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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, computational studies, and preliminary pharmacological evaluation of new arylpiperazines as potential antipsychotics

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Abstract A series of long-chain arylpiperazines bearing a salicylamide fragment were synthesized, and the target compounds were evaluated for atypical antipsychotic activity in apomorphine-induced climbing behavior (D_2 antagonism) and 5-HTP-induced head twitches (5-HT_{2A} antagonism) along with catalepsy studies in mice. The physicochemical similarity values of the target compounds with respect to standard drugs, clozapine, ketanserin, and risperidone, were determined using software programs. The test compounds demonstrated good similarity values with respect to the standard drugs. The compounds **3a$_4$** showed maximum atypical antipsychotic like profile.

Keywords Arylpiperazines · Salicylamide · Atypical antipsychotic · 5-HT_{2A} antagonist · D_2 antagonists

Introduction

Schizophrenia is a complex psychiatric disorder that affects approximately 1% of the population (Reynolds, 1992, Jibson *et al.*, 2004). The symptoms of the disease may be divided into two broad categories: the positive symptoms, which add to the normal psyche (aggression, hallucinations, etc.) and the negative ones, which detract from the normal psyche (e.g., flat affect, poverty of speech, social withdrawal, etc.). The use of classical (typical) neuroleptics (e.g., haloperidol and chlorpromazine) for the treatment of this disease is associated with severe mechanism-related side effects, including induction of extrapyramidal symptoms (EPS) (Altar *et al.*, 2003). Furthermore, these drugs are ineffective against the negative symptoms of schizophrenia. The introduction of clozapine for treatment-resistant schizophrenia gave rise to a new group of atypical or nonclassical antipsychotics which have no EPS and are effective against negative symptoms (Fitton and Hell, 1990). Unfortunately, its therapeutic use has been hampered by serious side effects, for example, agranulocytosis (Griffith and Saameli, 1975). It has been observed that clozapine and other antipsychotic drugs which show a reduced propensity for the development of EPS have demonstrated a higher affinity for the 5-HT_2 receptor than the D_2 receptor (Meltzer, 1989). This has led to the hypothesis that a combination of serotonin 5-HT_2 and dopamine D_2 receptor antagonism play critical role in the mechanism of action of atypical antipsychotic drugs. This so-called serotonin-dopamine hypothesis (Meltzer *et al.*, 2003) has become a useful model for developing new antipsychotics to achieve superior efficacy with a lower incidence of extrapyramidal side effects compared to classical antipsychotics (Kuroki *et al.*, 2008). Arylpiperazine derivatives display diverse pharmacological activity which can be mediated by different subpopulations of serotonin, dopamine, and aderenergic receptors (Obniska *et al.*, 2003; Tomic *et al.*, 2004; Kolaczkowski *et al.*, 2005).

Their general chemical structure consists of the arylpiperazine moiety connected by an alkyl chain with the terminal amide or imide fragment (Gonalez-Gomez *et al.*, 2003, Perrone *et al.*, 1999; Lopez-Rodriguez *et al.*, 2001). As part of our ongoing study on the development of

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strategies for the preparation of new D_2/5-HT_{2A} receptor antagonists as antipsychotics, we herein report the synthesis, computational studies, and preliminary pharmacological evaluation of new amide arylpiperazines.

Materials and methods

Chemistry

Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. The IR spectra of synthesized compounds were recorded in potassium bromide disks on Schimadzu FTIR Spectrophotometer 8300. The ^{1}H NMR spectra of the synthesized compounds were recorded in DMSO using AV-300 BROKE JEOL Spectrophotometer and tetramethylsilane (TMS) as an internal standard. Elemental analyses were performed on Perkin Elmer 2400 analyzer. The mass spectra were recorded on a Micromass Quattro II triple quadrupole mass spectrometer. All the reagents were of commercial quality and were used without further purification.

General procedure for the alkylation of salicylamide (**2a**, **2b,** and **2c**)

A mixture of salicylamide (5.48 g, 0.04 mol), dihaloalkane (1,2-dibromoethane or 1-bromo-3-chloropropane or 1,4-dibromobutane, 0.04 mol), and K_2CO_3 (5.52 g, 0.04 mol) in acetonitrile was refluxed for 8 h. The solvent was removed under vacuum. The residue was dissolved in $CHCl_3$ and washed with water. The organic extract was dried over Na_2SO_4. The solvent was removed, and the residue was recrystallized from methanol and chloroform (1:1).

