Synthesis and Computational Studies on Aryloxypropyl Piperazine Derivatives as Potential Atypical Antipsychotic Agents

Alka Bali*, Abhishek Bhalla, Suman Bala and Rajesh Kumar

University Institute of Pharmaceutical Sciences, UGC Center of Advanced Study, Panjab University, Chandigarh, 160 014, India

Received July 08, 2011: Revised November 02, 2011: Accepted November 02, 2011

Abstract: A series of aryloxypropyl derivatives have been synthesized and evaluated for atypical antipsychotic activity in apomorphine induced mesh climbing and stereotypy assays in mice and the compounds displayed good efficacy coupled with an atypical profile. Investigation of the selected physicochemical parameters important for CNS activity suggested a good potential for CNS activity. All compounds showed excellent compliance with lipinski's rules for oral and CNS activity. Good physicochemical similarity was noted for the test compounds with respect to standard drugs and good brain permeation was suggested by their log BB values computed through an online software program.

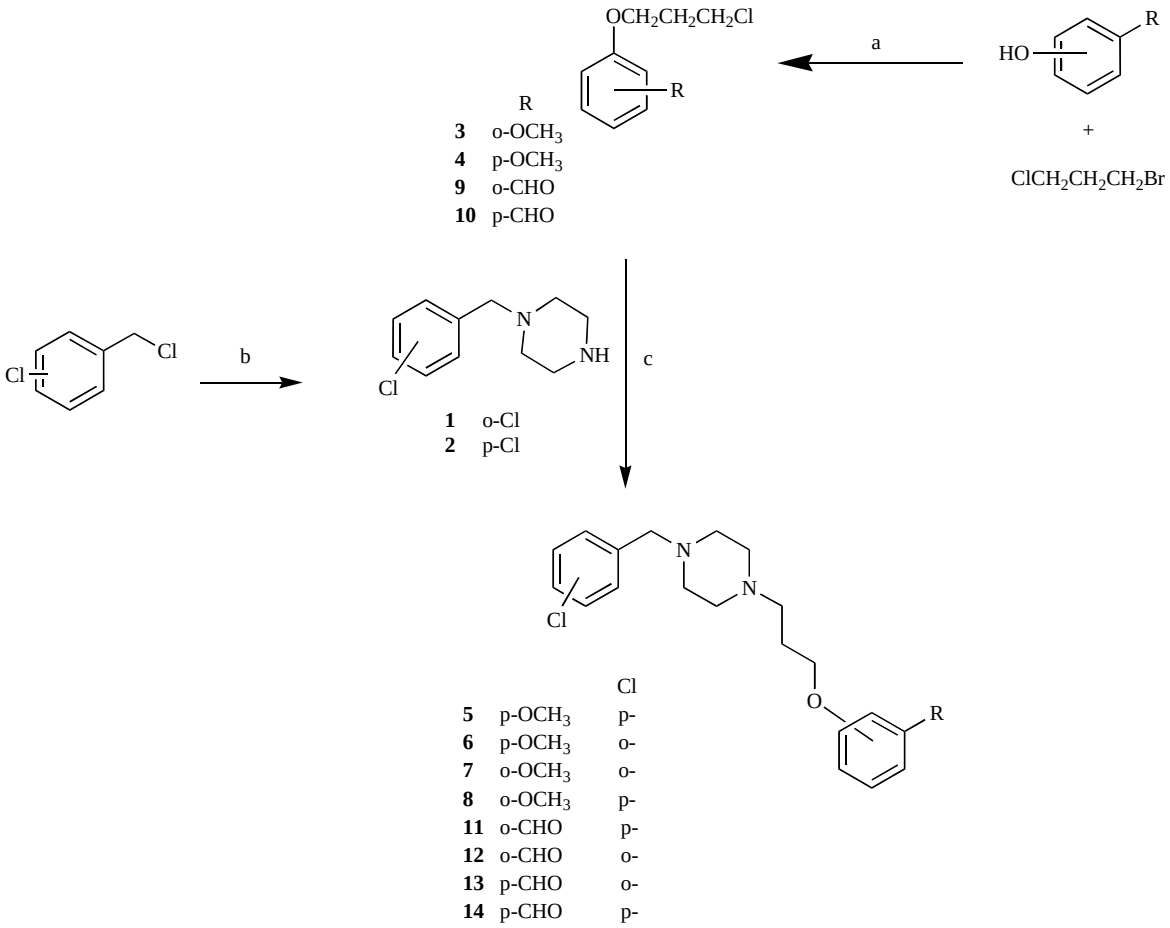
Keywords: Atypical antipsychotics, CNS agents, Lipinski rules, Log BB, Aryloxypiperazines, Piperazine.

