1253, 1227, 1036 and 773.

^{1}H-NMR (DMSO-d_6): δ 7.63-7.60 (d, 1H, *J* = 7.6 Hz), 7.59 (s, 1H), 7.54-7.52 (m, 1H), 7.32 (bs, 2H), 7.11-7.09 (d, 1H, *J* = 7.6 Hz), 7.06-7.04 (m, 1H), 7.02 (s, 1H), 6.13 (s, 2H), 3.53 (s, 2H), 3.17-3.15 (t, 4H, *J* = 4.5 Hz) and 2.72-2.69 (t, 4H, *J* = 4.5 Hz).

LC-MS/MS: t_R 11.44 min, 389.18 $(M+H)^+$.

4-Amino-2-[4-(2-methoxyphenyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (215)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(2-methoxyphenyl)piperazine (0.56 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**215**) (0.30 g, 79.0%) m. p. 231-33 °C dec.

Anal.:

TLC: R_f 0.37 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3439, 3308, 3201, 2946, 2911, 2687, 1621, 1560, 1499, 1472, 1241, 1209, 1041, 1013, 833 and 758.

^{1}H-NMR (DMSO-d_6): δ 7.60 (s, 1H), 7.20 (bs, 2H), 7.03 (s, 1H), 6.94-6.90 (d, 1H), 6.87-6.85 (m, 3H), 6.12 (s, 2H), 3.80 (s, 3H), 3.57 (s, 2H), 3.03 (bs, 4H) and 2.71 (bs, 4H).

MS (EI) m/z: 393.6 (M^+).

LC-MS/MS: t_R 11.33 min, 394.17 (M+H).

4-Amino-2-[4-(4-nitrophenyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (216)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(4-nitrophenyl)piperazine (0.60 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**216**) (0.32 g, 82.1%) m. p. 279-81 °C dec.

Anal.:

TLC: R_f 0.38 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3288, 3124, 2932, 2826, 1667, 1595, 1562, 1504, 1470, 1333, 1244, 1031 and 926.

^{1}H-NMR (DMSO-d_6): δ 8.05-8.03 (d, 2H, *J* = 9.5 Hz), 7.60 (s, 1H), 7.30 (bs, 2H), 7.01 (s, 1H), 6.97-6.95 (d, 2H, *J* = 9.5 Hz), 6.14 (s, 2H), 3.54 (s, 2H), 3.48-3.45 (t, 4H, *J* = 4.9 Hz) and 2.68-2.66 (t, 4H, *J* = 4.9 Hz).

MS (EI) m/z: 408.5 (M^+).

LC-MS/MS: t_R 10.72 min, 409.18 (M+H).

4-Amino-2-[4-(4-methylphenyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (217)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(4-methylphenyl)piperazine (0.51 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**217**) (0.30 g, 83.3%) m. p. 273-75 °C.

Anal.:

TLC: R_f 0.36 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3299, 3133, 3032, 2930, 2825, 1664, 1614, 1561, 1512, 1469, 1331, 1257, 1220, 1143, 1037, 994, 940, 854 and 809.

^{1}H-NMR (DMSO-d_6): δ 7.59 (s, 1H), 7.27 (bs, 2H), 7.02 (s, 1H), 7.01-6.98 (d, 2H, *J* = 8.5 Hz), 6.79-6.77 (d, 2H, *J* = 8.5 Hz), 6.13 (s, 2H), 3.52 (s, 2H), 3.09-3.07 (t, 4H, *J* = 4.7 Hz), 2.68-2.66 (t, 4H, *J* = 4.7 Hz) and 2.21 (s, 3H).

LC-MS/MS: t_R 11.80 min, 378.19 (M+H).

4-Amino-2-[4-(3,4,5-trimethoxyphenyl)piperazin-1-yl]methyl-6,7-methylenedioxy-quinazoline (218)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(3,4,5-trimethoxyphenyl)piperazine (0.73 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**218**) (0.36 g, 83.7%) m. p. 232-34 °C dec.

Anal.:

TLC: R_f 0.65 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3341, 3183, 2930, 2832, 1661, 1589, 1562, 1507, 1471, 1243, 1201, 1127, 1036 and 853.

^{1}H-NMR ($CDCl_3$): δ 7.20 (s, 1H), 7.01 (s, 1H), 6.16 (s, 2H), 6.10 (s, 2H), 5.59 (bs, 2H), 3.84 (s, 6H), 3.78 (s, 3H), 3.74 (s, 2H), 3.23-3.21 (t, 4H) and 2.78-2.76 (t, 4H).

MS (EI) m/z: 453.3 (M^+).

LC-MS/MS: t_R 11.24 min, 455.17 (M+H).

4-Amino-2-[4-(2-pyridyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (219)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(2-pyridyl)piperazine (0.47 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method K** afforded compound (**219**) (0.19 g, 54.3%) m. p. >275 °C.

Anal.:

TLC: R_f 0.39 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3308, 3138, 3041, 2974, 2936, 2821, 2780, 1663, 1594, 1561, 1510, 1474, 1434, 1257, 1227, 1145, 1038, 937, 853 and 776.

^{1}H-NMR (DMSO-d_6): δ 8.10-8.08 (d, 1H), 7.59 (s, 1H), 7.49-7.45 (m, 1H), 7.19 (bs, 2H), 7.02 (s, 1H), 6.71-6.69 (d, 1H, *J* = 7.5 Hz), 6.60-6.57 (m, 1H), 6.13 (s, 2H), 3.55 (s, 2H), 3.52-3.49 (t, 4H, *J* = 4.8 Hz) and 2.65-2.63 (t, 4H, *J* = 4.8 Hz).

MS (EI) m/z: 364.4 (M^+).

LC-MS/MS: t_R 11.04 min, 365.16 (M+H).

4-Amino-2-[4-(2-pyrimidinyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (220)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(2-pyrimidinyl)piperazine (0.48 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**220**) (0.28 g, 80.0%) m. p. 247-249 °C.

Anal.:

TLC: R_f 0.35 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3301, 3135, 2974, 2933, 2906, 2823, 1664, 1613, 1582, 1551, 1470, 1443, 1261, 1221, 1144, 1037, 938 and 853.

