Synthesis of New 1-Aryl-4-(biarylmethylene)piperazine Ligands, Structurally Related to Adoprazine (SLV313)

Nisar Ullah

Chemistry Department & Centre of Research Excellence in Nanotechnology, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia

Reprint requests to Professor Nisar Ullah. Fax: + 966 3 860 4277. E-mail: nullah@kfupm.edu.sa

Z. Naturforsch. **2012**, *67b,* 75 – 84; received November 26, 2011

A series of new 1-aryl-4-(biarylmethylene)piperazines has been synthesized. These ligands are structurally related to SLV-313, a potential atypical antipsychotic having potent D_2 receptor antagonist and 5-HT_{1A} receptor agonist properties. Buchwald-Hartwig coupling reactions of 1-boc-piperazine with appropriate aryl halides and subsequent removal of the boc group rendered arylpiperazines. The reductive amination of the latter with suitable biarylaldehydes accomplished the synthesis of these ligands.

Key words: Schizophrenia, Aryl-(biarylmethylene)piperazines, Buchwald-Hartwig Amination, Reductive Amination

Introduction

Schizophrenia is a lifelong, chronic, complex neuropsychiatric illness, afflicting approximately 1 % of the world population [1]. In general, schizophrenia involves alterations in cognitive and emotional functioning, and the symptoms can be grouped as positive and negative. The typical antipsychotic drugs such as haloperidol or chlorpromazine block D_2 receptors. However, although the blockade of D_2 receptors improves the positive symptoms, it also accounts for side effect that undermines compliance, in particular extrapyramidal side effects (EPS) [2, 3]. Various atypical or second-generation antipsychotics, such as clozapine, have been discovered that combine D_2 receptor antagonism with activity at other receptors, on the premise that a suitable balance of pharmacological activity should broaden the spectrum of therapeutic efficacy and reduce EPS. It is evident that the therapeutic window, side-effect profile and therapeutic efficacy of antipsychotic agents, could be improved by the combination of a dopamine D_2 receptor antagonist with 5-HT_{1A} receptor agonist properties [4]. Consequently adoprazine (**1**) (SLV-313) and bifeprunox (**2**), having potent D_2 receptor antagonist and 5-HT_{1A} receptor agonist properties, were developed [5]. However, **1** and **2** failed to oppose phencyclidine-induced social interaction deficits, suggesting that an appropriate 'balance' of activity at these sites is necessary for activity in this model [4]. There is a growing need to develop compounds having varying ratios of D_2 and 5-HT_{1A} activities [6]. This report describes the synthesis of a series of new 1-aryl-4-(biarylmethylene)piperazines **3a** – **3f**, **4a** – **4f** and **5a** – **5f**, structurally related to **1** (Fig. 1).

Results and Discussion

The synthesis of compounds **3a** – **3f**, **4a** – **4f** and **5a** – **5f** required the preparation of aldehydes **6b** – **6f**. Suzuki coupling of 4-bromobenzaldehyde with 4-fluoroboronic acid yielded **6b** in a high yield (95 %) [7]. Bromination of aldehyde **7** with bromine in acetic acid to the known bromoaldehdye **8** [8], followed by Suzuki coupling of the latter with the appropriate boronic acid, rendered the desired aldehydes **6c** [9] and **6d** [10], respectively. The known aldehydes **6e** and **6f** were synthesized from their corresponding bromides **10** and **11** by employing literature-known procedures [11] (Scheme 1).

The synthesis of the required arylpiperazines was accomplished as depicted in Scheme 2. Acetylation of 2-bromoaniline (**12**) with cinnamoyl chloride afforded **14** which was reacted with $AlCl_3$ at 125 °C to afford 48 % isolated yield of the quinolin-2-one **15**. The latter was transformed to bromochloroquinoline **16** in high yield by refluxing it with $POCl_3$ [12]. Condensation of **16** with sodium methoxide in refluxing methanol afforded quinoline **17** [13]. The Buchwald-Hartwig coupling of **17** with 1-boc-piperazine in toluene at 110 °C, using cesium carbon-

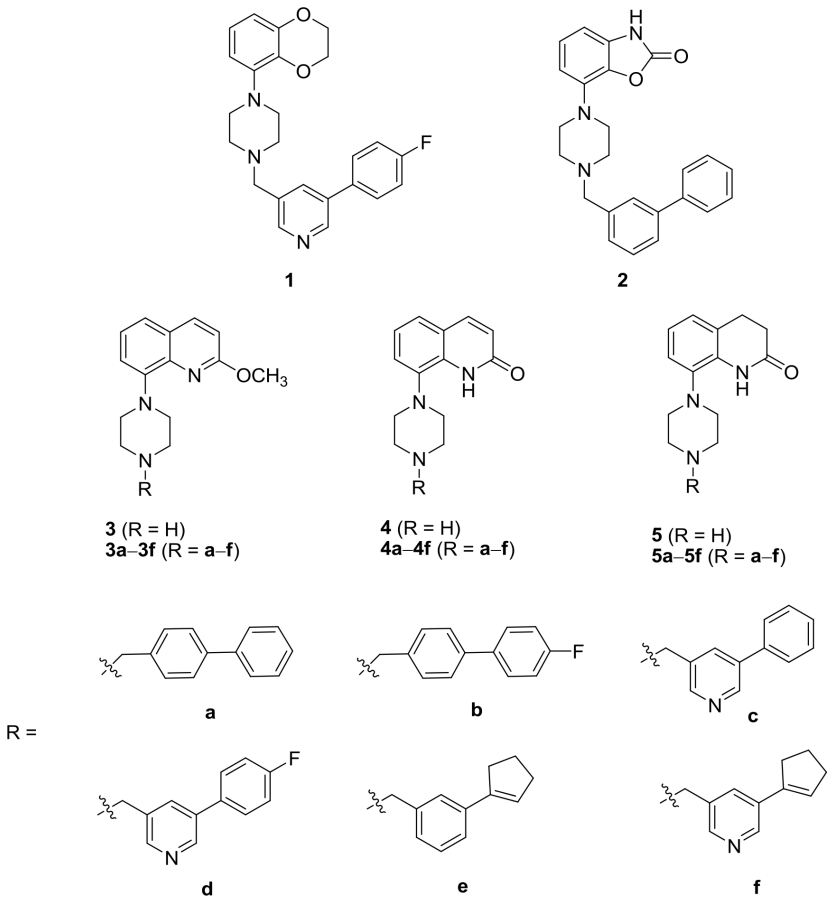


Fig. 1. 1-Aryl-4-(biarylmethylene)piperazines **3a** – **3f**, **4a** – **4f**, and **5a** – **5f**.

ate as a base, rendered the arylpiperazine adduct **18** in 72 % yield. Exposure of **18** to trifluoroacetic acid at r. t. smoothly afforded the required arylpiperazine salt **3** [14]. Attempts to convert compound **18** into the intermediate **4** proved to be unsuccessful; treating it with HCl at r. t. resulted in the formation of **3** only, whereas at higher temperature the reaction was sluggish and yielded fewer side products (Scheme 2).

Thus, to obtain the required intermediate **4**, bromochloroquinoline **16** was condensed with sodium phenylmethanolate, derived from the reaction of benzyl alcohol with sodium hydride, to produce bromoquinoline **19**. The Buchwald-Hartwig coupling of **19** with 1-boc-piperazine in toluene at 110 °C yielded the arylpiperazine adduct **20** in 82 % yield. Hydrogenation of intermediate **20** in a pressure vessel in a Parr apparatus at 50 psi for 3 h afforded compound **21**, which in turn was subjected to further hydrogenation at 65 psi for 20 h to obtain compound **22** in a high yield (96 %) [14]. Exposure of both compounds **21** and **22** to trifluoroacetic acid at r. t. produced the required intermediates **4** and **5**, respectively (Scheme 3).

Having the desired arylpiperazines (**4** – **5**) and biarylaldehydes (**b** – **f**) in hand, we next performed the reductive amination of arylpiperazines and aldehydes in 1,2-dichloroethane, using $NaBH(OAc)_3$ as a reducing agent to accomplish the final ligands (**3a** – **3f**, **4a** – **4f** and **5a** – **5f**).

