Synthesis of New 4-Aryl-1-(biarylmethylene)piperidines. Structural Analogs of Adoprazine (SLV313)

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A series of new 4-aryl-1-(biarylmethylene)piperidines have been synthesized. They are structurally related to SLV-313, a potential atypical antipsychotic agent with potent D_2 receptor antagonist and 5-HT_{1A} receptor agonist properties. Suzuki-Miyaura reaction of cyclic vinyl boronates, derived from the vinyl triflates of *N*-protected tetrahydropyridines, with appropriate aryl halides yielded 4-aryl-piperidines. The reductive amination of the latter with suitable biarylaldehdyes accomplished the synthesis of the new compounds.

Key words: Aryl-(biarylmethylene)piperidines, Suzuki-Miyaura Reaction, Reductive Amination, Schizophrenia

Introduction

Schizophrenia is a complex lifelong chronic neuropsychiatric illness, afflicting approximately 1 % of the world population. The symptoms of the disease can be grouped as positive and negative. Positive symptoms include delusions, hallucinations, and conceptual disorganization. The most characteristic negative symptoms are affective flattening, social withdrawal, anhedonia, and poverty of thought and content of speech [1]. The typical antipsychotic drugs, for example haloperidol or chlorpromazine, were the most widely used drugs for this disease because they block D_2 receptors. However, although the blockade of D_2 receptors improves the positive symptoms, the development of neurological side effects such as dystonia, muscle rigidity, tremor and akathisia, and tardive dyskinesia, and in particular of extrapyramidal side effects (EPS) [2, 3] undermine compliance. Various atypical or second-generation antipsychotics, such as clozapine and more recently aripiprazole have been developed to reduce EPS liability and to treat negative symptoms. The atypical antipsychotics combine D_2 receptor antagonism with activity at other receptors such as serotonergic receptors, on the premise that a suitable balance of pharmacological activity should broaden the spectrum of therapeutic efficacy and reduce EPS. It has been demonstrated that the combination of a dopamine D_2 receptor antagonist with 5-HT_{1A} receptor agonist properties could improve the therapeutic window, side-effect profile and therapeutic efficacy of antipsychotic agents [4]. As a result adoprazine (**1**) (SLV-313) and bifeprunox (**2**), possessing potent D_2 receptor antagonist and 5-HT_{1A} receptor agonist properties, were developed [5]. However, the failure of **1** and **2** to oppose phencyclidine-induced social interaction deficits suggested that an appropriate 'balance' of activity at these sites is necessary for activity in this model [4]. Thus, the need to discover compounds having varying ratios of D_2 and 5-HT_{1A} activities continued [6]. This report describes the synthesis of a series of new 4-aryl-1-(biarylmethylene)piperidines **3a – f**, **4a – f** and **5a – f**, structurally related to **1** (Fig. 1).

Results and Discussion

The synthesis of compounds **3a – f**, **4a – f** and **5a – f** required the synthesis of aldehydes **6b – f**. Suzuki reaction of 4-bromobenzaldehyde with 4-fluoroboronic acid yielded **6b** whereas the reaction between 5-bromonicotinaldehyde (**7**) with the appropriate boronic acid gave the desired aldehydes **6c** and **6d** [7 – 10]. The known aldehydes **6e** and **6f** were synthesized from their corresponding bromides **8** and **9** by employing literature-known procedures [11] (Scheme 1).

The synthesis of the required arylpiperidines was commenced from lithiation of **10** in THF at −78 °C fol-

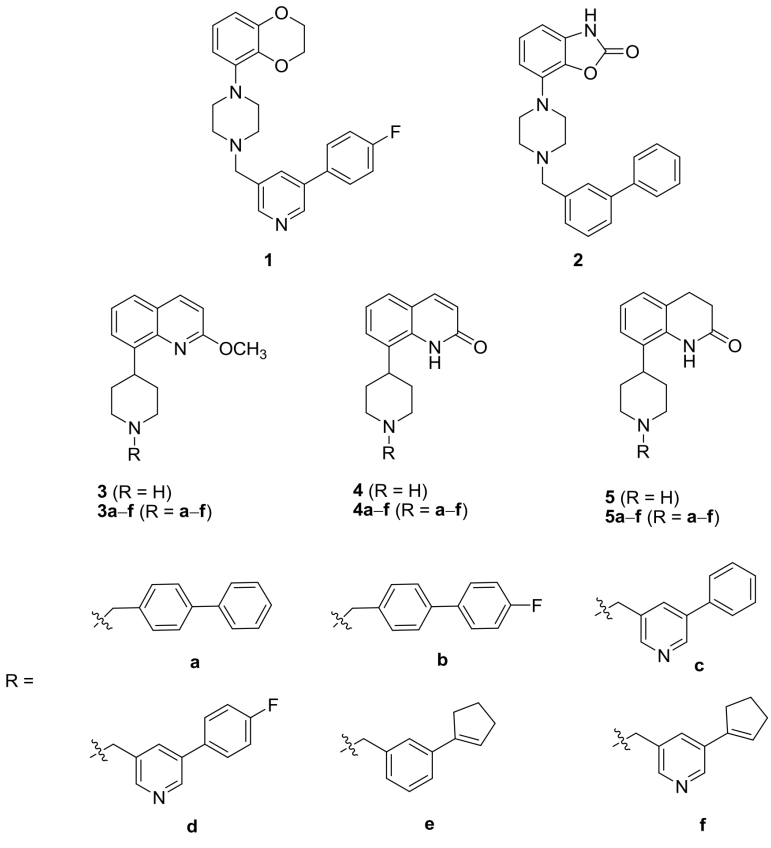
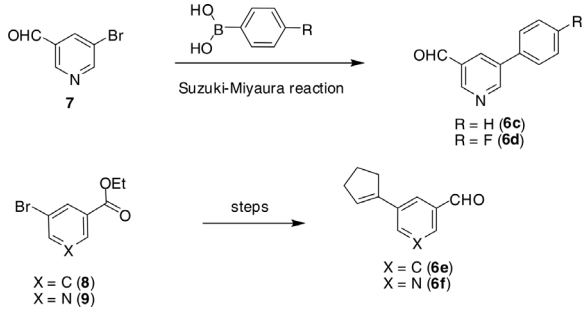


Fig. 1. 1-Aryl-4-(biarylmethylene)piperidines **3a – f**, **4a – f** and **5a – f**.

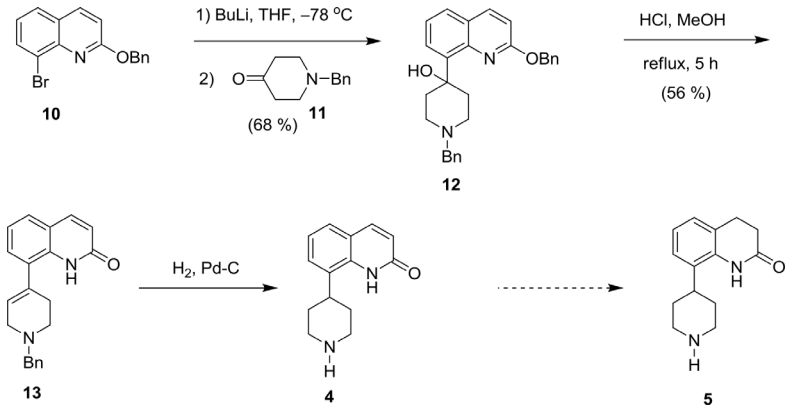


Scheme 1. Synthesis of aldehydes **6c – f**.