2-(2-Bromoethoxy) benzamide (**2a**)

Yield: 7.45 g (76.41%); R_f: 0.72 (Ethylacetate/Methanol, 2:0.4); mp: 199–201°C; IR (cm^{-1}): 3455, 3159, 2961, 1657, 1029, 748; ^{1}H NMR (DMSO-d_6): 3.40 (t, 2H, CH_2Br), 4.50 (t, 2H, OCH_2), 7.82 (s, 2H, $CONH_2$), 7.0–7.50 (m, 4H, Ar).

2-(3-Chloropropoxy) benzamide (**2b**)

Yield: 5.4 g (42.18%); R_f: 0.74 (Ethylacetate/Methanol, 2:0.4); mp: 123–125°C; IR (cm^{-1}): 3455, 3163, 2958, 1645, 1029, 749; ^{1}H NMR (δppm, DMSO-d_6): 1.92–2.21 (m, 2H, CH_2), 3.31 (t, 2H, CH_2Cl), 4.21 (t, 2H, OCH_2), 7.80 (s, 2H, $CONH_2$), 7.0–7.48 (m, 4H, Ar).

2-(4-Bromobutoxy) benzamide (**3c**)

Yield: 4.70 g (43%); R_f: 0.67 (Ethylacetate/Methanol, 2:0.4); mp: 211–213°C; IR (cm^1): 3455, 3159, 2981, 1657, 1029, 748, ^{1}H NMR (δppm, DMSO-d_6): 1.91–2.51 (m, 4H, CH_2CH_2), 3.36 (t, 2H, CH_2Br), 4.21 (t, 2H, OCH_2), 7.80 (s, 2H, $CONH_2$), 7.0–7.51 (m, 4H, Ar).

General procedure for the synthesis of $\mathbf{3a_1}$–$\mathbf{3a_6}$, $\mathbf{3b_1}$–$\mathbf{3b_2}$, and $\mathbf{3c_1}$–$\mathbf{3c_2}$

A mixture of **2a** or **2b** or **2c** (5 mmol), K_2CO_3 (0.69 g, 5 mmol), respective substituted phenylpiperazines (5 mmol), and a catalytic amount of potassium iodide in anhydrous dimethylformamide (100 ml) were stirred on a magnetic stirrer at 80°C temperature for 36 h. The reaction mixture was poured into 150–200 ml of water, and the precipitate was extracted with chloroform. The organic phase was dried over Na_2SO_4, and the solvent was removed. The crude products were purified by column chromatography (Ethyl acetate/Methanol, 4:1).

2-[2-(4-Phenylpiperazin-1-yl) ethoxy] benzamide ($\mathbf{3a_1}$)

Yield: 0.50 g (23%); R_f: 0.21 (Ethylacetate/Methanol, 2:0.4); mp: 205–207°C; IR (cm^{-1}): 3457, 3165, 2952, 1644, 1391, 1231, 1033; ^{1}H NMR(DMSO-d_6): 2.48–2.85 (m, 2H, CH_2N), 3.01–3.51 (m, 8H, pip ring), 4.15 (t, 2H, CH_2O), 6.88 (d, 2H, Ar–H), 6.97 (d, 2H, Ar–H), 7.01–7.37 (m, 5H, Ar–H), 7.82 (s, 2H, $CONH_2$); MS(EI) *m/z*: 326(M + 1); Anal. Calcd. for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91; O, 9.83; Found: C, 70.15; H, 7.14; N, 12.95; O, 9.86.

2-{2-[4-(3-Methylphenyl) piperazin-1-yl] ethoxy} benzamide ($3a_2$)

Yield: 0.54 g (31.95%); R_f: 0.28 (Ethylacetate/Methanol, 2:0.4); mp: 189–190°C; IR (cm^{-1}): 3458, 3163, 2889, 1648, 1390, 1228, 1033; ^{1}H NMR (DMSO-d_6): 2.31 (s, 3H, CH_3), 2.48–2.85 (m, 2H, CH_2N), 3.02–3.51 (m, 8H, pip ring), 4.15 (t, 2H, CH_2O), 6.88 (d, 2H, Ar–H), 6.97 (d, 2H, Ar–H), 7.02–7.48 (m, 4H, Ar–H), 7.82 (s, 2H, $CONH_2$); Anal.Calcd.for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.42; N, 12.38; O, 9.43; Found: C, 70.79; H, 7.43; N, 12.39; O, 9.41.

