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Synthesis of 6-Piperazinyl-3,4-dihydroquinazolin-2(1*H*)-ones

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A series of new 6-piperazinyl-3,4-dihydroquinazolin-2(1*H*)-ones have been synthesized. The described compounds are structurally related to adoprazine, a potential atypical antipsychotics bearing potent D_2 receptor antagonist and 5-HT_{1A} receptor agonist properties. Buchwald-Hartwig coupling of suitably modified aryl bromides with *tert*-butyl piperazine-1-carboxylate afforded the advanced intermediate piperazinyl-3,4-dihydroquinazolin-2(1*H*)-one. The reductive amination of the latter with appropriately designed biarylaldehydes accomplished the synthesis of 6-piperazinyl-3,4-dihydroquinazolin-2(1*H*)-ones.

Keywords: Schizophrenia, 6-Piperazinyl-3,4-Dihydroquinazolin-2(1*H*)-ones, Buchwald-Hartwig Coupling, 5-HT_{1A} receptor.

INTRODUCTION

Schizophrenia is a severe psychiatric illness afflicting 1 % of the population worldwide. The diagnosis of the disease is based on diverse and variably expressed symptoms which can be grouped as positive and negative. The positive symptoms include disorganized thought, delusions and auditory hallucinations whereas the most characteristic negative symptoms are emotional flattening, poverty of speech and motivational deficits[1]. The first-generation antipsychotics or typical antipsychotics such as chlorpromazine (**1**) and haloperidol (**2**) are dopamine antagonists which alleviate positive symptoms including hallucinations, agitation and delusions but fail to control the negative symptoms such as blunted affect, emotional withdrawal and cognitive deficits. In addition these therapeutics develop extrapyramidal symptoms (EPS) and hyperprolactinemia, respectively[2]. The 'second-generation' or atypical antipsychotics, such as clozapine (**3**), 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 extrapyramidal symptoms. With respect to classical neuroleptics, clozapine shows significantly greater efficacy, including an improved effect on negative symptoms and causes a marked increase in dopamine output in the prefrontal cortex[3]. Clozapine, however, is associated with its own set of serious side effects including weight gain, diabetes and an increased risk of seizures and agranulocytosis[4].

Several preclinical observations suggest that combining 5-HT_{1A} and D_2 receptor properties may provide a mutually complementary balance of pharmacological activity with reduced undesirable responses[5]. Indeed, numerous mechanistic considerations[6-8] and preclinical evidence[9-11] support the potential of such a combination. Consequently adoprazine (**4**) (SLV-313) and bifeprunox (**5**), bearing potent D_2 receptor antagonist and 5-HT_{1A} receptor agonist properties, were developed (Fig. 1)[12].

Although **5** has completed phase III clinical trials and has satisfactory tolerance profile, the FDA did not grant marketing approval. In addition, the failure of **4** and **5** to oppose phencyclidine-induced social interaction deficits suggested that an appropriate 'balance' of activity at these sites is necessary for activity in this model[13]. Thus, the need to discover compounds having varying ratios of D_2 and 5-HT_{1A} activities continued[14]. In an ongoing efforts to develop new antipsychotics[15-17], we have synthesized a series of 6-piperazinyl-3,4-dihydroquinazolin-2(1*H*)-ones (**6a-f**), which are structural analogs of adopraine (**4**) (Fig. 2). Herein we wish to disclose the synthesis of these compounds.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400. IR spectra were recorded on a Perkin Elmer 16F PC FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ and δ_6-DMSO using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Mass spectra were recorded on a GC-MS system (Agilent Technologies, 6890 N). Analytical TLC was carried out on silica gel 60 F_{254} plates; column