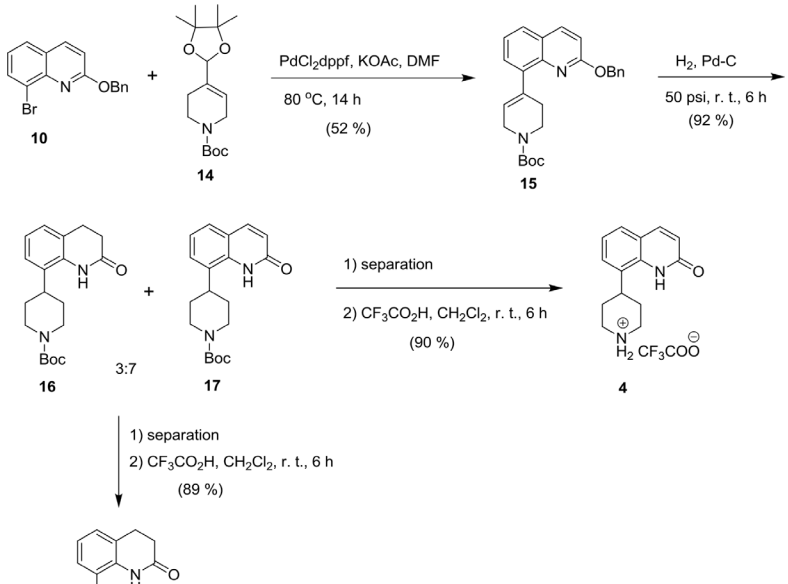
lowed by quenching with *N*-protected piperidinone **11** to obtain alcohol **12** in 68 % yield. The dehydration of the latter was ensued by refluxing it in concentrated HCl and MeOH to generate compound **13** in a moderate yield. To produce the desired intermediate **4** from compound **13**, removal of *N*-protection and reduction of the double bond were required. Hence compound **13** was subjected to hydrogenation in a Parr apparatus at 60 psi (1 psi = 6894.757 Pa) for 5 h. The benzyl deprotection, however, proved to be stubborn, and the reaction yielded a mixture of products which were difficult to separate (Scheme 2).

Thus, the desired intermediates **4** and **5** were synthesized by an alternative route as outlined in Scheme 3. Suzuki-Miyaura reaction of cyclic vinyl boronates **14** [12], derived from the vinyl triflates of *N*-protected tetrahydropyridines, with bromoquinoline **10** generated compound **15**. Hydrogenation of intermediate **15** in a Parr apparatus at 50 psi for 6 h followed by column-chromatographic purifications on silica gel produced intermediates **16** and **17** in a ratio of 3 : 7. Exposure of compounds **16** and **17** to trifluoroacetic acid at room temperature smoothly furnished the desired intermediates **4** and **5** in high yields (Scheme 3).

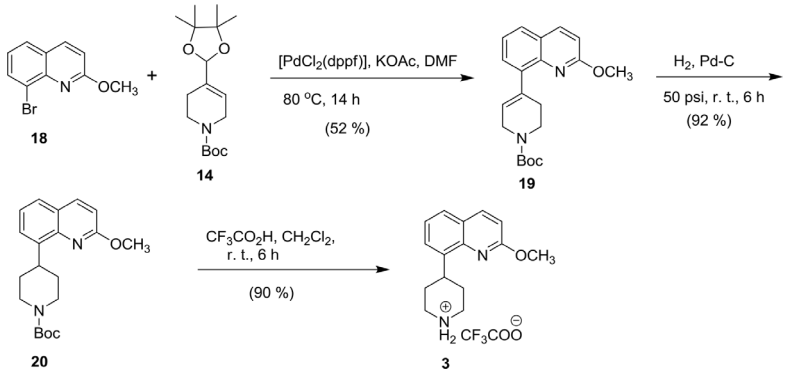
Likewise, to synthesize the required intermediate **3**, Suzuki-Miyaura reaction of cyclic vinyl boronates **14** with bromoquinoline **18** [13] generated compound **19**, which in turn was hydrogenated at 50 psi for 7 h to furnish intermediate **20**. Exposure of the latter to trifluoroacetic acid at r. t. smoothly produced the desired intermediate **5** in an overall yield of 36 % from **18** (Scheme 4).



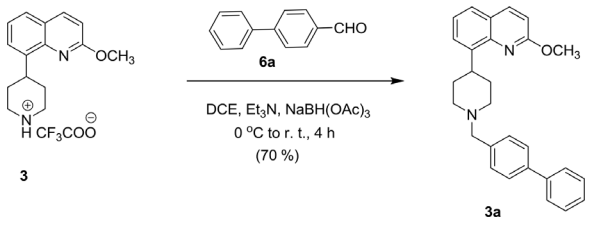
Scheme 2. Synthesis of arylpiperidines **4** and **5**.



Scheme 3. Synthesis of arylpiperidines **4** and **5**, an alternative route.



Scheme 4. Synthesis of arylpiperidine **3** (dppf = 1,1′-bis(diphenylphosphino)ferrocene).



Scheme 5. Synthesis of 1-aryl-4-(biarylmethylene)piperidines **3a**–**f**, **4a**–**f** and **5a**–**f**, **a** representative example.

Having the desired arylpiperidines **4** and **5** and biarylaldehdyes **6b**–**f** in hand, we next performed the reductive amination in 1,2-dichloroethane, using $NaBH(OAc)_3$ as reducing agent to obtain the desired piperidines **3a**–**f**, **4a**–**f** and **5a**–**f** (Scheme 5).

Conclusion

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

Experimental Section

*1-Benzyl-4-(2-(benzyloxy)quinolin-8-yl)piperidin-4-ol (**12**)*

A solution of 2-(benzyloxy)-8-bromoquinoline **10** (2.0 g, 6.4 mmol) in THF (20 mL) was added dropwise over 10 min to a solution of *n*-BuLi (2.5 M, 2.8 mL, 7 mmol) in hexane cooled to −78 °C. The mixture was stirred for 1 h at −78 °C, and a solution of 1-benzylpiperidone **11** (1.21 g, 6.4 mmol) in THF (10 mL) was added dropwise over a period of 10 min, maintaining the reaction temperature at −78 °C. The mixture was stirred at −78 °C for 0.5 h and at −10 °C for 1.5 h whereupon a saturated solution of ammonium chloride (4 mL) was added. The reaction mixture was stirred and warmed to r. t. Water (50 mL) was added, and the reaction mixture was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with water, dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (1 M NH_3 in MeOH/dichloromethane, 2 : 98 to 7 : 93) to afford the title compound as a dark-brown thick oil (1.84 g, 68 %). – IR (neat): ν = 3365, 3042, 3032, 2971, 1607, 1485, 1260, 1192 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 2.15 (br. s, 4 H, piperidine H), 2.73 – 2.78 (m, 5 H, piperidine H, OH), 3.62 (s, 2 H, NCH_2), 5.43 (s, 2 H, OCH_2), 6.99 (d, J = 9.0 Hz, 1 H, 3-H), 7.23 – 7.47 (m, 11 H, aromatic H), 7.60 (m, 2 H, aromatic H), 8.04 (d, J = 8.5 Hz, 1 H, 4-H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 37.26, 49.46 (all C_{piper}), 53.02 (OCH_2), 63.52 (NCH_2), 68.48 (C_{piper}), 113.21 (C-3), 124.75, 126.30, 127.48, 127.80, 128.05, 128.54, 128.70, 128.87, 129.08, 129.39, 129.93, 136.84, 141.18, 142.25, 144.64 (all C_{arom}), 160.31 (C-2). – $C_{42}H_{44}N_4O_3$ (652.82): calcd. C 77.27, H 6.79, N 8.58; found C 77.20, H 6.84, N 8.51.

