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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Synthesis and evaluation of *meta* substituted 1-(aryloxypropyl)-4-(chloroaryl) piperazines as potential atypical antipsychotics

**Alka Bali · A. C. Dinesh Kumar Reddy**

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**Abstract** A series of 1-(aryloxypropyl)-4-(chloroaryl) piperazines have been synthesized based upon their physicochemical similarity with respect to standard atypical antipsychotic drugs and their potential to cross the blood–brain barrier (log BB) as calculated by appropriate software programmes. The target compounds were evaluated for atypical antipsychotic activity in apomorphine-induced mesh climbing and stereotypy assays in mice. The compounds **8**, **9** and **10** bearing hydrogen bond acceptor substituents have emerged as important lead compounds showing higher efficacy along with potential atypical antipsychotic profile.

**Keywords** Atypical antipsychotics · *meta* substituted 1,4-diaryl piperazine derivatives · Physicochemical similarity · Log BB · CNS agents

## Introduction

Schizophrenia is a complex psychological disorder afflicting about 1 % of the population worldwide (Tandon *et al*., 2008). The aetiology of this disease is still unclear, but a general consensus is that the classical or 'typical' antipsychotic drugs ameliorate psychosis by blocking the postsynaptic dopaminergic receptors in the mesocorticolimbic regions of the brain, e.g. nucleus accumbens, olfactory tubercle, frontal cortex (related to behavioural aspects) (Davis *et al*., 1991) and alleviate the active or positive symptoms of the disease (Seeman and Van Tol, 1994; Seeman, 1995). The concomitant dopaminergic blockade in the nigrostriatal regions of the brain associated with locomotor coordination; however, results in severe mechanism related side effects including parkinsonism and akathisia (extrapyramidal symptoms), tardive dyskinesia and galactorrhoea (due to increased prolactin release) (Simpson *et al*., 1981; Costall and Naylor, 1974).

The dibenzodiazepine derivative clozapine (Meltzer, 1989) is considered as the prototype of the new group of non-classical or atypical antipsychotics indicated for treatment-resistant schizophrenia. This drug possesses a superior profile over conventional neuroleptics. It is nearly devoid of extrapyramidal side effects and is also effective in alleviation of negative symptoms of the disease. However, owing to concerns surrounding its haematological safety, metabolic and other adverse effects (Griffith and Saameli, 1975; Melkersson and Dahl, 2004), clozapine is used principally in patients refractory to treatment with other antipsychotic agents (Tandon and Jibson, 2003).

Several dopaminergic (Zhao *et al*., 2002; Geneste *et al*., 2006) and serotonergic approaches (Graham *et al*., 2008; Rotella *et al*., 2009, Cole *et al*., 2005), besides others (Xu *et al*., 2007; Weigl and Wunsch, 2007; Kinkead *et al*., 2000) have been investigated for the development of atypical antipsychotics; however, their exact significance is not clear yet. Hence, behavioural tests based upon locomotor activity and stereotyped behaviour induced by a dopaminergic agonist have been widely used to assess atypical antipsychotic profile (Vogel, 2007). In these models, significant reversal of the apomorphine-induced locomotor activity (mesh climbing) coupled with the inability of the compound to reverse the stereotyped behaviour suggests a selective action in the mesolimbic areas of the brain sparing the nigrostriatal system. This is indicative of antipsychotic effect along with low propensity to cause extrapyramidal symptoms.

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We had recently reported a series of quinoliloxypropyl piperazines (Bali *et al*., 2009) where the quinolin-8-yl derivative **I** (Fig. 1) had emerged as an important lead compound as a potential atypical antipsychotic. As USEPA has classified quinoline as a Group C carcinogen and it is considered 'likely to be carcinogenic in humans' in accordance with the EPA's proposed guidelines for carcinogenic risk assessment, we had subsequently investigated a series of 1,4-diaryl substituted piperazine derivatives incorporating a replacement of the quinoline system by aryl systems **II** (Fig. 1) (Bali *et al*., 2010) in which, the *ortho* acetyl substituted compounds had shown an atypical profile whereas, *para* acetyl substitution had generated a typical profile. In this paper, we are reporting the design and synthesis of *meta* carbonyl substituted 1-(aryloxypropyl)-4-(chloroaryl) piperazines based upon molecular parameter computation, particularly, their potential to cross the blood–brain barrier (log BB values), 2D similarity studies with respect to standard drugs and their pharmacological evaluation for potential atypical antipsychotic effect.

## Results and discussion

### Physicochemical similarity studies and compound design

According to the 'molecular similarity principle', compounds with similar chemical structures are more likely to possess similar physicochemical and hence, biological activities. The physicochemical and steric similarity of the target compounds was calculated with respect to the standard drugs (Nikolova and Jaworska, 2003). Firstly, the distance $d_i$ of a particular target compound $j$ to drug molecules, e.g. clozapine was calculated by the formula:

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

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, risperidone, etc. Then, the similarity of compound '$j$' to the standard drug was calculated as

$$\text{Similarity}\,(\%) = (1 - R) \times 100$$

where

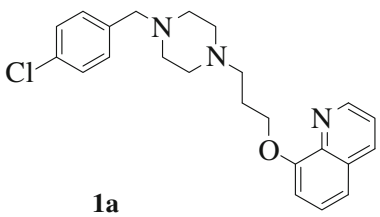
$$R = \sqrt{d^2}$$

is the quadratic mean (root mean square), a measure of central tendency.

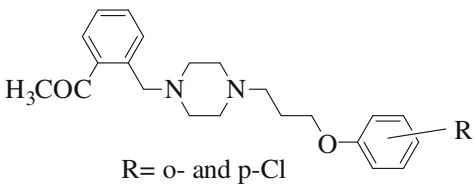
### *Computation of physicochemical properties*

Selected molecular parameters were computed for the target compounds as well as four established drugs possessing atypical antipsychotic profile, viz. clozapine, risperidone, ziprasidone and ketanserin using Chem3D Pro 12.0 (Table 1). Amongst the various molecular descriptors computed, the molecular surface area parameters, log *P* and volume parameters are particularly important for prediction of blood–brain barrier (BBB) penetration which is an essential feature required to be present in the compounds intended to be CNS active. Topological polar surface area, TPSA is a recognized parameter for prediction of drug transport properties (in this case, BBB penetration) and is specifically important for CNS compounds were also determined. Literature reports suggest 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. The values for these limits proposed in different literature reports are 90 $\text{Å}^2$ (van de Waterbeemd *et al*., 1998) and 60–70 $\text{Å}^2$ (Kelder *et al*., 1999). The TPSA values for our test compounds were found to be well within these limits (32.78–49.85) which shows that **7–14** have a potential to effectively cross the BBB. Further, lipophilicity correlates positively with BBB penetration and the values of Clog *P* for most of our test compounds were in the range (2.807–3.806) close to that of marketed CNS drugs.