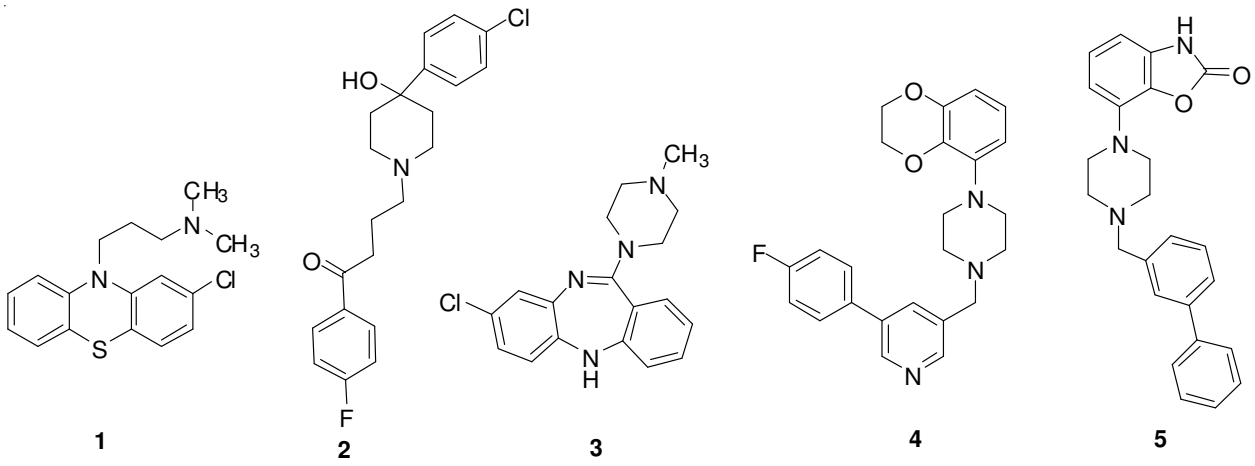


Fig. 1. Chlorpromazine, haloperidol, clozapine, adoprazine and bifeprunox

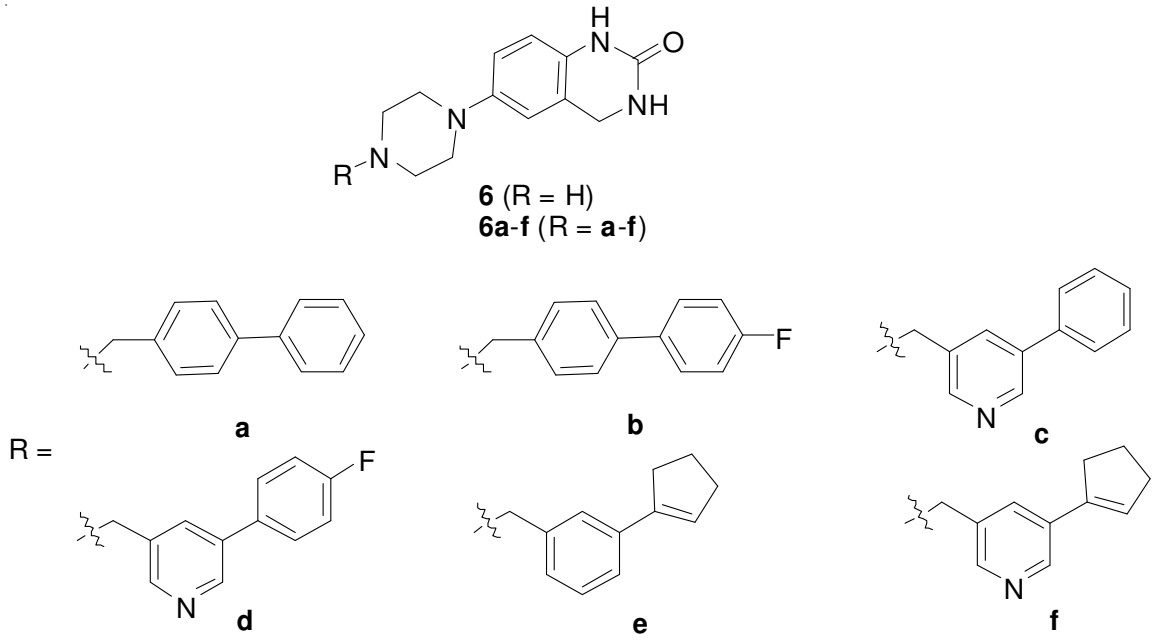


Fig. 2. 6-Piperazinyl-3,4-dihydroquinazolin-2(1*H*)-ones (**6a-f**)

chromatography was carried out on Merck silica gel (200-400 mesh).

(5-Bromo-2-nitrophenyl)methanamine (13): In a three neck round bottom flask solution of aldehyde (**12**) (3 g, 13 mmol) in THF (25 mL) was prepared at room temperature. To the solution were added ammonium hydroxide (28 %, 5 mL) and sodium borohydride (1.47 g, 39 mmol) simultaneously in portions in such a rate that addition of both was completed in 20 min. The mixture was left at room temperature for 4 h; ethyl acetate (30 mL) and brine (15 mL) were added. The organic layer was separated and washed with brine (15 mL), dried over Na_2SO_4 and evaporated to get an off-white solid, which was recrystallized from a mixture of ethanol and hexanes (3:7) to afford (5-bromo-2-nitrophenyl)methanamine (**13**) as an off-white solid (2.68 g, 89 %). IR (KBr, ν_{max}, cm^{-1}): 3431, 3319 (NH_2), 3052 (Ar-H), 2925 (Alph-H), 1606, 1554 (C=C), 1521, 1432 (NO_2), 1230 (C-N), 1188 (C-O). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.41 (br. s, 2H, NH_2), 5.02 (s, 2H, CH_2), 7.60 (dd, 1H, *J* = 2.2, 8.2 Hz, H-4), 7.99 (m, 2H, aromatic H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ = 61.95 (CH_2), 126.51 (C-3), 129.53 (C-1), 131.45 (C-6), 132.50 (C-4), 139.00 (C-5), 145.99 (C-2). Calculated (%) for $C_7H_7N_2O_2Br$ (229.97); C: 36.39, H: 3.05, N: 12.12, found (%); C: 36.33, H: 3.10, N: 12.02.

