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Preliminary communication

Synthesis, computational studies and preliminary pharmacological evaluation of 2–[4-(aryl substituted) piperazin-1-yl] N, N-diphenylacetamides as potential antipsychotics

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ABSTRACT

A series of 2-[4-(aryl substituted) piperazin-1-yl] N, N-diphenylacetamides have been synthesized and the target compounds (**3a**–**j**) were evaluated for atypical antipsychotic activity in apomorphine induced climbing, 5-HTP induced head twitches behavior and catalepsy studies in mice. The physicochemical similarity of the target compounds with respect to standard drugs clozapine, ketanserin and risperidone was calculated by using software programs. Among them, compound **3e** showed maximum atypical antipsychotic like profile.

1. Introduction

Schizophrenia is a complex psychological disorder affecting about 1% of the population worldwide [1,2]. The use of classical antipsychotics (phenothiazines, haloperidol, etc.) for the treatment of schizophrenia is associated with severe mechanism related side effects including induction of acute extra pyramidal symptoms [3,4]. Classical or typical antipsychotics share the ability to block D_2 dopamine receptor and their effectiveness in the treatment of positive symptoms of schizophrenia [5]. The adverse effects presented by classical antipsychotics, along with their ineffectiveness in the treatment of negative symptoms of schizophrenia has encouraged the search for atypical antipsychotic drugs. 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 [6]. The mechanism of their action is still controversial, since there are several models explaining 'atypicality' by specific drug action on subclasses of serotonergic, glutamatergic, muscarinic or α-adrenergic receptors. It was hypothesized that a combination of serotonin 5-HT_2 and dopamine D_2 receptor antagonism to play critical role in the mechanism of action of atypical antipsychotic drugs. This so-called 'serotonin-dopamine' hypothesis has become a useful model for developing new antipsychotics to achieve superior efficacy with a lower incidence of extra pyramidal side effects compared to classical antipsychotics [7,8]. This model suggests the ratio of 5-HT_{2A} to D_2 receptor affinities to be the major determinant of a drug's possibility to behave as an atypical antipsychotic [9]. Arylpiperazine derivatives display diverse pharmacological activity which can be mediated by different subpopulations of serotonin, dopamine and aderenergic receptors [10–15]. Their general chemical structure consists of the arylpiperazine moiety connected by an alkyl chain with the terminal amide or imide fragment (Chart 1) [16–21]. In view of these observations, we herein report the synthesis, computational studies of some new arylpiperazines and evaluate them for a possible atypical antipsychotic potential.

2. Results and discussion

2.1. Synthesis of compounds

The new arylpiperazines were prepared using the pathway shown in Scheme 1. The substituent of the compounds is given in