The BBB penetration potential of compounds is essential for their CNS activity. This feature can be assessed through various computational methods with overall accuracies ranging from 75 to 97 % (Zhao *et al*., 2007). We calculated the log BB values for our target compounds using an online software program based on topological descriptors (http://www.chemsilico.com/CS_prBBB/BBBhome.html) (Table 1). The values were also determined for the selection of antipsychotics for comparison. Literature reports suggest that log BB values greater than 0.30 result for the compounds




**1a**




R= o- and p-Cl

**1b**

**Fig. 1** Quinoline and acetophenone-based lead compounds with atypical antipsychotic profile

**Table 1** Calculation of molecular properties and log BB values for target compounds and standard drugs

| Compound no. | Log BB[a] | MW | MR | SAS (Å$^2$) | SA (Å$^2$) | SEV (Å$^3$) | Ovality | Log *P* | TPSA (Å$^2$) | MTI | WI |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **7** | 0.36 | 372.89 | 107.464 | 664.604 | 366.854 | 327.914 | 1.595 | 3.806 | 32.78 | 15848 | 2167 |
| **8** | 0.29 | 372.89 | 107.464 | 658.254 | 364.438 | 327.099 | 1.587 | 3.806 | 32.78 | 15670 | 2129 |
| **9** | 0.34 | 386.924 | 111.276 | 699.254 | 385.634 | 342.953 | 1.625 | 3.371 | 32.78 | 17901 | 2440 |
| **10** | 0.26 | 386.924 | 111.276 | 693.532 | 382.995 | 342.68 | 1.617 | 3.371 | 32.78 | 17713 | 2400 |
| **11** | −0.06 | 386.88 | 107.296 | 662.123 | 362.224 | 328.283 | 1.577 | 3.242 | 49.85 | 17071 | 2378 |
| **12** | −0.09 | 386.88 | 107.296 | 652.129 | 361.611 | 332.565 | 1.556 | 3.242 | 49.85 | 16887 | 2338 |
| **13** | −0.08 | 400.907 | 111.107 | 680.432 | 376.056 | 345.712 | 1.579 | 2.8071 | 49.85 | 18970 | 2587 |
| **14** | −0.12 | 400.907 | 111.107 | 680.434 | 377.771 | 347.608 | 1.579 | 2.8071 | 49.85 | 18776 | 2587 |
| **CLZ** | 0.75 | 362.82 | 95.226 | 506.405 | 256.884 | 216.638 | 1.473 | 3.707 | 30.87 | 8127 | 1082 |
| **KET** | 0.89 | 395.427 | 106.778 | 609.934 | 311.188 | 261.484 | 1.574 | 2.368 | 69.72 | 18646 | 2596 |
| **ZIP** | −0.08 | 412.936 | 116.981 | 625.053 | 320.158 | 268.640 | 1.590 | 4.668 | 47.94 | 16979 | 2344 |
| **RIS** | −0.20 | 484.00 | 114.60 | 631.449 | 324.651 | 274.282 | 1.590 | 2.100 | 57.5 | 20311 | 2793 |

*MW* molecular weight, *MR* molar refractivity, *SAS* connolly solvent accessible surface area, *SA* connolly molecular surface area, *SEV* connolly solvent excluded volume, *TPSA* topological polar surface area, *MTI* molecular topological index, *WI* Wiener index, CLZ clozapine, *KET* ketanserine, *ZIP* Ziprasidone, *RIS* risperidone

[a] Calcd. online (http://www.chemsilico.com/CS_prBBB/BBBhome.html)

which are able to cross the BBB readily. In comparison, log BB value below −1.00 for any compound signifies its poor distribution to the brain (Iyer *et al*., 2002). The log BB values for the chlorobenzyl-based compounds **7–10** (0.26–0.36) were found to be greater than or approaching 0.30, suggesting that these have an excellent potential for BBB penetration. The chlorobenzoyl derivatives **11–14** had values ranging from −0.12 to −0.06 suggesting a moderate BBB penetration.

The calculation results obtained for assessment of the structural similarity of the prepared compounds to standard drugs are presented in Table 2. The compounds **7–14** showed good physicochemical similarity to drugs with extended chain structure as risperidone (68–84 %), ziprasidone (82–85 %) and ketanserin (68–85 %). The similarity values were very less when compared with the fused system dibenzodiazepine derivative clozapine. In particular, the benzoyl derivatives **11–14** showed much lesser similarity values (27–33 %) with respect to clozapine compared to the benzyl derivatives **7–10** (50–61 %). Based upon these results, **7–14** were synthesized and subjected to pharmacological evaluation.

**Table 2** Similarity values of target compounds with respect to the standard drugs

| Compound no. | Clozapine | Similarity[a,b] (in %) to | | |
|---|---|---|---|---|
| | | Ketanserin | Ziprasidone | Risperidone |
| **7** | 50.03 | 67.59 | 85.02 | 67.71 |
| **8** | 51.65 | 72.02 | 85.08 | 67.78 |
| **9** | 61.76 | 75.00 | 82.57 | 73.26 |
| **10** | 60.42 | 75.06 | 85.13 | 73.43 |
| **11** | 27.19 | 83.39 | 82.22 | 83.95 |
| **12** | 28.78 | 84.91 | 82.60 | 84.01 |
| **13** | 31.25 | 82.85 | 82.92 | 83.68 |
| **14** | 33.33 | 83.65 | 83.37 | 84.06 |

[a] $(1 - R) \times 100$ where $R$ is the 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

## Synthesis of compounds

Synthetic scheme for preparation of target compounds is summarized in Fig. 2. In the first step, the starting compounds 3-hydroxybenzaldehyde and 3-hydroxyacetophenone were converted to their 3-chloropropyl ether derivatives 3-(3-chloropropoxy) benzaldehyde (**1**) and 1-[3-(3-chloropropoxy)phenyl] ethanone (**2**) by refluxing with 1-bromo-3-chloropropane and potassium carbonate in acetone by variation of a previously reported procedure (Murugananthan *et al*., 2004).