2-{2-[4-(4-Methylphenyl) piperazin-1-yl] ethoxy} benzamide ($\mathbf{3a_3}$)

Yield: 0.40 g (23.6%); R_f: 0.31 (Ethylacetate/Methanol, 2:0.4); mp:185–187°C; IR (cm^{-1}): 3389, 3188, 2885, 1643, 1390, 1238, 1035; ^{1}H NMR (DMSO-d_6): 2.32 (s, 3H, CH_3), 2.65–2.68 (m, 2H, CH_2N), 3.10–3.55 (m, 8H, pip ring),

4.15 (t, 2H, CH_2O), 6.88 (d, 2H, Ar–H), 6.97(d, 2H, Ar–H), 7.00–7.37 (m, 4H, Ar–H), 7.82 (s, 2H, $CONH_2$); Anal. Calcd. for $C_{20}H_{25}N_3O_2$: C, 70.79; H, 7.43; N, 12.38; O, 9.43; Found: C, 70.77; H, 7.40; N, 12.35; O, 9.40.

2-{2-[4-(2-Methoxyphenyl) piperazin-1-yl] ethoxy} benzamide (**3a$_4$**)

Yield: 0.31 g (17.5%); R_f: 0.59 (Ethylacetate/Methanol, 2:0.4); mp: 181–183°C; IR (cm^{-1}): 3377, 3177, 2883, 1641, 1400, 1237, 1023; ^{1}H NMR (δppm, DMSO-d_6): 2.48–2.97 (m, 2H, CH_2N), 3.00–3.59 (m, 8H, pipring), 3.97 (s, 3H, OCH_3), 4.15 (t, 2H, CH_2O), 6.88 (d, 2H, Ar–H), 6.98 (d, 1H, Ar–H), 7.00–7.32 (m, 5H, Ar–H), 7.82 (s, 2H, $CONH_2$); Anal.Calcd.for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82; O, 13.50; Found: C, 67.61; H, 7.13; N, 11.83; O, 13.48.

2-{2-[4-(3-Methoxyphenyl) piperazin-1-yl] ethoxy} benzamide (**3a$_5$**)

Yield: 0.38 g (22.0%); R_f: 0.46 (Ethylacetate/Methanol, 2:0.4); mp: 178–180°C; IR (cm^{-1}): 3392, 3193, 2875, 1638, 1393, 1235, 1047; ^{1}H NMR (δppm, DMSO-d_6): 2.55–2.98 (m, 2H, CH_2N), 3.01–3.54 (m, 8H, pipring), 3.94 (s, 3H, OCH_3), 4.15 (t, 2H, CH_2O), 6.88 (d, 2H, Ar–H), 6.87 (d, 2H, Ar–H), 7.02–7.58 (m, 4H, Ar–H), 7.82 (s, 2H, $CONH_2$); Anal. Calcd. for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82; O, 13.50; Found: C, 67.60; H, 7.10; N, 11.83; O, 13.49.

2-{2-[4-(2-Chlorophenyl) piperazin-1-yl] ethoxy} benzamide (**3a$_6$**)

Yield: 0.44 g (24.580%); R_f: 0.47 (Ethylacetate/Methanol, 2:0.4); mp: 154–156°C; IR (cm^{-1}): 3457, 3162, 2887, 1644, 1389, 1229, 1033; ^{1}H NMR (δppm, DMSO-d_6): 2.47–2.97 (m, 2H, CH_2N), 3.00–3.59 (m, 8H, pipring), 4.15 (t, 2H, CH_2O), 6.87 (d, 2H, Ar–H), 6.99 (d, 1H, Ar–H), 7.0–7.37 (m, 5H, Ar–H), 7.82 (s, 2H, $CONH_2$); Anal. Calcd. for $C_{19}H_{22}ClN_3O_2$: C, 63.42; H, 6.16; N, 11.68; O, 8.89; Found: C, 63.43; H, 6.17; N, 11.69; O, 8.88.