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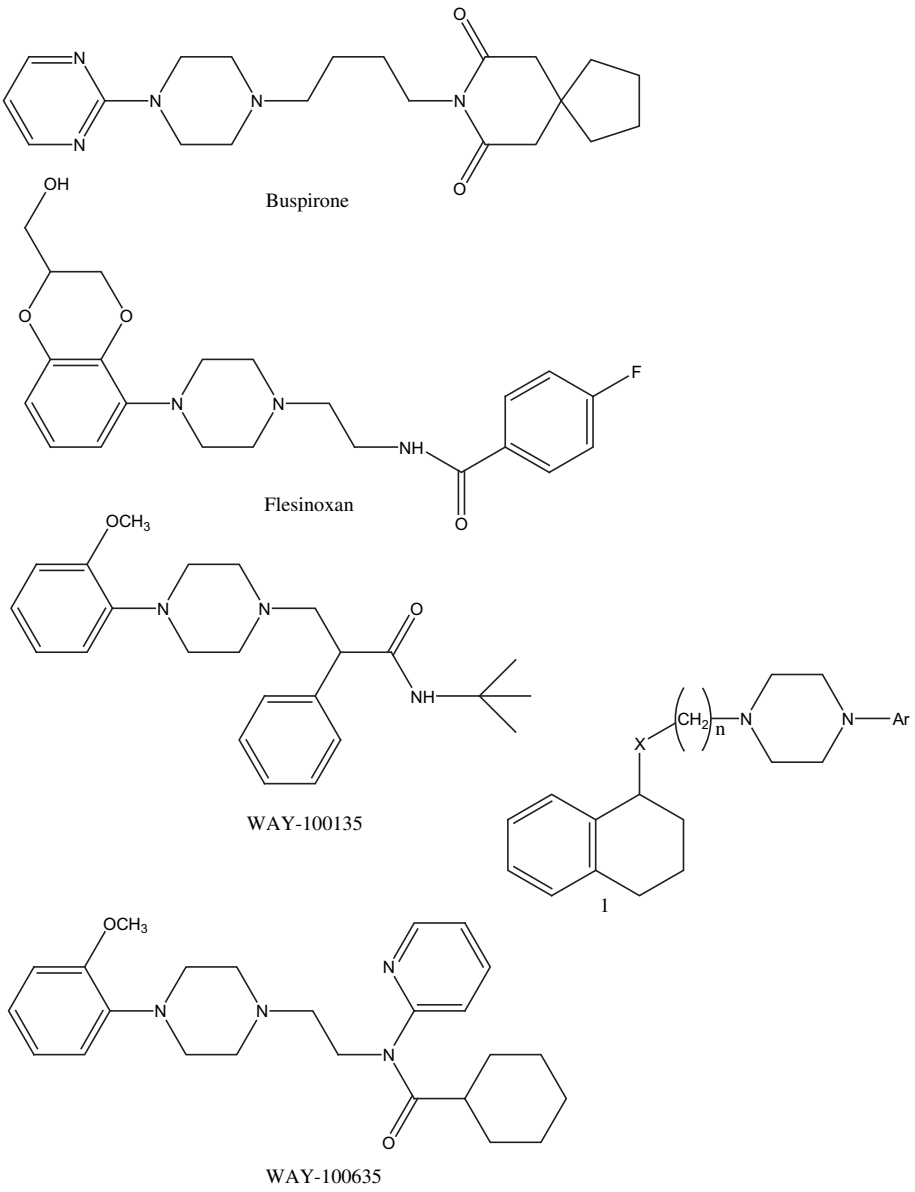
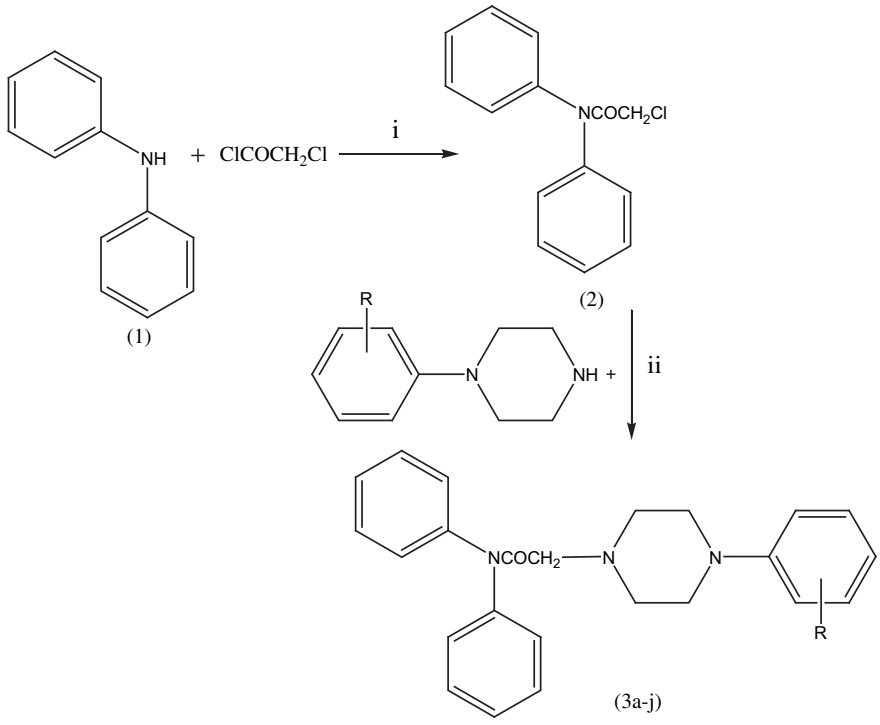


Chart 1. Structure of some amide and imides based arylpiperazines.