N-(5-Bromo-2-nitrobenzyl)acetamide (14): To a solution of compound **13** (2.5 g, 10.82 mmol) in pyridine (20 mL) was added acetic anhydride (2 mL, 21.60 mmol) and the mixture was stirred at room temperature for 12 h. The reaction was added ethyl acetate (30 mL) and the organic layer was washed sequentially with H_2O (20 mL), 1N HCl (15 mL × 3), brine (15 mL) and dried over Na_2SO_4 and evaporated to get N-(5-bromo-2-nitrobenzyl)acetamide as an off-white solid (2.89 g, 98 %). IR (KBr, ν_{max}, cm^{-1}): 3419 (NH), 3062 (Ar-H), 2925 (Alph-H), 1695 (C=O), 1604, 1564 (C=C), 1520, 1435 (NO_2), 1232 (C-N), 1168 (C-O). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.19 (s, 3H, CH_3); 5.50 (s, 2H, CH_2); 7.63 (dd, 1H, *J* = 2.3, 8.6 Hz, H-4); 7.75 (d, 1H, *J* = 2.3, H-6), 8.00 (d, 1H, *J* = 8.6 Hz, H-3). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ = 20.78 (CH_3), 62.27 (CH_2), 126.58 (C-3), 129.03 (C-1), 131.73 (C-6), 131.82 (C-4), 134.34 (C-5), 145.33 (C-2), 170.10 (CO). Calculated (%) for $C_9H_9N_2O_3Br$ (271.98); C: 39.58, H: 3.32, N: 10.26, found (%); C: 39.52, H: 3.36, N: 10.20.

***tert*-Butyl 4-[3-(acetamidomethyl)-4-nitrophenyl]-piperazine-1-carboxylate (15):** 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*(diphenylphos phino)-1,1'-binaphthyl (0.89 g, 1.43 mmol), toluene (8 mL) and compound **14** (3.89 g, 14.26 mmol) were added. While stirring the reaction mixture at room temperature, 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 stirred for 8 h. Ethyl acetate (40 mL) was added to the mixture at room temperature, washed with H_2O (15 mL), brine (10 mL), 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) to obtain the title compound **15** as light yellow solid (3.88 g, 72 %). IR (KBr, ν_{max}, cm^{-1}): 3441 (NH), 3060 (Ar-H), 2963 (Alph-H), 1696 (C=O), 1607, 1577 (C=C), 1484, 1421 (NO_2), 1243 (C-N), 1168 (C-O). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.49 (s, 9H, $(C(CH_3)_3)$, 2.17 (s, 3H, CH_3), 3.42 (br. s, 4H, $2CH_2$), 3.61 (br. s, 4H, $2CH_2$), 5.54 (s, 2H, CH_2), 6.76 (dd, 1H, *J* = 2.3, 9.3 Hz, H-6), 6.88 (br. s, 1H, H-2), 8.17 (d, 1H, *J* = 9.4 Hz, H-5). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ = 20.93 (CH_3), 28.39 ($C(CH_3)_3$), 46.82 (CH_2), 50.02 (CH_2), 66.12 (CH_2), 80.42 ($C(CH_3)_3$), 112.30 (aromatic-C), 112.48 (aromatic-C), 128.17 (aromatic-C), 135.60 (aromatic-C), 137.03 (aromatic-C), 153.02 (aromatic-C), 154.56 (CO), 170.29 (CO). Calculated (%) for $C_{18}H_{26}N_4O_5$ (378.19); C: 57.13, H: 6.93, N: 14.81, found (%); C: 57.07, H: 6.99, N: 14.71.

***tert*-Butyl 4-[3-(acetamidomethyl)-4-aminophenyl]-piperazine-1-carboxylate (16):** To a solution of compound **(15)** (1.13 g, 3 mmol) in EtOH (30 mL) was added Raney-Ni (0.20 g, 10 % wet basis) and the mixture was subjected to hydrogenation in Parr apparatus at 20 psi for 6 h. After filtering over the pad of celite, the solution was concentrated and purified over silica column, eluting with CH_2Cl_2:MeOH (95:5) and then changing to (92:8) afforded compound (**16**) as a light yellow thick oil (0.85 g, 82 %). IR (KBr, ν_{max}, cm^{-1}): 3441, 3421 (NH), 3042 (Ar-H), 2960 (Alph-H), 1699, 1696 (C=O), 1607, 1577 (C=C), 1240 (C-N), 1165 (C-O). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.48 (s, 9H, $(C(CH_3)_3)$, 2.16 (s, 3H, CH_3), 3.38 (br. s, 4H, $2CH_2$), 3.52 (br. s, 4H, $2CH_2$), 5.28 (br. s, 2H, NH_2), 5.49 (s, 2H, CH_2), 6.78 (dd, 1H, *J* = 2.3, 9.3 Hz, H-6), 6.80 (br. s, 1H, H-2), 6.87 (d, 1H, *J* = 9.2 Hz, H-5). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ = 20.97 (CH_3), 28.35 ($C(CH_3)_3$), 42.53 (CH_2), 46.26 (CH_2), 62.54 (CH_2), 79.85 ($C(CH_3)_3$), 112.10 (aromatic-C), 112.38 (aromatic-C), 117.09 (aromatic-C), 130.22 (aromatic-C), 135.03 (aromatic-C), 143.02 (aromatic-C), 154.58 (CO), 170.51 (CO). Calculated (%) for $C_{18}H_{28}N_4O_3$ (348.22); C: 62.05, H: 8.10, N: 16.08, found (%); C: 62.00, H: 8.15, N: 16.00.