*8-(1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl)quinolin-2(1H)-one (**13**)*

A solution of compound **12** (1.5 g, 5.35 mmol) in a mixture of methanol (15 mL) and concentrated HCl (15 mL) was heated at reflux temperature for 5 h. The reaction mixture was cooled, and the solvent was removed under reduced pressure to give the crude product as a hydrochloride salt, which was converted to the free base (aq. NaOH/ethyl acetate) and purified by column chromatography eluting with ethyl acetate/hexane (20 : 80 to 40 : 60) to afford the title compound as a light-yellow gum (0.95 g, 56 %). – IR (neat): ν = 3182, 3054, 3022, 2978, 1638, 1610, 1465 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 2.15 (br. s, 2 H, piperidine H), 2.97 (t, J = 5.5 Hz, 2 H, piperidine H), 3.34 (br. s, 2 H, piperidine H), 3.87 (s, 2 H, NCH_2Ph), 5.79 (br. s, 1 H, piperidine H), 6.62 (d, J = 9.5 Hz, 1 H, 3-H), 7.18 (t, J = 7.5 Hz, 1 H, aromatic H), 7.28 – 7.47 (m, 8 H, aromatic H), 7.76 (d, J = 9.5 Hz, 1 H, 4-H), 10.17 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 31.52, 48.1, 51.9, 115.82 (all C_{piper}), 120.93, 123.73, 124.66, 127.58, 128.07, 128.66, 128.88, 129.49, 129.99, 134.85, 136.44, 141.10, 141.85 (all C_{arom}), 160.32 (C-2). – $C_{21}H_{20}N_2O$ (316.40): calcd. C 79.72, H 6.37, N 8.85; found C 79.66, H 6.41, N 8.80.

*tert-Butyl 4-(2-(benzyloxy)quinolin-8-yl)-5,6-dihydropyridine-1(2H)-carboxylate (**15**)*

Nitrogen was flushed for 3 min in a flask containing a solution of boronate **14** (1.39 g, 4.5 mmol), K_2CO_3 (1.86 g, 13.5 mmol) and bromide **10** (1.49 g, 4.74 mmol) in DMF (30 mL), followed by the addition of [$PdCl_2$(dppf)] (0.23 g, 0.28 mmol) (dppf = 1,1′-bis(diphenylphosphino)ferrocene). The reaction mixture was heated to 80 °C and stirred under N_2 overnight, cooled to room temperature and filtered through a pad of celite. To the filtrate was added ethyl acetate (50 mL), and it was washed successively with water (20 mL) and brine (3 × 15 mL), dried over Na_2SO_4, and evaporated. Column chromatography of the brown oily material on silica gel, eluting with ethyl acetate : hexanes (10 : 90, then 25 : 75) gave the title compound as a light-yellow amorphous solid (0.97 g, 52 %). – IR (neat): ν = 3043, 3021, 2978, 1681, 1607, 1442, 1175 cm^{--1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, $OC(CH_3)_3$), 2.76 (br. s, 2 H, piperidine H), 3.68 (br. s, 2 H, piperidine H), 4.13 (br. s, 2 H, piperidine H), 5.49 (s, 2 H, OCH_2Ph), 5.85 (br. s, 1 H, piperidine H), 6.95 (d, J = 8.8 Hz, 1 H, aromatic H), 7.30 – 7.38 (m, 4 H, aromatic H), 7.46 – 7.48 (m, 3 H, aromatic H),

7.63 (dd, J = 1.5, 7.9 Hz, 1 H, aromatic H), 7.99 (d, J = 8.8 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.77 (OC(CH_3)$_3$), 30.18, 44.32, 67.73 (all C_{piper}), 79.74 (OC(CH$_3$)$_3$), 113.18, 124.14, 125.55, 127.22, 128.04, 128.20, 128.66, 129.12, 137.51, 139.51, 140.12, 144.24 (all C_{arom}), 155.60 (C=O), 161.02 (C_{arom}). – $C_{26}H_{28}N_2O_3$ (416.51): calcd. C 74.97, H 6.78, N 6.73; found C 74.91, H 6.83, N 6.67.

*tert-Butyl 4-(2-oxo-1,2,3,4-tetrahydroquinolin-8-yl)piperidine-1-carboxylate (**16**)*

To a solution of compound **15** (0.7 g, 1.68 mmol) in a mixture of THF (5 mL) and EtOH (10 mL) was added Pd-C (10 % wet basis, 0.5 g), and the mixture was subjected to hydrogenation in a Parr apparatus at 50 psi for 6 h (1 psi = 6894.757 Pa). After filtration through a pad of celite, the solution was concentrated to give a brown oily material, which was resolved over a silica column eluting with ethyl acetate : hexanes (30 : 70, then 60 : 40) to get compound **16** as an off-white solid (0.15 g, 27 %). M. p. 132 – 134 °C. – IR (neat): ν = 3245, 3019, 2971, 1668, 1603, 1472 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, OC(CH_3)$_3$), 1.61 (m, 2 H, piperidine H), 1.69 (m, 2 H, piperidine H), 2.61 (m, 2 H, 4-H), 2.79 (m, 1 H, piperidine H), 2.85 (br. s, 2 H, piperidine H), 2.93 (m, 2 H, 3-H), 4.28 (br. s, 2 H, piperidine H), 6.97 (t, J = 7.6 Hz, 1 H, aromatic H), 7.04 – 7.09 (m, 2 H, aromatic H), 8.30 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 26.00 (C-4), 28.45 (OC(CH$_3$)$_3$), 30.68 (C-3), 32.13, 35.62 (all C_{piper}), 79.56 (OC(CH$_3$)$_3$), 123.18, 124.48, 124.75, 126.02, 130.65, 134.23 (all C_{arom}), 154.75 (C=O), 172.03 (C-2). – $C_{19}H_{26}N_2O_3$ (330.42): calcd. C 69.06, H 7.93, N 8.48; found C 69.00, H 7.98, N 8.41.