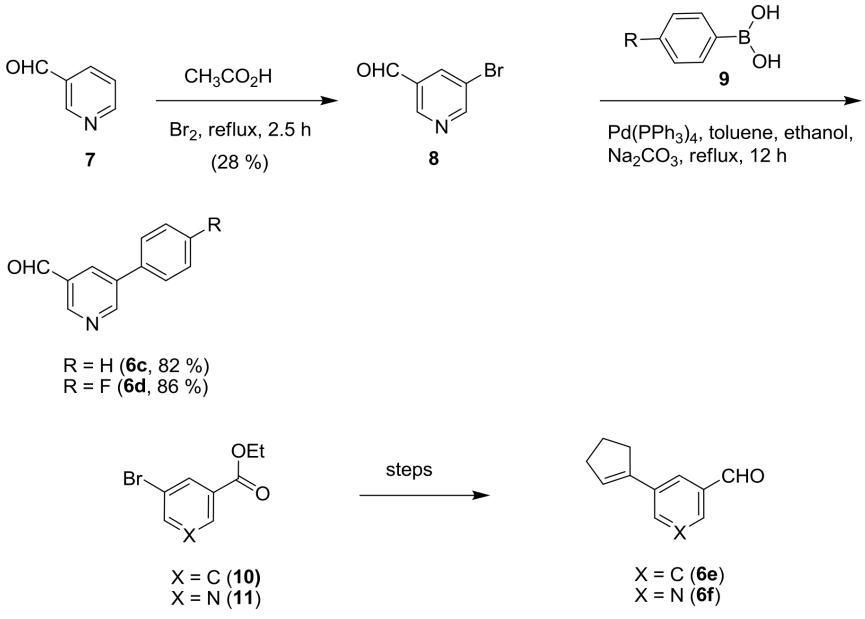
Conclusion

In conclusion we have accomplished the synthesis of a series of new 1-aryl-4-(biarylmethylene)piperazine ligands **3a** – **3f**, **4a** – **4f** and **5a** – **5f**, structurally related to SLV313.

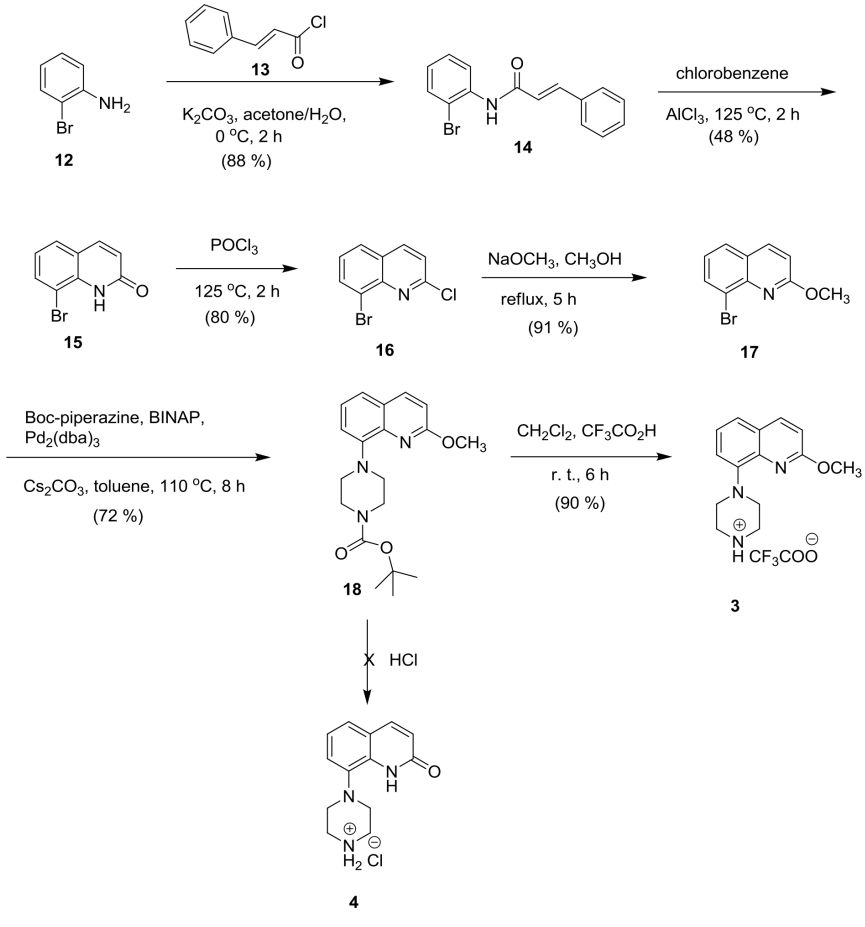
Experimental Section

*5-Phenylnicotinaldehyde (**6c**)*

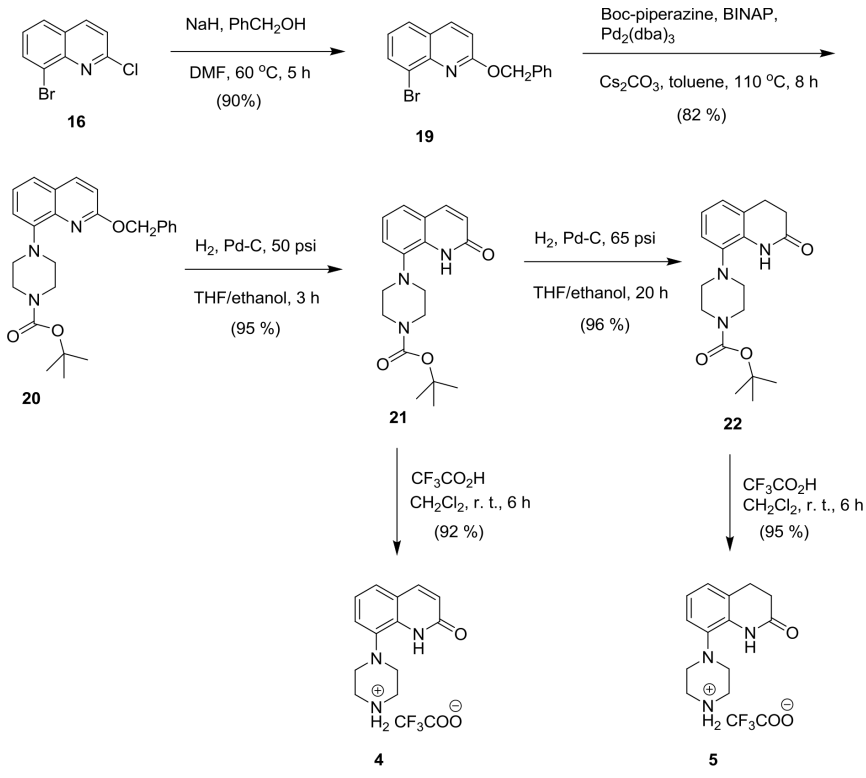
5-Bromonicotinaldehyde (**8**) (2.77 g, 14.92 mmol) was dissolved in toluene (100 mL) and an aqueous 2.0 M Na_2CO_3



Scheme 1. Synthesis of aldehydes **6c** – **6f**.



Scheme 2. Synthesis of arylpiperazine **3**.



Scheme 3. Synthesis of arylpiperazines **4** and **5**.

solution (47 mL) and an ethanolic solution (47 mL) of the phenylboronic acid (2.18 g, 17.86 mmol) were added. The mixture was deoxygenated under reduced pressure and flushed with nitrogen. After repeating this cycle several times, $Pd(PPh_3)_4$ (0.69 g, 0.6 mmol) was added, and the resulting suspension was heated under reflux for 8 h. After cooling ethyl acetate (20 mL) and water (20 mL) were added, and the organic phase was separated. The water phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered over a short plug of celite and evaporated under reduced pressure. Column chromatography on silica gel, eluting with ethyl acetate-hexanes = 3:7 gave 2.24 g (82 %) of the title compound as a light-yellow solid. M. p. 51 – 52 °C. – IR (neat): ν = 3054, 2844, 2737, 1701, 1587, 1443 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 7.45 (m, 1 H, aromatic H), 7.51 (m, 2 H, aromatic H), 7.62 (m, 2 H, aromatic H), 8.34 (d, J = 2.0 Hz, 1 H, 4-H), 9.04 (s, 1 H, 2-H), 9.07 (s, 1 H, 6-H), 10.18 (s, 1 H, CHO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 127.28 (C-3′, C-5′), 128.98 (C-4′), 129.44 (C-2′, C-6′), 131.48 (C-3), 133.78 (C-4), 136.38 (C-5), 137.38 (C-1′), 150.86 (C-2), 153.41 (C-6), 191.23 (CHO). – $C_{12}H_9NO$ (183.21): calcd. C 78.67, H 4.95, N 7.65; found C 78.60, H 5.00, N 7.58.