The *o*- and *p*-chloro benzyl/chlorobenzoyl piperazines **3–6** were obtained in good yields (80–85 %) by reaction of their corresponding aryl/aroyl chlorides with piperazine from our previously reported procedure (Bali *et al*., 2009). In these reactions, two disubstituted by-products, 1,4-bis-(2-chlorobenzyl) piperazine and 1,4-bis(4-chlorobenzyl) piperazine were also obtained in very low yields (nearly 2.5 %) which could be separated from the desired monosubstituted products by filtration. The quantity of disubstituted products was minimized by half molar quantity of

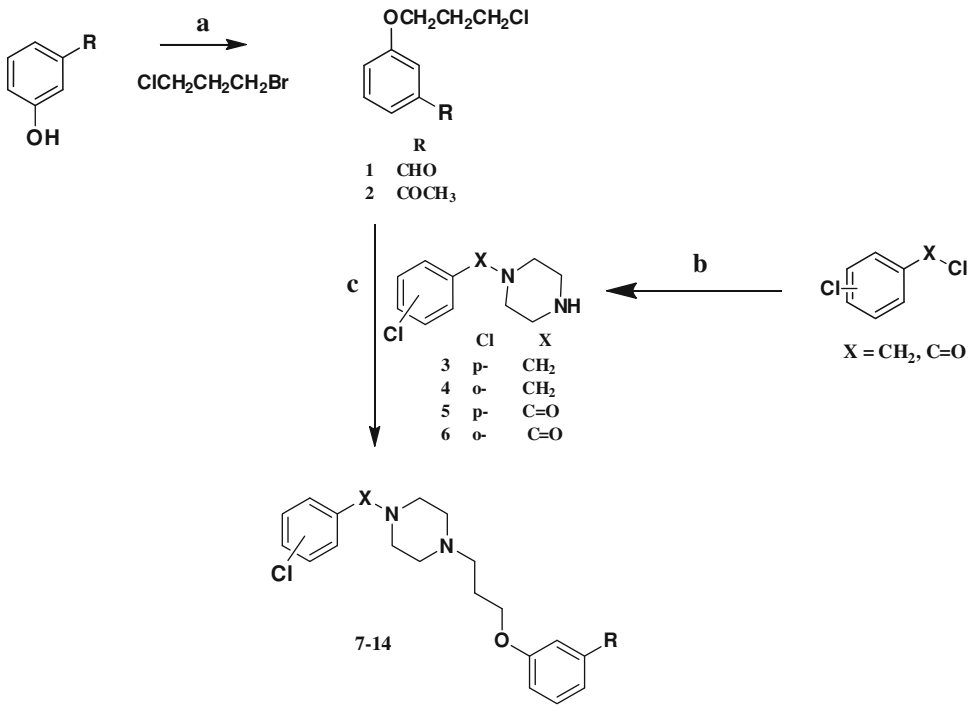


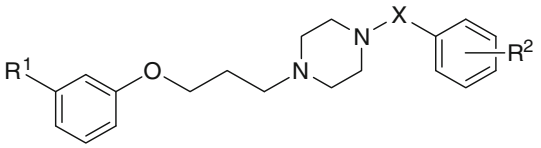

**Fig. 2** Synthetic scheme for preparation of the target compounds. Reagents and conditions: (*a*) acetone, $K_2CO_3$, reflux, (*b*) piperazine (twice molar quantity), abs. EtOH, and (*c*) $K_2CO_3$, DMF, 70 °C, 3–10 h reflux

aryl/aroyl chlorides, as compared to the piperazine. The final target compounds 3-[3-{4-(X-chlorobenzyl)piperazin-1-yl}propoxy]benzaldehydes **(7–8)**, 3-[3-{4-(X-chlorobenzoyl)piperazin-1-yl}propoxy]benzaldehydes **(11–12)**, 3-[3-{4-(X-chlorobenzyl)piperazin-1-yl}propoxy]phenylethanones **(9–10)** and 3-[3-{4-(X-chlorobenzoyl) piperazin-1-yl}propoxy] phenylethanones **(13–14)** were prepared by reacting the corresponding 3-chloropropyl ether derivatives with the chlorobenzyl piperazines/chlorobenzoyl piperazines in dimethyl formamide. All the reactions were monitored by TLC. The final products were purified by column chromatography and characterized through UV, IR, NMR and mass spectroscopic data.

## Preliminary pharmacological evaluation for atypical antipsychotic effect

The prepared test compounds were subjected to preliminary pharmacological evaluation for their potential atypical antipsychotic effect. Behavioural tests were performed to determine their ability to antagonize apomorphine-induced mesh climbing behaviour (indicative of dopaminergic antagonism in mesocorticolimbic pathway associated with antipsychotic effect) and apomorphine-induced stereotypy (characteristic of antagonism in nigrostriatal system linked to extrapyramidal symptoms) in mice (Vogel, 2007). In animal models, the atypical antipsychotics are identified by their inhibition of apomorphine-induced climbing response along with weak or no inhibition of apomorphine-induced stereotypy. The results from the pharmacological evaluation of the target compounds are given in Tables 3 and 4 and depicted graphically in Figs. 3 and 4. The test compounds **7**, **8**, **9** and **10** possessing chlorobenzyl systems produced statistically significant reversal of apomorphine-induced mesh climbing indicating potential antipsychotic effect. This also correlates well with their log BB values which suggest an excellent BBB penetration. However, the CHO-based compound **7** also reversed apomorphine-induced stereotypy signifying that it is also acting in nigrostriatal regions of the brain and hence, lacking an atypical profile. In comparison, the activity in mesh climbing assay for **8**, **9** and **10** was coupled with negative results in stereotypy assay, thus implying that these compounds have potential atypical antipsychotic profile. The results with the *m*-$COCH_3$-based compounds **9** and **10** ($ED_{50}$ values 7.2 and 8.0 mg $kg^{-1}$. respectively) suggest a potency slightly higher than their corresponding *o*-$COCH_3$ derivatives reported earlier ($ED_{50}$ values 10.0 and 10.5 mg $kg^{-1}$, respectively) and much higher than their *p*-$COCH_3$ analogues ($ED_{50}$ values 50.0 and 23.0 mg $kg^{-1}$, respectively) which also lack atypical antipsychotic profile (Bali *et al.*, 2010). Further, the *o*-Cl derivative possessing CHO group has shown atypical profile along with higher potency

