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Synthesis, Computational Studies and Preliminary Pharmacological Evaluation of New Arylpiperazines

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Abstract: A series of novel arylpiperazines were synthesized and the target compounds evaluated for atypical antipsychotic activity in apomorphine induced climbing behavior (D_2 antagonism), 5-HTP induced head twitches (5-HT_{2A} antagonism) and catalepsy studies in albino mice. The physicochemical similarity of the target compounds with respect to standard drugs clozapine, ketanserine and risperidone was assessed by calculating from a set of physiochemical properties using software programs. The test compounds (**3a-j**) demonstrated good similarity values with respect to the standard drugs. Among them, compound **3d** has emerged as an important lead compound showing potential atypical antipsychotic like profile.

Keywords: *N*-Cyclohexylacetamide, Arylpiperazines, Antipsychotic activity, 5-HT_{2A}, D_2 antagonists

Introduction

Schizophrenia has been referred to as the cancer of mental illnesses[1]. The vast amount of research directed towards the treatment of schizophrenia in recent years attests to the inadequacy of current methods of treatment and the need for new and improved therapeutic agents. Conventional agents such as haloperidol and chlorpromazine relieve only the positive symptoms such as delusion, hallucinations and thought disorders but ineffective in the treatment of negative symptoms of schizophrenia. The use of typical antipsychotics for the treatment of schizophrenia is associated with severe extrapyramidal side effects[2]. Clozapine is considered atypical because it is effective in treating both the positive and negative symptoms of schizophrenia without inducing extrapyramidal side effects. Meltzer *et al*.[3] suggested that in the efficacy of clozapine and other atypical antipsychotics such as olanzapine or risperidone, the most important factor is their relative affinities for D_2 and 5-HT_{2A} receptors. Arylpiperazines have been recognized as the largest and most diverse classes of compounds exerting actions on the central nervous system in particularly serotonin (5-HT) and dopamine affinity[4,5]. Their general chemical structure consists of the arylpiperazine moiety connected by an alkyl chain with the terminal amide or imide fragment[6]. As part of our ongoing work on the development of strategies for the preparation of new D_2/5-HT_{2A} receptor antagonists as atypical antipsychotics, we here in repot the synthesis and preliminary pharmacological evaluation of some novel amide arylpiperazines.

Experimental

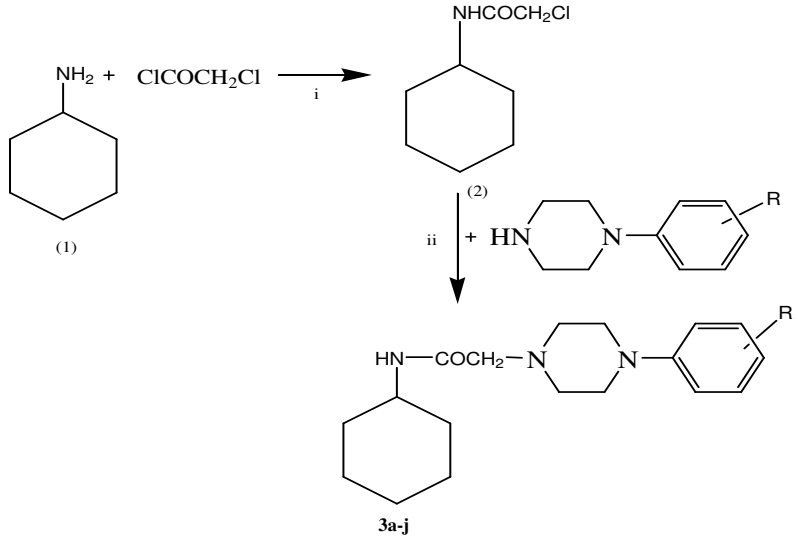
Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. The IR spectra of synthesized compounds were recorded in potassium bromide discs on Perkin Elmer Spectrum RX1. The ^{1}H NMR spectra were recorded on a Bruker DRX-300 spectrophometer at 300 MHz in $CDCl_3$ containing TMS as an internal standard. The electrospray mass spectra were recorded on a Thermo finnigan LCQ advantage max ion trap mass spectrometer. The reactions progress was monitored by thin-layer chromatography (TLC) using silica gel G and spots were visualized in an iodine chamber.