1. INTRODUCTION

Schizophrenia is a complex psychological disorder afflicting nearly 24 million people worldwide which accounts for 1% of the population worldwide [1]. Neurochemical and/or anatomical abnormalities in the central nervous system (CNS) are proposed to be the underlying cause of this disorder [2]. Although, multiple approaches have been explored as research and development tools [3], yet, the dopaminergic hypothesis of schizophrenia has dominated the drug development in this field [4]. The activity of classical or typical antipsychotics such as haloperidol to alleviate the positive symptoms of the disease is related to their ability to block D_2 receptors in the mesocorticolimbic system, and the intensity of their mechanism related side effects i.e. muscular rigidity, bradykinesia, akathesia and galactorroea (due to increased prolactin release) is closely correlated with their ability to block the dopaminergic receptors in the nigrostriatal pathway [5, 6]. The dibenzodiazepine derivative clozapine [7], considered as the prototype of the new group of non-classical or atypical antipsychotics is indicated for patients refractory to conventional antipsychotics. Atypical antipsychotics possess a superior profile over conventional neuroleptics in being nearly devoid of extrapyramidal side effects and in being effective in alleviation of negative symptoms of the disease. Many, but not all, atypicals have been found to improve cognitive function, which could be their most important advantage with regard to efficacy [8]. However, their hematological safety, metabolic and other adverse effects [9-11] have been the cause of constant concern in context of their therapeutic importance. The complex etiology of schizophrenia arises from the multireceptor involvement in the disease. The numerous receptor binding approaches being followed for the development of atypical antipsychotics, *viz* dopaminergic [12,13], serotonergic [14, 15] and several others [16-18] suggest that the strategies of "intramolecular polypharmacy," in which a single drug possesses the capacity to affect multiple receptor types should to be more relevant in this regard. Further, each atypical possesses a unique portfolio of activities at receptors that may contribute to therapeutic effects or side effects [19]. Hence, behavioural tests based upon locomotor activity and stereotyped behaviour induced by a dopaminergic agonist (e.g., apomorphine) have been widely used to assess atypical antipsychotic profile. In these models, a significant reversal of the locomotor activity (mesh climbing behaviour) induced by a dopaminergic agonist like apomorphine is indicative of a potential antipsychotic profile arising from dopaminergic blockade in the mesolimbic areas of the brain. Further, the inability of the compound to reverse the apomorphine induced stereotyped behaviour suggests a low propensity to cause extrapyramidal symptoms by sparing the nigrostriatal system [20]. We had recently reported a series of quinoliloxypropyl piperazines and 1, 4-diaryl substituted piperazine derivatives [21-22] as potential atypical antipsychotics bearing acetyl substituent on the phenyl ring. We found it worthwhile to extend the series further by replacing $COCH_3$ group with other H-bond acceptor groups (methoxy/CHO) and investigate the resultant effect on their pharmacological activity in the same animal models to extend the structure activity relationships. In this paper, we therefore, report the synthesis, pharmacological evaluation and computational studies on the aryloxypiperazine series of compounds bearing methoxy/CHO substituents in place of $COCH_3$ group. Since, the compounds were intended to be CNS active, their potential to cross the blood brain barrier was computed through an online software program in terms of their log BB values. The physicochemical and steric similarity between standard drugs clozapine, ketanserin, ziprasidone and risperidone and the new analogs was calculated from a set of physicochemical properties computed using software programs.

*Address correspondence to this author at the University Institute of Pharmaceutical Sciences, UGC Center of Advanced Study, Panjab University, Chandigarh,160 014, India; Tel: 91-172-2534104 ; Fax: 91-172-541142; E-mail: alka.bali@rediffmail.com, alkaa.bali@gmail.com

1875-628X/12 $58.00+.00



Scheme 1. Synthetic scheme for preparation of the final compounds **5-8** and **11-14**.
Reagents and conditions: (a) K_2CO_3, 16-18 h (b) piperazine (twice molar quantity), abs. EtOH, (c) K_2CO_3, DMF, 700C, 3-10 h reflux

2. RESULTS AND DISCUSSION

2.1. Synthesis

The synthetic scheme followed for the preparation of the final compounds and their chemical structures are given in Scheme **1**. The first step was the preparation of 2- and 4-chlorobenzyl piperazines **1** and **2** by reaction of the corresponding chlorobenzyl chlorides with piperazine in absolute ethanol at room temperature. In these reactions, the formation of the respective disubstituted derivatives, *viz* 1,4-bis-(2- or 4- chlorobenzyl) piperazines was minimized by using half molar quantity of chlorobenzyl chloride, as compared to the piperazine. The compounds **1** and **2** were obtained in good yields (80-85%) and the disubstituted compounds (nearly 2.5% yields) were removed from the products by filtration. In the second step, 2- or 4-methoxyphenols were refluxed with 1-bromo-3-chloropropane with potassium carbonate in acetone by variation of our previously reported procedure [21] yielding their corresponding 3-chloropropyl ether derivatives **3** and **4**. The final compounds 1-(X-chlorobenzyl)-4-(3-(X'-methoxyphenoxy)propyl) piperazines **5** – **8** were obtained in good yields (65-70%) by coupling reaction of the corresponding chlorobenzyl piperazines **1** and **2** with the chloropropyl ether derivatives **3** and **4** in dimethylformamide at a temperature of 70^0C. Further, the starting compounds 2- and 4- hydroxybenzaldehydes were similarly reacted with 1-bromo-3-chloropropane and potassium carbonate in acetone to prepare their 3-chloropropyl ether derivatives 2- and 4-(3- chloropropoxy)benzaldehydes **9** and **10**. The final target compounds X'-[3-{4-(X-chlorobenzyl)piperazin-1-yl}propoxy] benzaldehydes **(11-14)** were prepared by coupling of **9** and **10** with the the respective chlorobenzyl piperazines **1** and **2** in dimethyl formamide. All the reactions were monitored by TLC and the final products were purified by column chromatography and characterized through UV, IR, NMR and mass spectroscopic data.