**Table 3** Pharmacological evaluation for atypical antipsychotic profile




| Compound | $R^1$ | $R^2$ | X | Reversal of apomorphine-induced mesh climbing[a] | Reversal of apomorphine-induced stereotypy[a] | $ED^b_{50}$ (mg/kg) (mesh climbing) | Log $ED_{50}$ |
|---|---|---|---|---|---|---|---|
| **7** | CHO | *p*-Cl | $CH_2$ | + | + | 10.0 | 1 |
| **8** | CHO | *o*-Cl | $CH_2$ | + | − | 06.3 | 0.799 |
| **9** | $COCH_3$ | *p*-Cl | $CH_2$ | + | − | 07.2 | 0.857 |
| **10** | $COCH_3$ | *o*-Cl | $CH_2$ | + | − | 08.0 | 0.903 |
| **11** | CHO | *p*-Cl | C=O | − | + | – | – |
| **12** | CHO | *o*-Cl | C=O | − | + | – | – |
| **13** | $COCH_3$ | *p*-Cl | C=O | − | + | – | – |
| **14** | $COCH_3$ | *o*-Cl | C=O | − | + | – | – |

[a] Statistically significant reduction compared to control at $p < 0.05$

[b] Calculated from activity at three dose levels 5.0, 7.5 and 10.0 mg/kg

compared to the acetyl derivatives. Interestingly, the four chlorobenzoyl-based compounds **11**, **12**, **13** and **14** did not produce statistically significant reversal of apomorphine-induced mesh climbing at $p < 0.05$, but these caused statistically significant reversal in the stereotypy assay. These compounds otherwise possess a reasonable physicochemical profile in terms of moderate BBB penetration potential, good Clog *P* and TPSA values. These results are in good correlation with our previous results with the quinoline-based compounds and *o*- and *p*-based acetophenone derivatives. This suggests that the presence of carbonyl group next to phenyl group hinders their interactions with the mesocorticolimbic areas and such compounds may be only having the potential to bind to nigrostriatal areas of the brain instead of giving the desired action in the mesocorticolimbic regions.

## Experimental protocols

### Chemistry

Infrared spectra were recorded in KBr pellets on Perkin Elmer RX 1 spectrophotometer. Proton NMR was recorded on Bruker Avance-II, 400 MHz instrument. For NMR, solutions were made in deuterated chloroform and deuterated dimethyl sulfoxide (DMSO)-$d_6$ employing tetramethylsilane (TMS) as internal reference. Mass spectra were obtained using Vg-11-250 J70S spectrometer at 70 eV using electron ionization (EI source). For mass spectra, solutions were made in HPLC grade methanol.

*Preparation of 3-(3-chloropropoxy)benzaldehyde and 1-[3-(3-chloropropoxy)phenyl]ethanone (**1–2**)*

Mixture of 3-hydroxybenzaldehyde/3-hydroxyacetophenone (33 mmol), 1-bromo-3-chloro propane (10 ml, 100 mmol) and anhydrous potassium carbonate (6.91 g, 50 mmol) in 70 ml of acetone was heated under reflux for 8–12 h. After removal of solid material by filtration, the solvent was evaporated under vacuum yielding 3-(3-chloropropoxy) benzaldehyde (**1**) and 1-[3-(3-chloropropoxy) phenyl]ethanone (**2**) in their respective reactions.

*3-(3-Chloropropoxy)benzaldehyde (**1**)*

Light yellow oil. Yield 62 %. bp 89–92 °C. FTIR (KBr, $cm^{-1}$): 3068, 2961, 2880, 2827, 2731, 1698, 1593, 1483, 1450, 1388, 1261, 1041, 886, 787 and 652. $^1$H-NMR (400 MHz; $CDCl_3$, $\delta$, *J*): 9.97 (s, 1H); 7.48–7.46 (m, 2H); 7.40 (t, 1H, $J = 7.4$ Hz); 7.20–7.17 (m, 1H); 4.17 (t, 2H, $J = 7.2$ Hz); 3.76 (t, 2H, $J = 7.2$ Hz); 2.26 (quintet, 2H, $J = 7.2$ Hz). MS [EI, *m/z* (relative intensity)]: 200 (42) [M+2], 198 (100) [$M^{-+}$].

*1-[3-(3-Chloropropoxy)phenyl]ethanone (**2**)*

Light yellow oil. Yield 72 %. bp 86–89 °C. FTIR (KBr, $cm^{-1}$): 3072, 2963, 1684, 1587, 1440, 1272, 1215, 1042, 874, 784 and 687. $^1$H-NMR (400 MHz; $CDCl_3$, $\delta$, *J*): 7.54 (dt, 1H, $J = 7.6$ Hz, 1.2 Hz); 7.49 (t, 1H, $J = 2.6$ Hz); 7.37 (t, 1H, $J = 7.8$ Hz); 7.11 (dd, 1H, $J = 8.2$ Hz, 2.6 Hz); 4.16 (t, 2H, $J = 7.4$ Hz); 3.75 (t, 2H, $J = 7.4$ Hz); 2.59 (s, 3H);