2-[3-(4-Phenylpiperazin-1-yl) propoxy] benzamide (**3b$_1$**)

Yield: 0.26 g (30.95%); R_f: 0.30 (Ethylacetate/Methanol, 2:0.4); mp: 150–152°C, IR (cm^1): 3375, 3176, 2931, 1648, 1390, 1238, 1035; ^{1}H NMR (δppm, DMSO-d_6): 1.92–1.95 (m, 2H, CH_2), 2.21–2.97 (m, 2H, CH_2N), 3.00–3.59 (m, 8H, pipring), 4.12 (t, 2H, CH_2O), 6.84 (d, 2H, Ar–H), 6.97 (d, 2H, Ar–H), 7.01–7.30 (m, 5H, Ar–H), 7.82 (s, 2H, $CONH_2$); Anal. Calcd. for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.42; N, 12.38; O, 9.43; Found: C, 70.79; H, 7.43; N, 12.39; O, 9.42.

2-{3-[4-(2-Methoxyphenyl) piperazin-1-yl] propoxy} benzamide (**3b$_2$**)

Yield: 0.28 g (30.43%); R_f: 0.38 (Ethylacetate/Methanol, 2:0.4); mp: 143–145°C, IR (cm^1): 3375, 3176, 2931, 1648, 1390, 1238, 1035; ^{1}H NMR (δppm, DMSO-d_6): 1.92–2.21 (m, 2H, CH_2), 2.35–2.97 (m, 2H, CH_2N), 3.00–3.59 (m, 8H, pipring), 3.97 (s, 3H, OCH_3), 4.12 (t, 2H, CH_2O), 6.88 (d, 2H, Ar–H), 6.98 (d, 1H, Ar–H), 7.00–7.45 (m, 5H, Ar–H), 7.81 (s, 2H, $CONH_2$); Anal.Calcd.for $C_{21}H_{27}N_3O_3$: C, 68.27; H, 7.37; N, 11.37; O, 12.99; Found C, 68.24; H, 7.39; N, 11.36; O, 12.98.

2-[4-(4-Phenylpiperazin-1-yl) butoxy] benzamide (**3c$_1$**)

Yield: 0.24 g (27.27%); R_f: 0.39 (Ethylacetate/Methanol, 2:0.4); mp: 184–186°C, IR (cm^{-1}): 3457, 3162, 2968, 1641, 1389, 1229, 1033; ^{1}H NMR (δppm, DMSO-d_6): 1.20–1.28 (m, 4H, CH_2CH_2), 2.68–2.71 (m, 2H, CH_2N), 3.09–3.48 (m, 8H, pipring), 4.10 (t, 2H, CH_2O), 6.88 (d, 2H, Ar–H),6.98 (d, 2H, Ar–H), 7.00–7.45 (m, 5H, Ar–H), 7.81 (s, 2H, $CONH_2$); Anal.Calcd.for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.89; O, 9.05; Found: C, 71.34; H, 7.73; N, 11.86; O, 9.02.

2-{4-[4-(2-Methoxyphenyl) piperazine-1-yl] butoxy} benzamide (**3c$_2$**)

Yield: 0.38 g (40.0%); R_f: 0.57 (Ethylacetate/Methanol, 2:0.4); mp: 175–178°C; IR (cm^{-1}): 3457, 3160, 2968, 1641, 1387, 1229, 1031; ^{1}H NMR (δppm, DMSO-d_6): 1.24–1.28 (m, 4H, CH_2CH_2), 2.68–2.71 (m, 2H, CH_2N), 3.09–3.48 (m, 8H, pipring), 3.86 (s, 3H, OCH_3Ar), 4.10 (t, 2H, CH_2O), 6.88 (d, 2H, Ar–H), 6.98 (d, 1H, Ar–H), 7.00–7.45 (m, 5H, Ar–H), 7.81 (s, 2H, $CONH_2$); Anal.Calcd.for $C_{22}H_{29}N_3O_3$: C, 68.90; H, 7.62; N, 10.96; O, 12.52; Found C, 68.92; H, 7.60; N,10.97; O,12.51.

Preliminary pharmacological evaluation

All the target compounds were subjected to preliminary pharmacological evaluation to determine their ability to antagonize apomorphine-induced climbing behavior, inhibition of 5-hydroxy tryptophan (5-HTP)-induced head twitches behavior (Chung *et al.*, 2002) and catalepsy studies (Pemminati *et al.*, 2007; Ferre *et al.*, 1990). Prior permission of the Animal Ethics Committee was obtained, and all the experiments were conducted according to the approved protocol (837/ac/04/CPCSEA). Clozapine and haloperidol groups were employed as a standard (positive

control). Statistical analysis of the results in the test group was done by comparison with the results in the control group employing non-parametric Kruskal–Wallis test or one way ANOVA (Jandel Sigmastat version 2.0). Level of significance was fixed at $P < 0.05$.