*Synthesis of 2-chloro-N-cyclohexylacetamide (**2**)*

Cyclohexylamine **(1)** (4.61 mL, 0.04 mol) in 2 N aqueous sodium hydroxide (150 mL) at 0 ^{o}C temperature was treated with chloroacetylchloride (3.18 mL, 0.04 mol) as a solution in dichloromethane (100 mL). After 1 h, the layers were separated and the aqueous phase extracted with additional portion of dichloromethane. The organic phase was combined, washed with an aqueous solution of 1 N HCl, saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated to afford **2**. Yield: 75%. Mp. 100-102 ^{o}C. IR (KBr, cm^{-1}): 3414, 3290, 3012, 2937, 1658, 1219, 1093, 768. ^{1}H NMR (300 MHz; $CDCl_3$ δ): 1.22-1.45 (m, 5H), 1.61-1.76 (m, 3H), 1.90-1.94 (m, 2H), 3.73-3.85 (m, 1H), 4.03 (s, 2H, $COCH_2$), 6.44 (br s, NH).

*General procedure for the synthesis of **3a-j***

2-Chloro-*N*-cyclohexylacetamide **(2)** (0.87 g, 0.005 mol) was dissolved in 100 mL of acetonitrile in a 250 mL round bottom flask. Anhydrous K_2CO_3 (0.69 g, 0.005 mol), catalytic amount of potassium iodide and appropriate arylpiperazine (0.005 mol) were added into above solution. The mixture was allowed to reflux with continuous stirring on magnetic stirrer for 12 h. After completion of reaction the solvent was removed by vacuum distillation and residue was dissolved in chloroform and water. An organic layer was washed with brine and dried over $MgSO_4$, removal of the solvent to afford the target compounds **3a-j.** The reactions are outlined in Scheme 1 and the nature of the substituents is given in Table 1.



Scheme 1. Synthesis of the target compounds. *Reagents and condition*: (i) NaOH, dichloromethane (ii) acetonitrile, K_2CO_3, KI.

Table 1. Substituents of compounds **3a-j**

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

*2-[4-(Phenyl) piperazin-1-yl]-N-cyclohexylacetamide (**3a**)*

Yield: 0.75 g (50%). mp., 87-90 ^{0}C. IR (KBr, cm^{-1}): 3356, 3006, 2936, 1664, 1234, 1015, 752. ^{1}H NMR (300 MHz; $CDCl_3$ δ): 1.17-1.89 (m, 10H), 3.79- 3.82 (m,1H), 2.41 -2.86 (m, 4H, pip ring), 3.01-3.17 (m, 4H, pipring), 4.80 (s, 2H, $COCH_2$), 6.82 -7.24 (m, 5H, Ar-H), 7.27 (br s, NH). MS (EI) *m/z*: 302.3 (M+1). R_f 0.27 (Hexane: Ethylacetate 1:1).

*2-[4-(3-Methylphenyl) piperazin-1-yl]-N- cyclohexylacetamide (**3b**)*

Yield: 0.85 g (54.14%). mp., 78-82 ^{0}C. IR (KBr, cm^{-1}): 3246, 3006, 2938, 1660, 1234, 1015, 756. ^{1}H NMR (300 MHz; $CDCl_3$ δ): 1.20-1.88 (m, 10H), 3.69-3.96 (m, 1H), 2.31 (s, 3H, CH_3), 2.49 -2.89 (m, 4H, pip ring), 3.11-3.23 (m, 4H, pipring), 4.72 (s, 2H, $COCH_2$), 6.40 -8.17 (m, 4H, Ar-H), 7.27 (br s, NH). R_f : 0.23 (Hexane: Ethylacetate 1:1).