2.2. Preliminary Evaluation for Atypical Antipsychotic Effect

Amongst the established animal behavioural models, the inhibition of apomorphine induced climbing response in mice coupled with a weak or no inhibition of apomorphine induced stereotypy has been an accepted model for atypical profile. Prior permission of the Institutional Animal Ethics Committee (IAEC) was obtained and all experiments were conducted according to the approved protocol. The final compounds were evaluated for 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. Initial titration at different dose levels was done for selection of doses and three dose levels were employed for all the tested compounds. Clozapine was employed as a standard drug (positive control) in three 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). The results from the pharmacological evaluation of the target compounds are given in Tables **1** and **2** and depicted graphically in Figs. (**1** and **2**). A statistically significant reversal of apomorphine induced mesh climbing was noted for the test compounds **5**-**8** and **11**-**14**. Except for compound **11**, all other compounds did not produce a statistically significant reversal of apomorphine induced stereotypy. Negative results in stereotypy assay imply that nigrostriatal regions of the brain are being spared by the drug and this suggests the presence of a potential atypical profile. Compound **11**, on the other hand, displayed a conventional or 'typical' profile. In our previous studies, efficacy of the o-$COCH_3$ derivatives (ED_{50} values 10.0 and 10.5 mg kg^{-1} respectively) had been found to be much higher than their p-$COCH_3$ analogs (ED_{50} values 50.0 and 23.0 mg kg^{-1} respectively) and differences were noted in terms of atypical profile also, however, interestingly, this differentiation was not seen in case of the methoxy/CHO analogs with para- and ortho- analogs displaying very similar efficacies in the mesh climbing assay. The position of the substituents seems to be playing very little role in determining an atypical profile in this compound series. Considering the fact that both OCH_3 and CHO groups are electronically similar to acetyl group and can possibly show similar interactions with the target site(s), these differences may be attributed to their smaller steric bulk than acetyl moiety which seems to delineate the atypical profile from the position of the substituent on the phenyl ring. Moreover, the ED_{50} values of the compounds (calculated from the plot of log dose *vs* response at three dose levels) ranged from 3.1-5.7 mg kg^{-1}. These values are much lower in comparison with the values for the corresponding acetyl derivatives reported earlier (ED_{50} values 10.0 and 50.0 mg kg^{-1}) [22]. In order to correlate this enhanced efficacy with the change in the chemical structure, selected molecular parameters were calculated for the target compounds and some atypical antipsychotic drugs using Chem3D Pro 12.0 (Table **3**) and online softwares. Lipophilicity (ClogP) has been identified as important determinants for membrane permeability as well as blood brain barrier penetration. The values of ClogP for most of our test compounds were in the range (3.806-3.933) close to that of marketed CNS drugs. Further, the calculated log P values of the methoxy/CHO analogs (3.806-3.933) and their log BB values (0.27-0.53) were found to be quite close to the corresponding values for the $COCH_3$ derivatives (log P 3.371 and logBB 0.24-0.34). This signifies similarity in solubility profiles, permeability characteristics and BBB penetration potential of the methoxy/CHO and $COCH_3$ analogs. In this light, the observed differences in the activities of may be significantly (if not solely) attributable to the differences in chemical structures. Besides lipophilicity, several other molecular parameters have also been correlated with CNS activity, e.g.,cutoff limits have been given for molecular weights of CNS drugs for efficient BBB penetration. Mean value of MW for marketed CNS drugs is 310. Levin [23] and Van de Waterbeemd [24] have suggested these limits as 400 and 450 respectively and values (363-375) for all our compounds fall within these limits. Similarly, literature reports suggest that TPSA is a measure of a molecule's hydrogen bonding capacity and its value should not exceed a certain limit if the compound is intended to be CNS active. The values for these limits proposed are 60-70 $A^{\circ 2}$ [25] and should not exceed 90 $A^{\circ 2}$. The TPSA values for our test compounds were found to be well within these limits (32.78 - 49.85) which shows that all the test compounds have a potential to effectively cross the blood brain barrier. According to Lipinski's "Rule of five" [26], a good absorption and permeability is likely if MW is $\leq$500; LogP is $\leq$5; number of hydrogen bond donors (expressed as the sum of OHs and NHs) $\leq$5 and number of hydrogen bond acceptors (expressed as the sum of Ns and Os) $\leq$10 and number of rotatable bonds $\leq$10. These rules get more stringent for good CNS penetration as molecular weight $\leq$400; Log P $\leq$ 5; number of hydrogen bond donors $\leq$3 and number of hydrogen bond acceptors $\leq$7. As evident from Table **3**, all compounds comply well with these rules. Recently, several computational methods have been worked out to assess blood brain barrier penetration of compounds with overall accuracies ranging from 75% to 97% [27]. We calculated the log BB values for our target compounds using an online software program based on topological descriptors [28] (Table **3**). The values were also determined for the selection of antipsychotics for comparison. Experimental values of log BB published cover the range from about $^{-}$2.00 to +1.04. Literature reports suggest that log BB values greater than 0.30 result for the compounds which are able to cross the BBB readily. In comparison, log BB values below -1.00 signify a poor distribution to the brain [29]. The Log BB values for our present compound series (0.27 to 0.53) suggests an excellent potential for blood brain barrier penetration.

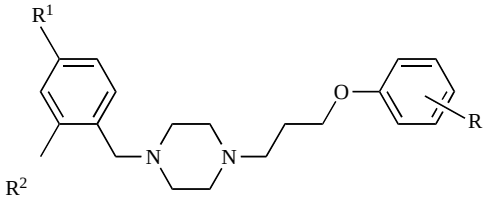
3. EXPERIMENTAL SECTION

The melting points reported are uncorrected. The Infrared spectra of these compounds were recorded in KBr pellets on Perkin Elmer PE RX 1 FTIR spectrophotometer. Proton NMR was recorded on Bruker Avance-II, 400 MHz instrument. For NMR, solutions were made in deuterated chloroform containing tetramethylsilane as internal reference. For mass spectra, solutions were made in HPLC grade methanol. Reactions were monitored and the homogeneity of the products was checked by TLC. Anhydrous sodium sulfate and anhydrous calcium chloride were used for drying solvent extracts.