**Table 4** Mean score in apomorphine-induced mesh climbing and stereotypy assays

| Treatment | Time (min) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 10 | | 15 | | 20 | | 25 | | 30 | |
| | C | St | C | St | C | St | C | St | C | St |
| Naïve group | 8.4 ± 0.40[a] | 6.6 ± 0.24[a] | 8.2 ± 0.37[a] | 6.2 ± 0.37[a] | 7.6 ± 0.40[a] | 5.8 ± 0.37[a] | 7.4 ± 0.24[a] | 5.4 ± 0.51[a] | 6.6 ± 0.24[a] | 4.2 ± 0.58 |
| Control | 12.8 ± 0.37 | 8.0 ± 0.44 | 13.0 ± 0.44 | 8.6 ± 0.4 | 10.8 ± 0.37 | 8.4 ± 0.24 | 12.6 ± 0.24 | 8.4 ± 0.40 | 12.2 ± 0.58 | 7.8 ± 0.37 |
| **Clozapine** | 5.2 ± 0.58[a] | 8.2 ± 0.37 | 5.0 ± 0.31[a] | 8.4 ± 0.24 | 5.0 ± 0.44[a] | 8.2 ± 0.37 | 4.8 ± 0.37[a] | 8.2 ± 0.37 | 4.8 ± 0.20[a] | 7.6 ± 0.40 |
| **7** | 6.6 ± 0.67[a] | 3.8 ± 0.37[b] | 6.4 ± 0.67[a] | 3.6 ± 0.24[b] | 6.6 ± 0.24[a] | 4.2 ± 0.37[b] | 5.8 ± 0.58[a] | 3.2 ± 0.20[b] | 5.2 ± 0.49[a] | 3.0 ± 0.31[b] |
| **8** | 5.2 ± 0.37[a] | 8.2 ± 0.37 | 5.2 ± 0.20[a] | 7.8 ± 0.37 | 4.8 ± 0.37[a] | 7.4 ± 0.4 | 4.2 ± 0.37[a] | 7.2 ± 0.37 | 4.0 ± 0.31[a] | 6.8 ± 0.37[a] |
| **9** | 5.4 ± 0.40[a] | 7.8 ± 0.37 | 5.0 ± 0.31[a] | 7.6 ± 0.40 | 5.2 ± 0.58[a] | 7.6 ± 0.40 | 4.4 ± 0.24[a] | 8.0 ± 0.31 | 3.8 ± 0.37[a] | 7.4 ± 0.24[a] |
| **10** | 5.6 ± 0.51[a] | 8.4 ± 0.24 | 5.4 ± 0.24[a] | 8.0 ± 0.31 | 6.4 ± 0.40[a] | 8.2 ± 0.37 | 4.8 ± 0.20[a] | 7.8 ± 0.20 | 4.0 ± 0.31[a] | 7.2 ± 0.37[a] |
| **11** | 11.8 ± 0.36 | 4.0 ± 0.36[b] | 12.2 ± 0.34 | 3.8 ± 0.30[b] | 11.9 ± 0.29 | 3.3 ± 0.29[b] | 12.4 ± 0.36 | 3.0 ± 0.30[b] | 12.3 ± 0.38 | 3.0 ± 0.28[b] |
| **12** | 12.0 ± 0.32 | 4.2 ± 0.38[b] | 12.8 ± 0.30 | 3.8 ± 0.34[b] | 12.6 ± 0.27 | 3.4 ± 0.32[b] | 12.5 ± 0.36 | 3.2 ± 0.27[b] | 12.2 ± 0.36 | 3.2 ± 0.29[b] |
| **13** | 11.9 ± 0.36 | 4.1 ± 0.38[b] | 12.6 ± 0.30 | 3.8 ± 0.33[b] | 12.5 ± 0.33 | 3.4 ± 0.30[b] | 12.2 ± 0.28 | 3.1 ± 0.28[b] | 11.9 ± 0.38 | 3.0 ± 0.29[b] |
| **14** | 12.1 ± 0.36 | 3.9 ± 0.40[b] | 13.0 ± 0.36 | 3.8 ± 0.35[b] | 12.2 ± 0.34 | 3.6 ± 0.28[b] | 12.2 ± 0.28 | 3.2 ± 0.30[b] | 12.0 ± 0.26 | 3.0 ± 0.30[b] |

All values are expressed as mean ± SEM. ($n = 5$)

*C* apomorphine-induced mesh climbing, *St* apomorphine-induced stereotypy

[a] Significantly different from control at $p < 0.001$(one way ANOVA)

[b] Significantly different from control at $p < 0.05$ (TUKEY test)

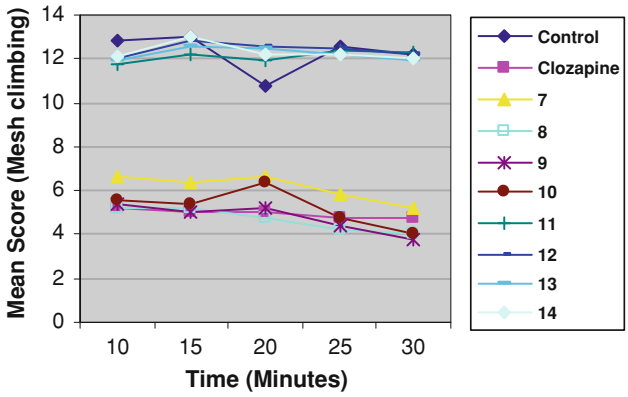



**Fig. 3** Mean score in apomorphine-induced mesh climbing assay

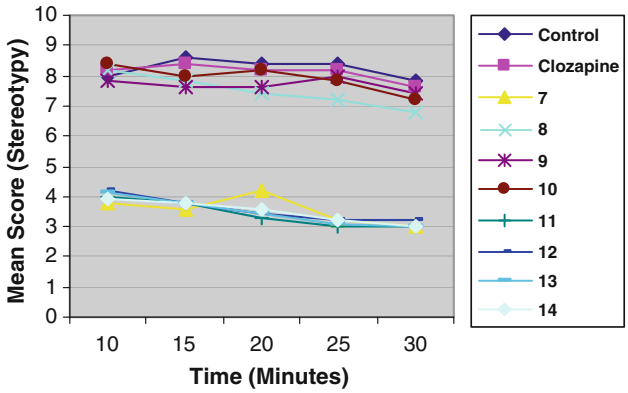



**Fig. 4** Mean score in apomorphine-induced stereotypy assay

2.25 (quintet, 2H, $J = 7.4$ Hz). MS [EI, *m/z* (relative intensity)]: 214 (45) [M+2], 212 (100) [$M^{\cdot+}$].

*Preparation of 1-(X-chlorobenzyl)-piperazines (**3–4**), the corresponding benzoyl derivatives (**5–6**)*

To the solution of piperazine (1.72 g, 20 mmol) in absolute ethanol (10 ml), the corresponding chlorobenzyl- and chlorobenzoyl-chlorides (10 mmol) were added dropwise and the reaction was allowed to proceed for 4–6 h at room temperature. To the contents of the reaction mixture, 100 mol of distilled water was then added and the precipitated disubstituted by-products were filtered out. Removal of the solvent under vacuum afforded the crude product which was recrystallized from methanol to obtain crystals of the pure compounds.