^{1}H-NMR (DMSO-d_6): δ 8.29-8.27 (d, 2H, *J* = 7.5 Hz), 7.59 (s, 1H), 7.14 (bs, 2H), 7.04 (s, 1H), 6.52-6.50 (m, 1H), 6.12 (s, 2H), 3.81-3.78 (t, 4H, *J* = 4.7 Hz), 3.57 (s, 2H) and 2.61-2.59 (t, 4H, *J* = 4.7 Hz).

MS (EI) m/z: 365.7 (M^+).

LC-MS/MS: t_R 11.14 min, 366.11 (M+H).

4-Amino-2-[4-(1-naphthyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (221)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(1-naphthyl)piperazine (0.61 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**221**) (0.32 g, 80.0%) m. p. 263-265 °C.

Anal.:

TLC: R_f 0.72 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3277, 3105, 2971, 2932, 2835, 2807, 1668, 1615, 1566, 1510, 1470, 1261, 1224, 1204, 1128, 1037, 938 and 772.

^{1}H-NMR (DMSO-d_6): δ 8.15-8.13 (d, 1H, *J* = 7.3 Hz), 7.82-7.79 (d, 1H, *J* = 6.8 Hz), 7.61 (s, 1H), 7.53-7.51 (d, 1H, *J* = 7.3 Hz), 7.48-7.44 (m, 2H), 7.40-7.36 (m, 1H), 7.19 (bs, 2H), 7.08-7.06 (d, 1H, *J* = 6.8 Hz), 7.05 (s, 1H), 6.13 (s, 2H), 3.65 (s, 2H), 3.12 (bs, 4H) and 2.85 (bs, 4H).

MS (EI) m/z: 413.2 (M^+).

LC-MS/MS: t_R 11.96 min, 414.21 (M+H).

4-Amino-2-(4-bezhydrylpiperazin-1-yl)methyl-6,7-methylenedioxyquinazoline (222)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-benzhydrylpiperazine (0.73 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**222**) (0.35 g, 79.5%) m. p. 210-212 °C.

Anal.:

TLC: R_f 0.34 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3640, 3336, 3148, 2962, 2912, 2825, 1665, 1569, 1508, 1465, 1257, 1219, 1136, 1041, 997, 850, 753 and 703.

^{1}H-NMR (DMSO-d_6): δ 7.56 (s, 1H), 7.40-7.38 (d, 4H, *J* = 7.4 Hz), 7.25-7.22 (m, 4H), 7.15-7.11 (m, 2H), 7.07 (bs, 2H), 7.00 (s, 1H), 6.09 (s, 2H), 4.20 (s, 1H), 3.52 (s, 2H), 2.57 (bs, 4H) and 2.38 (bs, 4H).

MS (EI) m/z: 454.0 (M^+).

4-Amino-2-(4-cyclohexylpiperazin-1-yl)methyl-6,7-methylenedioxyquinazoline (223)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-cyclohexylpiperazine (0.49 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**223**) (0.28 g, 80.0%) m. p. 235-237 °C.

Anal.:

TLC: R_f 0.37 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3328, 3148, 2924, 2857, 2818, 1657, 1613, 1558, 1507, 1466, 1257, 1222, 1141, 1042, 941 and 852.

^{1}H-NMR ($CDCl_3$): δ 7.19 (s, 1H), 6.99 (s, 1H), 6.09 (s, 2H), 5.69 (bs, 2H), 3.67 (s, 2H), 2.66 (bs, 8H), 1.89-1.87 (m, 2H), 1.79-1.76 (m, 2H), 1.63-1.60 (m, 1H), 1.26-1.17 (m, 4H) and 1.10-1.09 (m, 2H).

MS (EI) m/z: 369.4 (M^+).

LC-MS/MS: t_R 10.52 min, 370.24 (M+H).

4-Amino-2-[4-(2-bromobenzyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (224)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(2-bromobenzyl)piperazine (0.70 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**224**) (0.35 g, 79.6%) m. p. 241-243 °C.

Anal.:

TLC: R_f 0.30 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3312, 3144, 2927, 2817, 2773, 1661, 1613, 1562, 1505, 1468, 1367, 1324, 1261, 1224, 1141, 1035, 1001, 933, 852 and 751.

^{1}H-NMR (DMSO-d_6): δ 7.58 (s, 1H), 7.54-7.51 (d, 1H, J = 7.7 Hz), 7.47-7.45 (d, 1H, J = 7.7 Hz), 7.33-7.29 (m, 1H), 7.22 (bs, 2H), 7.16-7.12 (m, 1H), 7.00 (s, 1H), 6.12 (s, 2H), 3.53 (s, 2H), 3.48 (s, 2H), 2.54-2.53 (m, 4H) and 2.49 (bs, 4H).

MS (EI) m/z: 455.5 (M^+).

4-Amino-2-[4-(2-methylbenzyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (225)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(2-methylbenzyl)piperazine (0.55 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of

conditions described in **Method L** afforded compound (**225**) (0.30 g, 81.1%) m. p. 263-265 °C.

Anal.:

TLC: R_f 0.33 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3309, 3145, 2928, 2820, 2774, 1663, 1613, 1563, 1506, 1468, 1263, 1227, 1142, 1036, 1002, 933, 854 and 747.

^{1}H-NMR (DMSO-d_6): δ 7.57 (s, 1H), 7.19 (bs, 2H), 7.19-7.18 (d, 1H), 7.11-7.08 (m, 3H), 6.99 (s, 1H), 6.11 (s, 2H), 3.46 (s, 2H), 3.39 (s, 2H), 2.51 (bs, 4H), 2.42 (bs, 4H) and 2.32 (s, 3H).

MS (EI) m/z: 390.7 (M^+).

4-Amino-2-[4-(4-methoxybenzyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (226)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(4-methoxybenzyl)piperazine (0.60 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**226**) (0.28 g, 70.0%) m. p. 219-221 °C.

Anal.:

TLC: R_f 0.34 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3340, 3151, 2936, 2821, 1671, 1617, 1566, 1509, 1469, 1370, 1334, 1261, 1211, 1128, 1036, 1000, 937, 854 and 797.

^{1}H-NMR (DMSO-d_6): δ 7.57 (s, 1H), 7.18-7.16 (d, 2H, J = 8.5 Hz), 7.16 (bs, 2H), 6.99 (s, 1H), 6.83-6.80 (d, 2H, J = 8.5 Hz), 6.11 (s, 2H), 3.74 (s, 3H), 3.47 (s, 2H), 3.88 (s, 2H), 2.54 (bs, 4H) and 2.39 (bs, 4H).