3.1. General Procedure for Synthesis

A suspension of potassium carbonate (0.647g, 4.7mmol) was prepared in 5ml of DMF and 1-(X-chlorobenzyl) piperazines (4.7 mmol) were added with stirring. To the

Table 1. Chemical Structures and Pharmacological Evaluation of the Compounds for Atypical Antipsychotic Profile



Compound	R	R^1	R^2	Reversal of apomorphine induced mesh climbing[a]	Reversal of apomorphine induced stereotypy[a]	ED_{50}(mg/kg) (mesh climbing)	Log ED_{50}
5	p-OCH_3	Cl	H	+	_	3.10	0.49
6	p-OCH_3	H	Cl	+	_	3.10	0.49
7	o-OCH_3	H	Cl	+	_	5.01	0.70
8	o-OCH_3	Cl	H	+	_	5.20	0.72
11	o-CHO	Cl	H	+	+	5.70	0.755
12	o-CHO	H	Cl	+	_	4.50	0.653
13	p-CHO	H	Cl	+	_	4.60	0.662
14	p-CHO	Cl	H	+	_	5.00	0.698
Clozapine	-	-	-	+	_	3.01	0.479

[a]Statistically significant reduction compared to control assessed by one way ANOVA ($p < 0.001$) and TUKEY test ($p<0.05$).

Table 2. Mean Score in Apomorphine Induced Mesh Climbing and Stereotypy

Treatment	Average score at time (min)									
	10		15		20		25		30	
	C	St	C	St	C	St	C	St	C	St
Naïve	7.0 ±0.45	4.0±0.31	6.0±0.31[b]	3.0±0.31	6.0±0.55	3.2±0.20	5.4±0.51	2.2±0.20	5.8±0.37	1.4±0.51
Control	8.8 ±0.37	8.0±0.31	7.8±0.37	8.2±0.37	8.2±0.37	8.2±0.17	7.6±0.24	8.4±0.24	8.0±0.32	8.2±0.20
Clozapine (7.5mg/kg)	5.4±0.22[b]	8.4±0.10	5.2±0.09[b]	7.8±0.17	6.0±0.14[b]	8.2±0.17	5.0±0.20[b]	8.2±0.09	5.0±0.14[b]	7.6±0.17
5 (7.5mg/kg)	5.4±0.24[a]	8.2±0.20	4.2±0.29[a]	8.4±0.24	4.2±0.20[a]	7.4±0.24	4.6±0.24[a]	7.4±0.24	3.8±0.37[a]	7.6±0.20
6 (10mg/kg)	5.0±0.45[a]	7.8±0.20	5.0±0.31[a]	8.0±0.31	4.4±0.40[a]	8.0±0.31	4.4±0.24[a]	7.9±0.20	4.0±0.31[b]	7.8±0.20
7 (10mg/kg)	5.4±0.10[b]	8.0±0.18	5.4±0.18[b]	7.8±0.20	5.2±0.09[b]	7.6±0.11	4.8±0.09[b]	8.4±0.22	5.4±0.17[b]	7.9±0.11
8 (10mg/kg)	4.8±0.09[b]	8.2±0.11	4.8±0.21[b]	7.8±0.17	5.1±0.11[b]	8.0±0.14	4.4±0.11[b]	7.8±0.09	4.0±0.14[b]	7.2±0.17
11(10mg/kg)	4.8±0.37[a]	4.0±0.31[a]	4.6±0.24[a]	3.2±0.19[a]	4.6±0.24[a]	3.2±0.37	5.2±0.37[a]	4.0±0.31[a]	4.8±0.37[a]	3.6±0.24[a]
12(10mg/kg)	4.6±0.59[a]	8.0±0.54	4.8±0.58[a]	6.8±0.73	4.4±0.54[a]	7.8±0.73	4.4±0.48[a]	7.0±0.44	5.0 ±0.37[a]	7.6±0.51
13(7.5mg/kg)	5.0±.44[a]	7.6±0.73	4.0±0.31[a]	7.8±0.66[a]	4.4±0.24[a]	7.6±0.81	4.8±0.37[a]	7.8±0.37	4.6±0.51[a]	7.6±0.54
14(10mg/kg)	6.6±0.59[a]	8.0±0.54	6.2±0.58[a]	6.6±1.0	5.0±.54[a]	8.2±0.20	5.2±0.48[a]	6.8±0.48	5.2 ±0.37[a]	7.4±0.37

Readings shown are at highest dose level.
All values are expressed as mean ± S.E.M. (n=5); [a] significantly different from control at $p < 0.001$ (one way ANOVA).
[b]Significantly different from control at $P< 0.05$ (TUKEY test).
C: Apomorphine Induced mesh climbing St: Apomorphine Induced stereotypy.

resulting suspension, a solution of X-(3-chloropropoxy) benzaldehyde/X-(3-chloropropoxy)anisole (3.1 mmol) in DMF (5ml) was added dropwise with stirring. The solution was heated at a temperature of 70-80^{0}C for 3-10 hours and filtered. The filtrate was added to 60ml 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.