*5-(4-Fluorophenyl)nicotinaldehyde (**6d**)*

According to the procedure of the synthesis of compound **6c**, the Suzuki reaction of 5-bromonicotinaldehyde (**8**) and 4-fluorophenylboronic acid gave **6d** as a light-yellow solid (86 %). M. p. 78 – 79 °C. – IR (neat): ν = 3029, 2840, 2736, 1697, 1588, 1453 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 7.21 (m, 2 H, 3′-H, 5′-H), 7.57 (m, 2 H, 2′-H, 6′-H), 8.34 (d, J = 2.0 Hz, 1 H, 4-H), 9.04 (s, 2 H, 2-H, 6-H), 10.18 (s, 1 H, CHO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 116.49 (C-3′, C-5′), 129.25 (C-2′, C-6′), 131.61 (C-1′), 133.68 (C-4), 138.21 (C-5), 151.01 (C-2), 153.32 (C-6), 164.72 (C-4′), 191.19 (CHO). – $C_{12}H_8FNO$ (201.20): calcd. C 71.64, H 4.01, N 6.96; found C 71.60, H 4.05, N 6.90.

*8-Bromo-2-methoxyquinoline (**17**)*

To a solution of 8-bromo-2-chloroquinoline **16** (4.85 g, 20 mmol) in methanol (90 mL) was added NaOMe (2.4 g, 100 mmol) and the mixture refluxed for 5 h. The solvent was evaporated under reduced pressure, and ethyl acetate (150 mL) was added. The mixture was washed with H_2O and brine, dried over Na_2SO_4 and evaporated to obtain compound **17** as a light-violet solid (4.33 g, 91 %). M. p. 55 – 56 °C. – IR (neat): ν = 3062, 2980, 1610, 1493, 1270 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 4.15 (s, 3 H, OCH_3), 6.94

(d, J = 8.8 Hz, 1 H, 3-H), 7.22 (t, J = 7.9 Hz, 1 H, 6-H), 7.68 (d, J =7.9 Hz, 1 H, 5-H), 7.95 (m, 2 H, 4-H, 7-H). – ^{13}C NMR matched to the reported values [12].

*tert-Butyl 4-(2-methoxyquinolin-8-yl)piperazine-1-carboxylate (**18**)*

To an oven-dried flask, 1-boc-piperazine (3.19 g, 17.1 mmol), Cs_2CO_3 (5.82 g, 17.86 mmol), $Pd_2(dba)_3$ (1.44 g, 1.57 mmol), *rac*-2,2′ bis(diphenylphosphino)-1,1′-binaphthyl (0.89 g, 1.43 mmol), toluene (8 mL) and compound **17** (3.4 g, 14.28 mmol) were added. While stirring the reaction mixture at r. t., the air in the flask was removed and replaced by N_2. This process was repeated three times. The reaction temperature was brought to 110 °C and the mixture stirred for 8 h. Ethyl acetate was added to the mixture at r. t., washed with H_2O, brine, dried over Na_2SO_4 and evaporated. The brown oily material was chromatographed on a silica column eluting with hexanes-ethyl acetate (3 : 7), and then changing to (1 : 1), yielding compound **18** as a dark-brown thick oil (3.53 g, 72 %). – IR (neat): ν = 3054, 2978, 1710, 1604, 1490, 1276, 1185 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.49 (s, 9 H, OC(CH_3)$_3$), 3.36 (br. s, 4 H, piperazine H), 3.70 (br. s, 4 H, piperazine H), 4.06 (s, 3 H, OCH_3), 6.90 (d, J = 9.0 Hz, 1 H, 3-H), 7.08 (d, J = 8.3 Hz, 1 H, 5-H), 7.31 (m, 1 H, 6-H), 7.38 (d, J = 8.2 Hz, 1 H, 7-H), 7.97 (d, J = 9.0 Hz, 1 H, 4-H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.4 (OC(CH_3)$_3$), 51.41 (C_{piper}), 52.63 (C_{piper}), 79.68 (OC(CH$_3$)$_3$), 112.50 (C-3), 116.66 (C-7), 121.71 (C-5), 124.10 (C-6), 126.11 (C-10), 139.50 (C-4), 139.66 (C-9), 146.95 (C-8), 154.91 (COOC(CH$_3$)$_3$), 160.70 (C-2). – $C_{19}H_{25}N_3O_3$ (343.42): calcd. C 66.45, H 7.34, N 12.24; found C 66.40, H 7.38, N 12.18.

*2-Methoxy-8-(piperazin-1-yl)quinoline (**3**)*

To a solution of compound **18** (3 g, 8.74 mmol) in CH_2Cl_2 (30 mL) was added trifluoroacetic acid (10 mL) at 0 °C, and the mixture was stirred for 6 h at r. t. Solvents were evaporated under reduced pressure, and triturating with diethyl ether gave the trifluoroacetic acid salt of the title compound **3** as a grey solid (2.68 g, 90 %). M. p. 138 – 139 °C. – IR (neat): ν = 3034, 2978, 1616, 1445, 1200 cm^{-1}. – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.34 (br. s, 4 H, piperazine H), 3.50 (br. s, 4 H, piperazine H), 3.95 (s, 3 H, OCH_3), 6.98 (d, J = 8.5 Hz, 1 H, 3-H), 7.15 (m, 1 H, 6-H), 7.32 (d, J = 8.2 Hz, 1 H, 5-H), 7.48 (d, J = 8.5 Hz, 1 H, 7-H), 8.17 (d, J = 8.2 Hz, 1 H, 4-H), 8.93 (br. s, 2 H, *NH*). – ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): δ = 43.77 (C_{piper}), 48.11 (C_{piper}), 53.33 (OCH_3), 112.79 (C-3), 117.28 (C-5), 122.29 (C-7), 124.63 (C-6), 126.13 (C-10), 139.46 (C-4), 140.40 (C-9), 145.98 (C-8), 160.47 (C-2). – $C_{16}H_{18}F_3N_3O_3$(357.33): calcd. C 53.78, H 5.08, N 11.76; found C 53.73, H 5.13, N 11.69.

*2-(Benzyloxy)-8-bromoquinoline (**19**)*

To a solution of benzyl alcohol (3.57 g, 33.0 mmol) in DMF (30 mL) kept at 0 °C was added NaH (0.95 g, 39.6 mmol), and after stirring for 10 min at r. t., compound **16** (4 g, 16.5 mmol) was added. The mixture was stirred at 60 °C for 5 h. The reaction was diluted with ethyl acetate (100 mL) and washed with H_2O (20 mL) and brine (3 × 20 mL), dried over Na_2SO_4 and evaporated. Column chromatography on a silica column eluting with hexanes-ethyl acetate (1 : 1) yielded the title compound **19** as a colorless crystalline solid (4.67 g, 90 %). M. p. 38 – 39 °C. – IR (neat): ν = 3052, 3038, 2970, 1611, 1490, 1256 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.63 (s, 2 H, OCH_2Ph), 6.96 (d, J = 7.8 Hz, 1 H, 3-H), 7.24 (m, 1 H, aromatic H), 7.32 (m, 1 H, aromatic H), 7.37 – 7.40 (m, 2 H, aromatic H), 7.62 (m, 6 H, aromatic H), 7.67 (dd, J = 1.5, 8.0 Hz, 1 H, 5-H), 7.93 – 7.97 (m, 2 H, 4-H, 7-H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 68.0 (OCH_2Ph), 114.05 (C-3), 122.56 (C-8), 124.47 (C-6), 126.29 (C-10), 127.10 (C-5), 128.01 (C_{arom}), 128.41 (C_{arom}), 128.89 (C_{arom}), 133.10 (C-7), 137.10 (C_{arom}), 139.29 (C-4), 143.63 (C-9), 162.25 (C-2). – $C_{16}H_{12}BrNO$ (314.18): calcd. C 61.17, H 3.85, N 4.46; found C 61.10, H 3.89, N 4.39.