LC-MS/MS: t_R 10.67 min, 408.19 (M+H).

4-Amino-2-[4-(4-*t*.butylbenzyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (227)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(4-*t*.butylbenzyl)piperazine (0.67 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of

conditions described in **Method L** afforded compound (**227**) (0.32 g, 76.2%) m. p. 263-265 °C.

Anal.:

TLC: R_f 0.32 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3332, 3140, 2959, 2813, 1657, 1620, 1568, 1506, 1333, 1257, 1141, 1037, 1009, 937, 855 and 802.

^{1}H-NMR (DMSO-d_6): δ 7.57 (s, 1H), 7.29-7.27 (d, 2H, *J* = 8.2 Hz), 7.19-7.17 (d, 2H, *J* = 8.2 Hz), 7.17 (bs, 2H), 6.99 (s, 1H), 6.11 (s, 2H), 3.48 (s, 2H), 3.42 (s, 2H), 2.55 (bs, 4H), 2.41 (bs, 4H) and 1.29 (s, 9H).

LC-MS/MS: t_R 11.66 min, 434.24 (M+H).

4-Amino-2-[4-(1-naphthyl)methylpiperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (228)

Reaction of 4-amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) (0.2 g, 0.96 mM) and 1-(1-naphthyl)methylpiperazine (0.66 g, 2.90 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.25 g, 1.92 mM) as a base under a set of conditions described in **Method L** afforded compound (**228**) (0.32 g, 78.1%) m. p. 236-238 °C.

Anal.:

TLC: R_f 0.29 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3317, 3141, 2938, 2810, 2770, 1660, 1615, 1565, 1504, 1468, 1263, 1222, 1441, 1038, 1001, 939, 855 and 790.

^{1}H-NMR (DMSO-d_6): δ 8.26-8.24 (d, 1H, *J* = 8.0 Hz), 7.87-7.84 (d, 1H, *J* = 8.0 Hz), 7.79-7.76 (m, 1H), 7.58 (s, 1H), 7.52-7.46 (m, 2H), 7.41-7.38 (m, 2H), 7.23 (bs, 2H), 6.99 (s, 1H), 6.12 (s, 2H), 3.85 (s, 2H), 3.46 (s, 2H), 2.53 (bs, 4H) and 2.49 (bs, 4H).

LC-MS/MS: t_R 11.53 min, 428.20 (M+H).

5.1.9 Synthesis of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (229) & 4-amino-2-(4-substituted piperazin-1-yl)methyl-7,8-dimethoxyquinazolines (230-242) (Series VI)

4-Amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**)

2-Amino-3,4-dimethoxybenzonitrile (**145**) (0.5 g, 2.80 mM) was reacted with chloroacetonitrile (0.6 mL, 8.40 mM) under a set of conditions described in **Method K** but at a different range of temperature (-5 to 0 ^{0}C) to afford compound (**229**) (0.38 g, 53.5%) m. p. 195-97 ^{0}C.

Anal.:

TLC: R_f 0.44 (*n*-Hexane: ethyl acetate, 12:8).

IR (KBr, cm^{-1}): 3422, 3314, 3177, 2945, 2838, 1645, 1611, 1571, 1503, 1483, 1111 and 794.

^{1}H-NMR (DMSO-d_6): δ 8.00-7.97 (d, 1H, *J* = 9.1 Hz), 7.78 (bs, 2H), 7.33-7.31 (d, 1H, *J* = 9.1 Hz), 4.56 (s, 2H), 3.95 (s, 3H) and 3.91 (s, 3H).

MS (EI) m/z: 253.1 (M^+).

4-Amino-2-(4-phenypiperazin-1-yl)methyl-7,8-dimethoxyquinazoline (230)

Reaction of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**) (0.2 g, 0.79 mM) and 1-phenylpiperazine (0.38 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**230**) (0.35 g, 79.5%) m. p. 224-26 ℃.

Anal.:

TLC: R_f 0.34 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3379, 3297, 3158, 2936, 2837, 2802, 1641, 1607, 1568, 1502, 1484, 1455, 1247, 1117, 1068, 1038, 798 and 753.

^{1}H-NMR (DMSO-d_6): δ 7.96-7.93 (d, 1H, *J* = 9.3 Hz), 7.50 (bs, 2H), 7.23-7.20 (d, 1H, *J* = 9.3 Hz), 7.18-7.16 (m, 2H), 6.89-6.87 (d, 2H, *J* = 7.7 Hz), 6.77-6.73 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.61 (s, 2H), 3.17-3.15 (t, 4H, *J* = 4.9 Hz) and 2.76-2.73 (t, 4 H, *J* = 4.9 Hz).

^{13}C-NMR (DMSO-d_6): δ 162.61, 161.88, 153.90, 151.01, 145.12, 141.46, 128.67, 119.26, 118.64, 115.22, 111.83, 108.50, 65.21, 60.85, 56.09, 52.83, 48.29.

MS (ESI) m/z: 380.1 $(M + 1)^+$.

LC-MS/MS: t_R 11.37 min, 380.23 (M+H).

4-Amino-2-[4-(2-chlorophenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazoline (231)

Reaction of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**) (0.2 g, 0.79 mM) and 1-(2-chlorophenyl)piperazine (0.47 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**231**) (0.23 g, 70.0%) m. p. 225-27 °C.

Anal.:

TLC: R_f 0.35 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3410, 3167, 2970, 2937, 2818, 1640, 1615, 1570, 1484, 1322, 1282, 1239, 1116, 1041, 1011, 855, 793 and 761.

^{1}H-NMR (DMSO-d_6): δ 7.95-7.93 (d, 1H, *J* = 9.1 Hz), 7.44 (bs, 2H), 7.34-7.32 (d, 1H, *J* = 7.5 Hz), 7.26-7.24 (m, 1H), 7.22-7.19 (d, 1H, *J* = 9.1 Hz), 7.10-7.08 (d, 1H, *J* = 7.5 Hz), 6.99-6.95 (m, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.65 (s, 2H), 3.04 (bs, 4H) and 2.79 (bs, 4H).

MS (ESI) m/z: 414.2 $(M + 1)^+$.

LC-MS/MS: t_R 11.67 min, 414.20 (M+H).