*2-[4-(4-Methylphenyl) piperazin-1-yl]-N- cyclohexylacetamide (**3c**)*

Yield: 0.82 g (52.22%). mp., 76-80 ^{0}C. IR (KBr, cm^{-1}): 3246, 3006, 2938, 1660, 1234, 1015, 756. ^{1}H NMR (300 MHz; $CDCl_3$ δ): 1.20-1.88 (m, 10H), 3.79-3.96 (m, 1H), 2.29 (s, 3H, CH_3), 2.49 -2.80 (m, 4H, pip ring), 3.11-3.23 (m, 4H, pipring), 4.72 (s, 2H, $COCH_2$), 6.40 -7.94 (m, 4H, Ar-H), 7.27 (br s, NH). R_f 0.21 (Hexane: Ethylacetate 1:1).

*2-[4-(2-Methoxyphenyl) piperazin-1-yl]-N- cyclohexylacetamide (**3d**)*

Yield: 0.57 g (34.54%). mp., 85-89 ^{0}C. IR (KBr, cm^{-1}): 3355, 3003, 2937, 1666, 1242, 1036, 756. ^{1}H NMR (300 MHz; $CDCl_3$ δ): 1.25-1.89 (m, 10H), 3.79-3.96 (m, 1H), 3.54 (s, 3H, OCH_3), 2.17 -2.89 (m, 4H, pip ring), 3.10-3.42 (m, 4H, pipring), 4.69 (s, 2H, $COCH_2$), 6.57 -7.94 (m, 4H, Ar-H), 7.26 (br s, NH). R_f : 0.25 (Hexane: Ethylacetate 1:1).

*2-[4-(3-Methoxyphenyl) piperazin-1-yl]-N- cyclohexylacetamide (**3e**)*

Yield: 0.50 g (30.30%). mp., 66-70 ^{0}C. IR (KBr, cm^{-1}): 3353, 3003, 2935, 1665, 1241, 1036, 755. ^{1}H NMR (300 MHz; $CDCl_3$ δ): 1.25-1.89 (m, 10H), 3.79-3.96 (m, 1H), 3.54 (s, 3H, OCH_3), 2.17 -2.89 (m, 4H, pip ring), 3.10-3.42 (m, 4H, pipring), 4.69 (s, 2H, $COCH_2$), 6.57 -7.94 (m, 4H, Ar-H), 7.26 (br s, NH). R_f : 0.39 (Hexane: Ethylacetate 1:1).

*2-[4-(4-Methoxyphenyl) piperazin-1-yl]-N- cyclohexylacetamide (**3f**)*

Yield: 0.58 g (35.15%). mp., 94-98 ^{0}C. IR (KBr, cm^{-1}): 3353, 3003, 2935, 1665, 1241, 1036, 755. ^{1}H NMR (300 MHz; $CDCl_3$ δ): 1.13-1.90 (m, 10H), 3.79-3.86 (m, 1H), 3.54 (s, 3H, OCH_3), 2.67 -2.70 (m, 4H, pip ring), 3.04-3.47 (m, 4H, pipring), 4.67 (s, 2H, $COCH_2$), 6.77 -7.09 (m, 4H, Ar-H), 7.26 (br s, NH). R_f : 0.24 (Hexane: Ethylacetate 1:1).

*2-[4-(2-Chlorophenyl) piperazin-1-yl]-N- cyclohexylacetamide (**3g**)*

Yield: 0.97 g (58.08%). mp., 72-75 ^{0}C. IR (KBr, cm^{-1}): 3349, 3008, 2935, 1664, 1225, 1015, 757. ^{1}H NMR (300 MHz; $CDCl_3$ δ): 1.25-1.88 (m, 10H), 3.59- 3.81 (m, 1H), 2.14 -2.95 (m, 4H, pip ring), 3.01-3.45 (m, 4H, pipring), 4.68 (s, 2H, $COCH_2$), 6.65 -7.94 (m, 4H, Ar-H), 7.26 (br s, NH). R_f : 0.54 (Hexane: Ethylacetate 1:1).