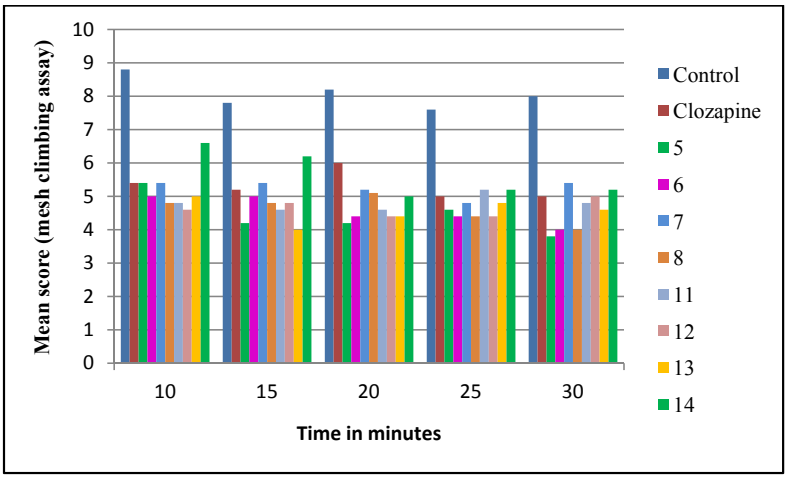


Fig. (1). Mean Score of Compounds in Apomorphine Induced Mesh Climbing Assay.

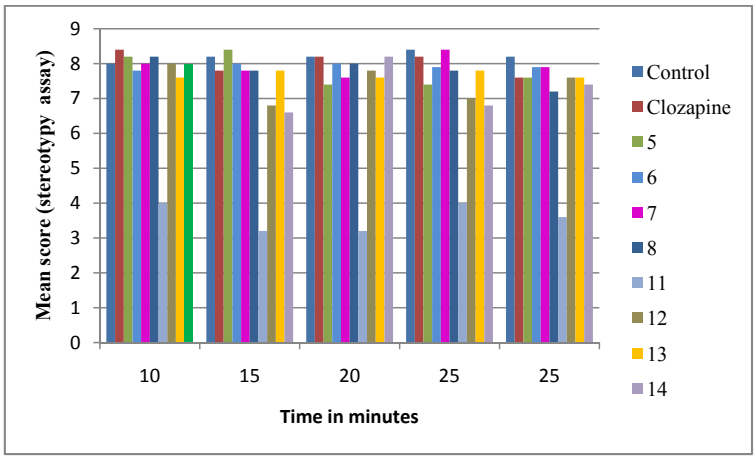


Fig. (2). Mean Score of Compounds in Apomorphine Induced Mesh Climbing Assay.

Table 3. Calculation of Molecular Properties and Log BB Values for Target Compounds and Standard Drugs

Comp. No.	Log BB[m]	M.W[a]	MR[b]	SAS[c] (A^2)	SA[d] (A^2)	SEV[e] (A^3)	Ovality	LogP	TPSA[f] (A^2)	MTI[g]	WI[h]	No. of H-bond acceptors	No. of H-bond donors	LR[n]
5	0.27	374.904	107.336	638.022	315.156	250.283	1.590	3.933	24.94	16370	2239	4	0	0
6	0.34	374.904	107.336	704.482	373.796	335.239	1.602	3.933	24.79	16192	2201	4	0	0
7	0.38	374.91	107.110	667.307	361.880	341.326	1.562	3.933	25.94	15716	2129	4	0	0
8	0.38	374.91	107.110	680.115	362.361	335.864	1.564	3.933	25.94	15894	2167	4	0	0
11	0.42	372.89	107.464	693.423	367.319	327.561	1.59	3.806	32.78	16324	2239	4	0	0
12	0.28	372.89	107.464	674.845	360.416	327.807	1.57	3.806	32.78	16146	2201	4	0	0
13	0.53	372.89	107.464	686.365	366.416	328.771	1.591	3.806	32.78	15848	2167	4	0	0
14	0.36	372.89	107.464	680.698	360.28	328.628	1.583	3.806	32.78	15640	2120	4	0	0
CLZ[i]	0.75	362.82	95.226	506.405	256.884	216.638	1.473	3.707	30.87	8127	1082	4	0	0
KET[j]	0.89	395.427	106.778	609.934	311.188	261.484	1.574	2.368	69.72	18646	2596	5	1	0
ZIP[k]	-0.08	412.936	116.981	625.053	320.158	268.640	1.590	4.668	47.94	16979	2344	5	0	0
RIS[l]	-0.20	484.00	114.60	631.449	324.651	274.282	1.590	2.100	57.5	20311	2793	6	0	0

[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]Wiener index; [i]Clozapine; [j]Ketanserine; [k]Ziprasidone; [l]Risperidone; [m]Calcd. Online[27]; [n]Violations from Lipinski's rules of five (CNS drugs).

1-(4-chlorobenzyl)-4-(3-(4-methoxyphenoxy)propyl)piperazine (5)

Reaction condition, 3 h. Yellowish solid; Yield 67.2%, mp 228-230^{0}C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 7.38 (2H, dd, *J*=7.0 Hz, 1.5 Hz), 7.26 (2H, dd, *J*=7.0 Hz, 1.5 Hz), 6.73 (4H, m), 3.86 (2H, t, *J*=6.4 Hz), 3.66 (3H, s), 3.54 (2H, s), 2.46 (10H, m), 1.89 (2H, quintet, *J*=7.4 Hz). FTIR (KBr) cm^{-1}: 3050, 2940, 2811, 1504, 1458, 1229, 1152, 1090, 1011, 943, 828, 768. MS [EI, m/z (relative intensity)]: 377 (9.7) [M+2], 375 (25.2) [$M^{\cdot +}$], 125 (100) [$ClC_6H_4CH_2^+$].