***tert*-Butyl 4-[4-amino-3-(aminomethyl)phenyl]piperazine-1-carboxylate (17):** To a solution of compound 16 (0.70 g, 2 mmol) in ethanol (20 mL) was added 4 M solution of KOH in H_2O (4 mL, 16 mmol) and the mixture was stirred at 90 °C for 12 h. The mixture was concentrated under reduced pressure to get a brown oil material, which was resolved over silica column eluting with CH_2Cl_2:MeOH (95:5) and then changing to (90:10) to get compound **17** as light brown thick oil (0.51 g, 84 %). IR (KBr, ν_{max}, cm^{-1}) : 3421, 3411 (NH), 3053 (Ar-H), 2936 (Alph-H), 1697 (C=O), 1606, 1578 (C=C), 1244 (C-N), 1166 (C-O). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.47 (s, 9H, $(C(CH_3)_3)$, 3.10 (br. s, 4H, $2CH_2$), 3.22 (br. s, 4H, $2CH_2$), 4.08 (s, 2H, CH_2), 4.58 (br. s, 2H, NH_2), 5.18 (br. s, 2H, NH_2), 6.68 (dd, 1H, *J* = 2.3, 9.3 Hz, H-6), 6.73 (br. s, 1H, H-2), 6.81 (d, 1H, *J* = 9.2 Hz, H-5). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ = 28.05 ($C(CH_3)_3$), 42.43 (CH_2), 45.26 (CH_2), 50.54 (CH_2), 79.75 ($C(CH_3)_3$), 112.01 (aromatic-C), 112.08 (aromatic-C), 117.00 (aromatic-C), 130.28 (aromatic-C), 134.08 (aromatic-C), 143.08 (aromatic-C), 154.70 (CO). Calculated (%) for $C_{16}H_{26}N_4O_2$ (306.21); C: 62.72, H: 8.55, N: 18.29, found (%); C: 62.66, H: 8.62, N: 18.20.

***tert*-Butyl 4-(2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-piperazine-1-carboxylate (10):** To a solution of compound 17 (1.38 g, 4.5 mmol) in THF (20 mL) at room temperature was CDI (0.80 g, 4.95 mmol) and the reaction was stirred at 80 °C for 6 h . The mixture was cooled to room temperature and the solid formed was filtered, washed with diethyl ether to afford 0.99g (72 %) of compound **10** as an off-white foam. IR (KBr, ν_{max}, cm^{-1}): 3210, 3162 (NH), 3032 (Ar-H), 1691 (C=O), 1607, 1515, 1419 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.47 (s, 9H, $(CH_3)_3C$); 3.06 (m, 4H, $2CH_2$); 3.52 (m, 4H, $2CH_2$); 4.49 (s, 2H, CH_2); 6.69 (m, 2H, aromatic-H), 6.74 (m, 1H, aromatic-H); 7.82 (br.s, 1H, NH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ = 28.60 ($CH_3)_3C$), 43.35 (CH_2), 43.90 (CH_2), 50.66 (CH_2), 80.10 ($CH_3)_3C$), 112.11 (aromatic-C), 112.28 (aromatic-C), 117.19 (aromatic-C), 130.18 (aromatic-C), 134.88 (aromatic-C), 143.18 (aromatic-C), 154.62 (CO), 155.93 (C=O). Calculated (%) for $C_{17}H_{24}N_4O_3$ (332.18); C: 61.43, H: 7.28, N: 16.86, found (%) C: 61.38, H: 7.32, N: 16.81.

6-(Piperazin-1-yl)-3,4-dihydroquinazolin-2(1*H*)-one (6): To a solution of compound **10** (0.7 g, 2.11 mmol) in a mixture of CH_2Cl_2 (15 mL) and THF (5 mL) at 0 °C was added TFA (5 mL) and the mixture was stirred at room temperature for 6 h. The solvent was evaporated under vacuum to afford 0.66 g (96 %) of compound **6** as a dark brown gum. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 3.17 (m, 4H, $2CH_2$), 3.40 (m, 4H, $2CH_2$), 4.28 (s, 2H, CH_2), 6.70 (m, 2H, aromatic-H), 6.73 (m, 1H, aromatic-H), 8.81 (br. s, 1H, NH), 8.86 (br. s, 1H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 46.11 (CH_2), 46.70 (CH_2), 48.68 (CH_2), 112.21 (aromatic-C), 112.27 (aromatic-C), 117.31 (aromatic-C), 130.28 (aromatic-C), 134.99 (aromatic-C), 143.38 (aromatic-C), 154.82 (C=O). Calculated (%) for $C_{14}H_{16}N_4O_2F_3$ (329.12); C: 51.06, H: 4.90, N: 17.01, found (%); C: 51.01, H: 4.95, N: 16.95.

6-[4-(Biphenyl-4-ylmethyl)piperazin-1-yl]-3,4-dihydro-quinazolin-2(1*H*)-one (6a): Representative procedure: To a solution of compound **6** (0.15 g, 0.43 mmol) and biphenyl-4-carbaldehyde **a** (0.1 g, 0.55 mmol) in DMSO (2 mL) at 0 °C was added Et_3N (0.13 mL, 0.97 mmol). After being stirred for 0.5 h at room temperature, $NaBH(OAc)_3$ (0.11 g, 0.53 mmol) was added and the mixture was stirred for 6 h. The reaction was mixed with sat. $NaHCO_3$ solution (5 mL) and stirred for 15 min, followed by the addition of ethyl acetate (20 mL). The organic layer was separated and washed with sat. $NaHCO_3$, brine and dried over Na_2SO_4 and evaporated. Column chromatography on silica gel, eluting with methanol: dichloromethane (5:95) and then changing (10:90) afforded 0.102 g (60 %) of compound **6a** as an off-white solid. IR (KBr, ν_{max}, cm^{-1}): 3436