4-Amino-2-[4-(2-cyanophenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazoline (232)

Reaction of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**) (0.2 g, 0.79 mM) and 1-(2-cyanophenyl)piperazine (0.44 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**232**) (0.28 g, 87.5%) m. p. 238-40 °C.

Anal.:

TLC: R_f 0.37 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3411, 3299, 3138, 3002, 2969, 2934, 2899, 2819, 2222, 1640, 1613, 1570, 1489, 1457, 1394, 1321, 1281, 1239, 1113, 1043, 1008, 792 and 769.

^{1}H-NMR (DMSO-d_6): δ 7.96-7.94 (d, 1H, *J* = 9.2 Hz), 7.61-7.59 (d, 1H, *J* = 7.8 Hz), 7.56-7.52 (m, 1H), 7.23-7.21 (d, 1H, *J* = 9.2 Hz), 7.11-7.09 (d, 1H, *J* = 7.8 Hz), 7.06-7.02 (m, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.65 (s, 2H), 3.22-3.19 (t, 4H, *J* = 4.5 Hz) and 2.82-2.80 (t, 4H, *J* = 4.5 Hz).

^{13}C-NMR (DMSO-d_6): δ 162.55, 161.87, 155.22, 153.92, 145.12, 141.47, 133.93, 133.85, 121.46, 119.26, 118.62, 118.00, 111.86, 108.09, 104.80, 65.03, 60.88, 56.10, 52.73 and 51.11.

MS (EI) m/z: 404.7 (M^{+}).

LC-MS/MS: t_R 11.44 min, 405.23 (M+H).

4-Amino-2-[4-(2-methoxyphenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazoline (233)

Reaction of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**) (0.2 g, 0.79 mM) and 1-(2-methoxyphenyl)piperazine (0.45 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**233**) (0.20 g, 62.0%) m. p. 233-35 °C.

Anal.:

TLC: R_f 0.33 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3411, 3299, 3157, 2971, 2934, 2796, 1640, 1615, 1572, 1489, 1323, 1241, 1110, 1009 and 761.

^{1}H-NMR (DMSO-d_6): δ 7.92-7.90 (d, 1H, *J* = 9.1 Hz), 7.43 (bs, 2H), 7.19-7.17 (d, 1H, *J* = 9.1 Hz), 6.91-6.87 (d, 1H), 6.85-6.79 (m, 3H), 3.93 (s, 3H), 3.92 (s, 3H), 3.76 (s, 3H), 3.59 (s, 2H), 2.99 (bs, 4H) and 2.72 (bs, 4H).

^{13}C-NMR (DMSO-d_6): δ 162.67, 161.85, 153.87, 151.80, 145.12, 141.45, 141.19, 122.15, 120.65, 119.24, 117.64, 111.78, 111.41, 108.50, 65.33, 60.86, 56.08, 55.06, 53.08 and 50.07.

LC-MS/MS: t_R 11.24 min, 410.22 (M+H).

4-Amino-2-[4-(2-methylphenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazoline (234)

Reaction of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**) (0.2 g, 0.79 mM) and 1-(2-methylphenyl)piperazine (0.42 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**234**) (0.22 g, 71.0%) m. p. 227-28 °C.

Anal.:

TLC: R_f 0.35 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3410, 3298, 3156, 2968, 2935, 2808, 1640, 1615, 1572, 1489, 1394, 1321, 1283, 1238, 1112, 1014 and 794.

^{1}H-NMR (DMSO-d_6): δ 7.96-7.94 (d, 1H, *J* = 9.1 Hz), 7.49 (bs, 2H), 7.24-7.21 (d, 1H, *J* = 9.1 Hz), 7.14-7.12 (d, 1H, *J* = 7.5 Hz), 7.12-7.10 (m, 1H), 7.01-6.99 (d, 1H, *J* = 7.5 Hz), 6.94-6.90 (m, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.64 (s, 2H), 2.90-2.88 (t, 4H, *J* = 4.4 Hz), 2.77 (bs, 4H) and 2.26 (s, 3H).

^{13}C-NMR (DMSO-d_6): δ 162.72, 161.87, 153.88, 151.42, 145.10, 141.45, 131.66, 130.58, 126.24, 122.51, 119.25, 118.47, 111.80, 108.50, 65.28, 60.86, 56.09, 53.31, 51.33 and 17.51.

MS (ESI) m/z: 394.5 $(M + 1)^+$.

4-Amino-2-[4-(4-nitrophenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazoline (235)

Reaction of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**) (0.2 g, 0.79 mM) and 1-(4-nitrophenyl)piperazine (0.49 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**235**) (0.25 g, 75.8%) m. p. 247-48 °C.

Anal.:

TLC: R_f 0.30 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3370, 3301, 3187, 2938, 2829, 1641, 1594, 1567, 1503, 1453, 1405, 1330, 1239, 1110, 1035, 994 and 801.

^{1}H-NMR (DMSO-d_6): δ 8.05-8.03 (d, 2H, *J* = 9.5 Hz), 7.95-7.93 (d, 1H, *J* = 9.3 Hz), 7.49 (bs, 2H), 7.23-7.21 (d, 1H, *J* = 9.3 Hz), 6.96-6.94 (d, 2H, *J* = 9.5 Hz), 3.95 (s, 3H), 3.93 (s, 3H), 3.63 (s, 2H),

3.49-3.47 (t, 4H, *J* = 5.0 Hz) and 2.77-2.74 (t, 4H, *J* = 5.0 Hz).

^{13}C-NMR (DMSO-d_6): δ 162.40, 161.88, 154.62, 153.94, 145.07, 141.43, 136.97, 125.46, 119.28, 112.30, 111.88, 108.48, 64.89, 60.83, 56.10, 52.27 and 46.40.

MS (ESI) m/z: 425.4 $(M + 1)^+$.

LC-MS/MS: t_R 11.48 min, 425.21 (M+H).

4-Amino-2-[4-(2-pyridinyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazoline (236)

Reaction of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**) (0.2 g, 0.79 mM) and 1-(2-pyridyl)piperazine (0.39 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**236**) (0.18 g, 60.0%) m. p. 170-72 °C dec.

Anal.:

TLC: R_f 0.32 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3387, 3297, 3158, 3013, 2931, 2830, 1641, 1611, 1588, 1481, 1246, 1117 and 732.