1-(2-chlorobenzyl)-4-(3-(4-methoxyphenoxy)propyl)piperazine (6)

Reaction condition, 3 h. Yellowish solid; Yield 67.2%, mp 212-214^{0}C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 7.38 (1H, dd, *J*=7.0 Hz, 1.4 Hz), 7.25 (1H, dd, *J*=7.0 Hz, 1.4 Hz), 7.10 (2H, m), 6.73 (4H, m), 3.86 (2H, t, *J*=6.4 Hz), 3.66 (3H, s), 3.54 (2H, s), 2.46 (10H, m), 1.89 (2H, quintet, *J*=7.4 Hz). FTIR (KBr) cm^{-1}: 3063, 2941, 2811, 1507, 1444, 1231, 1155, 1041, 1011, 947, 826, 753. MS [EI, m/z (relative intensity)]: 377 (7.8) [M+2], 375 (23.6) [$M^{\cdot +}$], 125 (100) [$ClC_6H_4CH_2^+$].

1-(2-chlorobenzyl)-4-(3-(2-methoxyphenoxy)propyl)piperazine (7)

Reaction condition, 6 h. Yellowish solid; Yield 62.0%, mp 190-192^{0}C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 7.46 (1H, dd, *J*=6.30 Hz, 1.68 Hz), 7.34 (1H, dd, *J*=6.28 Hz, 1.68 Hz), 7.18 (2H, m), 6.90 (4H, m), 4.10 (2H, t, *J*=6.20 Hz), 3.85 (3H, s), 3.64 (2H, s), 2.60 (10H, m, broadened), 2.34 (2H, quintet, *J*=6.8 Hz). FTIR (KBr) cm^{-1}: 3063, 2935, 2880, 1507, 1458, 1252, 1122, 1020, 1011, 947, 826, 753. MS [EI, m/z (relative intensity)]: 377 (40.7) [M+2], 375 (100) [$M^{\cdot +}$].

1-(4-chlorobenzyl)-4-(3-(2-methoxyphenoxy)propyl)piperazine (8)

Reaction condition, 6 h. Yellowish solid; Yield 62.0%, mp 190-192^{0}C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 7.26 (4H, m), 6.91 (4H, m), 4.17 (2H, t, *J*=6.10 Hz), 3.86 (3H, s), 3.45 (2H, s), 2.60 (10H, m, broadened), 2.30 (2H, quintet, *J*=6.1 Hz). FTIR (KBr) cm^{-1}: 3063, 2932, 2879, 1508, 1457, 1252, 1122, 1052, 1020, 943, 826, 741. MS [EI, m/z (relative intensity)]: 377 (26.5) [M+2], 375 (100) [$M^{\cdot +}$].

2-[3-{4-(4-chlorobenzyl)piperazin-1-yl}propoxy]benzaldehydes (11)

Creamy white solid; Yield 74.6%, mp 225-227^{0}C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 10.49 (1H, s), 7.84 (1H, dd, *J*=8.0 Hz, 1.8 Hz), 7.54 (1H, m), 7.25 (4H, m), 7.00 (2H, m), 4.25 (2H, t, *J*=7.2 Hz), 3.60 (2H, s), 2.60 (2H, t, *J*=7.2 Hz), 2.50 (8H, m, broadened), 2.04 (2H, quintet, *J*=7.2 Hz). FTIR (KBr) cm^{-1}: 3062, 2941, 2839, 1699, 1590, 1253, 1155, 1061, 1010, 946, 821 and 753. MS [EI, m/z (relative intensity)]: 375 (6.8) [M+2], 373 (20.6) [$M^{\cdot +}$], 125 (100) [$ClC_6H_4CH_2^+$].

2-[3-{4-(2-chlorobenzyl)piperazin-1-yl}propoxy]benzaldehydes (12)

Light yellow solid; Yield 77.6%, mp 205-207^{0}C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 10.50 (s, 1H), 7.84 (1H, dd, *J*=8.0 Hz, 1.8 Hz), 7.60 (1H, dd, *J*=8.0 Hz, 1.8 Hz), 7.50 (1H, dd, *J*=8.0 Hz, 1.8 Hz), 7.35 (1H, m), 7.25 (2H, m), 6.90 (2H, m), 4.23 (2H, t, *J*=7.2 Hz), 3.70 (2H, s), 3.40 (2H, t, *J*=7.2 Hz), 2.67 (8H, m, broadened), 2.04 (2H, quintet, *J*=7.2 Hz). FTIR (KBr) cm^{-1}: 3062, 2941, 2839, 1699, 1590, 1253, 1155, 1061, 1010, 946, 821 and 753. MS [EI, m/z (relative intensity)]: 375 (8.9) [M+2], 373 (26.8) [$M^{\cdot +}$], 125 (100) [$ClC_6H_4CH_2^+$].