*tert-Butyl 4-(2-(benzyloxy)quinolin-8-yl)piperazine-1-carboxylate (**20**)*

Following the same procedure as adopted for the synthesis of **18**, the title compound was obtained from compound **19** as a light-yellow semi-solid (80 %). – IR (neat): ν = 3042, 3032, 2971, 1708, 1607, 1485, 1260, 1192 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.50 (s, 9 H, OC(CH_3)$_3$), 3.28 (br. s, 4 H, piperazine H), 3.69 (br. s, 4 H, piperazine H), 5.55 (s, 2 H, OCH_2Ph), 6.99 (d, J = 9.0 Hz, 1 H, 3-H), 7.10 (m, 1 H, aromatic H), 7.33 (m, 2 H, 6-H, aromatic H), 7.37 (m, 3 H, 5-H, aromatic H), 7.46 (m, 2 H, 7-H, aromatic H), 8.00 (d, J = 9.0 Hz, 1 H, 4-H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.41 (OC(CH_3)$_3$), 51.53 (C_{piper}), 67.28 (OCH_2Ph), 79.71 (OC(CH$_3$)$_3$), 112.75 (C-3), 116.85 (C-5), 121.81 (C-7), 124.25 (C-6), 126.32 (C-10), 127.58 (C_{arom}), 127.80 (C_{arom}), 128.47 (C_{arom}), 137.09 (C-9), 139.86 (C-4), 147.04 (C-8), 154.85 (COOC(CH$_3$)$_3$), 160.36 (C-2). – $C_{25}H_{29}N_3O_3$ (419.52): calcd. C 71.57, H 6.97, N 10.02; found C 71.50, H 7.01, N 9.97.

*tert-Butyl 4-(2-oxo-1,2-dihydroquinolin-8-yl)piperazine-1-carboxylate (**21**)*

To a solution of compound **20** (4 g, 9.53 mmol) in a mixture of THF and ethanol (1 : 3, 40 mL) in a pressure vessel was added Pd-C (10 % w/w wet basis; 0.4 g). The mixture was subjected to hydrogenation in a Parr apparatus at 50 psi for 3 h. The solution was filtered through a pad of celite and evaporated under reduced pressure. Column chromatography

on a silica column, eluting with ethyl acetate-hexanes (8 : 2) and then changing to ethyl acetate (100 %) yielded the title compound **21** as a light-yellow amorphous solid (2.99 g, 95 %). M. p. 123 – 125 °C. – IR (neat): ν = 3054, 3032, 2978, 2972, 1710, 1680, 16010, 1475, 1190 cm^{-1}. – ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.50 (s, 9 H, OC(CH_3)$_3$), 2.89 (br. s, 4 H, piperazine H), 3.18 (br. s, 2 H, piperazine H), 4.18 (br. s, 2 H, piperazine H), 6.70 (d, J = 8.2 Hz, 1 H, 3-H), 7.20 (m, 1 H, 6-H), 7.33 (d, J = 7.5 Hz, 1 H, 7-H), 7.38 (d, J = 7.5 Hz, 1 H, 5-H), 7.79 (d, J = 8.2 Hz, 1 H, 4-H), 9.56 (br. s, 1 H, *NH*CO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.39 (OC(CH_3)$_3$), 52.52 (C_{piper}), 80.11 (OC(CH$_3$)$_3$), 120.43 (C-7), 122.67 (C-9, C-5), 124.56 (C-6, C-3), 133.56 (C-10), 138.76 (C-4), 140.94 (C-8), 154.62 (COOC(CH$_3$)$_3$), 162.25 (C-2). – $C_{18}H_{23}N_3O_3$ (329.39): calcd. C 65.63, H 7.04, N 12.76; found C 65.57, H 7.10, N 12.70.

*8-(Piperazin-1-yl)quinolin-2(1H)-one (**4**)*

Following the same procedure as adopted for the synthesis of **3**, the title compound was obtained from compound **21** as a light-yellow solid (85 %). M. p. 246 – 247 °C. – IR (neat): ν = 3050, 3036, 2982, 2970, 1682, 1618, 1478 cm^{-1}. – ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 3.02 (br. s, 4 H, piperazine H), 3.41 (br. s, 4 H, piperazine H), 6.54 (d, J = 8.2 Hz, 1 H, 3-H), 7.18 (m, 1 H, 6-H), 7.39 (d, J = 8.0 Hz, 1 H, 7-H), 7.48 (d, J = 8.1 Hz, 1 H, 5-H), 7.92 (d, J = 8.2 Hz, 1 H, 4-H), 8.91 (br. s, 1 H, *NH*CO). – ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): δ = 42.85 (C_{piper}), 49.06 (C_{piper}), 120.42 (C-9), 122.44 (C-3), 122.81 (C-7), 122.97 (C-5), 125.23 (C-6), 134.37 (C-10), 138.62 (C-8), 141.08 (C-4), 162.47 (C-2). – $C_{15}H_{16}F_3N_3O_3$ (343.30): calcd. C 52.48, H 4.70, N 12.24; found C 52.52, H 4.75, N 12.17.

*tert-Butyl 4-(2-oxo-1,2,3,4-tetrahydroquinolin-8-yl)piperazine-1-carboxylate (**22**)*

To a solution of compound **21** (1.6 g, 4.83 mmol) in a mixture of THF and ethanol (1 : 3, 20 mL) in a pressure vessel was added Pd-C (10 % w/w; 0.6 g). The mixture was subjected to hydrogenation in a Parr apparatus at 65 psi for 20 h. The solution was filtered through a pad of celite and evaporated under reduced pressure. Column chromatography on a silica column, eluting with ethyl acetate-hexanes: (8 : 2) and then changing to ethyl acetate (100 %) produced 1.54 g (96 %) of compound **22** as an off-white amorphous solid. M. p. 165 – 166 °C. – IR (neat): ν = 3044, 3030, 2978, 2972, 1711, 1678, 16010, 1475, 1178 cm^{-1}. – ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.49 (s, 9 H, OC(CH_3)$_3$), 2.64 (t, J = 7.9 Hz, 2 H, 3-H), 2.80 (br. s, 4 H, piperazine H), 2.98 (t, J = 7.3 Hz, 2 H, 4-H), 3.89 (br. s, 4 H, piperazine H), 6.96 (m, 2 H, 5-H, 7-H), 7.03 (m, 1 H, 6-H), 8.15 (br. s, 1 H, *NH*CO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 25.58 (C-4), 28.42 (OC(CH$_3$)$_3$), 30.71 (C-3), 39.21 (C_{piper}), 52.19 (C_{piper}), 80.01 (OC(CH$_3$)$_3$), 119.51 (C-7), 122.93 (C-5), 124.17 (C-9), 124.51 (C-6), 132.25 (C-10), 138.49 (C-8), 154.63 (COOC(CH$_3$)$_3$), 170.52 (C-2). – $C_{18}H_{25}N_3O_3$ (331.41): calcd. C 65.23, H 7.60, N 12.68; found C 65.19, H 7.66, N 12.60.

*8-(Piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (**5**)*

Following the same procedure as adopted for the synthesis of **3**, the trifluoroacetic acid salt of the title compound was obtained from compound **22** as an off-white solid (88 %). M. p. 235 – 236 °C. – IR (neat): ν = 3024, 1672, 1614, 1487, 1408 cm^{-1}. – ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 2.45 (m, 2 H, 3-H), 2.86 (m, 2 H, 4-H), 2.94 (br. s, 4 H, piperazine H), 3.32 (br. s, 4 H, piperazine H), 6.93 – 7.00 (m, 3 H, 5-H, 6-H, 7-H), 8.95 (br. s, 1 H, *NH*), 9.11 (s, 1 H, *NH*CO). – ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): δ = 25.05 (C-4), 30.58 (C-3), 42.99 (C_{piper}), 48.73 (C_{piper}), 119.52 (C-7), 122.95 (C-5), 124.80 (C-6), 125.49 (C-9), 133.20 (C-10), 138.77 (C-8), 170.91 (C-2). – $C_{15}H_{18}F_3N_3O_3$ (342.32): calcd. C 52.17, H 5.25, N 12.17; found C 52.21, H 5.29, N 12.11.