*tert-Butyl 4-(2-oxo-1,2-dihydroquinolin-8-yl)piperidine-1-carboxylate (**17**)*

Compound **17** was obtained from the reaction described for compound **16** as a light-yellow solid (0.36 g, yield 65 %). M. p. 101 – 103 °C. – IR (neat): ν = 3172, 3031, 2965, 1645, 1603, 1461, 1112 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50 (s, 9 H, OC(CH_3)$_3$), 1.69 (m, 2 H, piperidine H), 1.91 (m, 2 H, piperidine H), 3.10 (br. s, 2 H, piperidine H), 3.42 (m, 1 H, piperidine H), 4.30 (br. s, 2 H, piperidine H), 6.67 (d, J = 9.5 Hz, 1 H, 3-H), 7.20 (t, J = 7.6 Hz, 1 H, aromatic H), 7.40 – 7.45 (m, 2 H, aromatic H), 7.78 (t, J = 7.6 Hz, 1 H, 4-H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.48 (OC(CH_3)$_3$), 30.29, 32.33, 34.70 (all C_{piper}), 79.49 (OC(CH$_3$)$_3$), 120.20, 121.24, 122.54, 123.84, 126.41, 127.76, 131.38, 135.78, 141.74 (all C_{arom}), 154.83 (C=O), 163.99 (C_{arom}), 172.58 (C=O). – $C_{19}H_{24}N_2O_3$ (328.41): calcd. C 69.49, H 7.37, N 8.53; found C 69.45, H 7.43, N 8.46.

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

To a solution of **17** (0.5 g, 1.52 mmol) in CH_2Cl_2 (15 mL) was added trifluoroacetic acid (3 mL) at 0 °C, and the reaction mixture was stirred for 6 h at r. t. Solvents were evaporated under reduced pressure, and triturating with diethyl ether gave the title compound **4** as trifluoroacetic acid salt as an off-white solid (0.45 g, 90 %). M. p. 256 – 258 °C. – IR (neat): ν = 3266, 3031, 3011, 2990, 1672, 1618, 1445 cm^{--1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.86 (br. s, 4 H, piperidine H), 3.08 (m, 2 H, piperidine H), 3.42 (m, 2 H, piperidine H), 3.48 (m, 1 H, piperidine H), 6.51 (d, J = 9.4 Hz, 1 H, 3-H), 7.19 (t, J = 8.1 Hz, 1 H, aromatic H), 7.37 (d, J = 8.0 Hz, 1 H, aromatic H), 7.54 (d, J = 7.9 Hz, 1 H, aromatic H H), 7.91 (d, J = 9.5 Hz, 1 H, 4-H), 8.49 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): δ = 28.91, 31.68, 44.05 (all C_{piper}), 119.91, 121.60, 122.31, 127.09, 127.56, 129.40, 136.09, 141.55 (all C_{arom}), 162.92 (C=O). – $C_{16}H_{17}F_3N_2O_3$ (342.31): calcd. C 56.14, H 5.01, N 8.18; found C 56.08, H 5.06, N 8.11.

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

Following the same procedure as adopted for the synthesis of **4**, the title compound was obtained from compound **16** as an off-white solid (0.70 g, yield 89 %). M. p. 247 – 248 °C. – IR (neat): ν = 3221, 3021, 2988, 1660, 1603, 1445, 1186 cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.79 (m, 4 H, piperidine H), 2.51 (m, 2 H, 2-H), 2.85 (m, 2 H, 3-H), 2.99 – 3.06 (m, 3 H, piperidine H), 3.34 (m, 2 H, piperidine H), 6.96 (m, 1 H, aromatic H), 7.07 (m, 1 H, aromatic H), 9.63 (s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): δ = 25.88 (C-4), 29.22 (C_{piper}), 30.88 (C-3), 32.29, 44.82 (all C_{piper}), 123.05, 124.68, 125.63, 126.62, 130.45, 135.37 (all C_{arom}), 170.02 (C=O). – $C_{16}H_{19}F_3N_2O_3$ (344.33): calcd. C 55.81, H 5.56, N 8.14; found C 55.74, H 5.62, N 8.08.

*tert-Butyl 4-(2-methoxyquinolin-8-yl)-5,6-dihydropyridine-1(2H)-carboxylate (**19**)*

Following the same procedure as adopted for the synthesis of **15**, the title compound was obtained from Suzuki reaction of boronate **14** and bromoquinoline **18** as a dark-brown gum, (0.64 g, yield 42 %). M. p. 132 – 133 °C. – IR (neat): ν = 3037, 2978, 1677, 1604, 1486, 1176 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s, 9H, OC(CH_3)$_3$), 2.85 (br. s, 2 H, piperidine H), 3.70 (m, 2 H, piperidine H), 4.02 (s, 3 H, OCH$_3$), 4.13 (br. s, 2 H, piperidine H), 5.86 (br. s, 1 H, piperidine H), 6.90 (d, J = 8.5 Hz, 1 H, 3-H), 7.32 (t, J = 7.6 Hz, 1 H, aromatic H), 7.48 (dd, J = 1.5, 7.3 Hz, 1 H, aromatic H), 7.63 (dd, J = 1.2, 7.8 Hz, 1 H, aromatic H), 7.97 (d, J = 8.8 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 24.54 (C_{piper}), 28.51 (OC(CH_3)$_3$), 29.84, 42.32 (all

C_{piper}), 53.37 (OCH_3), 79.52 ($OC(CH_3)_3$), 112.71, 123.80, 125.13, 126.99, 128.81, 139.06, 139.74, 144.03, 161.37 (all C_{arom}). – $C_{20}H_{24}N_2O_3$ (340.42): calcd. C 70.56, H 7.11, N 8.23; found C 70.50, H 7.16, N 8.17.

*tert-Butyl 4-(2-methoxyquinolin-8-yl)piperidine-1-carboxylate (**20**)*

To a solution of compound **19** (0.6 g, 1.76 mmol) in a mixture of THF (5 mL) and EtOH (10 mL) was added Pd-C (10 % wet basis, 0.4 g), and the mixture was subjected to hydrogenation in a Parr apparatus at 60 psi for 7 h (1 psi = 6894.757 Pa). After filtration through a pad of celite, the solution was concentrated and chromatographed on a silica column, eluting with ethyl acetate:hexanes (20 : 80) to get the title compound as an off-white solid (0.57 g, yield 94 %). M. p. 72 – 73 °C. – IR (neat): ν = 3031, 2935, 1675, 1608, 1484 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, $OC(CH_3)_3$), 1.71 (m, 2 H, piperidine H), 1.95 (m, 2 H, piperidine H), 2.88 (m, 2 H, piperidine H), 3.82 (m, 1 H, piperidine H), 3.99 (s, 3 H, OCH_3), 4.22 (br. s, 2 H, piperidine H), 6.84 (d, J = 8.5 Hz, 1 H, 3-H), 7.28 (m, 1 H, aromatic H), 7.38 (m, 1 H, aromatic H), 7.51 (m, 1 H, aromatic H), 7.97 (d, J = 8.8 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.48 ($OC(CH_3)_3$), 32.15, 36.84, 42.84 (all C_{piper}), 53.23 (OCH_3), 79.30 ($OC(CH_3)_3$), 112.38, 123.89, 124.96, 125.64, 126.04, 139.40, 143.93 (all C_{arom}), 155.21 (C=O), 161.67 (C_{arom}). – $C_{20}H_{26}N_2O_3$ (342.43): calcd. C 70.15, H 7.65, N 8.18; found C 70.10, H 7.70, N, 8.11.