Apomorphine-induced mesh climbing assay

Swiss albino mice (six mice in each group) of either sex (24–26 g) were habituated by individually placing in a circular cage made of wire mesh of diameter 13 cm and height 14 cm. Mice in the test, control, and standard groups were injected, respectively, with test compounds, normal saline, and clozapine intraperitoneally and returned to the home cage. After a gap of 10 min, apomorphine (2.5 mg/kg) was injected intraperitoneally. Mesh-climbing behavior was noted at 5-min intervals for up to 20 min, starting 10 min after the apomorphine administration using the following scoring system: 0-no paws on the cage, 1-one paw on the cage, 2-two paws on the cage, 3-three paws on the cage, 4-four paws on the cage (Fig. 1). The score recorded for each animal was based on the position of the animal at the moment it was first observed.

Antagonism of 5-Hydoxytryptophan (5-HTP)-induced head twitches

Swiss albino mice in the control group ($n = 6$) were injected with pargyline (75 mg/kg) to prevent the rapid degradation of 5-HTP. Thirty minutes later, the test compound was administered. After a further 30 min, the mice received 5-HTP (50 mg/kg, sc). The mice were returned to the test cages and then head twitches were counted for 2 min at 10 min intervals for 30 min, starting 20 min after the 5-HTP treatment (Fig. 2).

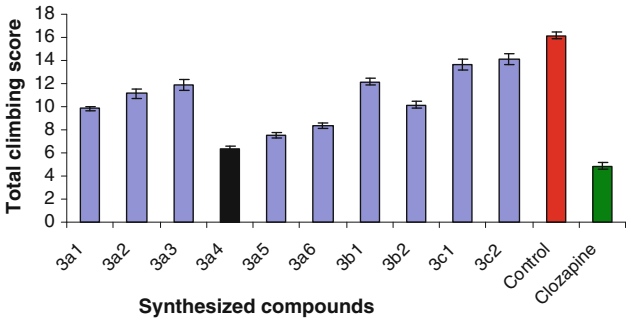

Fig. 1 Apomorphine-induced mesh climbing assay. The effects of synthesized compounds (**$3a_1$–$3a_6$, $3b_1$–$3b_2$, and $3c_1$–$3c_2$**) on the apomorphine-induced climbing behavior. Each column represents the mean ± SEM of total climbing score for group of six mice assessed at 5-min intervals for 20 min, starting 10 min after apomorphine treatment. A score of 20 is the maximum possible. All values statistically significant with respect to control at $P < 0.05$

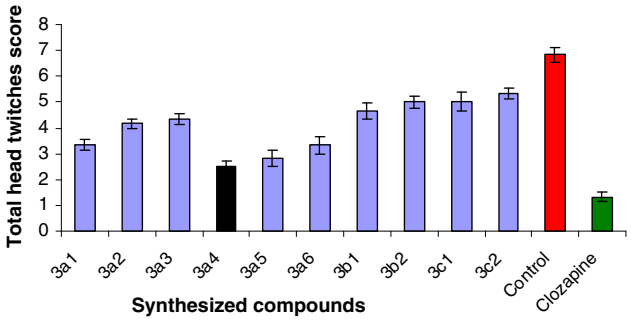

Fig. 2 Antagonism of 5-Hydoxytryptophan (5-HTP)-induced head twitches. The effect of synthesized compounds (**$3a_1$–$3a_6$, $3b_1$–$3b_2$,** and **$3c_1$–$3c_2$**) on the 5-HTP-induced head twitches behavior. Each column represents the mean ± SEM of total head twitches score for group of six mice assessed at 10-min intervals for 30 min, starting 20 after the 5-HTP treatment. A score of 8 is the maximum possible. All the values are statistically significant with respect to control at $P < 0.05$

Catalepsy

Catalepsy was induced in albino mice ($n = 6$) with haloperidol (1.0 mg/kg, i.p.) and was assessed at 30-min intervals until 120 min and at the end of 240 min by means of a standard bar test. Catalepsy was assessed in terms of the time(s) for which the mouse maintained an imposed position with both front limbs extended and resting on a 4-cm-high wooden bar (1.0 cm diameter). The endpoint of catalepsy was considered to occur when both front paws were removed from the bar, or if the animal moved its head in an exploratory manner. Severity of the cataleptic behavior was scored as 1 if it maintained the imposed posture for at least 20 s and for every additional 20 s, one extra point was given (Fig. 3).