*8-(4-(Biphenyl-4-ylmethyl)piperazin-1-yl)-2-methoxyquinoline (**3a**)*

To a solution of compound **3** (0.15 g, 0.42 mmol) and biphenyl-4-carbaldehyde **6a** (0.1 g, 0.55 mmol) in 1,2-dichloroethane (5 mL) at 0 °C was added Et_3N (0.13 mL, 0.97 mmol). After stirring for 10 min at r. t., $NaBH(OAc)_3$ (0.11 g, 0.53 mmol) was added, and the reaction mixture was stirred for 6 h. A saturated $NaHCO_3$ solution (10 mL) was added and the mixture stirred for 15 min, followed by the addition of ethyl acetate (30 mL). The organic layer was separated and washed with sat. $NaHCO_3$ and brine, and dried over Na_2SO_4. Purification of the brown oily material on a silica column, eluting with ethyl acetate-hexanes (6 : 4) and then changing to ethyl acetate (100 %) yielded 0.126 g (70 %) of the title compound **3a** as a light-yellow solid. M. p. 110 – 111 °C. – IR (neat): ν = 3060, 3034, 2972, 1616, 1580, 1445, 1210 cm^{-1}. – ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.84 (br. s, 4 H, piperazine H), 3.47 (br. s, 4 H, piperazine H), 3.69 (s, 2 H, NCH_2Ar), 4.06 (s, 3 H, OCH_3), 6.87 (d, J = 8.5 Hz, 1 H, 3-H), 7.11 (dd, J = 1.2, 7.6 Hz, 1 H, 5-H), 7.29 (t, J = 7.9 Hz, 1 H, aromatic H), 7.34 – 7.36 (m, 2 H, aromatic H), 7.42 – 7.48 (m, 2 H, aromatic H), 7.57 – 7.61 (m, 4 H, aromatic H), 7.94 (d, J = 8.8 Hz, 1 H, 4-H). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 51.42 (C_{piper}), 53.00 (C_{piper}), 53.54 (OCH_3), 62.71 (NCH_2Ar), 112.40, 116.56, 121.28, 124.19, 126.12, 126.92, 126.96, 127.10, 127.12, 128.67, 128.72, 129.63, 129.67, 137.06, 139.50, 139.69, 139.98, 140.1, 140.94, 147.23, 160.56 (all C_{arom}). – $C_{27}H_{27}N_3O$ (409.52): calcd. C 79.19, H 6.65, N 10.26; found C 79.15, H 6.70, N 10.20.

*8-(4-((4′-Fluorobiphenyl-4-yl)methyl)piperazin-1-yl)-2-methoxyquinoline (**3b**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as a light-yellow solid from the reductive amination of compound **3** in combination with **6b** (68 %). M. p. 136 – 137 °C. – IR (neat): ν = 3058, 3044, 2988, 2972, 1626, 1574, 1465, 1240 cm^{-1}. – ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.83 (br. s, 4 H, piperazine H), 3.48 (br. s, 4 H, piperazine H), 3.68 (s, 2 H, NCH_2Ar), 4.04 (s, 3 H, OCH_3), 6.87 (d, J = 8.8 Hz, 1 H, 3-H), 7.07 – 7.14 (m, 3 H, aromatic H), 7.27 (t, J = 8.8 Hz, 1 H, aromatic H), 7.34 (dd, J = 1.2, 7.9 Hz, 1 H, 5-H), 7.46 – 7.48 (m, 2 H, aromatic H), 7.51 – 7.57 (m, 4 H, aromatic H), 7.93 (d, J = 8.8 Hz, 1 H, 4-H). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 51.46 (C_{piper}), 53.11 (C_{piper}), 53.56 (OCH_3), 62.83 (NCH_2Ar), 112.40, 115.49, 115.66, 116.50, 121.32, 124.19, 126.11, 126.85, 128.51, 128.57, 129.71, 137.05, 137.25, 139.06, 139.60, 139.98, 147.24, 161.40, 163.36 (all C_{arom}). – $C_{27}H_{26}FN_3O$ (427.51): calcd. C 75.85, H 6.13, N 9.83; found C 75.79, H 6.17, N, 9.76.

*2-Methoxy-8-(4-((5-phenylpyridin-3-yl)methyl)piperazin-1-yl)quinoline (**3c**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as an off-white solid from compounds **3** and **6c** (63 %). M. p. 131 – 132 °C. – IR (neat): ν = 3068, 3045, 2982, 2976, 1636, 1570, 1455, 1242 cm^{-1}. – ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.86 (br. s, 4 H, piperazine H), 3.48 (br. s, 4 H, piperazine H), 3.73 (s, 2 H, NCH_2Ar), 4.06 (s, 3 H,OCH_3), 6.87 (d, J = 8.8 Hz, 1 H, 3-H), 7.08 (dd, J = 1.2, 7.8 Hz, 1 H, 5-H), 7.28 (t, J = 7.9 Hz, 1 H, aromatic H), 7.34 (dd, J = 1.2, 7.8 Hz, 1 H, aromatic H), 7.40 (m, 1 H, aromatic H), 7.48 (t, J = 7.9 Hz, 2 H, aromatic H), 7.61 (d, J = 7.3 Hz, 2 H, aromatic H), 7.93 (d, J = 8.8 Hz, 1 H, 4-H), 7.98 (br. s, 1H, 4′-H), 8.59 (d, J = 1.5 Hz, 1 H, 2′-H), 8.77 (d, J = 2.1 Hz, 1 H, 6′-H). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 51.42 (C_{piper}), 52.69 (C_{piper}), 53.54 (OCH_3), 59.74 (NCH_2Ar), 112.33, 116.05, 116.22, 116.49, 121.40, 124.10, 126.05, 127.13, 128.13, 129.02, 133.42, 135.55, 136.54, 137.54, 139.62, 139.94, 146.88, 147.04, 148.89, 160.73, 164.23 (all C_{arom}). – $C_{26}H_{26}N_4O$ (410.51): calcd. C 76.07, H 6.38, N 13.65; found C 76.00, H 6.42, N 13.60.

*8-(4-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)-2-methoxyquinoline (**3d**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as a light-brown solid from compounds **3** and **6d** (54 %). M. p. 160 – 161 °C. – IR (neat): ν = 3058, 3040, 2988, 2973, 1646, 1572, 1448, 1238 cm^{-1}. – ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.86 (br. s, 4 H, piperazine H), 3.48 (br. s, 4 H, piperazine H), 3.74 (s, 2 H, NCH_2Ar), 4.05 (s, 3 H,OCH_3), 6.87 (d, J = 9.0 Hz, 1 H, 3-H), 7.09 (d, J = 8.2 Hz, 1 H, 5-H), 7.16 (d, J = 8.5 Hz, 2 H, aromatic H), 7.28 (m, 2 H, aromatic H), 7.34 (d, J = 8.2 Hz, 1 H, 7-H), 7.57 (m, 2 H, aromatic H), 7.93 (m, 2 H, 4-H, 4′-H), 8.60 (d, J = 2.0 Hz, I H, 2′-H), 8.73 (d, J = 2.0 Hz, I H, 6′-H). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 50.94 (C_{piper}), 52.86 (C_{piper}), 53.18 (OCH_3), 59.89 (NCH_2Ar), 112.54, 116.05, 116.22, 116.70, 121.64, 124.30, 126.26, 128.99, 129.05, 133.52, 133.85, 135.47, 135.77, 139.82, 140.12, 147.07, 147.19, 149.24, 160.92, 164.23 (all C_{arom}). – $C_{26}H_{25}FN_4O$ (428.50): calcd. C 72.88, H 5.88, N 13.08; found C 72.81, H 5.94, N 13.02.

*8-(4-(3-Cyclopentenylbenzyl)piperazin-1-yl)-2-methoxyquinoline (**3e**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as a light-yellow solid from compounds **3** and **6e** (57 %). M. p. 115 – 116 °C. – IR (neat): ν = 3047, 3032, 2982, 2976, 2970, 1631, 1545, 1450, 1260 cm^{-1} (C-O). – ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.02 (m, 2 H, cyclopent H), 2.53 (m, 2 H, cyclopent H), 2.73 (m, 2 H, cyclopent H), 2.79 (br. s, 4 H, piperazine H), 3.45 (br. s, 4 H, piperazine H), 3.62 (s, 2 H, NCH_2Ar), 4.05 (s, 3 H, OCH_3), 6.21 (s, 1 H, cyclopent H), 6.86 (d, J = 9.8 Hz, 1 H, 3-H), 7.08 (d, J = 7.3 Hz, 1 H, 5-H), 7.24 – 7.29 (m, 3 H, aromatic H), 7.32 (m, 2 H, aromatic H), 7.46 (br. s, 1 H, 3′-H), 7.94 (d, J = 8.5 Hz, 1 H, 4-H). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 23.33 ($C_{cyclopent}$), 33.23 ($C_{cyclopent}$), 33.30 ($C_{cyclopent}$), 51.48 (C_{piper}), 53.09 (C_{piper}), 53.55 (OCH_3), 63.29 (NCH_2Ar), 112.34 (C-3), 116.49 ($C_{cyclopent}$), 121.21, 124.15, 124.32, 126.09, 126.17, 126.31, 127.74, 128.15, 136.74, 138.20, 139.54, 139.97, 142.40, 147.31, 160.51 (all C_{arom}). – $C_{26}H_{29}N_3O$ (399.53): calcd. C 78.16, H 7.32, N 10.52; found C 78.11, H 7.37, N 10.47.