*2-Methoxy-8-(piperidin-4-yl)quinoline (**3**)*

Following the same procedure as adopted for the synthesis of **4**, the title compound was obtained from compound **20** as an off-white solid (0.46 g, yield 92 %). M. p. 142 – 144 °C. – IR (neat): ν = 3031, 2982, 1612, 1441, 1213 cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): δ = 1.99 (m, 2 H, piperidine H), 2.14 (m, 2 H, piperidine H), 3.16 (m, 2 H, piperidine H), 3.45 (m, 2 H, piperidine H), 4.01 (s, 3 H, OCH_3), 7.01 (d, J = 8.2 Hz, 1 H, 3-H), 7.41 (m, 1 H, aromatic H), 7.51 (m, 1 H, aromatic H), 7.92 (d, J = 8.3 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, [D_6]DMSO): δ = 28.72, 31.00, 34.40, 36.02, 44.33 (all C_{piper}), 53.28 (OCH_3), 112.76, 114.52, 116.83, 124.23, 126.19, 126.48, 140.10, 158.76, 161.23 (all C_{arom}). – $C_{17}H_{19}F_3N_2O_3$ (356.34): calcd. C 57.30, H 5.37, N 7.86; found C 57.24, H 5.42, N 7.80.

*8-(1-(Biphenyl-4-ylmethyl)piperidin-4-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 being stirred 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 sat. solution of $NaHCO_3$(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. $NaHCO_3$, brine, and dried over Na_2SO_4. Purification of the brown oily material on a silica column, eluting with ethyl acetate : hexanes (70 : 30) and then changing to ethyl acetate (100 %) yielded the titled compound **3a** as a light-yellow solid 0.126 g, yield 45 %). M. p. 84 – 85 °C. – IR (neat): ν = 3031, 3021, 2936, 1609, 1444, 1186, 1120 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 2.15 (m, 2 H, piperidine H), 2.36 (m, 2 H, piperidine H), 2.85 (br. s, 2 H, piperidine H), 3.64 (m, 2 H, piperidine H), 4.03 (s, 3 H, OCH_3), 4.20 (s, 2 H, NCH_2), 6.88 (d, J = 8.8 Hz, 1 H, 3-H), 7.32 – 7.38 (m, 2 H, aromatic H), 7.45 (t, J = 7.3 Hz, 2 H, aromatic H), 7.51 (d, J = 7.3 Hz, 1 H, aromatic H), 7.56 – 7.59 (m, 4 H, aromatic H), 7.63 (m, 2 H, aromatic H), 7.95 (d, J = 8.5 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.47, 34.92 (all C_{piper}), 53.14 (OCH_3), 61.71 (NCH_2), 112.62 (C-3), 123.98, 124.98, 126.21, 127.06, 127.72, 128.85, 131.30, 139.31, 139.55, 140.02, 142.37, 143.86 (all C_{arom}), 161.44 (C-2). – $C_{28}H_{28}N_2O$ (408.53): calcd. C 82.32, H 6.91, N 6.86; found C 82.25, H 6.96, N 6.79.

*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 by reductive amination of compounds **3** and **6b** as an off-white solid (yield 37 %). M. p. 94 – 95 °C. – IR (neat): ν = 3042, 3011, 2926, 1603, 1440, 1183, 1132 cm^{-1} – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.92 (m, 2 H, piperidine H), 2.02 (m, 2 H, piperidine H), 2.30 (m, 2 H, piperidine H), 3.18 (m, 2 H, piperidine e H), 3.70 (s, 2 H, NCH_2), 3.83 (m, 1 H, piperidine H), 4.05 (s, 3 H, OCH_3), 6.88 (d, J = 8.5 Hz, 1 H, 3-H), 7.09 – 7.12 (m, 2 H, aromatic H), 7.32 (t, J = 7.6 Hz, 1 H, aromatic H), 7.45 – 7.56 (m, 8 H, aromatic H), 7.94 (d, J = 8.8 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.03, 36.07 (all C_{piper}), 53.07 (OCH_3), 54.66 (C_{piper}), 62.95 (NCH_2), 112.36 (C-3), 115.49, 115.66, 123.85, 124.91, 125.41, 125.81, 126.84, 128.52, 128.57, 129.97, 136.71, 136.98, 139.17, 142.32, 144.13 (all C_{arom}), 161.20 (C-2). – $C_{28}H_{27}FN_2O$ (426.53): calcd. C 78.85, H 6.38, N 6.57; found C 78.79, H 6.44, N 6.50.

*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 by reductive amination of compounds **3** and **6c** as an off-white solid (yield

35 %). M. p. 135 – 137 °C. – IR (neat): ν = 3021, 2945, 1601, 1433, 1263, 1228 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.90 (m, 2 H, piperidine H), 2.02 (m, 2 H, piperidine H), 2.30 (m, 2 H, piperidine H), 3.09 (m, 2 H, piperidine H), 3.67 (s, 2 H, NCH_2), 3.82 (m, 1 H, piperidine H), 4.07 (s, 3 H, OCH_3), 6.88 (d, J = 8.8 Hz, 1 H, 3-H), 7.33 (t, J = 7.6 Hz, 1 H, aromatic H), 7.41 (d, J = 7.3 Hz, 1 H, aromatic H), 7.47 – 7.53 (m, 3 H, aromatic H), 7.64 (m, 2 H, aromatic H), 7.94 (m, 2 H, aromatic H), 8.59 (d, J = 1.8 Hz, 1 H, aromatic H), 8.77 (d, J = 2.1 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.33, 36.36 (all C_{piper}), 53.05 (OCH_3), 54.79 (C_{piper}), 60.65 (NCH_2), 112.32 (C-3), 124.88, 125.33, 125.77, 127.16, 127.98, 128.97, 134.08, 135.05, 136.23, 137.81, 139.11, 142.49, 144.13, 146.95, 149.17 (all C_{arom}), 161.13 (C-2). – $C_{27}H_{27}N_3O$ (409.52): calcd. C 79.19, H 6.65, N 10.26; found C 79.12, H 6.71, N 10.19.

*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 by reductive amination of compounds **3** and **6d** as a light-brown solid (yield 32 %). M. p. 156 – 158 °C. – IR (neat): ν = 3025, 2931, 1607, 1431, 1266 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.89 (m, 2 H, piperidine H), 2.01 (m, 2 H, piperidine H), 2.28 (m, 2 H, piperidine H), 3.05 (m, 2 H, piperidine H), 3.65 (s, 2 H, NCH_2), 3.81 (m, 1 H, piperidine H), 4.06 (s, 3 H, OCH_3), 6.88 (d, J = 8.5 Hz, 1 H, 3-H), 7.16 (m, 2 H, aromatic H), 7.33 (t, J = 7.6, 1 H, aromatic H), 7.51 (dd, J = 1.2, 7.3 Hz, 1 H, aromatic H), 7.54 – 7.59 (m, 3 H, aromatic H), 7.89 (m, 1 H, aromatic H), 7.94 (d, J = 8.8 Hz, 1 H, aromatic H), 8.59 (d, J = 1.5 Hz, 1 H, aromatic H), 8.77 (d, J = 2.1 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.33, 36.35 (all C_{piper}), 53.04 (OCH_3), 54.82 (C_{piper}), 60.62 (NCH_2), 112.34 (C-3), 115.86, 116.03, 123.78, 124.90, 125.36, 125.77, 128.80, 128.85, 133.92, 134.22, 134.89, 135.33, 139.12, 142.47, 144.13, 146.76, 149.17, 161.13, 163.82 (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 6.19, N 9.76.