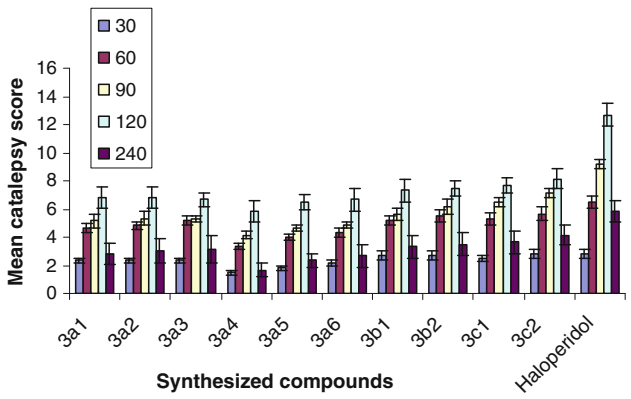

Fig. 3 Induction of catalepsy. The effect of synthesized compounds (**$3a_1$–$3a_6$, $3b_1$–$3b_2$,** and **$3c_1$–$3c_2$**) on induction of catalepsy in mice. Results are expressed as the mean ± SEM ($n = 6$). All the values are statistically significant with respect to control at $P < 0.05$

Results and discussion

Synthesis

The new arylpiperazines were prepared using the pathway shown in Scheme 1. The substituent of the compounds is given in Table 1. The target compounds were prepared by a two-step procedure: alkylation of salicylamide (**1**) with dihaloalkanes (1,2-dibromoethane, 1-bromo-3-chloropropane and 1,4-dibromobutane) in acetonitrile in the presence of potassium carbonate, followed by condensation of intermediates (**2a**, **2b**, and 2c) with substituted phenylpiperazines in dimethylformamide in the presence of potassium carbonate and potassium iodide as catalyst afforded the target compounds (**3a$_1$**–**3a$_6$**, **3b$_1$**–**3b$_2$**, and **3c$_1$**–**3c$_2$**). All the target compounds were obtained in low yield (17.5–40%) and characterized by analytic and spectroscopic methods. The reaction progress was monitored by thin-layer chromatography (TLC) using silica gel G, and spots were visualized in an iodine chamber.

Computation of physicochemical properties

A set of molecular parameters was computed for the target compounds as well as three standard drugs, clozapine, ketanserin and risperidone, using Chem 3D Ultra version, 11.0, and Chem Silico online free software, which is shown in Table 2. The important molecular parameters for antipsychotics are blood–brain barrier (BBB), log P, and topological polar surface area (TPSA). The review of the existing literature suggests that TPSA is a measure of a molecule's hydrogen bonding capacity, and its value should not exceed certain limit if the compound is intended to be CNS active. Two differing limits have been proposed: van de Waterbeemed *et al.* (1998) suggested a limit of 90 A^2, where, Kelder *et al.* (1999) suggested 60–70 A^2. The TPSA value for test compounds were well within these limits (58.8–68.03), showing that these compounds have a potential to effectively cross the BBB. Further, lipophilicity correlates positively with BBB penetration, and the values of log P for most of our test compounds were very close to the marketed drugs (2.52–3.2).

Table 1 Substituent of compounds

Cpd. code	*n*	R
3a$_1$	2	H
3a$_2$	2	3–CH_3
3a$_3$	2	4–CH_3
3a$_4$	2	2–OCH_3
3a$_5$	2	3–OCH_3
3a$_6$	2	2–Cl
3b$_1$	3	H
3b$_2$	3	2–OCH_3
3c$_1$	4	H
3c$_2$	4	2–OCH_3

Similarity calculations

The physicochemical similarity of the target compounds was calculated with respect to the standard drugs (Bali *et al.*, 2010) and is shown in Table 3.