Table 1. The target compounds (**3a**–**j**) were prepared by a two-step procedure: chloroacetylation of diphenylamine (**1**) in toluene, followed by condensation of intermediate (**2**) with substituted phenylpiperazines in acetonitrile in the presence of K_2CO_3 and KI as catalyst. All the reactions were monitored by TLC. The target compounds were obtained in good yields (46–76%). The structural assignments to new compounds were based through analytical and spectroscopic data. In the IR spectrum of compound **2** a peak at 1678 cm^{-1} assigned to C=O str and the appearance of a new band at 695 cm^{-1} due to C–Cl str along with the absence of band at 3240 cm^{-1} due to NH str. The NMR spectrum showed a characteristic singlet peak at δ 4.02 indicated its formation. The target compounds (**3a**–**j**) were confirmed by the absence of C–Cl str at 695 cm^{-1}, presence of C=O str at 1673–1685 cm^{-1}, C–N str (aliphatic) at 1217–1237 cm^{-1}, C–N str (aromatic) at 1448–1496 and by the presence of singlet proton at δ 4.47–4.58 (2H, $COCH_2$) in the proton NMR. Mass spectra of the target compounds exhibited characteristic M + 1 peak.

2.2. 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 are shown in Table 2. The important molecular parameters for antipsychotics are blood–brain barrier (BBB), log P and topological polar surface area (TPSA) [22,23]. Literature review suggested 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. [24] suggested a limit of 90 A^2, where, Kelder et al. [25] suggested 60–70 A^2. The TPSA value for test compounds were well within these limits (26.79–78.60) which shows that these compounds have a potential to effectively cross the blood–brain barrier. The log BB values (0.01–0.41) and log *P* values (4.04–5.6) for the compounds were noted and suggesting that these have an excellent potential for CNS activity.



Scheme 1. Synthesis of the target compounds. Reagents and condition: (i) toluene, reflux, 4 h (ii) Acetonitrile, K_2CO_3, KI.

2.3. Similarity calculations

The physicochemical similarity of the target compounds was calculated with respect to the standard drugs [26] and is shown in Table 3.

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

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

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:

Similarity $(\%) = (1 - R) \times 100$. where $R = \sqrt{d^2}$ is the quadratic mean (root mean square), a measure of central tendency. Similarity of target compounds was noted less with respect to clozapine. However, a much higher similarity was found with respect to ketanserin and risperidone. Among them, compounds **3e** and **3f** showed maximum structural similarity with respect to risperidone (86.33% and 86.39%).

Table 1
Substituent of compounds **3a**–**j**.

Cpd. no.	Cpd. code	R
1	3a	H
2	3b	4-CH_3
3	3c	2,3-CH_3
4	3d	3-CF_3
5	3e	2-OCH_3
6	3f	3-OCH_3
7	3g	3-Cl
8	3h	3,4-Cl
9	3i	4-F
10	3j	4-NO_2

2.4. Preliminary pharmacological evaluation for atypical antipsychotic effect

All the target compounds were subjected to preliminary pharmacological evaluation to determine their ability to inhibition of apomorphine induced climbing behavior, inhibition of 5-hydroxy tryptophan (5-HTP) induced head twitches behavior [27–30] and catalepsy studies [31–33]. Prior permission of the Animal Ethics Committee was obtained and all experiments were conducted according to the approved protocol (837/ac/04/CPCSEA). Clozapine and haloperidol groups were employed as 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 $p < 0.05$. The results from the pharmacological evaluation of the target compounds are given in Table 4 and depicted graphically in Figs. 1–3. All ligands showed significant interactions with the dopamine and serotonin receptors, which were found to be dependent, fundamentally on the substitution of N-aryl group of piperazines. With respect to dopamine receptor, the compounds **3e** and **3f** ($ED_{50} = 8.2$ and 10.0 mg/kg, respectively) possessing methoxy group at ortho and meta position of aryl group of piperazine showed statistically significant reversal of apomorphine induced climbing behavior than chloro, trifluoromethyl and dichloro analogs **3g, 3d and 3h** ($ED_{50} = 16.5$, 21.3 and 24.0 mg/kg, respectively). The analogs **3a** and **3i** ($ED_{50} = 20.5$ and 13.4 mg/kg, respectively) exhibited a modest interaction for dopamine receptor. Significant reduction in activity was observed, when methyl, dimethyl and nitro group was present at aryl moiety of piperazine **3b**, **3c** and **3j** ($ED_{50} > 20$, 28.5, and 30.0 mg/kg, respectively). Regarding the inhibition of 5-HTP induced head twitches study showed that ortho and meta-methoxy analogs **3e and 3f** ($ED_{50} = 12.7$ and 15.5 mg/kg, respectively) produced significant activity than chloro, trifluoromethyl and dichloro analogs **3g, 3d and 3h** ($ED_{50} = 18.0$, 30.0 and >20.0 mg/kg, respectively). The