*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 by reductive amination of compounds **3** and **6e** as a light-yellow solid (yield 46 %). M. p. 125 – 126 °C. – IR (neat): ν = 3028, 2982, 2898, 1605, 1472, 1445, 1263, 1258 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.85 – 192 (m, 2 H, piperidine H), 1.98 – 2.04 (m, 4 H, piperidine H, cyclopent H), 2.24 (m, 2 H, cyclopent H), 2.72 (m, 2 H, cyclopent H), 3.05 (m, 2 H, piperidine H), 3.60 (s, 2 H, NCH_2), 3.79 (m, 1 H, piperidine H), 4.05 (s, 3H, OCH_3), 6.20 (s, 1 H, cyclopent H), 6.85 (d, J = 8.8 Hz, 1 H, 3-H), 7.24 – 7.34 (m, 4 H, aromatic H), 7.45 – 7.54 (m, 3 H, aromatic H), 7.91 (d, J = 8.8 Hz, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.33 ($C_{cyclopent}$), 32.33 (C_{piper}), 33.22, 33.30 (all $C_{cyclopent}$), 36.32 (C_{piper}), 53.05 (OCH_3), 54.74 (C_{piper}), 63.62 (NCH_2), 112.34 ($C_{cyclopent}$), 123.80, 124.27, 124.87, 125.28, 125.80, 126.12, 126.46, 127.88, 128.10, 136.67, 138.29, 139.11, 142.41, 142.67, 144.13, 161.12 (all C_{arom}). – $C_{27}H_{30}N_2O$ (398.54): calcd. C 81.37, H 7.59, N 7.03; found C 81.31, H 7.64, N 6.97.

*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 by reductive amination of compounds **3** and **6f** as a light-yellow amorphous solid (yield 39 %). M. p. 85 – 86 °C. – IR (neat): ν = 3021, 2992, 2828, 1601, 1472, 1445, 1255 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.89 – 194 (m, 2 H, piperidine H), 2.02 – 2.09 (m, 4 H, piperidine H, cyclopent H), 2.26 – 2.31 (m, 2 H, cyclopent H), 2.73 (m, 2 H, cyclopent H), 3.09 (m, 2 H, piperidine H), 3.61 (s, 2 H, NCH_2), 3.80 (m, 1 H, piperidine H), 4.05 (s, 3 H, OCH_3), 6.30 (s, 1 H, cyclopent H), 6.87 (d, J = 8.5 Hz, 1 H, 3-H), 7.32 (m, 1 H, aromatic H), 7.49 (d, J = 7.3 Hz, 1 H, aromatic H), 7.55 (d, J = 7.9 Hz, 1 H, aromatic H), 7.76 (s, 1 H, aromatic H), 7.95 (d, J = 8.8 Hz, 1 H, aromatic H), 8.42 (s, 1 H, aromatic H), 8.59 (s, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.16 ($C_{cyclopent}$), 32.09 (C_{piper}), 32.88, 33.36 (all $C_{cyclopent}$), 36.24 (C_{piper}), 53.03 (OCH_3), 54.57 (C_{piper}), 60.46 (NCH_2), 112.32 ($C_{cyclopent}$), 123.77, 124.87, 125.36, 125.78, 128.35, 132.04, 133.14, 133.59, 139.10, 139.38, 142.34, 144.10, 145.74, 148.46 (all C_{arom}), 161.14 (C-2). – $C_{26}H_{29}N_3O$ (399.53): calcd. C 78.16, H 7.32, N 10.52; found C 78.10, H 7.38, N 10.45.

*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 by reductive amination of compounds **4** and **6a** as a light-yellow solid (yield 45 %). M. p. 146 – 148 °C. – IR (neat): ν = 3193, 3038, 3021, 2938, 1641, 1601, 1437, 1218 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.81 (m, 4 H, piperidine H), 2.26 (m, 2 H, piperidine H), 3.00 (br. s, 3 H, piperidine H), 3.60 (s, 2 H, NCH_2), 6.65 (d, J = 9.4 Hz, 1 H, 3-H), 7.10 (t, J = 8.7 Hz, 1 H, aromatic H), 7.34 – 7.55 (m, 5 H, aromatic H), 7.61 (d, J = 9.4 Hz, 1 H, 4-H), 10.12 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.41, 34.93, 53.83 (all C_{piper}), 63.03 (NCH_2), 119.99, 121.17, 122.47, 126.18,

126.92, 127.03, 127.16, 127.78, 128.73, 129.75, 131.41, 135.71, 137.02, 139.95, 140.92, 141.61 (all C_{arom}), 163.46 (C=O). – $C_{27}H_{26}N_2O$ (394.51): calcd. C 82.20, H 6.64, N 7.10; found C 82.14, H 6.70, N 7.03.

*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 by reductive amination of compounds **4** and **6b** as an off-white solid (yield 41 %). M. p. 159 – 161 °C. – IR (neat): ν = 3213, 3028, 2928, 1637, 1609, 1447, 1171 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.88 (m, 4 H, piperidine H), 2.24 (m, 2 H, piperidine H), 2.90 (m, 1 H, piperidine H), 3.08 (m, 2 H, piperidine H), 3.65 (s, 2 H, NCH_2), 6.62 (d, J = 9.4 Hz, 1 H, 3-H), 7.12 (t, J = 8.7 Hz, 1 H, aromatic H), 7.20 (t, J = 8.5 Hz, 1 H, aromatic H), 7.41 – 7.44 (m, 4 H, aromatic H), 7.52 – 7.58 (m, 5 H, aromatic H), 7.73 (d, J = 9.4 Hz, 1 H, 4-H), 9.55 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.32, 35.36, 54.03 (all C_{piper}), 63.02 (NCH_2), 115.52, 115.73, 120.06, 121.21, 122.62, 126.32, 126.86, 127.82, 128.56, 128.64, 129.77, 130.08, 135.66, 137.05, 137.07, 139.03, 141.70 (all C_{arom}), 161.32 (C=O), 163.11 (C_{arom}). – $C_{27}H_{25}FN_2O$ (412.50): calcd. C 78.62, H 6.11, N 6.79; found C 78.56, H 6.16, N 6.72.

*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 by reductive amination of compounds **4** and **6c** as a light-yellow solid (yield 38 %). M. p. 158 – 160 °C. – IR (neat): ν = 3363, 3051, 3018, 2932, 1643, 1600, 1433, 1208 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.90 (m, 4 H, piperidine H), 2.17 (m, 2 H, piperidine H), 3.07 (m, 3 H, piperidine H), 3.71 (s, 2 H, NCH_2), 6.59 (d, J = 9.5 Hz, 1 H, 3-H), 7.21 (t, J = 7.6 Hz, 1 H, aromatic H), 7.41 – 7.43 (m, 2 H, aromatic H), 7.47 – 7.51 (m, 4 H, aromatic H), 7.64 (m, 2 H, aromatic H), 7.7 (d, J = 9.4 Hz, 1 H, 4-H), 7.92 (s, 1 H, aromatic H), 8.57 (d, J = 1.8 Hz, 1 H, aromatic H), 8.78 (d, J = 1.6 Hz, 1 H, aromatic H), 10.52 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.28, 34.67, 53.84 (all C_{piper}), 60.47 (NCH_2), 120.03, 121.06, 122.55, 126.26, 127.19, 127.81, 128.07, 129.02, 131.34, 133.55, 135.16, 135.69, 136.31, 137.71, 141.73, 147.06, 149.16 (all C_{arom}), 163.65 (C=O). – $C_{26}H_{25}N_3O$ (395.50): calcd. C 78.96, H 6.37, N 10.62; found C 78.90, H 6.43, N 10.57.