(NH), 3052 (Ar-H), 2953 (Alph-H), 1702 (C=O), 1614, 1515, 1425 (C=C), 1229 (C-N), 1162 (C-O). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.76 (m, 4H, 2CH_2), 3.18 (m, 4H, 2CH_2), 3.67 (s, 2H, CH_2), 4.49 (s, 2H, CH_2), 6.60 (d, 1H, *J* = 2.3 Hz, aromatic H), 6.70 (dd, 1H, *J* = 2.2, 8.5 Hz, aromatic H), 7.43-7.48 (m, 6H, aromatic H), 7.58-7.62 (m, 4H, aromatic H). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 43.70 (CH_2), 48.23 (CH_2), 53.03 (CH_2), 62.64 (CH_2), 114.56 (aromatic-C), 117.64 (aromatic-C), 119.82 (aromatic-C), 124.58 (aromatic-C), 127.19 (aromatic-C), 127.26 (aromatic-C), 127.55 (aromatic-C), 127.90 (aromatic-C), 128.95 (aromatic-C), 129.26 (aromatic-C), 130.25 (aromatic-C), 130.59 (aromatic-C), 136.66 (aromatic-C), 138.22 (aromatic-C), 138.66 (aromatic-C), 140.95 (aromatic-C), 146.88 (aromatic-C), 156.32 (C=O). Calculated (%) for $C_{25}H_{26}N_4O$ (398.21); C: 75.35, H: 6.58, N: 14.06, found (%); C: 75.27, H: 6.65, N: 13.96.

6-[4-{(4'-fluorobiphenyl-4-yl)methyl}piperazin-1-yl]-3,4-dihydroquinazolin-2(1*H*)-one (6b): Following the same procedure adopted for the synthesis of **6a**, the reductive amination of compound **6** with aldehyde b afforded 0.101 g (55 %) of compound **6b** as an off-white solid. IR (KBr, ν_{max}, cm^{-1}): 3421 (NH), 3048 (Ar-H), 2953 (Alph-H), 1702 (C=O), 1615, 1515, 1420 (C=C), 1228 (C-N), 1161 (C-O). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.71 (m, 4H, 2CH_2), 3.17 (m, 4H, 2CH_2), 3.65 (s, 2H, CH_2), 4.43 (s, 2H, CH_2), 6.66 (d, 1H, *J* = 2.3 Hz, aromatic H), 6.73 (dd, 1H, *J* = 2.2, 8.5 Hz, aromatic H), 7.13-7.15 (m, 3H, aromatic H), 7.40-7.45 (m, 2H, aromatic H), 7.44-7.56 (m, 4H, aromatic H). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 43.76 (CH_2), 48.28 (CH_2), 53.08 (CH_2), 62.66 (CH_2), 114.66 (aromatic-C), 115.29 (aromatic-C), 116.18 (aromatic-C), 117.69 (aromatic-C), 119.88 (aromatic-C), 124.65 (aromatic-C), 127.52 (aromatic-C), 129.39 (aromatic-C), 129.46 (aromatic-C), 130.85 (aromatic-C), 131.15 (aromatic-C), 136.69 (aromatic-C), 136.79 (aromatic-C), 138.79 (aromatic-C), 140.89 (aromatic-C), 146.89 (aromatic-C), 156.38 (C=O), 161.64 (aromatic-C). Calculated (%) for $C_{25}H_{25}N_4OF$ (416.20); C: 72.09, H: 6.05, N: 13.45, found (%); C: 72.00, H: 6.11, N: 13.37.

6-[4-{(5-Phenylpyridin-3-yl)methyl}piperazin-1-yl]-3,4-dihydroquinazolin-2(1*H*)-one (6c): Following the same procedure adopted for the synthesis of **6a**, the reductive amination of compound **6** with aldehyde **c** afforded 0.082 g (48 %) of compound **6c** as light yellow gum. IR (KBr, ν_{max}, cm^{-1}): 3436, 3192 (NH), 3042 (Ar-H), 2932 (Alph-H), 1690 (C=O), 1622, 1518, 1440 (C=C), 1175 (C-O). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.72 (m, 4H, 2CH_2), 3.12 (m, 4H, 2CH_2), 3.62 (s, 2H, CH_2), 4.45 (s, 2H, CH_2), 6.64-6.72 (m, 3H, aromatic H), 7.10-7.13 (m, 2H, aromatic H), 7.40-7.42 (m, 2H, aromatic H), 7.44-7.48 (m, 3H, aromatic H), 7.62 (m, 2H, aromatic H), 7.91 (s, 1H, aromatic H), 8.55 (s, 1H, aromatic H), 8.92 (s, 1H, aromatic H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ = 43.67 (CH_2), 48.13 (CH_2), 52.92 (CH_2), 62.40 (CH_2), 114.46 (aromatic-C), 117.54 (aromatic-C), 119.70 (aromatic-C), 124.38 (aromatic-C), 126.94 (aromatic-C), 127.86 (aromatic-C), 128.38 (aromatic-C), 128.70 (aromatic-C), 128.78 (aromatic-C), 128.89 (aromatic-C), 132.98 (aromatic-C), 133.16 (aromatic-C), 136.18 (aromatic-C), 136.49 (aromatic-C), 136.60 (aromatic-C), 137.36 (aromatic-C), 146.10 (aromatic-C), 146.87 (aromatic-C), 148.86 (aromatic-C), 155.41 (C=O). Calculated (%) for $C_{24}H_{25}N_5O$ (399.21); C: 72.16, H: 6.31, N: 17.53, found (%); C: 72.07, H: 6.37, N: 17.41.

