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Original article

Design, synthesis, pharmacological evaluation and computational studies of 1-(biphenyl-4-yl)-2-[4-(substituted phenyl)-piperazin-1-yl] ethanones as potential antipsychotics

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ABSTRACT

This article describes the design of biphenyl moiety linked with aryl piperazine and syntheses of fourteen 1-(biphenyl-4-yl)-2-[4-(substituted phenyl)-piperazin-1-yl]ethanone derivatives along with their pharmacological evaluation for antipsychotic activity and computational studies including quantitative structure activity relationship (QSAR) and descriptor based similarity study. All compounds were found to exhibit considerable anti-dopaminergic and anti-serotonergic activity in behavioural models. Among all derivatives, compound 1-(biphenyl-4-yl)-2-[4-(2-methoxyphenyl)-piperazin-1-yl]ethanone (**3c**) and 1-(biphenyl-4-yl)-2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]ethanone (**3k**) showed impressive antipsychotic profile with lower potency for catalepsy induction. These results were found to be sturdily matching with docking study in designing of compounds with homology model of human dopamine D_2 receptor. Also the QSAR study strongly supports the obtained results.

1. Introduction

Schizophrenia is the overwhelming mental disorder characterized by severe distortions of reality and disturbances in perception, intellectual performance, behaviour and motor activities [1]. The symptoms of schizophrenia are categorized in to positive symptoms which include delusion, hallucination, illusion and negative symptoms that include apathy, reduced motivation, and alogia [2]. Various typical antipsychotics like chlorpromazine, haloperidol have been introduced which showed improvement in positive symptoms of schizophrenia by blocking dopaminergic transmission in the brain [3]. This non-selective inhibition of dopamine not only reduces psychoses symptoms, but also creates extrapyramidal symptoms (EPS) like Parkinsonism and tardive dyskinesia as side effects due to blockade of dopaminergic activity in motor areas of the brain [4]. Other side effects of these typical antipsychotics include hyperprolactinemia, sexual disturbances, malignant neuroleptic syndromes and cardiac arrhythmias [5]. In search of new antipsychotic agents to treat either types of symptoms of schizophrenia and to obtain broader efficacy, second generation or atypical antipsychotics like clozapine, ziprasidone, aripiprazole were introduced. It was believed that the newer atypical antipsychotics are effective against both positive and negative symptoms of schizophrenia by blocking dopaminergic as well as serotonergic neurotransmission in brain [6,7]. But these atypical antipsychotics, on chronic medication, have limitations like substantial weight gain, agranulocytosis, blood dyscrasias and hyperglycemia [8–10].

In 2007 Bifeprunox, was filed with US-FDA for its potential atypical antipsychotic activity. In fact Bifeprunox has better anti-dopaminergic and anti-serotonergic activity than many of the other atypical antipsychotics. Previously many molecular modifications of parent bifeprunox have been performed and tested for their antipsychotic profile [11]. Various substituted phenyl piperazines were also reported for anti-dopaminergic and anti-serotonergic activity with less EPS induction [12,13]. Furthermore, biphenyl has been reported to comprise with diverse biological activities like, anti-inflammatory [14], nitric oxide synthase inhibitor [15], anti-diabetics [16], and fungicidal activity [17]. Here we

Abbreviations: QSAR, quantitative structure activity relationship; EPS, extrapyramidal symptoms; GPCR, G-protein coupled receptors; DMF, *N*,*N*-dimethyl formamide; 5-HTP, DL-5-hydroxytryptophan; EA, electron affinity; BBB, blood brain barrier; QPlogBB, predicted brain/blood partition coefficient; WFI, water for injection; i.p, intraperitoneal.

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have designed hybrid structure with biphenyl and aryl-piperazine moiety with acetyl linker (Fig. 1). In previous study our group has reported the homology model for human dopamine D_2 receptor and here we used same for docking of designed molecules [18]. While designing the molecule we considered various factors required for receptor affinity such as; i) the presence of nitrogen attached with aliphatic chain which gets protonated and becomes quaternary in physiological conditions to produce hydrogen bonding with dopamine receptor, ii) the presence of hydrophobic groups to bind with two hydrophobic microdomain of 7-transmembrane GPCR [18]. On design, we conceived it interesting to evaluate anti-dopaminergic and anti-serotonergic activity along with catalepsy profile of designed biphenyl moiety linked with substituted aryl piperazine by acetyl linker.

2. Results and discussion

2.1. Docking study

The compounds were docked on 3D structure of human D_2 receptor using Glide XP docking. The binding mode of most active compound (**3c**) is shown in Fig. 2. The nitrogen of piperazine attached to the aliphatic chain protonates at physiological pH and it showed hydrogen bonding interaction with the carboxylate ion of Asp85 residue. The distance between the charged nitrogen and Asp85 carboxylate ion was found to be ~1.47 Å. Further, the hydrophobic interaction of aryl piperazine ring of ligand with Val82, Ile137, Val161 and Trp357 of receptor stabilized the complex. Additionally, the biphenyl moiety was found to be stabilized by Val62 and Trp384.