^{1}H-NMR (DMSO-d_6): δ 8.09-8.08 (d, 1H), 7.96-7.93 (d, 1H, *J* = 9.1 Hz), 7.52 (bs, 2H), 7.49-7.45 (m, 1H), 7.24-7.21 (d, 1H, *J* = 9.1 Hz), 6.73-6.71 (d, 1H), 6.60-6.57 (m, 1H), 3.94 (s, 6H), 3.60 (s, 2H), 3.51-3.49 (t, 4H, *J* = 4.8 Hz) and 2.70-2.67 (t, 4H, *J* = 4.8 Hz).

^{13}C-NMR (DMSO-d_6): δ 162.61, 161.88, 159.04, 153.93, 147.36, 145.10, 141.48, 137.12, 119.25, 112.65, 111.91, 108.50, 106.74, 65.25, 60.83, 56.13, 52.63 and 44.65.

LC-MS/MS: t_R 11.35 min, 380.23 (M+H).

4-Amino-2-[4-(2-pyrimidinyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazoline (237)

Reaction of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**) (0.2 g, 0.79 mM) and 1-(2-pyrimidinyl)piperazine (0.39 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**237**) (0.20 g, 66.7%) m. p. 228-30 °C.

Anal.:

TLC: R_f 0.30 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3386, 3295, 3192, 2981, 2936, 2876, 2821, 1637, 1615, 1587, 1569, 1487, 1452, 1362, 1248, 1111, 1005 and 795.

^{1}H-NMR (DMSO-d_6): δ 8.29-8.28 (d, 2H, *J* = 4.7 Hz), 7.93-7.91 (d, 1H, *J* = 9.1 Hz), 7.54 (bs, 2H), 7.23-7.21 (d, 1H, *J* = 9.1 Hz), 6.55-6.52 (m, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.75-3.73 (t, 4H, *J* = 4.9 Hz), 3.57 (s, 2H) and 2.63-2.62 (t, 4H, *J* = 4.9 Hz).

^{13}C-NMR (DMSO-d_6): δ 162.58, 161.88, 161.21, 157.56, 153.95, 145.07, 141.64, 119.26, 112.00, 109.71, 103.79, 65.02, 60.80, 56.13, 52.59 and 43.80.

LC-MS/MS: t_R 11.09 min, 282.24 (M+H).

4-Amino-2-[4-(1-naphthyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazoline (238)

Reaction of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**) (0.2 g, 0.79 mM) and 1-(1-naphthyl)piperazine (0.50 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**238**) (0.28 g, 82.4%) m. p. 234-36 °C.

Anal.:

TLC: R_f 0.36 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3354, 3298, 3120, 3008, 2964, 2930, 2829, 1669, 1611, 1572, 1514, 1486, 1456, 1403, 1289, 1252, 1125, 1057, 1002 and 773.

^{1}H-NMR (DMSO-d_6): δ 8.12-8.07 (m, 2H), 7.92-7.91 (d, 1H, *J* = 9.1 Hz), 7.79-7.77 (d, 1H, *J* = 8.5 Hz), 7.50-7.48 (d, 1H, *J* = 8.5 Hz), 7.45-7.39 (m, 1H), 7.39 (bs, 2H), 7.37-7.32 (m, 1H), 7.19-7.16 (d, 1H, *J* = 9.1 Hz), 7.06-7.04 (d, 1H, *J* = 7.4 Hz), 3.96 (s, 3H), 3.93 (s, 3H), 3.69 (s, 2H), 3.07 (bs, 4H) and 2.88 (bs, 4H).

^{13}C-NMR (DMSO-d_6): δ 163.36, 162.58, 161.89, 153.89, 149.34, 145.07, 134.18, 128.17, 127.97, 125.68, 124.97, 124.03, 123.26, 122.78,

119.59, 114.19, 112.47, 108.52, 65.39, 60.91, 56.07, 53.27 and 52.59.

MS (ESI) m/z: 429.8 $(M + 1)^+$.

LC-MS/MS: t_R 11.90 min, 430.26 (M+H).

4-Amino-2-(4-benzhydrylpiperazin-1-yl)methyl-7,8-dimethoxyquinazoline (239)

Reaction of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**) (0.2 g, 0.79 mM) and 1-benzhydrylpiperazine (0.60 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**239**) (0.24 g, 64.9%) m. p. 248-50 °C.

Anal.:

TLC: R_f 0.37 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3376, 3296, 3187, 3024, 2973, 2946, 2832, 2801, 1636, 1611, 1565, 1484, 1456, 1413, 1335, 1280, 1251, 1118, 1044, 998, 866, 795, 750, 737 and 699.

^{1}H-NMR (DMSO-d_6): δ 7.93-7.90 (d, 1H, *J* = 9.2 Hz), 7.49 (bs, 2H), 7.41-7.39 (d, 4H, *J* = 7.6 Hz), 7.27-7.23 (m, 4H), 7.22-7.20 (d, 1H, *J* = 9.2 Hz), 7.16-7.12 (m, 2H), 4.22 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.52 (s, 2H), 2.60 (bs, 4H) and 2.34 (bs, 4H).

^{13}C-NMR (DMSO-d_6): δ 162.67, 161.82, 153.88, 145.07, 142.84, 141.46, 128.25, 127.45, 126.58, 119.20, 111.90, 108.46, 75.39, 65.15, 60.82, 56.13, 52.96 and 51.49.

MS (ESI) m/z: 470.2 $(M + 1)^+$.

LC-MS/MS: t_R 11.81 min, 470.26 (M+H).

4-Amino-2-(4-benzylpiperazin-1-yl)methyl-7,8-dimethoxyquinazoline (240)

Reaction of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**) (0.2 g, 0.79 mM) and 1-benzylpiperazine (0.42 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**240**) (0.18 g, 58.1%) m. p. 209-11 °C.

Anal.:

TLC: R_f 0.35 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3315, 3141, 2925, 2829, 1663, 1609, 1569, 1510, 1484, 1457, 1406, 1279, 1255, 1121, 1067, 1002 and 732.

^{1}H-NMR (DMSO-d_6): δ 7.93-7.91 (d, 1H, *J* = 9.1 Hz), 7.54 (bs, 2H), 7.29-7.27 (d, 1H, *J* = 9.1 Hz), 7.26-7.17 (m, 5H), 3.91 (s, 3H), 3.89 (s, 3H), 3.50 (s, 2H), 3.43 (s, 2H), 2.56 (bs, 4H) and 2.38 (bs, 4H).