Table 2
Calculation of molecular properties 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	0.25	4.49	371.47	113.32	641.894	344.355	308.409	26.79	17130	2193	1.5599
3b	0.36	4.98	385.50	119.22	582.422	313.211	291.582	26.79	19148	2450	1.4729
3c	0.39	5.46	399.53	125.12	679.816	371.123	336.247	26.79	20677	2644	1.5870
3d	0.41	5.41	439.47	119.83	690.253	373.577	335.839	26.79	22826	3226	1.5988
3e	0.21	4.36	401.50	120.57	676.270	367.637	333.074	36.02	20277	2648	1.5821
3f	0.27	4.36	401.50	120.57	687.020	370.267	331.754	36.02	20575	2692	1.5976
3g	0.32	5.05	405.92	117.93	666.463	359.201	322.774	26.79	18269	2428	1.5785
3h	0.33	5.60	440.36	122.53	686.713	372.494	336.839	26.79	19519	2688	1.5910
3i	0.31	4.65	389.47	113.73	648.109	348.009	311.631	26.79	18374	2450	1.5655
3j	0.01	4.04	416.47	119.57	686.144	371.220	332.383	78.60	22209	3024	1.5997
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	589.340	298.729	253.386	69.72	18646	2596	1.5420
RIS[m]	−0.20	2.10	410.48	114.21	690.021	375.090	351.810	57.50	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 [35].
[k] Clozapine.
[l] Ketanserin.
[m] Risperidone.

fluoro analog **3i** ($ED_{50} = 20.0$ mg/kg) exhibited a modest interaction for serotonin receptor than the methyl, dimethyl analogs **3b** and **3c** ($ED_{50} = 31.2$ and >30.0 mg/kg, respectively) suggesting a potential steric effect of the phenyl ring in the binding site. Nitro analog **3j** ($ED_{50} > 40.0$ mg/kg) showed lowest activity with serotonin receptor. The catalepsy results showed all the new compounds were less cataleptogenic than haloperidol. Among them, methoxy analogs **3e and 3f** ($ED_{50} = 50.4$ and 55.5 mg/kg, respectively) exhibited lower propensity to produce catalepsy.

3. Conclusion

A new series of arylpiperazines have been synthesized and their preliminary pharmacological evaluation has shown potential atypical antipsychotic effect in animal models. However, in vivo results are insufficient for prediction of an atypical antipsychotic profile with similar to clozapine. Among the compounds, **3e** has shown potent atypical antipsychotic activity probably by inhibition of dopamine D_2 and serotonin 5-HT_2 receptors and low induction of catalepsy. Moreover, TPSA, log BB, log P values suggested that this compound has the potential to penetrate the blood–brain barrier and showed good similarity with respect to standard drugs, particularly risperidone. Further studies on this lead including in vitro assays are required for the refinement of the atypical antipsychotic activity.

4. Experimental

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 discs on Perkin Elmer RX1. The ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 spectrophometer (^1H at 300 MHz and ^{13}C at 75 MHz) in $CDCl_3$ containing TMS as an internal standard. The signals are quoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet and are expressed in δ ppm. Elemental analyses were performed on Perkin Elmer 2400 analyzer. The mass spectra were recorded on a Micromass Quattro II triple

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

Cpd.Code.	Similarity[a,b] (in %) to		
	Clozapine	Ketanserin	Risperidone
3a	41.72	75.10	77.86
3b	32.69	77.01	77.91
3c	18.99	72.37	80.61
3d	0.22	70.12	79.56
3e	20.44	76.74	86.33
3f	16.61	76.45	86.39
3g	31.70	74.29	79.90
3h	20.78	72.28	80.61
3i	32.24	75.57	79.56
3j	8.15	81.27	86.04

[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.

