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Research Article

Synthesis and Preliminary Pharmacological Evaluation of 2-[4-(Aryl substituted) piperazin-1-yl]-N-phenylacetamides: Potential Antipsychotics

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Abstract

Purpose: *Arylpiperazines have been recognized as the largest and most diverse class of compounds exerting actions on the central nervous system with strong affinity for serotonin and dopamine receptors. We here report the synthesis of some novel arylpiperazines and their evaluation for possible antipsychotic properties.*
Methods: *The target compounds 2-[4-(aryl substituted) piperazin-1-yl]-N-phenylacetamides (**3a-j**) were synthesized by first reacting aniline (**1**) in 2 N sodium hydroxide with chloroacetylchloride in dichloromethane to obtain 2-chloro-N-phenylacetamide (**2**) and subsequently treating with appropriate phenylpiperazine in acetonitrile in the presence of K_2CO_3 and KI. All the compounds were characterized by analytical and spectroscopic methods. The compounds were evaluated for antipsychotic activity using three animal models.*
Results: *All the 10 new arylpipeazines showed variable antipsychotic activity with compound 3h being the least effective in the induction of catalepsy. Their effect may involve interaction with 5-HT_{2A} and D_2 receptors.*
Conclusion: *A synthetic method and possible antipsychotic effect have been established for 2-[4-(Aryl substituted) piperazin-1-yl]-N-phenylacetamides.*

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

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INTRODUCTION

Schizophrenia is a complex psychological disorder affecting about 1 % of the population worldwide [1,2]. The use of classical neuroleptics such as phenothiazines and butyrophenones for the treatment of schizophrenia is associated with severe mechanism-related side effects including induction of acute extrapyramidal symptoms. They all share the ability to block D_2 dopamine receptors and effectiveness in the treatment of positive symptoms of schizophrenia [3,4]. The adverse effects presented by classical antipsychotics, along with their ineffectiveness in the treatment of negative symptoms of schizophrenia has encouraged the search for other drugs [5]. Both serotonergic and dopaminergic systems have been proposed to be involved in the mechanism of action of antipsychotic drugs. Most atypical antipsychotic drugs have in common relatively strong blockade of 5-HT_{2A} receptors coupled with weaker antagonism of the D_2 receptors [6, 7]. This so-called "serotonin-dopamine hypothesis" has become the basis for developing new antipsychotics with the view to achieving superior efficacy with a lower incidence of extrapyramidal side effects compared to earlier drugs . Molecules based on arylpiperazine core were classified as ligands of serotonin (5-HT), dopamine and adrenergic receptors and some of them became clinically useful drugs in the treatment of anxiety, depression and psychiatric disorders [8]. Long-chain arylpiperazines have been (LCAPs) recognized as the largest and most diverse classes of compounds exerting actions on the central nervous system particularly serotonin and dopamine affinity [9,10]. Their general chemical structure consists of the arylpiperazine moiety connected by an alkyl chain with the terminal amide or imide fragment. As part of our ongoing work on the development of strategies for the preparation of new antipsychotics, we here report the synthesis of some novel amide arylpiperazines and the evaluation of their antipsychotic activity.

EXPERIMENTAL

Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. The infrared (IR) spectra of synthesized compounds were recorded in potassium bromide discs on Perkin Elmer Spectrum RX1. ^1H and ^{13}C NMR (nuclear magnetic resonance) 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. Elemental analyses were performed on Elementar Vario EL III analyzer. The electrospray mass spectra were recorded on a Thermo Finnigan LCQ Advantage Max ion trap mass spectrometer. All reagents were of commercial quality and were used without further purification. The reaction's 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-phenylacetamide (**2**)

Aniline **1** (3.65 ml, 0.04 mol) in 2N aqueous sodium hydroxide (150 ml) at room 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 (100 ml). The organic phase was combined, washed with an aqueous solution of 1N HCl, saturated $NaHCO_3$, dried with Na_2SO_4, and concentrated to afford **2**. Yield: 68.12 %; m.p.: 130-132 ^oC; IR (KBr, cm^{-1}): 3311, 3021, 2862, 1681, 1217, 769, 670; ^1H NMR (300 MHz; $CDCl_3$ δ): 4.19 (s, 2H), 7.11-7.39 (m, 3H, Ar-H), 7.53 (d, J= 7.8, 2H, Ar-H), 8.24 (br, s, 1H). Anal.Calcd.for C_8H_8ClNO: C, 56.65; H, 4.75; N, 8.26; Found: C, 56.59; H, 4.66; N, 8.18.