^{13}C-NMR (DMSO-d_6): δ 162.74, 161.84, 153.91, 145.08, 141.44, 138.16, 128.66, 127.92, 126.66, 119.23, 111.93, 108.45, 65.24, 62.24, 60.81, 56.14, 52.83 and 52.64.

MS (ESI) m/z: 394.5 $(M + 1)^{+}$.

LC-MS/MS: t_R 11.54 min, 394.25 (M+H).

4-Amino-2-[4-(2-cyanobenzyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazoline (241)

Reaction of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**) (0.2 g, 0.79 mM) and 1-(2-cyanobenzyl)piperazine (0.48 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**241**) (0.17 g, 51.5%) m. p. 208-10 °C.

Anal.:

TLC: R_f 0.40 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3394, 3342, 3235, 2932, 2819, 2222, 1655, 1611, 1567, 1510, 1483, 1323, 1284, 1245, 1115 and 793.

^{1}H-NMR (DMSO-d_6): δ 7.95-7.93 (d, 1H, *J* = 9.2 Hz), 7.76-7.74 (d, 1H, *J* = 7.6 Hz), 7.66-7.62 (m, 1H), 7.58 (bs, 2H), 7.56-7.54 (d, 1H, *J* = 7.6 Hz), 7.45-7.41 (m, 1H), 7.26-7.24 (d, 1H, *J* = 9.2 Hz), 3.93 (s, 3H), 3.91 (s, 3H), 3.63 (s, 2H), 3.52 (s, 2H), 2.58 (bs, 4H) and 2.46 (bs, 4H).

^{13}C-NMR (DMSO-d_6): δ 162.69, 161.85, 153.92, 145.07, 141.99, 141.41, 132.74, 132.71, 129.91, 127.71, 119.24, 117.47, 112.10, 111.94, 108.43, 65.17, 60.81, 59.85, 56.13, 52.70 and 52.63.

MS (ESI) m/z: 418.9 $(M + 1)^{+}$.

4-Amino-2-[4-(2-methylbenzyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazoline (242)

Reaction of 4-amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**) (0.2 g, 0.79 mM) and 1-(2-methylbenzyl)piperazine (0.45 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**242**) (0.19 g, 59.4%) m. p. 203-04 °C.

Anal.:

TLC: R_f 0.36 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3403, 3292, 3153, 2986, 2935, 2813, 1637, 1613, 1567, 1484, 1405, 1322, 1284, 1241, 1118, 1001 and 743.

^{1}H-NMR (DMSO-d_6): δ 7.93-7.91 (d, 1H, *J* = 8.5 Hz), 7.38 (bs, 2H), 7.20 (bs, 2H), 7.10 (bs, 3H), 3.95 (s, 6H), 3.55 (s, 2H), 3.41 (s, 2H), 2.55 (bs, 4H), 2.43 (bs, 4H) and 2.32 (s, 3H).

MS (ESI) m/z: 408.4 $(M + 1)^+$.

LC-MS/MS: t_R 11.14 min, 408.68 (M+H).

5.1.10 Synthesis of 2-chloromethyl-7,8-dimethoxyquinazolin-4(3*H*)-one (244) & 2-(4-substituted piperazin-1-yl)methyl-7,8-dimethoxyquinazolin-4(3*H*)-ones (245-251) (Series VII)

4-Chloro-2-chloromethyl-7,8-dimethoxyquinazoline (**243**)

Reaction of 2-amino-3,4-dimethoxybenzonitrile (**145**) (0.5 g, 2.80 mM) with chloroacetonitrile (0.6 mL, 8.40 mM) under a set of conditions described in **Method K** afforded compound (**243**) (0.50 g, 65.8%) m. p. 129-31 ^{0}C.

Anal.:

TLC: R_f 0.41 (*n*-Hexane: ethyl acetate, 8:12).

IR (KBr, cm^{-1}): 2977, 2937, 2841, 166, 1559, 1468, 1430, 1270, and 702.

MS (ESI) m/z: 274.6 $(M + 1)^+$, 276.6 $(M + 3)^+$.

2-Chloromethyl-7,8-dimethoxyquinazolin-4(3*H*)-one (244)

4-Chloro-2-chloromethyl-7,8-dimethoxyquinazoline (**243**) (0.5 g, 1.83 mM) was hydrolyzed by adding a few drops of concentrated hydrochloric acid under microwave irradiations at 600 W for 2-4 minutes. The residue was poured into cold diethyl ether to

give a brown precipitate which was filtered, washed several times with diethyl ether and dried to afford compound (**244**) (0.43 g, 60.6%) m. p. 202-04 ^{0}C.

Anal.:

TLC: R_f 0.39 (*n*-Hexane: ethyl acetate, 10:10).

IR (KBr, cm^{-1}): 3138, 2801, 1683 and 1099.

^{1}H-NMR (DMSO-d_6): δ 7.91-7.89 (d, 1H, *J* = 7.9 Hz), 7.33-7.31 (d, 1H, *J* = 7.9 Hz), 4.63 (s, 2H), 3.96 (s, 3H) and 3.91 (s, 3H).

MS (ESI) m/z: 255.5 $(M + 1)^+$, 256.5 $(M + 2)^+$.

2-[4-(Phenylpiperazin-1-yl]methyl-7,8-dimethoxyquinazolin-4(3*H*)-one (245)

Reaction of 2-chloromethyl-7,8-dimethoxyquinazolin-4(3*H*)-one (**244**) (0.2 g, 0.79 mM) and 1-phenylpiperazine (0.38 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**245**) (0.18 g, 60.0%) m. p. 186-88 °C.

Anal.:

TLC: R_f 0.40 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3255, 2940, 2876, 2834, 1678, 1600, 1497, 1457, 1422, 1332, 1289, 1250, 1180, 1150, 1092, 1046, 997, 915, 880, 802 and 770.

^{1}H-NMR ($CDCl_3$): δ 10.02 (bs, 1H), 8.05-8.03 (d, 1H, *J* = 8.9 Hz), 7.30-7.26 (m, 2H), 7.12-7.10 (d, 1H, *J* = 8.9 Hz), 6.95-6.93 (d, 2H, *J* = 7.8 Hz), 6.91-6.87 (m, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 3.70 (s, 2H), 3.27-3.25 (t, 4H, *J* = 4.8) and 2.78-2.76 (t, 4H, *J* = 4.8).