*2-[4-(3-Chlorophenyl) piperazin-1-yl]-N- cyclohexylacetamid (**3h**)*

Yield: 0.95 g (56.88%). mp., 86-90 ^{0}C. IR (KBr, cm^{-1}): 3349, 3008, 2935, 1664, 1225, 1015, 757. ^{1}H NMR (300 MHz; $CDCl_3$ δ): 1.25-1.88 (m, 10H), 3.59- 3.81 (m, 1H), 2.14 -2.95 (m, 4H, pip ring), 3.01-3.45 (m, 4H, pipring), 4.68 (s, 2H, $COCH_2$), 6.65 -7.94 (m, 4H, Ar-H), 7.26 (br s, NH). R_f : 0.47 (Hexane: Ethylacetate 1:1).

*2-[4-(4-Fluorophenyl) piperazin-1-yl]-N- cyclohexylacetamide (**3i**)*

Yield: 1 g (62.89%). mp., 88-91 ^{0}C. IR (KBr, cm^{-1}): 3248, 3009, 2936, 1662, 1224, 1015, 756. ^{1}H NMR (300 MHz; $CDCl_3$ δ): 1.15-1.87 (m, 10H), 3.55- 3.97 (m, 1H), 2.63 -2.92 (m, 4H, pip ring), 3.10-3.45 (m, 4H, pipring), 4.82 (s, 2H, $COCH_2$), 6.74 -7.97 (m, 4H, Ar-H), 7.28 (br s, NH). R_f : 0.28 (Hexane: Ethylacetate 1:1).

*2-[4-(4-Nitrophenyl) piperazin-1-yl]-N- cyclohexylacetamide (**3j**)*

Yield: 0.98 g (56.64%). mp., 134-136 ^{0}C. IR (KBr, cm^{-1}): 3249, 3008, 2937, 1663, 1225, 1015, 754. ^{1}H NMR (300 MHz; $CDCl_3$ δ): 1.18-1.91 (m, 10H), 3.55- 3.97 (m, 1H), 2.63-2.70 (m, 4H, pip ring), 3.06-3.46 (m, 4H, pipring), 4.82 (s, 2H, $COCH_2$), 6.82 -8.13 (m, 4H, Ar-H), 7.27 (br s, NH). R_f: 0.26 (Hexane: Ethylacetate 1:1).

Computation of physiochemical properties

A set of molecular parameters was computed for the target compounds as well as three standard drugs clozapine, ketanserine and risperidone using Chem 3D ultra version 11.0, Chem Silico online free software and are shown in Table 2. The important molecular parameters for antipsychotics are blood brain barrier (BBB), log P and topological polar surface area. Literature review 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.*[7] suggest a limit of 90 A^2, where, Kelder *et al.*[8] suggest 60-70 A^2.

Similarity calculations

The physicochemical similarity of the target compounds was calculated with respect to the standard drugs[9] and 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:

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

Where, $X_{i,\,j}$ is the value of molecular parameter 'i' for compound 'j', $X_{i,\,std}$ is the value of the same molecular parameter for the standard drug, *e.g.,* clozapine, ketanserine and risperidone. Then, the similarity of compound 'j' to the standard drug was calculated as: Similarity (%) = (1-R) x 100. Where R =$\sqrt{d^2}$ is the quadratic mean (root mean square), a measure of central tendency.