*8-(4-((5-Cyclopentenylpyridin-3-yl)methyl)piperazin-1-yl)-2-methoxyquinoline (**3f**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as a light-yellow semi-solid from compounds **3** and **6f** (47 %). – IR (neat): ν = 3062, 3042, 2980, 2976, 2964, 1636, 1546, 1451, 1261 cm^{-1}. – ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.05 (m, 2 H, cyclopent H), 2.56 (m, 2 H, cyclopent H), 2.73 (m, 2 H, cyclopent H), 2.80 (br. s, 4 H, piperazine H), 3.46 (br. s, 4 H, piperazine H), 3.64 (s, 2 H, NCH_2Ar), 4.07 (s, 3 H, OCH_3), 6.31 (m, 1 H, cyclopent H), 6.88 (d, J = 8.8 Hz, 1 H, 3-H), 7.08 (dd, J = 1.2, 7.8 Hz, 1 H, 5-H), 7.27 (m, 1 H, aromatic H), 7.35 (dd, J = 1.2, 7.9 Hz, 1 H, 7-H), 7.76 (br. s, 1 H, 4′-H), 7.96 (d, J = 8.8 Hz, 1 H, 4-H), 8.44 (d, J = 1.8 Hz, 1 H, 2′-H), 8.59 (d, J = 2.1 Hz, 1 H, 6′-H). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 23.20 ($C_{cyclopent}$), 32.95 ($C_{cyclopent}$), 33.40

($C_{cyclopent}$), 51.34 (C_{piper}), 53.10 (C_{piper}), 53.46 (OCH_3), 60.30 (NCH_2Ar), 112.42 (C-3), 116.55 ($C_{cyclopent}$), 121.38, 124.16, 126.11, 128.43, 132.10, 133.04, 133.47, 139.42, 139.58, 139.96, 145.91, 147.11, 148.11, 160.58 (all C_{arom}). – $C_{25}H_{28}N_4O$ (400.52): calcd. C 74.97, H 7.05, N 13.99; found C 74.91, H 7.10, N 13.93.

*8-(4-(Biphenyl-4-ylmethyl)piperazin-1-yl)quinolin-2(1H)-one (**4a**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as a light-yellow solid from compounds **4** and **6a** (46 %). M. p. 141 – 142 °C. – IR (neat): ν = 3052, 3038, 2980, 1681, 1618, 1535, 1478 cm^{-1}. – ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.52 (br. s, 2 H, piperazine H), 2.99 (br. s, 6 H, piperazine H), 3.67 (s, 2 H, NCH_2Ar), 6.65 (d, J = 9.1 Hz, 1 H, 3-H), 7.17 (t, J = 8.8 Hz, 1 H, 5-H), 7.34 – 7.37 (m, 2 H, 6-H, 7-H), 7.38 (dd, J = 1.5, 8.1 Hz, 1 H, aromatic H), 7.43 – 7.46 (m, 4 H, aromatic H), 7.58 – 7.62 (m, 4 H, aromatic H), 7.74 (d, J = 9.2 Hz, 1 H, 4-H), 9.47 (br. s, 1 H, *NH*CO). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 52.29 (C_{piper}), 53.28 (C_{piper}), 62.57 (NCH_2Ar), 120.33, 122.53 (all C_{arom}), 122.62 (C-3), 124.28, 127.26, 127.41, 128.93, 129.93, 133.93, 139.21 (all C_{arom}), 140.93 (C-4), 162.70 (C-2). – $C_{26}H_{25}N_3O$ (395.50): calcd. C 78.96, H 6.37, N 10.62; found C 78.90, H 6.41, N 10.56.

*8-(4-((4′-Fluorobiphenyl-4-yl)methyl)piperazin-1-yl)quinolin-2(1H)-one (**4b**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as an off-white solid from compounds **4** and **6b** (44 %). M. p. 156 – 157 °C. – IR (neat): ν = 3062, 3042, 2981, 1682, 1628, 1542, 1479 cm^{-1}. – ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.62 (br. s, 2 H, piperazine H), 2.99 (br. s, 6 H, piperazine H), 3.69 (s, 2 H, NCH_2Ar), 6.65 (d, J = 9.5 Hz, 1 H, 3-H), 7.10 – 7.14 (m, 2 H, 5-H, 7-H), 7.17 (t, J = 7.5 Hz, 1 H, 6-H), 7.34 – 7.38 (m, 2 H, aromatic H), 7.43 – 7.45 (m, 2 H, aromatic H), 7.52 – 7.57 (m, 4 H, aromatic H), 7.74 (d, J = 9.5 Hz, 1 H, 4-H), 9.58 (br. s, 1 H, *NH*CO). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 52.19 (C_{piper}), 53.12 (C_{piper}), 62.41 (NCH_2Ar), 115.65, 115.82, 120.39, 122.48 (all C_{arom}), 122.69 (C-3), 124.34, 127.16, 128.77, 128.83, 130.09, 133.92, 137.21, 139.24, 139.61 (all C_{arom}), 141.02 (C-4), 162.81 (C_{arom}), 163.80 (C-2). – $C_{26}H_{24}FN_3O$ (413.49): calcd. C 75.52, H 5.85, N 10.16; found C 75.45, H 5.91, N 10.10.

*8-(4-((5-Phenylpyridin-3-yl)methyl)piperazin-1-yl)quinolin-2(1H)-one (**4c**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as an off-white solid from compounds **4** and **6c** (47 %). M. p. 150 – 151 °C. – IR (neat): ν = 3057, 3040, 2979, 1683, 1621, 1540, 1465 cm^{-1}. – ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.63 (br. s, 2 H, piperazine H), 3.00 (br. s, 2 H, piperazine H), 3.81 (s, 2 H, NCH_2Ar), 6.69 (d, J = 10.0 Hz, 1 H, 3-H), 7.21 (t, J = 7.6 Hz, 1 H, aromatic H), 7.39 – 7.47 (m, 3 H, aromatic H), 7.53 (m, 2 H, aromatic H), 7.67 (m, 2 H, aromatic H), 7.78 (d, J = 9.4 Hz, 1 H, 4-H), 8.63 (s, 1 H, 2′-H), 8.84 (s, 1 H, 6′-H), 9.45 (br. s, 1 H, *NH*CO). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 52.09 (C_{piper}), 53.21 (C_{piper}), 59.92 (NCH_2Ar), 120.37, 122.53, 122.64 (all C_{arom}), 122.71 (C-3), 124.44, 127.39, 128.36, 129.27, 133.91, 135.48, 136.70, 137.82, 138.97 (all C_{arom}), 140.94 (C-4), 147.69, 149.44 (all C_{arom}), 162.70 (C-2). – $C_{25}H_{24}N_4O$ (396.48): calcd. C 75.73, H 6.10, N 14.13; found C 75.67, H 6.14, N 14.07.

*8-(4-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)quinolin-2(1H)-one (**4d**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained by as a light-yellow solid from compounds **4** and **6d** (41 %). M. p. 151 – 152 °C. – IR (neat): ν = 3068, 3043, 2989, 1681, 1623, 1565, 1458 cm^{-1}. – ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.72 – 3.12 (br. s, 8 H, piperazine H), 3.83 (s, 2 H, NCH_2Ar), 6.70 (d, J = 9.5 Hz, 1 H, 3-H), 7.17 – 7.21 (m, 2 H, aromatic H), 7.38 (d, J = 8.0 Hz, 1 H, 5-H), 7.42 (d, J = 8.0 Hz, aromatic H), 7.59 – 7.62 (m, 2 H, aromatic H), 7.81 (d, J = 9.5 Hz, 1 H, 4-H), 8.00 (s, 1 H, 4′-H), 8.60 (s, 1 H, 2′-H), 8.78 ((s, 1 H, 6′-H), 10.12 (br. s, 1 H, *NH*CO). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 51.63 (C_{piper}), 52.50 (C_{piper}), 59.34 (NCH_2Ar), 116.14, 116.31, 120.64, 121.94 (all C_{arom}), 123.03 (C-3), 124.56, 129.02, 129.08, 132.50, 133.37, 133.71, 136.15, 136.37, 139.31 (all C_{arom}), 141.48 (C-4), 146.71, 148.58, 162.37 (all C_{arom}), 164.36 (C-2). – $C_{25}H_{23}FN_4O$ (414.47): calcd. C 72.45, H 5.59, N 13.52; found C 72.39, H 5.65, N 13.45.