*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 reductive amination of compounds **4** and **6d** as a light-yellow solid (yield 34 %). M. p. 161 – 163 °C. – IR (neat): ν = 3373, 3058, 3040, 2928, 1640, 1602, 1430, 1228 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.91 (m, 4 H, piperidine H), 2.39 (m, 2 H, piperidine H), 3.09 (m, 3 H, piperidine H), 3.71 (s, 2 H, NCH_2), 6.62 (d, J = 11.8 Hz, 1 H, 3-H), 7.18 – 7.22 (m, 4 H, aromatic H), 7.44 – 7.48 (m, 2 H, aromatic H), 7.59 – 7.62 (m, 2 H, aromatic H), 7.80 (d, J = 11.2 Hz, 1 H, 4-H), 7.91 (br. s, 1 H, NH), 8.59 (d, J = 1.8 Hz, 1 H, aromatic H), 8.75 (d, J = 1.8 Hz, 1 H, aromatic H), 10.20 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.26, 34.89, 53.99 (all C_{piper}), 60.46 (NCH_2), 115.97, 116.18, 120.07, 121.15, 123.63, 126.38, 127.85, 128.89, 131.10, 133.87, 135.03, 135.48, 141.77, 147.01, 149.24, 163.50, 164.36 (all C_{arom}). – $C_{26}H_{24}FN_3O$ (413.49): calcd. C 75.52, H 5.85, N 10.16; found C 75.46, H 5.91, N 10.09.

*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 by reductive amination of compounds **4** and **6e** as a colorless solid (yield 42 %). M. p. 123 – 125 °C. – IR (neat): ν = 3164, 3110, 3022, 3011, 2936, 2886, 1639, 1599, 1471, 1116 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.83 – 191 (m, 6 H, piperidine H, cyclopent H), 2.21 – 2.29 (m, 2 H, cyclopent H), 2.51 – 2.59 (m, 2 H, piperidine H), 2.73 (m, 2 H, cyclopent H), 2.83 (m, 1 H, piperidine H), 3.08 (m, 2 H, piperidine H), 3.60 (s, 2 H, NCH_2), 6.22 (s, 1 H, cyclopent H), 6.60 (d, J = 9.4 Hz, 1 H, 3-H), 7.11 – 7.28 (m, 2 H, aromatic H), 7.29 (t, J = 7.8 Hz, 1 H, aromatic H), 7.33 (m, 1 H, aromatic H), 7.42 (m, 2 H, aromatic H), 7.52 (m, 1 H, aromatic H), 7.75 (d, J = 9.4 Hz, 1 H, 4-H), 9.36 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.37 ($C_{cyclopent}$), 32.27 (C_{piper}), 33.28, 33.34 (all $C_{cyclopent}$), 35.47, 53.99 (all C_{piper}), 63.44 (NCH_2), 119.94, 121.21, 122.58, 124.37, 126.26, 126.43, 127.81, 128.18, 130.84, 135.47, 136.77, 137.01, 141.64, 142.42 (all C_{arom}), 162.98 (C=O). – $C_{26}H_{28}N_2O$ (384.51): calcd. C 81.21, H 7.34, N 7.29; found C 81.15, H 7.40, N 7.22.

*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 by reductive amination of compounds **4** and **6f** as an off-white solid (yield 31 %). M. p. 133 – 135 °C. – IR (neat): ν = 3169, 3026, 2934, 1639, 1601, 1411, 1190, 1127 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.81 – 191 (m, 4 H, piperidine H), 1.98 – 2.10 (m, 2 H, cyclopent H), 2.25 – 2.36 (m, 2 H, cyclopent H), 2.52 – 2.59 (m, 2 H, piperidine H), 2.72 (m, 2 H, cyclopent H), 3.00 (m, 3 H, piperidine H), 3.59 (s, 2 H, NCH_2), 6.30

(s, 1 H, cyclopent H), 6.57 (d, J = 9.4 Hz, 1 H, 3-H), 7.18 (t, J = 8.8 Hz, 1 H, aromatic H), 7.41 (m, 2 H, aromatic H), 7.68 (s, 1 H, aromatic H), 7.76 (d, J = 9.4 Hz, 1 H, 4-H), 8.40 (s, 1 H, aromatic H), 8.59 (s, 1 H, aromatic H), 10.18 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.33 ($C_{cyclopent}$), 32.33 (C_{piper}), 33.22, 33.30 (all $C_{cyclopent}$), 36.32 (C_{piper}), 53.05 (OCH_3), 54.74 (C_{piper}), 63.62 (NCH_2), 113.98 ($C_{cyclopent}$), 120.14 (Ar-C), 122.26, 122.41, 124.11, 128.50, 132.05, 132.59, 133.36, 133.58, 138.80, 139.29, 140.65, 145.98, 148.45 (all C_{arom}), 162.28 (C-2). – $C_{25}H_{27}N_3O$ (385.50): calcd. C 77.89, H 7.06, N 10.90; found C 77.83, H 7.12, N 10.83.

*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 by reductive amination of compounds **5** and **6a** as an off-white solid (yield 41 %). M. p. 116 – 118 °C. – IR (neat): ν = 3217, 3053, 2912, 2872, 1668, 1601, 1482, 1211 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.76 – 184 (m, 4 H, piperidine H), 2.15 (m, 4 H, piperidine H), 2.53 (m, 1 H, piperidine H), 2.59 (t, J = 7.6, 2 H, 4-H), 2.94 (t, J = 6.7, 2 H, 3-H), 3.05 (m, 2 H, piperidine H), 3.60 (s, 2 H, NCH_2), 6.97 – 7.03 (m, 2 H, aromatic H), 7.15 (m, 1 H, aromatic H), 7.34 (m, 1 H, aromatic H), 7.41 – 7.45 (m, 4 H, aromatic H), 7.55 (d, J = 7.3, 1 H, aromatic H), 7.60 (d, J = 7.3, 1 H, aromatic H), 7.87 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 25.95 (C-4), 30.62 (C-3), 32.24, 35.82, 54.07 (all C_{piper}), 63.00 (NCH_2), 123.09, 124.21, 124.80, 125.69, 126.92, 127.01, 127.12, 128.69, 129.62, 130.91, 134.20, 137.22, 139.95, 140.91 (all C_{arom}), 171.68 (C-2). – $C_{27}H_{28}N_2O$ (396.52): calcd. C 81.78, H 7.12, N 7.06; found C 81.72, H 7.17, N 7.00.