General procedure for the synthesis of 3a-j

2-Chloro-N-phenylacetamide **2** (0.84 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), catalytic amount of potassium iodide and appropriate arylpiperazine (0.005 mol) were added into above solution. The above 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 the residue dissolved in chloroform and water. The separated organic layer was washed with brine and dried over anhydrous magnesium sulphate. Removal of the solvent under vacuum afforded the crude product which was recrystallized from ethanol to obtain crystals of the pure compounds (**3a-j)**.

Animals

Swiss albino mice (six in each group) of either sex (20 - 25 g) were housed per cage in standard laboratory conditions (12 h light/dark cycle, 22±2 ^{o}C room temperature). Food and water were available to them *ad libitum*. The animal experiments were approved by institutional ethical committee.

Apomorphine-induced mesh climbing assay

Each mouse was placed in a cylindrical wire mesh cage (height 13 cm, diameter 14 cm and mesh size 3mm) for 1h prior to the experiments. Mice in the test, control and standard groups were injected respectively with test compounds (ED_{min} 20 mg/kg), normal saline and clozapine intraperitoneally and returned to the home cage. After 30 min, apomorphine (2.5 mg/kg, i.p.) was injected. Mesh climbing behavior was assessed 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. The score recorded for each animal was based on the position of the animal at the moment it was first observed. The maximum possible score was 20. Recording was undertaken by an observer who was unaware of the specific drug treatments [11].

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

The head twitches were measured after placing a mouse in a Perspex cage for a 30 min habituation period. The mice were then injected with pargyline (75 mg/kg, i.p.) in order to prevent the rapid degradation of 5-HTP. Thirty minutes later, the test compound (ED_{min} 20 mg/kg, i.p) was administered. After a further 30 min, the mice received 5-HTP (50 mg/kg, i.p.) and then returned to the test cages. Twenty minutes after 5-HTP injections, head twitches were assessed every 10 min for 30 min. The head twitches were monitored using the following scoring system, 0- absent, 1-moderate, 2-marked. The maximum possible score was 8. An observer made all observations unaware of the specific drug treatments [12].

Catalepsy

Catalepsy was induced in albino mice (n=6) with haloperidol (1.0 mg/kg, i.p.) and was assessed at 30, 60, 90, 120, and 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 given a score of 1 if the animal maintained the imposed posture for at least 20 s and every additional 20 sec one extra point would be given. 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

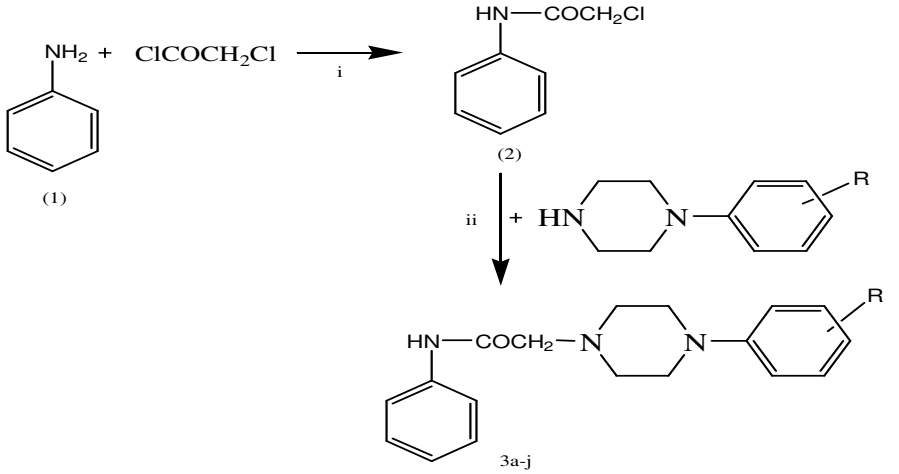

Figure 1: Synthesis of the target compounds. Reagents and condition: (i) NaOH; dichloromethane (ii) acetonitrile, K_2CO_3, KI.

determinations. All observations were made between 10.00 and 16.00 hrs in a quiet room at 23-25ºC. The animals in the test group were administered with test drug (ED_{min} 80 mg/kg, i.p.) instead of haloperidol and the remaining procedure for assessment of catalepsy was the same as indicated above [13,14].

Statistical analysis

The results are expressed as mean ± SEM. Statistical analysis of the results in the test group was carried out by comparison with the results in the control group, employing non-parametric Kruskal Wallis test or one-way ANOVA (Jandel Sigmastat version 2.0). The statistical level of significance was fixed at $p<0.05$.