*1-(4-Chlorobenzyl)-piperazine (**3**)*

Yield 60.5 %. mp 150 °C. FTIR (KBr, $cm^{-1}$): 3500–3200, 3017, 2938, 2804, 1609, 1475, 1426, 1186, 1090 and 661. $^1$H-NMR (400 MHz; $CDCl_3$, $\delta$, $J$): 7.27 (d, 2H, $J = 9.0$ Hz); 7.25 (d, 2H, $J = 9.0$ Hz); 3.48 (s, 2H); 2.97 (t, 4H, $J = 7.0$ Hz); 2.51 (broadened s, 4H); 1.83 (s, 1H, NH proton). MS [EI, *m/z* (relative intensity)]: 212 (0.9) [M+2], 210 (2.1) [$M^{\cdot+}$], 125(100) [Cl–$C_6H_4$–$CH_2$], 89.

*1-(2-Chlorobenzyl)-piperazine (**4**)*

Yield 66.7 %. mp 157 °C. FTIR (KBr, $cm^{-1}$): 3500–3200, 3011, 2932, 2844, 1623, 1426, 1143, 1046, 753 and 680. $^1$H-NMR (400 MHz; $CDCl_3$, $\delta$, $J$): 7.45 (dd, 1H, $J =$ 7.8 Hz, 1.3 Hz); 7.34 (dd, 1H, $J = 7.5$, 1.4 Hz); 7.24–7.15 (m, 2H); 3.47 (s, 2H); 2.87 (t, 4H, $J = 5.0$ Hz); 2.34 (broadened m, 4H); 2.14 (br, s, 1H, NH). MS [EI, *m/z* (relative intensity)]: 212 (0.9) [M+2], 210 (2.3) [$M^{\cdot+}$], 125 (100) [Cl–$C_6H_4$–$CH_2$], 89.

*1-(4-Chlorobenzoyl)-piperazine (**5**)*

Yield 82.6 %. mp 200 °C. FTIR (Nujol, $cm^{-1}$): 3500–3100, 3120, 2950, 2900, 2850, 1640, 1590, 1450, 1240, 1110, 740 and 710. $^1$H-NMR (400 MHz; $CDCl_3$, $\delta$, $J$): 7.40 (d, 2H, $J = 11.0$ Hz); 7.32 (d, 2H, $J = 11.0$ Hz); 3.71 (s, 2H), 3.41 (s, 2H); 2.86 (s, 4H); 2.08 (s, 1H, NH). MS [EI, *m/z* (relative intensity)]: 226 (0.7) [M+2], 224 (2.6) [$M^{\cdot+}$], 139 (26.8), 105 (100) [$C_6H_5CO$], 85, 77.

*1-(2-Chlorobenzoyl)-piperazine (**6**)*

Yield 80.5 %. mp 195 °C. FTIR (Nujol, $cm^{-1}$): 3500–3150, 3100, 2940, 2900, 2850, 1679, 1595, 1450, 1230, 1100, 745 and 710. $^1$H-NMR (400 MHz; $CDCl_3$, $\delta$, $J$): 7.57 (m, 2H); 7.42 (t, 1H, $J = 8.0$ Hz); 7.32 (dd, 1H, $J = 8.0$, 1.8 Hz); 3.61 (broadened s, 2H), 3.41 (s, 2H); 2.86 (s, 4H); 2.08 (s, 1H, NH). MS [EI, *m/z* (relative intensity)]: 226 (1.7) [M+2], 224 (3.5) [$M^{\cdot+}$], 139 (30.8), 105 (100) [$C_6H_5CO$], 85, 77.

*Preparation of 3-[3-{4-(X-chlorobenzyl) piperazin-1-yl}propoxy] benzaldehydes (**7–8**), corresponding phenyl ethanones (**9–10**) and corresponding chlorobenzoyl derivatives (**11–14**)*

A suspension of potassium carbonate (0.647 g, 4.7 mmol) was prepared in 5 ml of DMF and 1-(X-chlorobenzyl) piperazines/their corresponding chlorobenzoyl analogues (4.7 mmol) were added with stirring. To the resulting suspension, a solution of 3-(3-chloropropoxy)benzaldehyde/1-[3-(3-chloropropoxy) phenyl]ethanone (3.1 mmol) in DMF (5 ml) was added dropwise with stirring. The solution was heated at a temperature of 70–80 °C for 3–10 h and filtered. The filtrate was added to 60 ml water. The resulting solution was extracted with chloroform, the

chloroform layer was washed with saline and dried over anhydrous sodium sulphate. Removal of the solvent under vacuum afforded the crude product which was purified by column chromatography using silica gel (60–80 mesh), employing petroleum ether along with varying amounts of ethyl acetate and methanol as solvent.

*3-[3-{4-(4-Chlorobenzyl) piperazin-1-yl}propoxy]benzaldehyde (**7**)*

Yield 63.9 %. mp 275–278 °C. FTIR (KBr, $cm^{-1}$): 3022, 2941, 2812, 1698, 1593, 1452, 1386, 1262, 1150, 1089, 1010, 933, 841, 760 and 681. $^1$H-NMR (400 MHz; $CDCl_3$), $\delta$: 9.89 (s, 1H); 7.38–7.36 (m, 2H); 7.30 (t, 1H, $J = 7.5$ Hz); 7.22–7.18 (m, 4H); 7.11–7.08 (m, 1H); 4.00 (t, 2H, $J = 7.4$ Hz); 3.42 (s, 2H), 2.54–2.46 (broadened m, 10H); 1.96 (quintet, 2H, $J = 7.4$ Hz). MS [EI, *m/z* (relative intensity)]: 375 (49.0) [M+2], 373 (100) [$M^{\cdot+}$], 262 (18) [M–PhCl], 247 (10) [M–($ClC_6H_4CH_3$], 126 (1.8) [$ClC_6H_4CH_3$], 100, 99. Anal. Calcd. for $C_{21}H_{25}N_2O_2Cl$: C, 67.64; H, 6.76; N, 6.65. Found: C, 66.08; H, 6.12; N, 6.45.