6-[4-{5-(4-fluorophenyl)pyridin-3-yl}methyl]piperazin-1-yl)-3,4-dihydroquinazolin-2(1*H*)-one (6d): Following the same procedure adopted for the synthesis of **6a**, the reductive amination of compound **6** with aldehyde **d** afforded 0.083 g (49 %) of compound **6d** as a light yellow solid. IR (KBr, ν_{max}, cm^{-1}): 3426, 3175 (NH), 3040 (Ar-H), 2962 (Alph-H), 1688 (C=O), 1622, 1525, 1420 (C=C), 1172 (C-O). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.79 (m, 4H, 2CH_2), 3.19 (m, 4H, 2CH_2), 3.66 (s, 2H, CH_2), 4.48 (s, 2H, CH_2), 6.62-6.69 (m, 2H, aromatic H), 6.70-6.72 (m, 2H, aromatic H), 7.17 (m, 1H, aromatic H), 7.56-7.58 (m, 2H, aromatic H), 7.89 (s, 1H, aromatic H), 8.54 (s, 1H, aromatic H), 8.70 (s, 1H, NH), 8.96 (s, 1H, aromatic H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ = 43.60 (CH_2), 48.19 (CH_2), 52.90 (CH_2), 61.41 (CH_2), 114.32 (aromatic-C), 114.48 (aromatic-C), 115.85 (aromatic-C), 116.76 (aromatic-C), 117.54 (aromatic-C), 119.70 (aromatic-C), 124.38 (aromatic-C), 128.61 (aromatic-C), 129.75 (aromatic-C), 135.28 (aromatic-C), 136.63 (aromatic-C), 146.89 (aromatic-C), 146.96 (aromatic-C), 148.83 (aromatic-C), 150.49 (aromatic-C), 152.80 ((aromatic-C)), 155.06 (C=O), 161.73 (aromatic-C), 163.68 (aromatic-C). Calculated (%) for $C_{24}H_{24}FN_5O$ (417.20); C: 69.05, H: 5.79, N: 16.78, found (%); C: 68.96, H: 5.86, N: 16.71.

6-[4-(3-cyclopentenylbenzyl)piperazin-1-yl]-3,4-dihydroquinazolin-2(1*H*)-one (6e): Following the same procedure adopted for the synthesis of **6a**, the reductive amination of compound **6** with aldehyde e afforded 0.111 g (60 %) of compound **6e** as light brown foam. IR (KBr, ν_{max}, cm^{-1}): 3416, 3182 (NH), 3045 (Ar-H), 2933 (Alph-H), 1690 (C=O), 1622, 1518, 1421 (C=C), 1167 (C-O). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.00-2.04 (m, 2H, CH_2), 2.51 (m, 2H, CH_2), 2.60 (m, 2H, 2CH_2), 2.73 (m, 4H, 2CH_2), 3.12 (m, 4H, 2CH_2), 3.60 (s, 2H, CH_2), 4.46 (s, 2H, CH_2), 6.19 (s, 1H, CH), 6.58-6.75 (m, 3H, aromatic H), 7.18 (m, 1H, aromatic H), 7.24 (m, 1H, aromatic H), 7.31 (m, 1H, aromatic H), 7.40 (s, 1H, aromatic H), 7.95 (br. s, 1H, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ = 23.52 (CH_2), 33.46 (CH_2), 33.58 (CH_2), 43.62 (CH_2), 48.18 (CH_2), 52.90 (CH_2), 62.48 (CH_2), 114.48 (aromatic-C), 115.12 (aromatic-C), 117.58 (aromatic-C), 119.72 (aromatic-C), 123.52 (aromatic-C), 124.42 (aromatic-C), 126.59 (aromatic-C), 128.06 (aromatic-C), 128.45 (aromatic-C), 130.07 (aromatic-C), 136.60 (aromatic-C), 137.79 (aromatic-C), 142.58 (aromatic-C), 146.92 (aromatic-C), 156.19 (C=O). Calculated (%) for $C_{24}H_{28}N_4O$ (388.23); C: 74.20, H: 7.26, N: 14.42, found (%); C: 74.13, H: 7.33, N: 14.33.