RESULTS

The reactions are outlined in Figure 1 and the nature of constituents is given in Table 1.

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

Yield: 66%; m.p.: 124-125 ^oC; IR (KBr, cm^{-1}): 3311, 3016, 2829, 1683, 1221, 1017, 759; ^1H NMR (300 MHz; $CDCl_3$ δ): 2.65 -2.68 (m, 4H), 2.96-3.16 (m, 4H), 3.18 (s, 2H, $COCH_2$), 6.83 -6.91 (m, 3H, Ar-H), 7.09 -7.32 (m, 5H, Ar-H), 7.56 (d, J=7.5, 2H), 9.10 (br s,1H); ^{13}C NMR (75 MHz, $CDCl_3$ δ): 48.9, 53.0, 76.5, 115.3, 116.6, 119.6, 123.8, 128.7, 128.8, 137.2, 150.6, 167.7; MS (EI) m/z: 296.3 (M+1). Anal.Calcd. for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 72.98; H, 6.34; N, 14.03.

Table1: 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-(3-Methylphenyl) piperazin-1-yl]-N-phenylacetamide (3b)

Yield: 62%; m.p.: 92-94 ^oC; IR (KBr, cm^{-1}): 3307, 3016, 2829, 1682, 1219, 1016, 766; ^1H NMR (300 MHz; $CDCl_3$ δ): 2.29 (s, 3H), 2.78 - 2.81 (m, 4H), 3.11-3.32 (m, 4H), 3.21 (s, 2H,

$COCH_2$), 6.85-6.88 (m, 3H), 7.09-7.36 (m, 4H, Ar-H), 7.56 (d, J=9, 2H), 9.14 (s,1H); MS (EI) m/z: 310 (M+1). Anal.Calcd.for $C_{20}H_{25}N_3O_2$: C,70.77; H, 7.42; N,12.38. Found: C, 72.97; H, 7.40; N, 13.45.

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

Yield: 56%; m.p.: 109-111 ^oC; IR (KBr, cm^{-1}): 3307, 3016, 2825, 1681, 1238, 1017, 759; ^1H NMR (300 MHz; $CDCl_3$ δ): 2.28 (s, 3H), 2.79 -2.82 (m, 4H), 3.11-3.32 (m, 4H), 3.22 (s, 2H, $COCH_2$), 6.80-6.87 (m, 3H), 7.08-7.36 (m, 4H, Ar-H), 7.56 (d, J=8.1, 2H), 9.15 (s, 1H); MS (EI) m/z: 310 (M+1). Anal.Calcd.for $C_{19}H_{23}N_3O$: C, 73.76; H, 7.49; N, 13.58. Found: C, 73.28; H, 7.38; N, 13.43.

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

Yield: 52%; m.p.: 119-120 ^oC; IR (KBr, cm^{-1}): 3309, 3013, 2831, 1681, 1237, 1032, 762; ^1H NMR (300 MHz; $CDCl_3$ δ): 3.87 (s, 3H), 2.83-2.98 (m, 4H), 3.15-3.31 (m, 4H), 3.21 (s, 2H, $COCH_2$), 6.87 - 6.96 (m, 3H, Ar-H), 7.00-7.36 (m, 4H, Ar-H), 7.57 (d, J=8.1, 2H), 9.19 (s,1H); MS (EI) m/z: 326 (M+1). Anal.Calcd.for $C_{19}H_{23}N_3O$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.19; H, 7.10; N, 12.87.

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

Yield: 48%; m.p.: 86-88 ^oC; IR (KBr, cm^{-1}): 3309, 3013, 2831, 1681, 1237, 1032, 762; ^1H NMR (300 MHz; $CDCl_3$ δ): 3.87 (s,3H), 2.83 -2.98 (m, 4H), 3.15-3.31 (m, 4H), 3.21 (s, 2H, $COCH_2$), 6.87 - 6.96 (m, 3H, Ar-H), 7.00-7.36 (m, 4H, Ar-H), 7.57 (d, J=8.1, 2H), 9.19 (s,1H); MS (EI) m/z: 326 (M+1). Anal.Calcd.for $C_{19}H_{23}N_3O$: C, 70.13; H, 7.12; N,12.91. Found: C, 70.08; H, 7.07; N, 12.86.