Table 2. Calculation of molecular properties for 2-[4-(aryl substituted) piperazin-1-yl]-*N*-cyclohexylacetamides (**3a-j**) and standard drugs

Compd No.	log BB[i]	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]
3a	0.3	2.47	301.43	91.17	580.26	309.45	297.08	35.58	9668	1248
3b	0.34	2.96	315.45	97.07	611.49	328.11	313.97	35.58	10915	1408
3c	0.34	2.96	315.45	97.07	611.47	328.10	313.96	35.58	11038	1424
3d	0.09	2.35	331.45	98.42	633.86	336.43	311.66	44.81	11801	1559
3e	0.07	2.35	331.45	98.42	642.35	338.88	311.45	44.81	12015	1591
3f	0.07	2.35	331.45	98.42	644.60	339.97	311.78	44.81	12229	1623
3g	0.27	3.03	335.87	98.78	588.70	317.12	310.21	35.58	10357	1392
3h	0.32	3.03	335.87	95.78	604.78	324.26	311.41	35.58	10432	1408
3i	0.24	2.63	319.42	91.58	586.41	313.07	300.27	35.58	10507	1424
3j	-0.87	1.6	346.42	95.77	622.69	336.23	321.55	87.39	13142	1824
CLZ[j]	0.75	3.71	326.82	94.58	508.99	259.12	215.89	30.87	8127	1082
KET[k]	-0.48	2.37	395.43	106.67	589.34	298.72	253.38	69.72	18646	2596
RIS[l]	-0.20	2.10	410.48	114.21	690.02	375.09	351.81	57.5	20311	2793

[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, iCalcd.online[10], [j]Clozapine, [k]Ketanserine, [l]Risperidone

Table 3. Similarity values of 2-[4-(aryl substituted)piperazin-1-yl]-*N*-cyclohexyl-acetamides (**3a-j**) with respect to standard drugs

Compd.No	Similarity[a,b], in % to		
	Clozapine	Ketanserine	Risperidone
3a	81.01	67.40	64.74
3b	73.74	69.62	70.13
3c	73.28	69.84	70.36
3d	65.53	74.29	76.03
3e	64.30	74.63	75.39
3f	63.32	75.00	75.89
3g	76.31	69.70	69.42
3h	76.36	69.65	69.71
3i	76.82	69.84	68.80
3j	24.90	78.87	72.76

[a](1 - R) X 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

Preliminary pharmacological evaluation for atypical antipsychotic effect

All the target compounds were subjected to preliminary pharmacological evaluation to determine their ability to antagonize apomorphine induced climbing behaviour, inhibition of 5-hydroxy tryptophan (5-HTP) induced head twitches behavior and catalepsy studies[11-14].

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). The results from the pharmacological evaluation of the target compounds at their respective ED_{min} values are depicted graphically in Figures 1, 2 and 3. ED_{min} of the synthesized compounds were 40mg/kg for inhibition of apomorphine induced climbing behaviour, inhibition of 5-hydroxy tryptophan (5-HTP) induced head twitches behavior and EDmin 80 mg/kg was for catalepsy studies. Statistical analysis of the results in the test group was done by comparison with the results in the control group employing one way ANOVA. 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 (Figure 1). The score recorded for each animal was based on the position of the animal at the moment it was first observed.

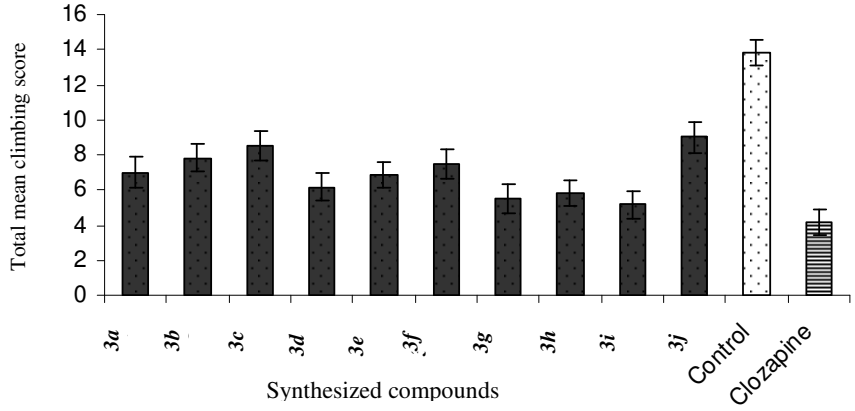


Figure 1. The effect of synthesized compounds (**3a-j**) on the apomorphine induced climbing behavior. *(Each column represents the mean ±SEM of total climbing score for group of six mice assessed at 5-min intervals for 20 min, starting 10 min after apomorphine treatment. A score of 20 is the maximum possible. All values statistically significant with respect to control at p<0.05).*

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

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, s.c). 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.