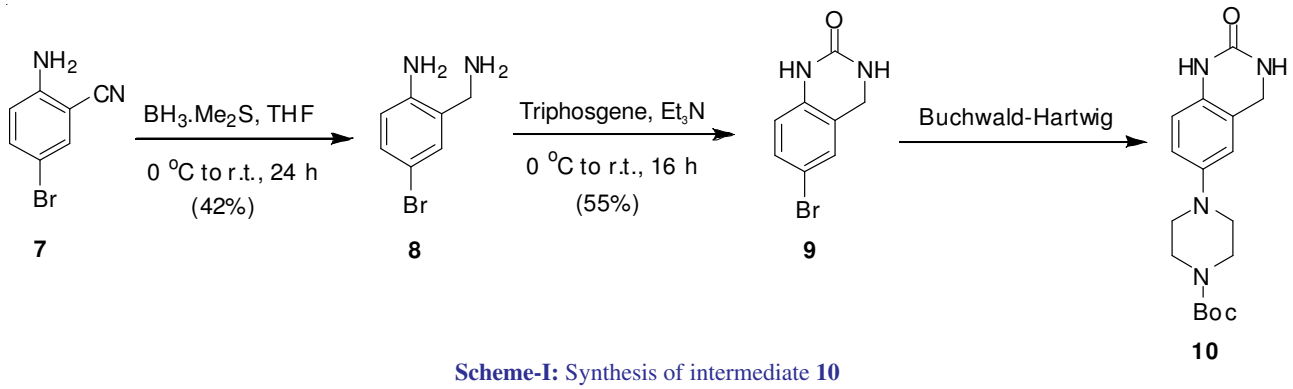
6-[4-{(5-cyclopentenylpyridin-3-yl)methyl}piperazin-1-yl]-3,4-dihydroquinazolin-2(1*H*)-one (6f): Following the same procedure adopted for the synthesis of **6a**, the reductive amination of compound **6** with aldehyde **f** afforded 0.090 g (54 %) of compound **6f** as an off-white solid. IR (KBr, ν_{max}, cm^{-1}): 3412, 3190 (NH), 3061 (Ar-H), 2961 (Alph-H), 1690 (C=O), 1626, 1523, 1422 (C=C), 1170 (C-O). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.00-2.06 (m, 2H, CH_2), 2.50 (m, 2H, CH_2), 2.61 (m, 2H, 2CH_2), 2.71 (m, 4H, 2CH_2), 3.15 (m, 4H, 2CH_2), 3.61 (s, 2H, CH_2), 4.45 (s, 2H, CH_2), 6.20 (s, 1H, CH), 6.58-6.75 (m, 3H, aromatic H), 6.78 (m, 1H, aromatic H), 7.71 (s, 1H, NH), 8.09 (s, 1H, aromatic H), 8.42 (s, 1H, aromatic H), 8.58 (s, 1H, aromatic H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ = 23.92 (CH_2), 33.56 (CH_2), 33.88 (CH_2), 43.69 (CH_2), 48.12 (CH_2), 52.92 (CH_2), 62.68 (CH_2), 114.43 (aromatic-C), 115.92

(aromatic-C), 117.44 (aromatic-C), 119.76 (aromatic-C), 124.39 (aromatic-C), 130.92 (aromatic-C), 133.09 (aromatic-C), 133.69 (aromatic-C), 136.60 (aromatic-C), 140.37 (aromatic-C), 146.90 (aromatic-C), 147.91 (aromatic-C), 149.46 (aromatic-C), 156.90 (C=O). Calculated (%) for $C_{23}H_{27}N_5O$ (389.22); C: 70.92, H: 6.99, N: 17.98, found (%); C: 70.86, H: 7.06, N: 17.91.