MS (ESI) m/z: 380.8 $(M + 1)^+$.

2-[4-(2-Chlorophenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazolin-4(3*H*)-one (246)

Reaction of 2-chloromethyl-7,8-dimethoxyquinazolin-4(3*H*)-one (**244**) (0.2 g, 0.79 mM) and 1-(2-chlorophenyl)piperazine (0.47 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**246**) (0.17 g, 51.5%) m. p. 203-05 °C.

Anal.:

TLC: R_f 0.41 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3159, 3077, 2996, 2969, 2937, 2831, 1670, 1631, 1597, 1506, 1461, 1426, 1293, 1270, 1228, 1096 and 764.

^{1}H-NMR ($CDCl_3$): δ 10.05 (bs, 1H), 8.07-8.04 (d, 1H, *J* = 8.9 Hz), 7.38-7.35 (d, 1H, *J* = 7.9 Hz), 7.27-7.22 (m, 1H), 7.14-7.12 (d, 1H, *J* = 8.9 Hz), 7.06-7.04 (d, 1H, *J* = 7.9 Hz), 7.02-6.98 (m, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.73 (s, 2H), 3.14 (bs, 4H) and 2.82-2.80 (t, 4H, *J* = 4.5).

^{13}C-NMR ($CDCl_3$): δ 161.48, 157.19, 153.37, 148.85, 143.77, 142.74, 130.68, 128.83, 127.70, 124.02, 122.73, 120.47, 116.06, 111.77, 61.91, 60.62, 56.32, 53.54 and 51.12.

MS (ESI) m/z: 415.1 $(M + 1)^+$.

2-[4-(2-Cyanophenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazolin-4(3*H*)-one (247)

Reaction of 2-chloromethyl-7,8-dimethoxyquinazolin-4(3*H*)-one (**244**) (0.2 g, 0.79 mM) and 1-(2-cyanophenyl)piperazine (0.40 mL, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**247**) (0.23 g, 71.9%) m. p. 184-85 °C.

Anal.:

TLC: R_f 0.36 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3145, 3034, 2998, 2942, 2835, 2217, 1676, 1602, 1479, 1451, 1429, 1286, 1227, 1099 and 800.

^{1}H-NMR (DMSO-d_6): δ 11.65 (bs, 1H), 7.87-7.85 (d, 1H, *J* = 8.9 Hz), 7.62-7.60 (d, 1H, *J* = 8.0 Hz), 7.56-7.52 (m, 1H), 7.22-7.20 (d, 1H, *J* = 8.9 Hz), 7.12-7.10 (d, 1H, *J* = 8.0 Hz), 7.06-7.03 (m, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.56 (s, 2H), 3.21-3.19 (t, 4H, *J* = 4.3) and 2.78-2.76 (t, 4H, *J* = 4.3).

^{13}C-NMR (DMSO-d_6): δ 161.23, 160.30, 156.35, 155.12, 153.32, 143.33, 142.28, 133.98, 121.72, 121.66, 118.81, 117.97, 115.68, 111.82, 104.94, 61.06, 60.43, 56.02, 52.46 and 51.06.

MS (ESI) m/z: 405.9 $(M + 1)^+$.

LC-MS/MS: t_R 14.29 min, 406.20 (M+H).

2-[4-(2-Methoxyphenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazolin-4(3*H*)-one (248)

Reaction of 2-chloromethyl-7,8-dimethoxyquinazolin-4(3*H*)-one (**244**) (0.2 g, 0.79 mM) and 1-(2-methoxyphenyl)piperazine (0.46 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**248**) (0.17 g, 53.1%) m. p. 173-75 °C.

Anal.:

TLC: R_f 0.38 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3162, 3087, 2933, 2815, 1679, 1597, 1501, 1461, 1426, 1335, 1295, 1234, 1091, 1050, 1019, 879, 796 and 753.

^{1}H-NMR ($CDCl_3$): δ 9.97 (bs, 1H), 7.99-7.97 (d, 1H, *J* = 8.9 Hz), 7.06-7.03 (d, 1H, *J* = 8.9 Hz), 6.95-6.93 (m, 1H), 6.88-6.86 (m, 2H), 6.81-6.79 (d, 1H, *J* = 7.7 Hz), 3.94 (s, 3H), 3.92 (s, 3H), 3.79 (s, 3H), 3.64 (s, 2H), 3.07 (bs, 4H) and 2.75-2.73 (t, 4H).

^{13}C-NMR ($CDCl_3$): δ 161.46, 157.18, 153.47, 152.27, 143.79, 142.76, 140.87, 123.28, 122.74, 121.07, 118.37, 116.10, 111.77, 111.24, 61.89, 60.69, 56.32, 55.40, 53.62 and 50.57.

MS (ESI) m/z: 411.4 $(M + 1)^+$.

LC-MS/MS: t_R 14.19 min, 411.21 (M+H).

2-[4-(4-Nitrophenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazolin-4(3*H*)-one (249)

Reaction of 2-chloromethyl-7,8-dimethoxyquinazolin-4(3*H*)-one (**244**) (0.2 g, 0.79 mM) and 1-(4-nitrophenyl)piperazine (0.49 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**249**) (0.25 g, 73.5%) m. p. 251-52 °C.

Anal.:

TLC: R_f 0.37 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3225, 2925, 2848, 1666, 1601, 1488, 1455, 1425, 1319, 1250, 1114, 995, 922 and 833.

^{1}H-NMR (DMSO-d_6): δ 11.51 (bs, 1H), 8.06-8.04 (d, 2H, *J* = 9.5 Hz), 7.91-7.89 (d, 1H, *J* = 8.9 Hz), 7.19-7.17 (d, 1H, *J* = 8.9 Hz), 6.94-6.91 (d, 2H, *J* = 9.5 Hz), 3.95 (s, 3H), 3.92 (s, 3H), 3.59 (s, 2H), 3.52-3.50 (t, 4H, *J* = 4.9) and 2.76-2.74 (t, 4H, *J* = 4.9).

MS (ESI) m/z: 425.9 $(M + 1)^+$.