First, the distance d_i of a particular target compound j to drug molecules, e.g., clozapine was calculated by the formula:

$$d_i^2 = \sum_{j=1}^{n} \left(1 - X_{i,j}/X_{i,\mathrm{std}}\right)^2/n$$

where, $X_{i,j}$ is the value of molecular parameter "*i*" for compound "*j*," $X_{i,\mathrm{std}}$ is the value of the same molecular parameter for the standard drug, e.g., clozapine, ketanserin, and risperidone. Then, the similarity of compound "*j*" to the standard drug was calculated as:

Scheme 1 Synthesis route of the target compounds

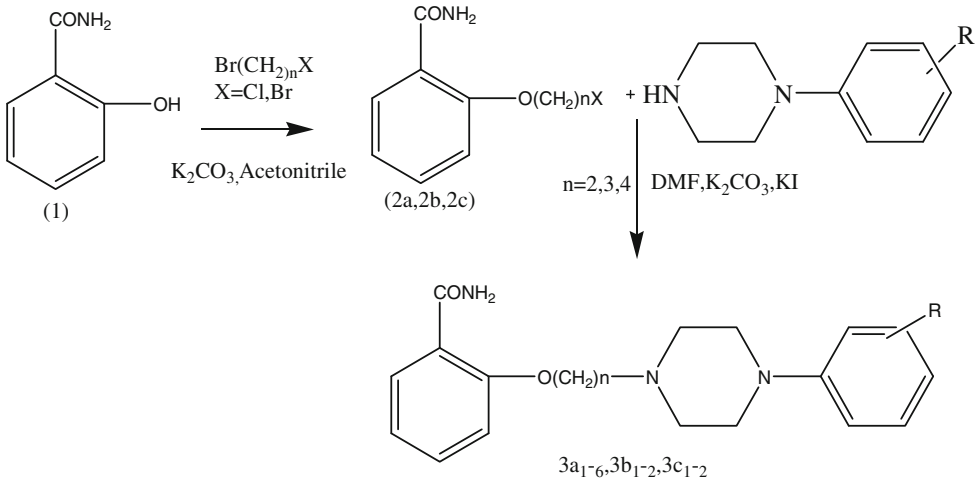

Table 2 Calculation of molecular properties and log BB values for target compounds and standard drugs

Cpd. code	Log BB[j]	Log P	M.W[a]	MR[b]	SAS[c] (A^2)	MSA[d] (A^2)	SEV[e] (A^2)	TPSA[f]	MTI[g]	WI[h]	Ov[i]
3a$_1$	0.23	2.64	325.40	96.5	596.869	314.792	281.008	58.8	12122	1607	1.5172
3a$_2$	0.16	3.13	339.43	102.4	628.141	333.488	297.919	58.8	13585	1798	1.5459
3a$_3$	0.16	3.13	339.43	102.4	628.116	333.469	297.902	58.8	13722	1816	1.5459
3a$_4$	−0.02	2.52	355.43	103.75	635.134	338.812	304.225	68.03	14615	1978	1.5488
3a$_5$	−0.15	2.52	355.43	103.75	641.975	340.692	304.338	68.02	14853	2014	1.5570
3a$_6$	0.16	3.2	359.85	101.11	608.65	324.119	292.986	58.8	12926	1780	1.5193
3b$_1$	0.18	2.75	339.43	101.1	629.429	333.603	298.018	58.8	14070	1864	1.5461
3b$_2$	−0.12	2.62	369.46	108.35	667.699	357.203	320.803	68.03	16827	2274	1.5761
3c$_1$	0.11	3.2	353.46	105.7	660.925	352.171	314.99	58.8	16211	2146	1.5730
3c$_2$	−0.26	3.08	383.48	112.95	699.174	376.186	338.223	68.03	19246	2597	1.6024
CLZ[k]	0.75	3.71	326.82	94.58	508.991	259.124	215.892	30.87	8127	1082	1.4889
KET[l]	−0.48	2.37	395.43	106.67	589.34	298.729	253.386	69.72	18646	2596	1.542
RIS[m]	−0.20	2.10	410.48	114.21	690.021	375.09	351.81	57.5	20311	2793	1.5563

[a] Molecular weight

[b] Molar refractivity

[c] Connolly solvent accessible surface area

[d] Connolly molecular surface area

[e] Connolly solvent excluded volume

[f] Topological polar surface area

[g] Molecular topological index

[h] Wienner index

[i] Ovality

[j] Calcd. online (Chemsilico.com/CS_prBBB/BBBdata.html)