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

Yield: 45%; m.p.: 95-98 ^oC; IR (KBr, cm^{-1}): 3309, 3013, 2831, 1681, 1237, 1032, 762; ^1H NMR (300 MHz; $CDCl_3$ δ): 3.78 (s, 3H), 2.81 -2.97 (m, 4H), 3.15-3.32 (m, 4H), 3.22 (s, 2H, $COCH_2$), 6.80 - 6.95 (m, 3H, Ar-H), 7.10-7.36 (m, 4H, Ar-H), 7.59 (d, J=9, 2H), 9.19 (s,1H); MS (EI) m/z: 326 (M+1). Anal.Calcd.for $C_{19}H_{23}N_3O$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.07; H, 7.15; N, 12.78.

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

Yield: 52%; m.p: 126-127 ^oC; IR (KBr, cm^{-1}): 3311, 3013, 2829, 1683, 1238, 1015, 758; ^1H NMR (300 MHz; $CDCl_3$ δ): 2.77 -2.80 (m, 4H), 3.26-3.29 (m, 4H), 3.21 (s, 2H, $COCH_2$), 6.79 - 6.90 (m, 3H, Ar-H), 7.10-7.37 (m, 4H, Ar-H), 7.58 (d, J=9, 2H), 9.08 (s, 1H); MS (EI) m/z: 330 (M+1). Anal.Calcd.for $C_{18}H_{20}ClN_3O$: C, 65.55; H, 6.11; N, 12.74. Found: C, 65.40; H, 6.09; N, 12.69.

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

Yield: 57%; m.p.: 104-105 ^oC; IR (KBr, cm^{-1}): 3311, 3013, 2829, 1683, 1238, 1015, 758; ^1H NMR (300 MHz; $CDCl_3$ δ): 2.77 -2.80 (m, 4H), 3.26-3.29 (m, 4H), 3.21 (s, 2H, $COCH_2$), 6.79 - 6.90 (m, 3H, Ar-H), 7.10-7.37 (m, 4H, Ar-H), 7.59 (d, J=9, 2H), 9.08 (s, 1H); MS (EI) m/z: 330 (M+1). Anal.Calcd.for $C_{18}H_{20}ClN_3O$: C, 65.55; H, 6.11; N, 12.74. Found: C, 65.38; H, 6.07; N, 12.67.

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

Yield: 54%; m.p.: 106-107 ^oC; IR (KBr, cm^{-1}): 3307, 3016, 2829, 1682, 1219, 1016, 766; ^1H NMR (300 MHz; $CDCl_3$ δ): 2.63-2.83 (m, 4H), 3.18-3.32 (m, 4H), 3.22 (s, 2H, $COCH_2$), 6.88-6.92 (m, 3H), 7.10-7.37 (m, 4H, Ar-H), 7.56 (d, J=9, 2H), 9.12 (s,1H); MS (EI) m/z: 314 (M+1). Anal.Calcd.for $C_{18}H_{20}FN_3O$: C, 68.99; H, 6.43; N, 13.41. Found: C, 68.03; H, 6.35; N, 13.21.

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

Yield: 58%; m.p.: 168-169 ^{o}C; IR (KBr, cm^{-1}): 3307, 3016, 2829, 1682, 1219, 1016, 766; ^{1}H NMR (300 MHz; $CDCl_3$ δ): 2.59-2.82 (m, 4H), 3.24 (s, 2H, $COCH_2$), 3.48-3.52 (m, 4H), 6.84 (d, J=7.6,1H), 7.11-7.16 (m, 2H, Ar-H), 7.26-7.58 (m, 3H, Ar-H), 7.69 (d, J=7.8, 2H), 8.13 (d, J=9.3,1H), 9.14 (s, 1H); MS (EI) m/z: 341 (M+1). Anal.Calcd.for $C_{18}H_{20}N_4O_3$: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.35; H, 5.78; N, 16.38.

Aniline (**1**) was converted to 2-chloro-N-phenylacetamide (**2**) by treating with chloroacetylchloride in dichloromethane. The IR spectrum of compound (**2)** showed characteristic carbonyl group absorption at 1681 $cm^{-1}$and ^{1}H NMR spectrum exhibited a broad singlet due to NH group at 8.24. The final target compounds 2–[4-(arylsubstituted) piperazin-1-yl]-N-phenylacetamides (**3a-j**) were prepared by coupling the 2-chloro-N-phenylacetamide (**2**) with appropriate phenylpiperazine in acetonitrile in the presence of K_2CO_3 and KI. All the target compounds (**3a-j**) were obtained in good yield (45-66%) and characterized by analytical and spectroscopic methods as described. Mass spectra of newly synthesized compounds showed M+1 peak.