*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 by reductive amination of compounds **5** and **6b** as a light-yellow solid (yield 33 %). M. p. 132 – 134 °C. – IR (neat): ν = 3223, 3050, 2902, 2862, 1667, 1600, 1489, 1231 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.67 – 173 (m, 4 H, piperidine H), 2.07 (m, 2 H, piperidine H), 2.50 (m, 3 H, piperidine H, 4-H), 2.83 (t, J = 7.6, 2 H, 3-H), 2.96 (m, 2 H, piperidine H), 3.51 (s, 2 H, NCH_2), 6.88 – 6.94 ((m, 2 H, aromatic H), 7.01 – 7.12 ((m, 3 H, aromatic H), 7.32 (d, J = 7.6 Hz, 2 H, aromatic H), 7.39 – 7.49 ((m, 4 H, aromatic H), 7.94 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 26.02 (C-4), 30.71 (C-3), 32.30, 35.78, 54.10 (all C_{piper}), 63.02 (NCH_2), 115.52, 115.73, 123.16, 124.31, 124.87, 125.87, 126.84, 128.56, 129.78, 131.05, 134.31, 137.08, 137.24, 139.04, 161.32, 163.62 (all C_{arom}), 170.87 (C=O). – $C_{27}H_{27}FN_2O$ (414.51): calcd. C 78.23, H 6.57, N 6.76; found C 78.26, H 6.62, N 6.69.

*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 by reductive amination of compounds **5** and **6c** as a light-yellow gum (yield 34 %). – IR (neat): ν = 3213, 3032, 2922, 1662, 1608, 1472, 1201 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.76 – 189 (m, 4 H, piperidine H), 2.27 (m, 2 H, piperidine H), 2.56 – 2.66 (m, 3 H, piperidine H, 4-H), 2.93 (m, 2 H, 3-H), 3.05 (m, 2 H, piperidine H), 3.67 (s, 2 H, NCH_2), 6.97 (m, 2 H, aromatic H), 7.07 (m, 1 H, aromatic H), 7.43 (m, 1 H, aromatic H), 7.50 (t, J = 7.5 Hz, 2 H, aromatic H), 7.89 (s, 1 H, aromatic H), 8.41 (s, 1 H, aromatic H), 8.54 (s, 1 H, NHCO), 8.72 (s, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 25.93 (C-4), 30.63 (C-3), 31.93, 35.26, 53.85 (all C_{piper}), 60.13 (s, 2 H, NCH_2), 115.99, 116.20, 123.34, 124.43, 124.91, 125.96, 128.87, 128.95, 130.99, 133.68, 134.21, 135.43, 146.80, 148.93, 161.76, 164.22 (all C_{arom}), 172.50 (C=O). – $C_{26}H_{27}N_3O$ (397.51): calcd. C 78.56, H 6.85, N 10.57; found C 78.50, H 6.91, N 10.50.

*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 by reductive amination of compounds **5** and **6d** as a light-yellow solid (yield 30 %). M. p. 136 – 138 °C. – IR (neat): ν = 3198, 3051, 2931, 1660, 1608, 1468, 1186 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.74 – 189 (m, 4 H, piperidine H), 2.31 (m, 2 H, piperidine H), 2.56 (m, 2 H, 4-H), 2.72 (m, 1 H, piperidine H), 2.89 (m, 2 H, 3-H), 3.07 (m, 2 H, piperidine H), 3.70 (s, 2 H, NCH_2), 6.93 – 7.06 (m, 2 H, aromatic H), 7.13 (d, J = 8.2 Hz, 1 H, aromatic H), 7.35 – 7.55 (t, J = 9.0 Hz, 3 H, aromatic H), 7.62 (m, 2 H, aromatic H), 7.93 (s, 1 H, aromatic H), 8.54 (s, 1 H, aromatic H), 9.61 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 25.95 (C-4), 30.68 (C-3), 31.95, 35.04, 53.69 (all C_{piper}), 60.07 (NCH_2), 123.30, 124.46, 124.93, 125.90, 127.20, 128.23, 129.10, 131.25, 133.00, 134.37, 135.69, 136.55, 137.51, 146.91, 148.90 (all C_{arom}), 172.66 (C=O). – $C_{26}H_{26}FN_3O$ (415.50): calcd. C 75.16, H 6.31, N 10.11; found C 75.10, H 6.37, N 10.03.

*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 by reductive am-

ination of compounds **5** and **6e** as a light-green solid (yield 45 %). M. p. 115 – 117 °C. – IR (neat): ν = 3191, 3067, 2922, 2842, 1665, 1603, 1431, 1188 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.71 – 189 (m, 4 H, piperidine H), 1.98 – 2.08 (m, 2 H, cyclopent H), 2.11 – 2.18 (m, 2 H, cyclopent H), 2.48 – 2.56 (m, 5 H, piperidine H, 4-H), 2.74 (m, 2 H, cyclopent H), 2.95 (m, 2 H, 3-H), 3.03 (m, 2 H, piperidine H), 3.57 (s, 2 H, NCH_2), 6.22 (br. s, 1 H, cyclopent H), 6.94 – 7.13 (m, 2 H, aromatic H), 7.16 (d, J = 7.7 Hz, 1 H, aromatic H), 7.23 (d, J = 7.6 Hz, 1 H, aromatic H), 7.25 – 7.32 (m, 2 H, aromatic H), 7.41 (s, 1 H, aromatic H), 7.98 (br. s, 1 H, NHCO). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.40 ($C_{cyclopent}$), 26.04 (C-4), 30.71 (C-3), 32.31 (C_{piper}), 33.29, 33.37 (all $C_{cyclopent}$), 35.83, 54.07 (all C_{piper}), 63.49 (NCH_2), 123.13 ($C_{cyclopent}$), 124.28, 124.37, 124.88, 125.83, 126.27, 126.26, 127.88, 128.18, 131.11, 134.30, 136.82, 137.04, 142.42 (all C_{arom}), 171.82 (C=O). – $C_{26}H_{30}N_2O$ (386.53): calcd. C 80.79, H 7.82, N 7.25; found C 80.73, H 7.88, N 7.18.

*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 by reductive amination of compounds **5** and **6f** as a light-yellow solid (yield 39 %). M. p. 123 – 125 °C. – IR (neat): ν = 3195, 3057, 2932, 2832, 1667, 1600, 1437, 1182 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.73 – 188 (m, 4 H, piperidine H), 2.00 – 2.11 (m, 2 H, cyclopent H), 2.12 – 2.16 (m, 2 H, cyclopent H), 2.51 – 2.66 (m, 4 H, piperidine H, 4-H), 2.69 – 2.76 (m, 2 H, cyclopent H), 2.92 – 3.06 (m, 4 H, piperidine H, 3-H), 3.57 (s, 2 H, NCH_2), 6.31 (br. s, 1 H, cyclopent H), 6.92 – 7.12 (m, 2 H, aromatic H), 7.16 (d, J = 7.7 Hz, 1 H, aromatic H), 7.69 (s, 1 H, aromatic H), 8.12 (br. s, 1 H, NHCO), 8.41 (s, 1 H, aromatic H), 8.59 (s, 1 H, aromatic H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.25 ($C_{cyclopent}$), 26.03 (C-4), 30.71 (C-3), 32.25 (C_{piper}), 32.99, 33.44 (all $C_{cyclopent}$), 35.62, 54.04 (all C_{piper}), 60.57 (NCH_2), 123.13 ($C_{cyclopent}$), 124.34, 124.84, 125.88, 128.35, 130.98, 132.02, 133.07, 133.31, 134.33, 139.49, 146.02, 148.68 (all C_{arom}), 171.87 (C=O). – $C_{25}H_{29}N_3O$ (387.52): calcd. C 77.48, H 7.54, N 10.84; found C 77.42, H 7.60, N 10.77.

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