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	20.5	27.0	50
3b	>20	31.2	>40
3c	28.5	>30	>40
3d	21.3	30.0	48.0
3e	8.2	12.7	50.4
3f	10.0	15.5	55.4
3g	16.5	18.0	48.4
3h	24.0	>20	45
3i	13.4	20.0	>40
3j	30.0	>40	>40
Clozapine	8.7	2.8	–
Haloperidol	–	–	nd[a]

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

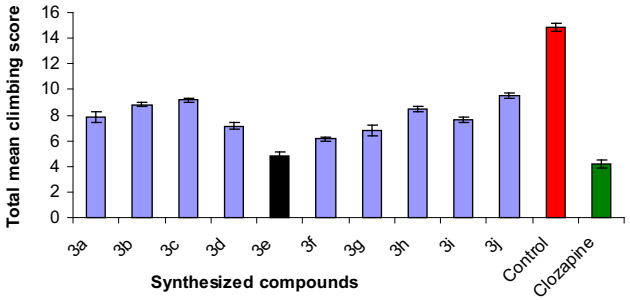


Fig. 1. The effect of synthesized compounds (**3a**–**j**) on climbing behavior induced by apomorphine (2.5 mg/kg, i.p.). Each column represents the mean ± SEM of total climbing score for groups of six mice assessed at 5 min intervals for 20 min, starting 10 min after apomorphine treatment. A score 20 is the maximum possible. Clozapine (ED_{50} 8.7 mg/kg, i.p) was used for comparison with respect to test compounds (**3a**–**j**). $p < 0.05$.

quadrupole mass spectrometer. All reagents were of commercial quality and were used without further purification. The reactions progress was monitored by thin-layer chromatography (TLC) using silica gel G and spots were visualized in an iodine chamber.

4.1. Synthesis of compounds

4.1.1. Synthesis of 2-chloro-N, N-diphenylacetamide (**2**)

Diphenylamine (6.76 g, 0.04 mol) was dissolved in toluene (200 ml) in a 250 ml round bottom flask and chloroacetylchloride (3.18 ml, 0.04 mol) was added. The reaction mixture was refluxed for 4 h. A total of 400 ml of water was then added to the reaction mixture and kept overnight for precipitation of the product, which was filtered, washed with water, dried and recrystallized from ethanol [34]. Yield: 73.49 %. mp: 116–118 °C. $R_f = 0.44$ (Hexane/EtOAc 5:1). IR (KBr, cm^{-1}): 3005, 2942, 1678, 1364, 1263, 695. ^1H NMR (300 MHz; $CDCl_3$) δ: 4.02 (s, 2H); 7.26–7.39 (m, 10H, Ar–H).

4.1.2. General procedure for the synthesis of ***3a–j***

2-Chloro-N, N-diphenylacetamide (1.22 g, 0.005 mol) was dissolved in acetonitrile (100 ml) in a 250 ml round bottom flask, anhydrous K_2CO_3 (0.69 g, 0.005 mol), appropriate arylpiperazine (0.005 mol) and catalytic amount of potassium iodide were added. The above mixture was allowed to reflux with continuous stirring on magnetic stirrer for 10 h. After completion of reaction the solvent was removed by vacuum distillation and residue was dissolved in 1:1 mixture of chloroform and water. The organic layer was separated, washed with brine and dried over $MgSO_4$, removal of the solvent afforded target compounds **3a**–**j**.