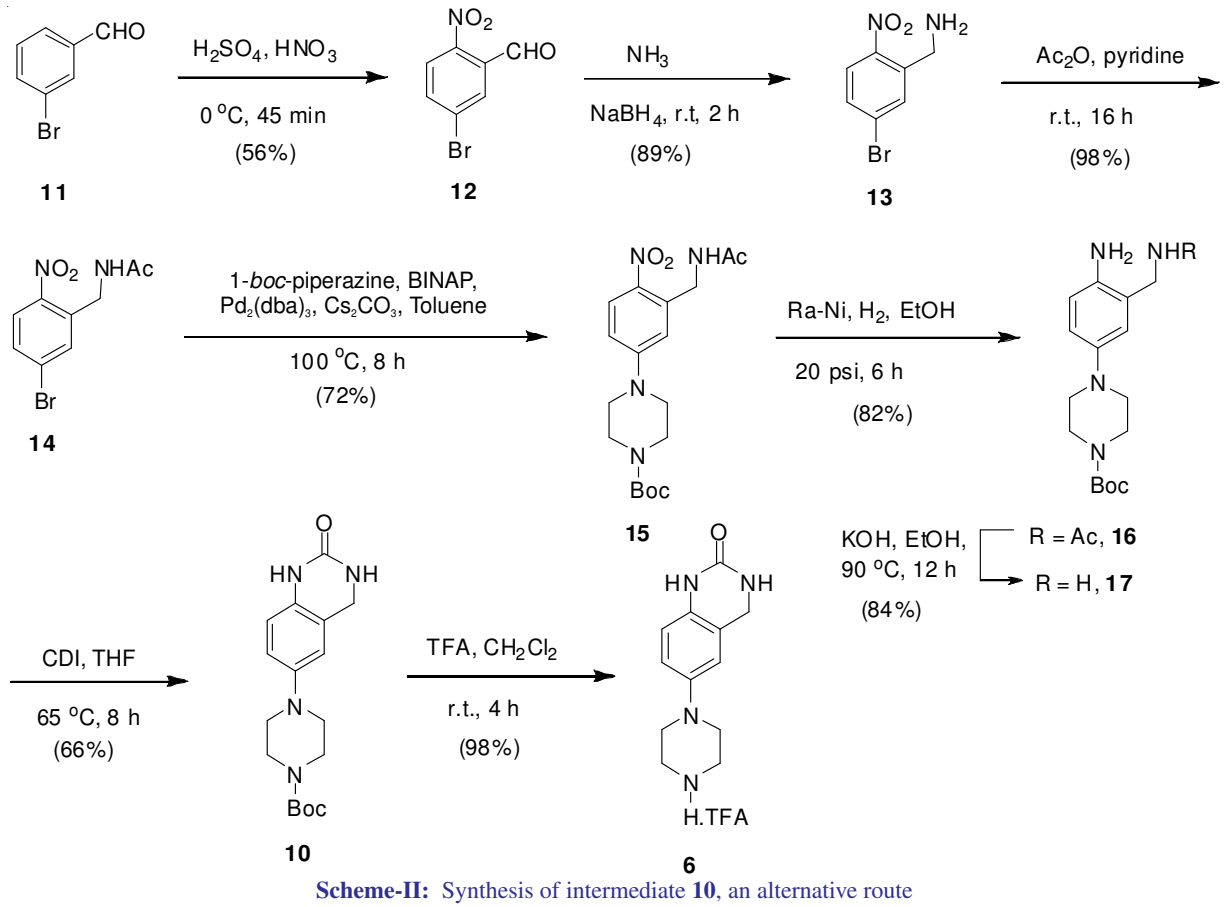
RESULTS AND DISCUSSION

To accomplish the synthesis of the desired compounds **6a-f**, synthesis of the key intermediate **10** was required, which in turn was envision from the Buchwald-Hartwig coupling reaction of known 6-bromo-3,4-dihydroquinazolin-2(1*H*)-one (**9**)[18] with *tert*-butyl piperazine-1-carboxylate. Thus the synthesis of compound **9** was commenced with the reduction of bromobenzonitrile with borane to afford diamine (**8**), which was reacted with triphosgene to get the desired bromide (**9**) in 23 % overall yield from (**7**). However, the Buchwald-Hartwig coupling of bromides **9** with *tert*-butyl piperazine-1-carboxylate, under different reaction conditions ($PdCl_2$dppf, KOAc, DMF, 80 °C; $Pd(PPh_3)_4$, toluene, ethanol, Na_2CO_3, reflux) were not successful; the desired **10** was not observed in any case (**scheme-I**).

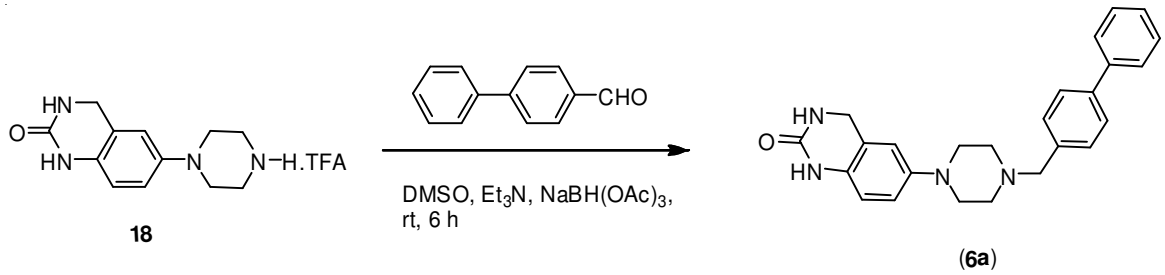
Therefore an alternative approach was adopted in which benzaldehyde **11** was nitrated to the known benzaldehyde **12**[18], which in turn was subjected to reductive amination by condensing it with ammonium hydroxide, using sodium borohydride as reducing agent to produce amine **13** in high yield. Acetylation amine **13** generated acetamide **14**, which was reacted with *tert*-butyl piperazine-1-carboxylate under Buchwald-Hartwig conditions to afford intermediate **15** in good yield. Reduction of nitro group of **15** over Pd-C in a Parr apparatus produced intermediate **16** in 91 % yield high yield. Exposure of intermediate **16** under basic conditions rendered the desired diamine **17** in good yield after column purifications. Reaction of **17** with CDI in THF, heating the mixture at 80 °C for 6 h,



Scheme-I: Synthesis of intermediate **10**



Scheme-II: Synthesis of intermediate **10**, an alternative route



Scheme-III: Synthesis of **6a**, a representative example

gave access to the key intermediate **10** in an overall yield of 33 % from **14**. Exposure of intermediate **10** to trifluoroacetic acid in a mixture of methanol and dichloromethane finally furnished the desired key intermediate **18** (**Scheme-II**).

Having the desired intermediates **18** in hands, we next performed reductive amination of **18** with aldehydes (**a-f**)[15] in DMSO, using $NaBH(OAc)_3$ as reducing agent to accomplish the synthesis of final compounds (**6a-f**) (**Scheme-III**).

Conclusion

A series of new 6-piperazinyl-3,4-dihydroquinazolin-2(1*H*)-ones have been synthesized. The described compounds are structurally related to adoprazine, a potential atypical antipsychotics bearing potent D_2 receptor antagonist and 5-HT_{1A} receptor agonist properties.

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