*3-[3-{4-(2-Chlorobenzyl)piperazin-1-yl}propoxy]benzaldehyde (**8**)*

Yield 66.7 %. mp 274–277 °C. FTIR (KBr, $cm^{-1}$): 3064, 2942, 2812, 1698, 1594, 1448, 1386, 1263, 1150, 1048, 1010, 933, 831, 754 and 683. $^1$H-NMR (400 MHz; $CDCl_3$), $\delta$: 9.96 (s, 1H); 7.46 (dd, 1H, $J = 7.8$, 1.5 Hz); 7.44–7.43 (m, 2H); 7.38 (t, 1H, $J = 7.6$ Hz); 7.35 (dd, 1H, $J = 7.8$, 1.5 Hz); 7.23 (td, 1H, J = 7.4, 1.5 Hz); 7.20–7.16 (m, 2H); 4.07 (t, 2H, $J = 7.2$ Hz); 3.63 (s, 2H), 2.56–2.48 (broadened m, 10H); 2.00 (quintet, 2H, $J = 7.2$ Hz). MS [EI, *m/z* (relative intensity)]: 375 (45.0) [M+2], 373 (100) [$M^{\cdot+}$], 262 (5.8) [M–PhCl], 247 (10) [M–($ClC_6H_4CH_3$], 125 (3.0) [$ClC_6H_4CH_2$], 100, 99. Anal. Calcd. for $C_{21}H_{25}N_2O_2Cl$: C, 67.64; H, 6.76; N, 6.65. Found: C, 66.68; H, 6.23; N, 6.55.

*1-(3-[3-{4-(4-Chlorobenzyl)piperazin-1-yl}propoxy]phenyl)ethanone (**9**)*

Yield 61.1 %. mp 282–285 °C. FTIR (KBr, $cm^{-1}$): 3068, 2941, 1682, 1592, 1487, 1272, 1156, 1046, 1011, 956, 841, 791 and 688. $^1$H-NMR (400 MHz; $CDCl_3$, $\delta$, *J*): 7.52 (dt, 1H, $J = 7.7$, 1.1 Hz); 7.48–7.45 (m, 1H); 7.35 (t, 1H, $J = 7.9$ Hz); 7.27–7.25 (m, 4H); 7.10 (dd, 1H, $J = 8.2$, 2.6 Hz); 4.05 (t, 2H, $J = 7.1$ Hz); 3.47 (s, 2H), 2.59 (s, 3H), 2.55–2.49 (broadened m, 10H); 1.98 (quintet, 2H, $J = 7.1$ Hz). MS [EI, *m/z* (relative intensity)]: 389 (40.0) [M+2], 387 (100) [$M^{\cdot+}$], 261 (7.4) [M–($ClC_6H_4CH_3$], 125 (1.8) [$ClC_6H_4CH_2$]. Anal. Calcd. for $C_{22}H_{27}N_2O_2Cl$: C, 68.29; H, 7.03; N, 7.24. Found: C, 67.68; H, 6.73; N, 6.98.

*1-(3-[3-{4-(2-Chlorobenzyl)piperazin-1-yl}propoxy]phenyl)ethanone (**10**)*

Yield 58.3 %. mp 284–287 °C. FTIR (KBr, $cm^{-1}$): 3065, 2941, 1683, 1592, 1440, 1272, 1156, 1049, 1011, 830, 755, and 687. $^1$H-NMR (400 MHz; $CDCl_3$, $\delta$, *J*): 7.52 (dt, 1H, $J = 7.8$, 1.2 Hz); 7.47–7.45 (m, 2H); 7.36–7.32 (m, 2H); 7.22 (dt, 1H, $J = 7.8$, 1.4 Hz); 7.17 (dt, 1H, $J = 7.8$, 1.4 Hz); 7.10 (dd, 1H, $J = 8.2$, 2.6 Hz); 4.06 (t, 2H, $J = 7.2$ Hz); 3.63 (s, 2H), 2.57 (s, 3H), 2.55–2.51 (broadened m, 10H); 2.00 (quintet, 2H, $J = 7.2$ Hz). MS [EI, *m/z* (relative intensity)]: 389 (42.0) [M+2], 387 (100) [$M^{\cdot+}$], 261 (3.6) [M–($ClC_6H_4CH_3$], 125 (0.3) [$ClC_6H_4CH_2$]. Anal. Calcd. for $C_{22}H_{27}N_2O_2Cl$: C, 68.29; H, 7.03; N, 7.24. Found: C, 67.90; H, 6.88; N, 7.08.

*3-[3-{4-(4-Chlorobenzoyl) piperazin-1-yl}propoxy]benzaldehyde (**11**)*

Yield 62.5 %. mp 298–300 °C. FTIR (KBr, $cm^{-1}$): 3012, 2921, 2832, 1695, 1593, 1452, 1380, 1256, 1138, 1070, 1009, 923, 851, 765 and 670. $^1$H-NMR (400 MHz; $CDCl_3$, $\delta$, *J*): 9.80 (s, 1H); 7.86 (d, 2H, $J = 7.6$ Hz); 7.74 (t, 1H, $J = 7.5$ Hz); 7.56 (d, 2H, $J = 7.6$ Hz); 7.32–7.25 (m, 2H); 7.16 (dt, 1H, $J = 7.5$, 1.5 Hz); 4.02 (t, 2H, $J = 7.4$ Hz); 3.40–3.38 (m, 4H); 2.50–2.46 (broadened m, 6H); 1.85 (quintet, 2H, $J = 7.4$ Hz). MS [EI, *m/z* (relative intensity)]: 389 (49.0) [M+2], 387 (100) [$M^{\cdot+}$], 247 (18) [M–Cl $C_6H_4CHO$], 140 (9.8) [$ClC_6H_4CHO$]. Anal. Calcd. for $C_{21}H_{23}N_2O_3Cl$: C, 65.20; H, 5.99; N, 7.24. Found: C, 64.18; H, 5.65; N, 7.08.