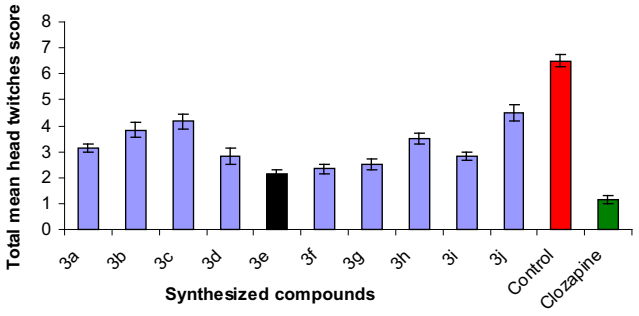


Fig. 2. The effect of synthesized compounds (**3a**–**j**) on the 5-HTP (50 mg/kg, i.p.) induced head twitches behavior. Each column represents the mean ± SEM of total score for groups of six mice assessed at 10 min intervals for 30 min, starting 20 min after the 5-HTP treatment. A score 8 is the maximum possible. Clozapine (ED_{50} 2.8 mg/kg, i.p) was used for comparison with respect to test compounds (**3a**–**j**). $p < 0.05$.

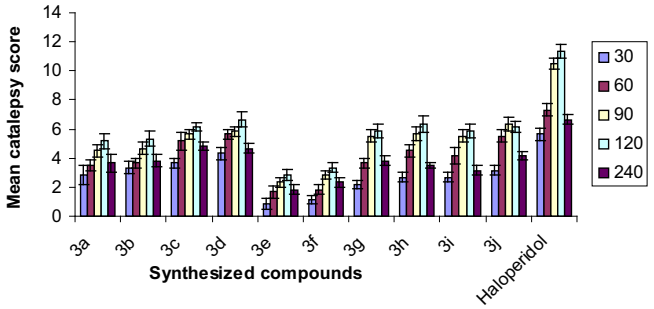


Fig. 3. Induction of catalepsy of synthesized compounds (**3a**–**j**). Haloperidol (1.0 mg/kg, i.p) was used for comparison with respect to test compounds. Results are expressed as the mean ± SEM. ($n = 6$), $p < 0.05$.

*4.1.2.1. 2-[4-(Phenyl) piperazin-1-yl] N, N-diphenyl acetamide (**3a**).* Yield: 76%. mp: 125–127 °C. $R_f = 0.34$ (Hexane/EtOAc 2:1). IR (KBr, cm^{-1}): 3056, 2826, 1673, 1448, 1237. ^1H NMR (300 MHz; $CDCl_3$) δ: 2.64–2.67 (m, 4H, pip ring); 3.15–3.66 (m, 4H, pip ring); 4.56 (s, 2H, $COCH_2$); 6.80–6.90 (m, 6H, Ar–H); 7.20–7.54 (m, 9H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$ δ): 48.92, 53.15, 76.58, 115.91, 116.62, 119.50, 120.25, 127.13, 128.97, 142.31, 151.19, 154.64, 169.29. MS (EI, m/z): 372.2 (M + 1). Anal.Calcd.for $C_{24}H_{25}N_3O$: C, 77.60; H, 6.78; N, 11.31. Found: C, 77.66; H, 6.74; N, 11.35.

*4.1.2.2. 2-[4-(4-Methylphenyl) piperazin-1-yl] N, N-diphenylacetamide (**3b**).* Yield: 72%. mp: 86–88 °C. $R_f = 0.28$ (Hexane/EtOAc 2:1). IR (KBr, cm^{-1}): 3014, 2826, 1674, 1453, 1218. ^1H NMR (300 MHz; $CDCl_3$) δ: 2.25 (s, 3H, CH_3); 2.69–2.97 (m, 4H, pip ring); 3.12- 3.77 (m, 4H, pip ring); 4.47 (s, 2H, $COCH_2$); 6.65–6.72 (m, 6H, Ar–H); 7.10–7.48 (m, 8H, Ar–H). MS (EI, m/z): 386.2 (M + 1). Anal.Calcd.for $C_{25}H_{27}N_3O$: C, 77.89; H, 7.06; N, 10.90. Found: C, 77.85; H, 7.09; N, 10.94.