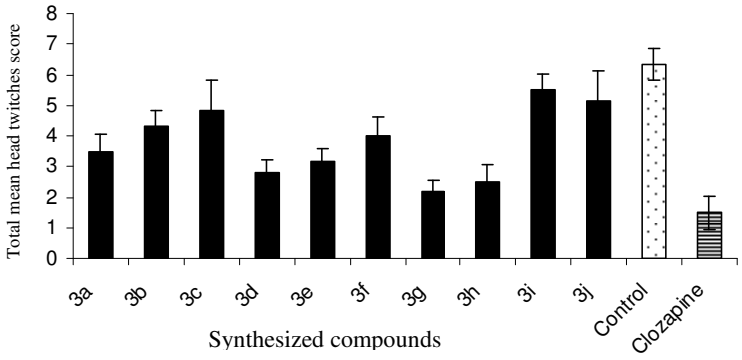


Figure 2. The effect of synthesized compounds (**3a-j**) on the 5-HTP induced head twitches behavior. (*Each column represents the mean ±SEM of total head twitches score for group of six mice assessed at 10 min intervals for 30 min, starting 20 after the 5-HTP treatment. A score of 8 is the maximum possible. All values 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 (sec) 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 sec and every additional 20 sec one extra point would be given (Figure 3).

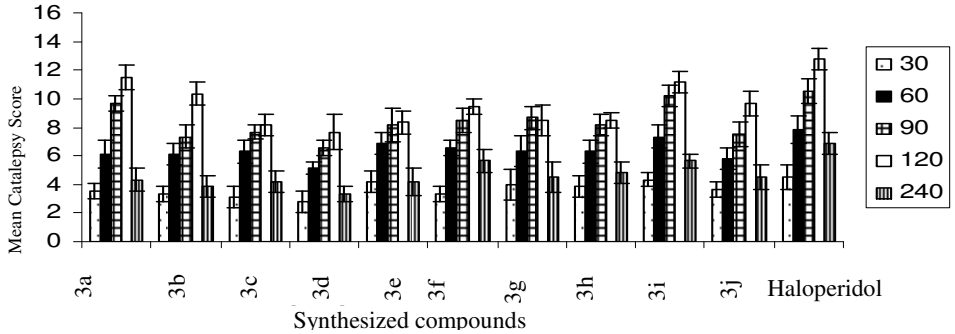


Figure 3. The effect of synthesized compounds (**3a-j**) on induction of catalepsy in mice. Results are expressed as the mean ±SEM. (n=6), p<0.05.

Results ad Discussion

The target compounds (**3a-j**) were synthesized as outlined in Scheme 1 and obtained in good yields (30.30-62.89%). The purity of the compounds was monitored by TLC and the structure of the compounds was deduced on the basis of spectroscopic methods. A set of molecular parameters and physicochemical similarity of the target compounds was calculated with respect to the standard drugs. The compounds (**3a-j**) showed good structural similarity with respect to standard drugs (24.90 - 81.01%). The results from the pharmacological

evaluation of the target compounds at their respective ED_{min} values were showed significant reduction in apomorphine induced climbing behaviour, inhibition of 5-hydroxy tryptophan (5-HTP) induced head twitches behavior and low propensity to induce catalepsy.

Conclusion

We have synthesized a new series of arylpiperazines and their preliminary pharmacological evaluation has shown potential atypical antipsychotic effect. Test compounds have shown good structural similarity with respect to the standard drugs. Among the compounds, **3d** has shown potent binding affinities for D_2 and 5-HT_{2A} receptors and low propensity to induce catalepsy and further studies on this lead are required for the refinement of the atypical antipsychotic activity.

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