4-[3-{4-(2-chlorobenzyl)piperazin-1-yl}propoxy]benzaldehydes (13)

Light yellow solid; Yield 75.6%, mp 205-207^{0}C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 9.87 (1H, s), 7.89 (2H, d, *J*=8.6 Hz), 7.48 (1H, dd, *J*=7.2 Hz, 1.4 Hz), 7.39 (1H, dd, *J*=7.2 Hz, 1.4 Hz), 7.20 (2H, m), 7.00 (2H, d, *J*=8.6 Hz), 4.30 (2H, t, *J*=7.0 Hz), 4.15 (2H, t, *J*=7.0 Hz), 3.54 (2H, s), 2.56 (8H, m, broadened), 2.00 (2H, quintet, *J*=7.0 Hz). FTIR (KBr) cm^{-1}: 3063, 2940, 2811, 1669, 1600, 1509, 1393, 1256, 1159, 1049, 1011, 947, 832 and 754. MS [EI, m/z (relative intensity)]: 375 (6.8) [M+2], 373 (20.2) [$M^{\cdot +}$], 125 (100) [$ClC_6H_4CH_2^+$].

4-[3-{4-(4-chlorobenzyl)piperazin-1-yl}propoxy]benzaldehydes (14)

Light yellow solid; Yield 72.4%, mp 235-237^{0}C. ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 9.87 (1H, s), 7.80 (2H, d, *J*=8.0 Hz), 7.27 (4H, m), 6.98 (2H, d, *J*=8.0 Hz), 3.56 (2H, t, *J*=6.8 Hz), 3.50 (2H, s), 3.30 (2H, t, *J*=7.0 Hz), 2.46 (8H, m, broadened), 2.01 (2H, quintet, *J*=7.0 Hz). FTIR (KBr) cm^{-1}: 3065, 2942, 2814, 1687, 1599, 1404, 1256, 1159, 1088, 1012, 951, 834 and 690. MS [EI, m/z (relative intensity)]: 375 (7.0) [M+2], 373 (24.2) [$M^{\cdot +}$], 125 (100) [$ClC_6H_4CH_2^+$].

3.2. Atypical Antipsychotic Activity

Albino lyka mice (6 mice in each group) of either sex (26-38 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 groups, control groups and clozapine groups were injected with the test compound, normal saline and clozapine intraperitoneally and returned to the home cage. After a gap of ten minutes, 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 seconds. 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). The same albino lyka mice employed in the mesh climbing assay were used for the stereotypy assay and response was 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 seconds. Scoring of stereotypy was done as: 1 (rearing, sniffing, grooming) and 2 (licking, biting).

4. CONCLUSION

A series of aryloxypiperazines having OCH_3/CHO substituents have been synthesized and a potential atypical antipsychotic effect was noted in the compounds **5-8** and **11-14**. Excellent efficacy was observed which was comparable to clozapine. The results further strengthen our previous hypothesis that in our compound series, the presence of

hydrogen bond acceptor substituents on the phenyl ring is important for antipsychotic activity. Further, smaller size of the substituents seems to reduce the tendency of the compounds to bind to nigrostriatal regions. The computational studies suggest a good correlation between activity profile and the chemical structures. The values of the various computed parameters e.g., log BB values (⁻2.00 - 1.04), TPSA (24.79 – 32.78) and log P (3.806-3.933) for the test compounds indicate a good potential to penetrate the blood brain barrier and an excellent compliance with lipinski's rules for CNS activity.

ACKNOWLEDGEMENTS

The research grant provided by the University Grants Commission is duly acknowledged.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES AND NOTES

[1] Tandon, R.; Keshavan, M.S.; Nasrallah, H.A. Schizophrenia, "Just the Facts" What we know in 2008. 2. Epidemiology and etiology. *Schiz. Res.*, **2008**, *102*, 1-18.

[2] Baldessarini, R.J.; Tarazi, F. Drugs and the treatment of psychiatric disorders: Psychosis and mania. *The Pharmacol. Basis Ther.*, **2001**, *9*, 485-520.

[3] Marino, M.J.; Knutsen, L.J.S.; Williams, M. Emerging opportunities for antipsychotic drug discovery in postgenomic era, *J. Med. Chem.*, **2008**, *51*, 1077-1107.

[4] Kapur, S.; Mamo, D. Half a century of antipsychotics and still a central role for dopamine D_2 receptors. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry.*, ***2003***, *27*, 1081-1090.

[5] Hartman, D.S.; Civelli, O. Dopamine receptor diversity: Molecular and pharmacological perspectives. *Prog. Drug Res.*, **1997**, *48*, 173-194.

[6] Seeman, P. In: *Psychopharmacology: The Fourth Generation of Progress*, Bloom, F. E.; Kupfer, D. V. Eds.; Raven Press: New York, **1995**; pp. 295-302.

[7] Fitton, A.; Heel, R.C. Clozapine: A review of its pharmacological properties and therapeutic use in schizophrenia. *Drugs*, **1990**, *40*, 722-747.

[8] Meltzer, H.Y. What's atypical about atypical antipsychotic drugs? *Curr. Opin. Pharmacol.*, **2004**, *4*, 53-57.

[9] Stanniland, C.; Taylor, D. Tolerability of atypical antipsychotics. *Drug Saf.*, **2000**, *22*, 195-214.

[10] Melkersson, K.; Dahl, M.L. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. *Drugs*, **2004**, *64*, 701-723.

[11] Haddad, P.M.; Sharma, S.G. Adverse effects of atypical antipsychotics: differential risk and clinical implications. *CNS Drugs*, **2007**, *21*, 911–936.