[k] Clozapine

[l] Ketaserin

[m] Risperidone

Table 3 Similarity values of target compounds with respect to the standard drugs

Cpd. code	Similarity[ab] (in %) to		
	Clozapine	Ketanserin	Risperidone
3a$_1$	57.23	79.15	59.55
3a$_2$	50.03	81.86	83.57
3a$_3$	49.47	82.14	80.23
3a$_4$	37.62	85.03	82.05
3a$_5$	36.48	85.36	82.63
3a$_6$	52.26	81.97	78.99
3b$_1$	47.97	82.81	80.91
3b$_2$	26.48	85.99	65.80
3c$_1$	37.14	87.22	86.95
3c$_2$	13.29	83.41	92.30

[a] $(1 - R) \times 100$ where $R =$ Quadratic mean (Root mean square mean)

[b] Calcd. from physicochemical properties: Molecular weight; Molar refractivity; Connolly solvent accessible surface area; Connolly molecular surface area; Connolly solvent excluded volume; Topological polar surface area; Molecular topological index; Wiener index

Similarity (%) $= (1-R) \times 100$, where $R = \sqrt{d^2}$ is the quadratic mean (root mean square), a measure of central tendency. The target compounds showed good structural similarity with respect to standard drugs (13.29–92.30%).

Preliminary pharmacological evaluation for antipsychotic effect

The results from the pharmacological evaluation of the target compounds are given in Table 4 and depicted graphically in Figs. 1, 2, and 3. All the ligands showed significant interactions with the D_2 and 5-HT_{2A} receptors, which were found to be dependent, fundamentally on the substitution of the N^4-aryl group of the piperazine ring. The compounds possessing methoxy group (**3a$_4$** and **3a$_5$**) at ortho and meta positions of aryl moiety of piperazine produced statistically significant reversal of apomorphine-induced climbing behavior than chloro analog (**3a$_6$**). A significant reduction in activity was observed, when methyl group was present at meta and para positions of aryl moiety of piperazine (**3a$_2$** and **3a$_3$**). Other compounds (**3a$_1$**,

Table 4 Potential for atypical antipsychotic activity in vivo

Cpd. code	Inhibition of apomorphine-induced climbing behavior (ED_{50}, mg/kg, i.p.)	Inhibition of 5-HTP-induced head twitches behavior ($ED_{50,}$ mg/kg, i.p.)	Induction of catalepsy (ED_{50}, mg/kg, i.p.)
$3a_1$	35.3	30	50
$3a_2$	40.0	>20	70
$3a_3$	40.5	27.2	>80
$3a_4$	40.0	10.0	100
$3a_5$	>40	25.0	>80
$3a_6$	>40	>20	>80
$3b_1$	>40	>20	>60
$3b_2$	50.0	18.2	>60
$3c_1$	>40	>40	>60
$3c_2$	50.8	>40	>70
Clozapine	8.7	2.8	–
Haloperidol	–	–	nd[a]

[a] *nd* Not determined, 1 mg/kg dose was used

$3b_1$–$3b_2$, and **$3c_1$–$3c_2$**,) have lesser interaction at the D_2 receptor. The data also revealed that the compounds with alkyl side chain length $n = 2$ showed better activity than compounds with chain length $n = 3$ and 4. The study on inhibition of 5-HTP-induced head twitches behavior (5-HT_{2A} antagonism) showed that methoxy analogs (**$3b_4$**) with shorter alkyl side chain ($n = 2$) produced more significant activity than chloro analog (**$3a_6$**). The methyl analogs (**$3a_2$** and **$3a_3$**) showed lesser interaction with receptor. The data also revealed that compounds with alkyl side chain length $n = 2$ showed better activity than compounds with chain length $n = 3$ and 4. The catalepsy results showed that all the new compounds were less cataleptogenic than haloperidol. Among them ortho-methoxy analogs (**$3a_4$**) exhibited lower propensity to produce catalepsy.

Conclusion

A new series of arylpiperazines have been synthesized, and their preliminary pharmacological evaluation has shown potential atypical antipsychotic effect. The results suggest that the presence of methoxy group in the phenyl group of piperazine ring and compound with shorter alkoxy side chain ($n = 2$) increased the atypical antipsychotic activity (higher D_2 antagonistic and 5-HT_{2A} antagonistic activity) with minimum induction of catalepsy. Test compounds have shown good similarity with respect to the standard drugs. The log BB, TPSA, and log P values indicate that these have a good potential to penetrate the blood brain barrier and show CNS activity. The compound **$3a_4$** emerged as potential atypical antipsychotic effect and showed maximum similarity to ketanserin (85.03%).

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Competing Interests The authors declare no conflict of interest.

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