*4.1.2.3. 2-[4-(2,3-Dimethylphenyl)piperazin-1-yl] N, N-diphenylacetamide (**3c**).* Yield: 60%. mp: 107–109 °C. $R_f = 0.26$ (Hexane/EtOAc 2:1). IR (KBr, cm^{-1}): 3012, 2820, 1675, 1490, 1219. ^1H NMR (300 MHz; $CDCl_3$) δ: 2.18 (s, 3H, CH_3); 2.24 (s, 3H, CH_3); 2.35–2.94 (m, 4H, pip ring); 3.05–3.97 (m, 4H, pip ring); 4.57 (s, 2H, $COCH_2$); 6.64–6.87 (m, 5H, Ar–H); 7.18–7.56 (m, 8H, Ar–H). MS(EI, m/z): 400.2 (M + 1). Anal. Calcd. for $C_{26}H_{29}N_3O$: C, 78.16; H, 7.32; N, 10.52. Found: C, 77.19; H, 7.37; N, 10.49.

*4.1.2.4. 2-[4-(3-Trifluoromethylphenyl) piperazin-1-yl] N, N-diphenylacetamide (**3d**).* Yield: 57%. mp: 60–62 °C. $R_f = 0.27$ (Hexane/EtOAc 2:1). IR (KBr, cm^{-1}): 3016, 2828, 1674, 1490, 1218. ^1H NMR (300 MHz; $CDCl_3$) δ: 2.64–2.67 (m, 4H, pip ring); 3.15–3.66 (m, 4H, pip ring); 4.56 (s, 2H, $COCH_2$); 6.65–6.80 (m, 6H, Ar–H); 7.21–7.35 (m, 8H, Ar–H). MS (EI, m/z): 440.1 (M + 1). Anal. Calcd. for $C_{25}H_{24}F_3N_3O$: C, 68.32; H, 5.50; N, 9.56. Found: C, 68.36; H, 5.54; N, 9.52.

*4.1.2.5. 2-[4-(2-Methoxyphenyl) piperazin-1-yl] N, N-diphenylacetamide (**3e**).* Yield: 48%. mp: 79–81 °C. $R_f = 0.22$ (Hexane/EtOAc 2:1). IR (KBr, cm^{-1}): 3083, 2822, 1685, 1493, 1218. ^1H NMR (300 MHz; $CDCl_3$) δ: 2.64–2.68 (m, 4H, pip ring); 3.15–3.20 (m, 4H, pip ring); 3.78 (s, 3H, OCH_3); 4.57 (s, 2H, $COCH_2$); 6.39–6.52 (m, 6H, Ar–H); 7.04–7.37 (m, 8H, Ar–H); MS (EI, m/z): 402.2 (M + 1). Anal.Calcd.for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47. Found: C, 74.75; H, 6.74; N, 10.49.

*4.1.2.6. 2-[4-(3-Methoxyphenyl) piperazin-1-yl] N, N-diphenylacetamide (**3f**).* Yield: 46%. mp: 110–112 °C. $R_f = 0.24$ (Hexane/EtOAc 2:1). IR (KBr, cm^{-1}): 3083, 2822, 1685, 1493, 1218. ^1H NMR

(300 MHz; $CDCl_3$ δ): 2.64–2.68 (m, 4H, pip ring); 3.15–3.20 (m, 4H, pip ring); 3.77 (s, 3H, OCH_3); 4.57 (s, 2H, $COCH_2$); 6.39–6.52 (m, 6H, Ar–H); 7.04–7.37 (m, 8H, Ar–H); MS (EI, *m*/*z*): 402.2 (M + 1). Anal. Calcd. for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47. Found: C, 74.75; H, 6.79; N, 10.51.

*4.1.2.7. 2-[4-(3-Chlorophenyl) piperazin-1-yl] N, N-diphenylacetamide (**3g**).* Yield: 56%. mp: 102–104 °C. $R_f = 0.32$ (Hexane/EtOAc 2:1). IR (KBr, cm^{-1}): 3016, 2828, 1674, 1490, 1218. ^1H NMR (300 MHz; $CDCl_3$) δ: 2.63–2.66 (m, 4H, pip ring); 3.15–3.20 (m, 4H, pip ring); 4.54 (s, 2H, $COCH_2$); 6.73–6.98 (m, 6H, Ar–H); 7.20–7.36 (m, 8H, Ar–H). MS (EI, *m*/*z*): 406.1 (M + 1). Anal. Calcd. for $C_{24}H_{24}ClN_3O$: C, 71.01; H, 5.96; N, 10.35. Found: 71.07; H, 5.99; N, 10.39.