[12] Nakane, M.; Cowart, M.D.; Hsieh, G.C.; Miller, L.; Chang, R.; Terranovo, M.A.; Namovic, M.T.; Miller, T.R.; Wetter, J.M.; Marsh, K.; Stewart, A.O.; Moreland, R.B. 2-[4-(3,4-Dimethylphenyl)piperazin-1-ylmethyl]*1H* benzimidazole (A-381393), a selective dopamine D_4 receptor antagonist. *Neuropharmacology*, **2005**, *49*, 112-121.

[13] Geneste, H.; Backfisch, G.; Braje, W.; Delzer, J.; Haupt, A.; Hutchins, C.W.; King, L.L.; Lubisch, W.; Steiner, G.; Teschendorf, H.; Unger, L.; Wernet, W. Synthesis and SAR of highly potent and selective dopamine D_3-receptor antagonists: Quinolin(di)one and benzazepin(di)one derivatives. *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 658-662.

[14] Galici, R.; Boggs, J.D.; Miller, K.L.; Bonaventure, P.; Atack, J.R. Effects of SB-269970, a 5-HT_7 receptor antagonist, in mouse models predictive of antipsychotic-like activity. *Behav. Pharmacol.*, **2008**, *19*, 153-159.

[15] Stephane, C.; Bourdiol, N.; Lacharme, V.; Newman-Tancredi, A.; Colpaert, F.; Vacher, B. Towards a new generation of potential antipsychotic agents combining D_2 and 5-HT_{1A} receptor activities. *J. Med.Chem.*, **2007**, *50*, 865-876.

[16] Bedurftig, S.; Wunsch, B. 1, 4-diazepanes derived from (S)-serine-Homopiperazines with improved σ_1 (sigma) receptor affinity and selectivity. *Eur. J. Med. Chem.*, **2009**, *44*, 519-525.

[17] Olincy, A.; Stevens, K.E. Treating schizophrenia symptoms with an α_7 nicotinic agonist, from mice to men. *Biochem. Pharmacol.*, **2007**, *74*, 1192–1201.

[18] Pinard, E.; Alanine, A.; Alberati, D.; Bender, M.; Borroni, E.; Bourdeaux, P.; Brom, V.; Burner, S.; Fischer, Hainzl, D.; Halm, R.; Hauser, N.; Jolidon, S.; Lengyel, J.; Marty, H.; Meyer, T.; Moreau, J.; Mory, R.; Narquizian, R.; Nettekoven, M.; Norcross, R.D.; Puellmann, B.; Schmid, P.; Schmitt, S.; Stalder, H.; Wermuth, R.; Wettstein, J.G.; Zimmerli, D. Selective GlyT1 Inhibitors: Discovery of [4-(3-Fluoro-5-trifluoromethyl- pyridine-2-yl)piperazin-1-yl]-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methylethoxy)phenyl]methanone (RG1678), a promising novel medicine to treat schizophrenia. *J. Med. Chem.*, **2010**, *53*, 4603-4614.

[19] Kim, D.H.; Maneen, M.J.; Stahl, S.M. Building a better antipsychotic: receptor targets for the treatment of multiple symptom dimensions of schizophrenia. *Neurotherapeutics*, **2009**, *6*, 78-85.

[20] Vogel, H.G. Ed. In *Drug discovery and evaluation: Pharmacological assays*, 3rd ed.; Springer: New York, **2007**; pp. 761-762.

[21] Bali, A.; Malhotra, S.; Dhir, H.; Kumar, A.; Sharma, A. Synthesis and evaluation of 1-(quinoliloxypropyl)-4-aryl piperazines for atypical antipsychotic effect. *Bioorg. Med. Chem. Lett.*, **2009**, *19*, 3041-3044.

[22] A. Bali, A.; Sharma, K.; Bhalla, A.; Bala, S.; Reddy, D.; Singh, A.; Kumar, A. Synthesis, evaluation and computational studies on a series of acetophenone based 1-(aryloxypropyl)-4-(chloroaryl) piperazines as potential atypical antipsychotics. *Eur. J. Med. Chem.*, **2010**, *45*, 2656-2662.

[23] Levin, V.A. Relationship of octanol/water partition coefficient and molecular weight to rat brain capillary permeability. *J. Med. Chem.*, **1980**, *23*, 682–684.

[24] Van de waterbeemed, H.; Atkinson, F.; Cole, S.; Green, C. Lipophilicity and other parameters affecting brain penetration. *Curr. Med. Chem.- Central Nervous System Agents*, **2002**, *2*, 229–240.

[25] Kelder, J.; Grootenhuis, P.D.J.; Bayada, D.M.; Delbressine, L.P.C.; Ploemen, J.P. Polar molecular surface as a dominating determinant for oral absorption and brain penetration of drugs. *Pharm. Res.*, **1999**, *16*, 1514-1519.

[26] Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug. Deliv. Rev.*, **1997**, *23*, 3–25.

[27] Zhao, Y.H.; Abraham, M.H.; Ibrahim, A.; Fish, P.V.; Cole, S.; Lewis, M.L.; deGroot, M.J.; Reynolds, D.P. Predicting penetration across the blood brain barrier from simple descriptors and fragmentation schemes. *J. Chem. Inf. Model.*, **2007**, *47*, 170-175.

[28] ChemSilico LLC, Tewksbury, MA 01876. http://www.chemsilico.com/CS_prBBB/BBBhome.html (Accessed July 24, **2010**).

[29] Iyer, M.; Mishra, R.; Han, Y.; Hopfinger, A. Predicting blood-brain partitioning of organic drugs using membrane-interaction QSAR analysis. *J. Pharm. Res.*, **2007**, *19*, 1611-1621.