*8-(4-(3-Cyclopentenylbenzyl)piperazin-1-yl)quinolin-2(1H)-one (**4e**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as an off-white solid from compounds **4** and **6e** (51 %). M. p. 133 – 135 °C. – IR (neat): ν = 3060, 3034, 2989, 2968, 1680, 1612, 1535, 1448 cm^{-1}. – ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.99 (m, 2 H, cyclopent H), 2.53 (m, 2 H, cyclopent H), 2.53 (m, 2 H, cyclopent H), 2.94 (br. s, 8 H, piperazine H), 3.60 (s, 2 H, NCH_2Ar), 6.21 (d, J = 2.4 Hz, 1 H, cyclopent H), 6.66 (d, J = 8.5 Hz, 1 H, 3-H), 7.16 (t, J = 7.3 Hz, 1 H, 7-H), 7.21 (d, J = 7.7 Hz, 1 H, 5-H), 7.29 (t, J = 7.3 Hz, 6-H), 7.32 – 7.36 (m, 3 H, aromatic H), 7.43 (br. s, 1 H, 2′-H), 7.72 (d, J = 9.8 Hz, 1 H, 4-H), 9.48 (br. s, 1 H, *NH*CO). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 23.26 ($C_{cyclopent}$),

33.15 ($C_{cyclopent}$), 33.24 ($C_{cyclopent}$), 52.44 (C_{piper}), 53.38 (C_{piper}), 63.06 (N*C*H$_2$Ar), 120.07 (C_{arom}), 122.26 (C-3), 122.34, 123.95, 124.43, 126.23, 126.33, 127.71, 128.17, 133.60, 136.75, 137.55, 138.95 (all C_{arom}), 140.57 (C-4), 142.24 (C_{arom}), 162.20 (C-2). – $C_{25}H_{27}N_3O$ (385.50): calcd. C 77.89, H 7.06, N 10.90; found C 77.84, H 7.10, N 10.82.

*8-(4-((5-Cyclopentenylpyridin-3-yl)methyl)piperazin-1-yl)quinolin-2(1H)-one (**4f**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as an off-white solid from compounds **4** and **6f** (43 %). M. p. 126 – 127 °C. – IR (neat): ν = 3058, 3032, 2979, 2972, 1681, 1610, 1538, 1438 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.04 (m, 2 H, cyclopent H), 2.57 (m, 2 H, cyclopent H), 2.73 (m, 2 H, cyclopent H), 2.96 (br. s, 8 H, piperazine H), 3.62 (s, 2 H, N*CH*$_2$Ar), 6.32 (s, 1 H, cyclopent H), 6.66 (d, *J* = 9.4 Hz, 1 H, 3-H), 7.18 (t, *J* = 7.9 Hz, 1 H, 7-H), 7.36 (m, 2 H, 5-H, 6-H), 7.74 (m, 2 H, 4-H, 4′-H), 8.43 (s, 1 H, 2′-H), 8.60 (s, 1 H, 6′-H), 9.51 (br. s, 1 H, *NH*CO). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 23.15 ($C_{cyclopent}$), 32.87 ($C_{cyclopen}$), 33.36 ($C_{cyclopen}$), 52.36 (C_{piper}), 53.34 (C_{piper}), 60.15 (N*C*H$_2$Ar), 120.14 (C_{arom}), 122.26 (C-3), 122.41, 124.11, 128.50, 132.05, 132.59, 133.36, 133.58, 138.80, 139.29 (all C_{arom}), 140.65 (C-4), 145.98, 148.45 (all C_{arom}), 162.28 (C-2). – $C_{24}H_{26}N_4O$ (386.49): calcd. C 74.58, H 6.78, N 14.50; found C 74.51, H 6.83, N 14.43.

*8-(4-(Biphenyl-4-ylmethyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (**5a**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as an off-white solid from compounds **5** and **6a** (58 %). M. p. 111 – 112 °C. – IR (neat): ν = 3051, 3044, 2989, 2976, 1682, 1611, 1548, 1458 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.62 (m, 2 H, 4-H), 2.96 (m, 2 H, 3-H), 2.65 – 3.38 (br. s, 8 H, piperazine H), 3.70 (N*CH*$_2$Ar), 6.95 (m, 2 H, 6-H, 7-H), 7.08 (dd, *J* = 2.0, 6.9 Hz, 1 H, 5-H), 7.35 (m, 1 H, aromatic H), 7.42 – 7.45 (m, 4 H, aromatic H), 7.57 – 7.61 (m, 4 H, aromatic H), 8.21 (br. s, 1 H, *NH*CO). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 25.18 (C-4), 30.39 (C-3), 51.70 (C_{piper}), 53.11 (C_{piper}), 62.39 (N*C*H$_2$Ar), 119.71, 123.10, 124.10, 127.26, 127.30, 127.43, 128.93, 130.11, 132.42, 139.15, 140.65, 141.08 (all C_{arom}), 171.08 (C-2). – $C_{26}H_{27}N_3O$ (397.51): calcd. C 78.56, H 6.85, N 10.57; found C 78.50, H 6.90, N 10.50.

*8-(4-((4′-Fluorobiphenyl-4-yl)methyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (**5b**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as a light-yellow solid from compounds **5** and **6b** (56 %). M. p. 128 – 129 °C. – IR (neat): ν = 3055, 3042, 2984, 2973, 1683, 1608, 1538, 1436 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.61 (m, 2 H, 4-H), 2.96 (m, 2 H, 3-H), 2.65 – 3.08 (br. s, 8 H, piperazine H), 3.68 (N*CH*$_2$Ar), 6.92 – 6.97 (m, 2 H, 6-H, 7-H), 7.05 – 7.12 (m, 3 H, 5-H, aromatic H), 7.40 (d, *J* = 8.0 Hz, 2 H, aromatic H), 7.50 – 7.55 (m, 4 H, aromatic H), 8.23 (m, 1 H, aromatic H), 9.86 (br. s, 1 H, *NH*CO). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 24.86 (C-4), 30.07 (C-3), 51.31 (C_{piper}), 52.63 (C_{piper}), 61.88 (N*C*H$_2$Ar), 115.35, 115.53, 119.38, 122.87, 123.84, 124.00, 126.85, 128.47, 128.53, 129.95, 132.08, 135.74, 136.85, 138.87, 139.35, 163.48 (all C_{arom}), 170.89 (C-2). – $C_{26}H_{26}FN_3O$ (415.50): calcd. C 75.16, H 6.31, N 10.11; found C 75.09, H 6.36, N 10.03.

*8-(4-((5-Phenylpyridin-3-yl)methyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (**5c**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as a light-yellow gum from compounds **5** and **6c** (51 %). – IR (neat): ν = 3045, 3028, 2980, 2976, 1681, 1618, 1542, 1430 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.62 (m, 2 H, 4-H), 2.68 (br. s, 4 H, piperazine H), 2.91 (br. s, 4 H, piperazine H), 2.96 (m, 2 H, 3-H), 3.69 (N*CH*$_2$Ar), 6.97 (m, 2 H, 6-H, 7-H), 7.07 (dd, *J* = 2.2, 6.9 Hz, 1 H, 5-H), 7.43 (m, 1 H, aromatic H), 7.50 (t, *J* = 7.5 Hz, 2 H, aromatic H), 7.63 (m, 2 H, aromatic H), 7.93 (s, 1 H, 4′-H), 8.18 (s, 1 H, *NH*CO), 8.59 (d, *J* = 1.5 Hz, 1 H, 2′-H), 8.79 (d, *J* = 1.5 Hz, 1 H, 6′-H). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 25.07 (C-4), 30.28 (C-3), 51.70 (C_{piper}), 53.13 (C_{piper}), 59.82 (N*C*H$_2$Ar), 119.50, 122.97, 124.02, 124.19, 127.27, 128.26, 129.16, 132.30, 133.36, 135.45, 136.60, 137.66, 138.99, 147.19, 149.09 (all C_{arom}), 170.90 (C-2). – $C_{25}H_{26}N_4O$ (398.50): calcd. C 75.35, H 6.58, N 14.06; found C 75.28, H 6.64, N 14.00.