*4.1.2.8. 2-[4-(3, 4-Dichlorophenyl) piperazin-1-yl] N, N-diphenylacetamide (**3h**).* Yield: 51%. mp: 80–82 °C. $R_f = 0.29$ (Hexane/EtOAc 2:1). IR (KBr, cm^{-1}): 3016, 2829, 1675, 1480, 1219. ^1H NMR (300 MHz; $CDCl_3$) δ: 2.60–2.66 (m, 4H, pip ring); 3.14–20 (m, 4H, pip ring); 4.50 (s, 2H, $COCH_2$); 6.68–6.98 (m, 6H, Ar–H); 7.23–7.48 (m, 7H, Ar–H). MS (EI, *m*/*z*): 440.1 (M + 1). Anal. Calcd. for $C_{24}H_{23}Cl_2N_3O$: C, 65.46; H, 5.26; N, 9.54. Found: C, 65.42; H, 5.28; N, 9.58.

*4.1.2.9. 2-[4-(4-Fluorophenyl) piperazin-1-yl] N, N-diphenylacetamide (**3i**).* Yield: 49%. mp: 96–98 °C. $R_f = 0.21$ (Hexane/EtOAc 2:1). IR (KBr, cm^{-1}): 3021, 2840, 1674, 1480, 1217. ^1H NMR (300 MHz; $CDCl_3$) δ: 2.68–2.71 (m, 4H, pip ring); 3.09–3.34 (m, 4H, pip ring); 4.54 (s, 2H, $COCH_2$); 6.67–7.02 (m, 6H, Ar–H); 7.18–7.48 (m, 8H, Ar–H). MS (EI, *m*/*z*): 390.1 (M + 1). Anal. Calcd. for $C_{24}H_{24}FN_3O$: C, 74.01; H, 6.21; N, 10.79. Found: C, 74.05; H, 6.24; N, 10.77.

*4.1.2.10. 2-[4-(4-Nitrophenyl) piperazin-1-yl] N, N-diphenylacetamide (**3j**).* Yield: 47%. mp: 134–136 °C. $R_f = 0.30$ (Hexane/EtOAc 2:1). IR (KBr, cm^{-1}): 3020, 2848, 1673, 1496, 1217. ^1H NMR (300 MHz; $CDCl_3$) δ: 2.68–2.71 (m, 4H, pip ring); 3.19–3.43 (m, 4H, pip ring); 4.58 (s, 2H, $COCH_2$); 6.76–6.98 (m, 6H, Ar–H); 7.10–8.17 (m, 8H, Ar–H). MS (EI, *m*/*z*): 417.1 (M + 1). Anal. Calcd. for $C_{24}H_{24}N_4O_3$: C, 69.21; H, 5.81; N, 13.45. Found: C, 69.25; H, 5.84; N, 13.48.

4.2. Preliminary pharmacological evaluation for atypical antipsychotic effect

4.2.1. Apomorphine induced mesh climbing behavior

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 compound, 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. A maximum of 20 score is possible. Recording was done by an observer who was unaware of the specific drug treatments.

4.2.2. 5-Hydoxytryptophan (5-HTP) induced head twitches behavior

Swiss albino mice in the control group ($n = 6$) was injected with pargyline (75 mg/kg, i.p) in order 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, i.p). The mice were returned to the test cages and then head twitches were assessed at 10 min intervals for 30 min, starting 20 min after the 5-HTP treatment. Head twitches were monitored using the following scoring system: 0, absent; 1, moderate; 2, marked (Fig. 2). A maximum of 8 score is possible. An observer made all observations unaware of the specific drug treatments.

4.2.3. 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 maintained the imposed posture for at least 20 s and every additional 20 s one extra point was given (Fig. 3). A cut-off time of 1100 s was applied during the recording of observations. The animals were returned to their individual home cages in between determinations. All observations were made between 10.00 and 16.00 hrs in a quiet room at 23–25 °C. The animals in the test group were administered with test drugs instead of haloperidol and the remaining procedure for assessment of catalepsy was same as mentioned above.

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