2-[4-(3,4,5-Trimethoxyphenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazolin-4(3*H*)-one (250)

Reaction of 2-chloromethyl-7,8-dimethoxyquinazolin-4(3*H*)-one (**244**) (0.2 g, 0.79 mM) and 1-(3,4,5-trimethoxyphenyl)piperazine (0.60 g, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**250**) (0.31 g, 83.8%) m. p. 234-36 °C.

Anal.:

TLC: R_f 0.37 (Chloroform: methanol, 18:2).

IR (KBr, cm^{-1}): 3174, 2934, 2837, 1679, 1631, 1596, 1511, 1429, 1291, 1235, 1134, 1102, 1001 and 796.

^{1}H-NMR ($CDCl_3$): δ 9.88 (bs, 1H), 8.07-8.05 (d, 1H, *J* = 8.9 Hz), 7.15-7.13 (d, 1H, *J* = 8.9 Hz), 6.19 (s, 2H), 4.02 (s, 3H), 4.01 (s, 3H), 3.86 (s, 6H), 3.81 (s, 3H), 3.72 (s, 2H), 3.23-3.20 (t, 4H, *J* = 4.8 Hz) and 2.80-2.77 (t, 4H, *J* = 4.8 Hz).

^{13}C-NMR ($CDCl_3$): δ 160.94, 156.64, 153.11, 148.89, 146.43, 142.18, 142.05, 131.61, 121.95, 115.58, 112.21, 94.36, 61.32, 60.01, 56.40, 56.02, 55.71, 52.23 and 46.98.

MS (ESI) m/z: 471.0 $(M + 1)^+$.

2-[4-(2-Pyridyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazolin-4(3*H*)-one (251)

Reaction of 2-chloromethyl-7,8-dimethoxyquinazolin-4(3*H*)-one (**244**) (0.2 g, 0.79 mM) and 1-(2-pyridyl)piperazine (0.36 mL, 2.37 mM) in dried DMF (2 mL) using flame dried potassium carbonate (0.22 g, 1.58 mM) as a base under a set of conditions described in **Method L** afforded compound (**251**) (0.15 g, 50.0%) m. p. 168-70 °C.

Anal.:

TLC:	R_f 0.40 (Chloroform: methanol, 18:2).
IR (KBr, cm^{-1}):	3298, 2927, 2832, 1679, 1628, 1598, 1482, 1433, 1282, 1245, 1098, 1002 and 792.
^{1}H-NMR ($CDCl_3$):	δ 9.96 (s, 1H), 8.21-8.19 (d, 1H, *J* = 5.4 Hz), 8.06-8.04 (d, 1H, *J* = 8.9 Hz), 7.52-7.48 (m, 1H), 7.14-7.12 (d, 1H, *J* = 8.9 Hz), 6.67-6.66 (d, 1H), 6.66-6.65 (m, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.69 (s, 2H), 3.64-3.61 (t, 4H, *J* = 4.9) and 2.74-2.71 (t, 4H, *J* = 4.9).
MS (ESI) m/z:	382.4 $(M + 1)^+$.
LC-MS/MS:	t_R 11.63 min, 382.19 (M+H).

5.2 Biological Work

(**The biological work has been carried out by the researchers of pharmacology section and not by the candidate himself**)

General

All the experiments were performed on healthy adult male wistar rats (300-330 g) in accordance with guidelines provided by the committee for the purpose of control and supervision of experiments on animals (CPCSEA), New Delhi, India. All the experimental protocols were approved by the institutional animals ethics committee (IAEC) of Faculty of Pharmacy, The Maharaja Sayajirao University of Baroda (*approval no. MSU/ IAEC/2014-15/1435*).

5.2.1 Functional antagonism assay on rat aortic strip

Male wistar rats were sacrificed humanely. Descending segment of thoracic aortas were dissected free immediately and placed in ice-cold and aerated Kreb's bicarbonate solution of the following composition (mM): NaCl 112, $NaHCO_3$ 12, glucose 11.1, KCl

5.0, $MgSO_4$ 1.2, KH_2PO_4 1.0 and $CaCl_2$ 2.5.[149] Adherent fat was removed carefully and gentle rubbing was applied to denude endothelium. Following this, the aortic strip was prepared using surgical blade and both ends of the strips were tied by a thread. The strips were suspended in prewarmed oxygenated Kreb's solution under the resting tension of 2 g during experiment. Before performing of the experiment, the strip was allowed to stabilize for 60 minutes during which Kreb's solution was changed for every 10 minutes. Removal of the endothelium was confirmed by observing the "absence of relaxation" on strips precontracted with potassium chloride/phenylephrine. Isotonic contractions were recorded using a transducer (UGO BASILE, Italy) coupled to a Gemini 7070 recorder (UGO BASILE, Italy). Graded and cumulative contractions were induced by phenylephrine and AII separately and dose response curves were obtained. Frequent washings were given by Kreb's solution and the strip was allowed to relax completely. Test compounds/standard antagonists were then added to the organ tubes and incubated for 30 minutes prior to the addition of phenylephrine/AII. Control strips were incubated with solvent [DMSO (0.5%) or normal saline] for 30 minutes prior to recording the concentration response curves. Antagonism of test compounds were determined by finding out pA_2 values of the test compounds.[150]

5.2.2 Invasive measurement of blood pressure

The effects of compound (**179**) was found to have considerable antagonistic activity on both the receptors in the *in vitro* isolated tissue studies, so it was decided to challenge the *in vivo* effects of phenylephrine and AII on rat arterial blood pressure by compound (**179**) independently. This method involves measurement of arterial blood pressure via catheterization of the carotid artery and provides a direct measurement of blood pressure.[151-154] Briefly, after anesthetizing the animals, a partial cut was put on trachea that was cannulised for allowing unobstructed respiration. Vagotomy was performed to exclude the effect of vagus nerve on presser response. The left femoral vein was cannulated for administration of the test substances. The carotid artery was isolated and cannulated with a polyethylene catheter attached to a pressure transducer (MLT 844 pressure transducer, Power Lab) for measurement of intra-arterial blood pressure. The transducer was filled with heparinized saline (100 IU/ml) to prevent blood clotting in the transducer and connected to the Powerlab-4/35 data acquisition system (AD Instruments,

Australia) for recording of the blood pressure. Following this, the animal was allowed to stabilize for 30 to 45 minutes to remove surgical stress. Baseline blood pressure was recorded following which responses to the agonists (in absence and presence of the antagonists) were recorded.[155]