*8-(4-((5-(4-Fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (**5d**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as a light-yellow solid from compounds **5** and **6d** (47 %). M. p. 133 – 135 °C. – IR (neat): ν = 3065, 3038, 2981, 2973, 1680, 1613, 1548, 1432 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.62 (m, 2 H, 4-H), 2.68 (br. s, 4 H, piperazine H), 2.90 (br. s, 4 H, piperazine H), 2.97 (m, 2 H, 3-H), 3.68 (N*CH*$_2$Ar), 6.96 (m, 2 H, 6-H, 7-H), 7.06 (dd, *J* = 2.2, 6.9 Hz, 1 H, 5-H), 7.17 (t, *J* = 9.0 Hz, 1 H, aromatic H), 7.58 (m, 2 H, aromatic H), 7.89 (s, 1 H, 4′-H), 8.22 (1H, s, *NH*CO), 8.57 (d, *J* = 2.0 Hz, 1 H, 2′-H), 8.73 (d, *J* = 2.0 Hz, 1 H, 6′-H). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 24.84 (C-4), 30.03 (C-3), 51.44

(C_{piper}), 52.86 (C_{piper}), 59.51 (N*CH*$_2$Ar), 115.80, 115.97, 119.30, 122.81, 123.84, 123.99, 128.74, 128.80, 132.05, 133.24, 133.48, 135.27, 135.54, 138.77, 146.62, 148.70, 163.99 (all C_{arom}), 170.81 (C-2). – $C_{25}H_{25}FN_4O$ (416.49): calcd. C 72.09, H 6.05, N 13.45; found C 72.03, H 6.09, N 13.40.

*8-(4-(3-Cyclopentenylbenzyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (**5e**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as a light-green gum from compounds **5** and **6e** (61 %). – IR (neat): ν = 3062, 3048, 2981, 2976, 2973, 1681, 1623, 1545, 1422 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.02 (m, 2 H, cyclopent H), 2.53 (m, 2 H, cyclopent H), 2.62 (t, J = 7.9 Hz, 2 H, 4-H), 2.63 – 2.70 (br. s, 4 H, piperazine H), 2.71 (m, 2 H, cyclopent H), 2.88 (br. s, 4 H, piperazine H), 2.95 (t, J = 7.3 Hz, 2 H, 3-H), 3.59 (N*CH*$_2$Ar), 6.21 (s, 1 H, cyclopent H), 6.94 (m, 2 H, 6-H, 7-H), 7.05 (dd, J = 2.7, 6.7 Hz, 1 H, 5-H), 7.22 (m, 1 H, aromatic H), 7.26 (t, J = 7.6 Hz, 1 H, aromatic H), 7.35 (m, 1 H, aromatic H), 7.42 (br. s, 1 H, 2′-H), 8.10 (br. s, 1 H, *NH*CO). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 23.26 ($C_{cyclopent}$), 25.46 (C-4), 30.64 (C-3), 33.15 ($C_{cyclopent}$), 33.24 ($C_{cyclopent}$), 51.99 (C_{piper}), 53.38 (C_{piper}), 63.02 (N*CH*$_2$Ar), 119.39, 122.76, 123.78, 123.91, 124.47, 126.25, 126.41, 127.78, 128.17, 132.14, 136.76, 137.32, 138.90, 142.23 (all C_{arom}), 170.39 (C-2). – $C_{25}H_{29}N_3O$ (387.52): calcd. C 77.48, H 7.54, N 10.84; found C 77.40, H 7.58, N 10.77.

*8-(4-((5-Cyclopentenylpyridin-3-yl)methyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (**5f**)*

Following the same procedure as adopted for the synthesis of **3a**, the title compound was obtained as a light-yellow solid from compounds **5** and **6f** (52 %). M. p. 103 – 105 °C. – IR (neat): ν = 3052, 3033, 2980, 2972, 2970, 1682, 1633, 1541, 1426 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.05 (m, 2 H, cyclopent H), 2.55 (m, 2 H, cyclopent H), 2.62 (m, 2 H, 4-H), 2.63 – 2.70 (br. s, 4 H, piperazine H), 2.72 (m, 2 H, cyclopent H), 2.88 (br. s, 4 H, piperazine H), 2.97 (m, 2 H, 3-H), 3.59 (N*CH*$_2$Ar), 6.31 (s, 1 H, cyclopent H), 6.95 (m, 2 H, 6-H, 7-H), 7.05 (dd, J = 2.5, 6.8 Hz, 1 H, 5-H), 7.69 (br. s, 1 H, 4′-H), 8.12 (br. s, 1 H, *NH*CO), 8.42 (s, 1 H, 2′-H), 8.60 (s, 1 H, 6′-H). – ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 23.13 ($C_{cyclopent}$), 25.44 (C-4), 30.61 (C-3), 32.86 ($C_{cyclopent}$), 33.34 ($C_{cyclopent}$), 51.98 (C_{piper}), 53.35 (C_{piper}), 60.13 (N*CH*$_2$Ar), 119.37, 122.80, 123.84, 123.99, 128.45, 132.03, 132.12, 132.66, 133.39, 138.80, 139.27, 145.85, 148.35 (all C_{arom}), 170.47 (C-2). – $C_{24}H_{28}N_4O$ (388.51): calcd. C 74.20, H 7.26, N 14.42; found C 74.13, H 7.30, N 14.34.

Acknowledgements

Financial support from KACST Project No: AR-28-38 and lab facilities from KFUPM are gratefully acknowledged.

[1] M. Rowley, J. L. Bristow, H. H. Peter, *J. Med. Chem.* **2001**, *44*, 477 – 498.
[2] D. E. Casey, *Br. J. Psychiatr.* **1996**, *29*, 32 – 39.
[3] P. Seeman, T. Lee, M. Chau-Wong, K. Wong, *Nature* **1976**, *261*, 717 – 719.
[4] A. Newman-Tancredi, *Curr. Opin. Inves. Drugs* **2010**, *11*, 802 – 812.
[5] A. C. McCreary, J. C. Glennon, C. R. Ashby, Jr., H. Y. Meltzer, Z. Li, J. -H. Reinders, M. B. Hesselink, S. K. Long, A. H. Herremans, H. van Stuivenberg, R. W. Feenstra, C. G. Kruse, *Neuropsychopharmacology* **2007**, *32*, 78 – 94.
[6] S. Cuisiat, N. Bourdiol, V. Lacharme, A. Newman-Tancredi, F. Colpaert, B. Vacher, *J. Med. Chem.* **2007**, *50*, 865 – 876.
[7] Q. Hu, M. Negri, K. Jahn-Hoffmann, Y. Zhuang, S. Olgen, M. Bartels, U. Müller-Vieira, T. Lauterbach, R. W. Hartmann, *Bioorg. Med. Chem.* **2008**, *16*, 7715 – 7727.
[8] D. Desai, G. Lin, H. Morimoto, P. G. Williams, K. El-Bayoumy, S. Amin, *J. Label Compd Radiopharm.* **2002**, *45*, 1133 – 1141.
[9] D. L. Comins, J. J. Herrick, *Heterocycles* **1987**, *26*, 2159 – 2164.
[10] J. Kralik, US Patent 123682, **2005**.
[11] F. Cottet, M. Marull, O. Lefebvre, M. Schlosser, *Eur. J. Org. Chem.* **2003**, *8*, 1559 – 1568.
[12] A. G. Osborne, *J. Chem. Soc., Perkin Trans. I* **1993**, *2*, 181 – 184.
[13] J. D. Clark, J. M. Davis, D. Favor, L. K. Fay, L. Franklin, K. E. Henegar, D. S. Johnson, B. J. Nichelson, L. Ou, J. T. Repine, M. A. Walters, A. D. White, Z. Zhu, US Patent 0043309, **2005**.
[14] M. Tominaga, E. Yo, H. Ogawa, S. Yamashita, Y. Yabuuchi, K. Nakagawa, *Chem. Pharm. Bull.* **1984**, *32*, 2100 – 2110.