*3-[3-{4-(2-Chlorobenzoyl) piperazin-1-yl}propoxy]benzaldehyde (**12**)*

Yield 66.5 %. mp 296–298 °C. FTIR (KBr, $cm^{-1}$): 3022, 2911, 2820, 1688, 1590, 1445, 1376, 1248, 1140, 1065, 1015, 920, 856, 760 and 673. $^1$H-NMR (400 MHz; $CDCl_3$, $\delta$, *J*): 9.76 (s, 1H); 7.83 (t, 1H, $J = 7.6$ Hz); 7.66–7.62 (m, 2H); 7.48 (td, 1H, $J = 7.6$, 1.4 Hz); 7.42–7.37 (m, 3H); 7.22 (dt, 1H, $J = 7.6$, 1.5 Hz); 4.00 (t, 2H, $J = 8.0$ Hz); 3.41–3.39 (broadened m, 4H); 2.52–2.46 (broadened m, 6H); 1.82 (quintet, 2H, $J = 8.0$ Hz). MS [EI, *m/z* (relative intensity)]: 389 (35.0) [M+2], 387 (100) [$M^{\cdot+}$], 247 (14.5) [M–$ClC_6H_4CHO$], 140 (7.8) [$ClC_6H_4CHO$]. Anal. Calcd. for $C_{21}H_{23}N_2O_3Cl$: C, 65.20; H, 5.99; N, 7.24. Found: C, 64.67; H, 5.58; N, 6.98.

*1-(3-[3-{4-(4-Chlorobenzoyl)piperazin-1-yl}propoxy]phenyl)ethanone (**13**)*

Yield 68.5 %. mp 296–298 °C. FTIR (KBr, $cm^{-1}$): 3042, 2921, 1688, 1590, 1467, 1265, 1160, 1038, 1010, 950, 848,

798 and 683. $^1$H-NMR (400 MHz; $CDCl_3$, $\delta$, $J$): 7.89 (d, 2H, $J = 7.7$ Hz); 7.72 (t, 1H, $J = 7.5$ Hz); 7.58 (d, 2H, $J = 7.7$ Hz); 7.38–7.35 (m, 2H); 7.10 (dt, 1H, $J = 7.5$, 1.5 Hz); 4.02 (t, 2H, $J = 7.4$ Hz); 3.40–3.38 (m, 4H); 2.52–2.48 (broadened m, 6H); 1.86 (quintet, 2H, $J =$ 7.4 Hz). MS [EI, *m/z* (relative intensity)]: 403 (37.0) [M+2], 401 (100) [$M^{\cdot+}$], 261 (9.9) [M–$ClC_6H_4CHO$], 140 (7.8) [$ClC_6H_4CHO$]. Anal. Calcd. for $C_{22}H_{25}N_2O_3Cl$: Elemental Analysis: C, 65.91; H, 6.29; N, 6.99. Found: C, 64.97; H, 5.98; N, 6.48.

*1-(3-[3-{4-(2-Chlorobenzoyl)piperazin-1-yl}propoxy]phenyl)ethanone (**14**)*

Yield 67.5 %. mp 299–300 °C. FTIR (KBr, $cm^{-1}$): 3019, 2924, 1690, 1586, 1444, 1370, 1238, 1150, 1069, 1010, 918, 853, 758 and 683. $^1$H-NMR (400 MHz; $CDCl_3$, $\delta$, $J$): 7.87–7.82 (m, 2H); 7.70 (t, 1H, $J = 7.6$ Hz); 7.67–7.64 (m, 2H); 7.45–7.37 (m, 2H); 7.18 (dt, 1H, $J = 7.6$, 1.5 Hz); 4.02 (t, 2H, $J = 7.8$ Hz); 3.42–3.39 (broadened m, 4H); 2.54–2.48 (broadened m, 6H); 1.90 (quintet, 2H, $J = 7.8$ Hz). MS [EI, *m/z* (relative intensity)]: 403 (35.0) [M+2], 401 (100) [$M^{\cdot+}$], 261 (7.9) [M–Cl $C_6H_4CHO$], 140 (8.8) [$ClC_6H_4CHO$]. Anal. Calcd. for $C_{22}H_{25}N_2O_3Cl$: C, 65.91; H, 6.29; N, 6.99. Found: C, 64.87; H, 5.98; N, 6.49.

## Pharmacology

Albino lyka mice (six mice in each group) of either sex (26–38 g) were used for all the experiments. The animals were kept in colony cages (six mice each), maintained on standard pellet diet, water ad libitum and left for 2 days for acclimatization before the experimental session. Prior permission from the Institutional Animal Ethics Committee (IAEC) was obtained and all experiments were conducted according to the suggested ethical guidelines for the care of laboratory animals and as per the approved protocol. Doses were selected by initial titration at different dose levels. All compounds were tested at three dose levels (5.0, 7.5 and 10 mg/kg) in apomorphine-induced mesh climbing and stereotypy assays. Clozapine group was employed as a standard (positive control) in dose levels of 2.5, 5.0 and 7.5 mg/kg. A 0.1 % solution of the surfactant Tween 80 prepared in distilled water was used as a vehicle to dissolve the target compounds. 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 ($p < 0.001$) and TUKEY test ($p < 0.05$) (Jandel Sigmastat version 2.0).

### *Apomorphine-induced mesh climbing assay*

Mice 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 groups were injected with the test compound intraperitoneally and returned to the home cage. Mice in the control groups were injected with normal saline intraperitoneally and returned to the home cage. Mice in the clozapine test groups were injected with clozapine intraperitoneally and returned to the home cage. After a gap of 10 min, apomorphine (2.5 mg/kg) was injected intraperitoneally. Mesh climbing behaviour was noted for the naïve or untreated group at the start and then, readings were noted at 10, 15, 20, 25 and 30 min after the apomorphine injection by placing the mice in the mesh cage for 60 s. Severity of the climbing behaviour was scored as: 1 (one, two or three paws on the mesh) and 2 (all four paws on the mesh).

### *Apomorphine-induced stereotypy assay*

The same albino lyka mice employed in the mesh climbing assay were used. Each mouse was injected with either the vehicle or the test compound or clozapine and returned to its home cage. After a gap of 10 min, apomorphine (2.5 mg/kg) was injected. Stereotypy scores were noted similarly at 10, 15, 20, 25 and 30 min after apomorphine injection by placing the animal in an inverted 500-ml beaker for 60 s. Scoring of stereotypy was done as: 1 (rearing, sniffing and grooming) and 2 (licking and biting).

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