The results from the pharmacological evaluation of the target compounds are shown in Figures 2 - 4. The test compounds (3a-j) produced statistically significant reversal of apomorphine- induced mesh climbing behaviour; 5-hydroxytryptophan (5-HTP) induced head twitches behaviour and lower induction of catalepsy.

DISCUSSION

Arylpiperazine derivatives display diverse pharmacological activity which can be mediated by different subpopulations of serotonin (5-HT), dopamine and adrenergic receptors [15]. In view of the DA-5-HT hypothesis, regarding the development of

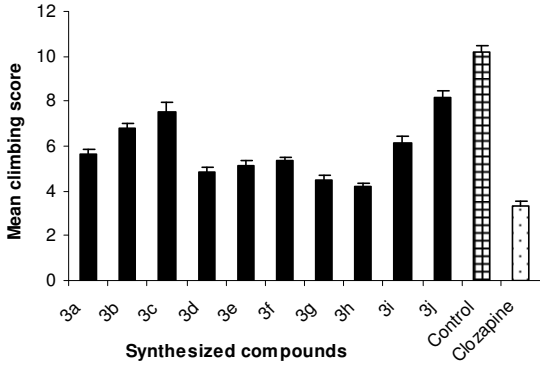

Figure 2: The effect of synthesized compounds (**3a-j**) on the apomorphine-induced climbing behaviour. Each column represents the mean ± SEM of climbing score (n = 6) assessed at 5 min intervals for 20 min, starting 10 min after apomorphine treatment.

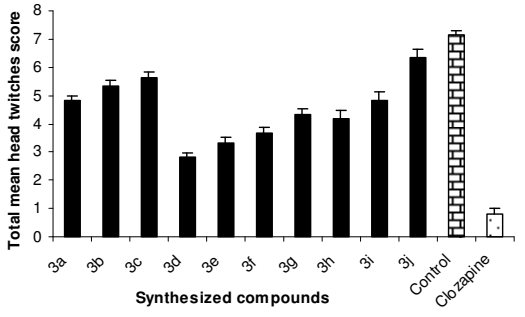

Figure 3: The effect of synthesized compounds (**3a-j**) on the 5-HTP-induced head twitches behavior. Each column represents the mean ±SEM of total head twitches score for (n = 6) assessed at 10-min intervals for 30 min, starting 20 min after the 5-HTP treatment.

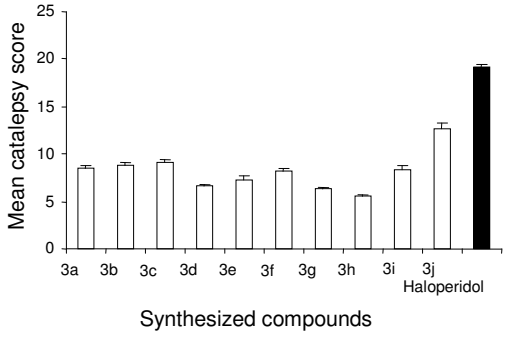

Figure 4: The effect of synthesized compounds (**3a-j**) on induction of catalepsy in mice. Results are expressed as the mean ± SEM (n = 6)

atypical antipsychotic potential [16] in the present work, we synthesized 10 new arylpiperazines. 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 (**3h, 3g)** possessing chloro group at ortho and meta positions of aryl moiety of piperazine produced a significant greater reversal of apomorphine-induced climbing behaviour than their methoxy analogs (**3d**, **3e**, **3f**). A significant reduction in activity was observed when nitro group was present at para position of aryl moiety (**3j).** Other compounds (**3a**, **3i**, **3b** and **3c**) showed lower efficacy at the D_2 receptor. The inhibition of 5-HTP induced head twitches behaviour (5-HT_{2A} antagonism) study showed that methoxy analogs produced significant higher activity than chloro analogs. The other compounds (**3a, 3b, 3c, 3f, and 3g**) showed lower antagonism of 5-HTP-induced head twitches behaviour. The catalepsy results showed all the new compounds (**3a**-**j**) were less cataletogenic than haloperidol. Among them, chloro analogs (**3h** and **3g**) exhibited the lowest propensity to produce catalepsy.

CONCLUSION

A new series of arylpiperazines have been synthesized and preliminary pharmacological evaluations show their potential antipsychotic activity. Among the compounds, **3h** displayed significant inhibition activity for D_2 and 5-HT_{2A} receptors and minimum induction of catalepsy. Further studies on this lead are required for the refinement of the atypical antipsychotic activity.

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COMPETING INTERESTS

The authors declare no conflict of interest.

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