2.2. Chemistry

The scheme for the synthesis of titled compounds 1-(biphenyl-4-yl)-2-[4-(substituted phenyl)-piperazin-1-yl]-ethanones (**3a**–**3n**) is depicted in Scheme 1. Compound 1-(biphenyl-4-yl)-2-chloroethanone (**2**) was prepared by Friedel–Crafts acylation of biphenyl (**1**) with chloroacetyl chloride in presence of anhydrous $AlCl_3$ in carbon disulphide (CS_2). Synthesis of derivatives **3a**–**3n** was accomplished by reacting **2** with various substituted aryl piperazines in *N*,*N*-dimethyl formamide (DMF) and K_2CO_3. Structures were confirmed on the basis of elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy (ESI). The yields of synthesized

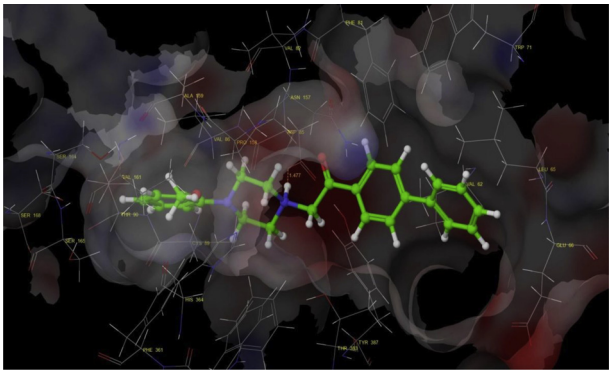


Fig. 2. Glide XP docking of compound **3c** docked in active site of D_2 receptor.

derivatives were in the range of 62–85% after recrystallization in ethanol–water.

2.3. Pharmacology

The inhibition of apomorphine induced climbing behaviour and inhibition of DL-5-Hydroxytryptophan (5-HTP) induced head twitches model along with haloperidol induced catalepsy model was used for the *in-vivo* evaluation of antipsychotic potential of synthesized derivatives. Taking compound **3n** as lead, various substitutions were made on aryl ring and the behavioural studies were performed. All the biological data statistically analysed and represented as percentage inhibition in Table 1.

Central anti-dopaminergic activity for all compounds was assessed by their ability to inhibit apomorphine induced climbing behaviour. By and large, antidopaminergic activity exhibited by *ortho* substituted derivatives was found more than *meta* and *para* substituted derivatives. Presence of chloro (**3a**), methyl (**3b**) on aryl ring resulted in increase in anti-dopaminergic activity as compared to lead (**3n**). While substitution methoxy (**3c**) at *ortho* position significantly reversed the apomorphine induced climbing behaviour. Further presence of methyl (**3e**) at *meta* position slightly improved the anti-dopaminergic activity. Whereas chloro (**3d**) and trifluoromethyl (**3f**) substitution at *meta* position exhibited reduction in the anti-dopaminergic activity. Replacement of hydrogen at *para* position with halogens (**3g** and **3h**) decreased the anti-dopaminergic activity. Whereas replacement with methyl (**3i**)

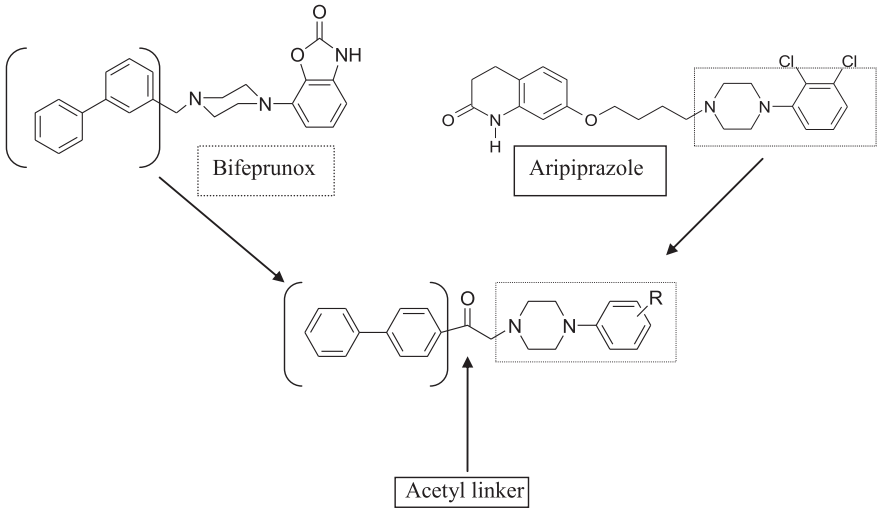
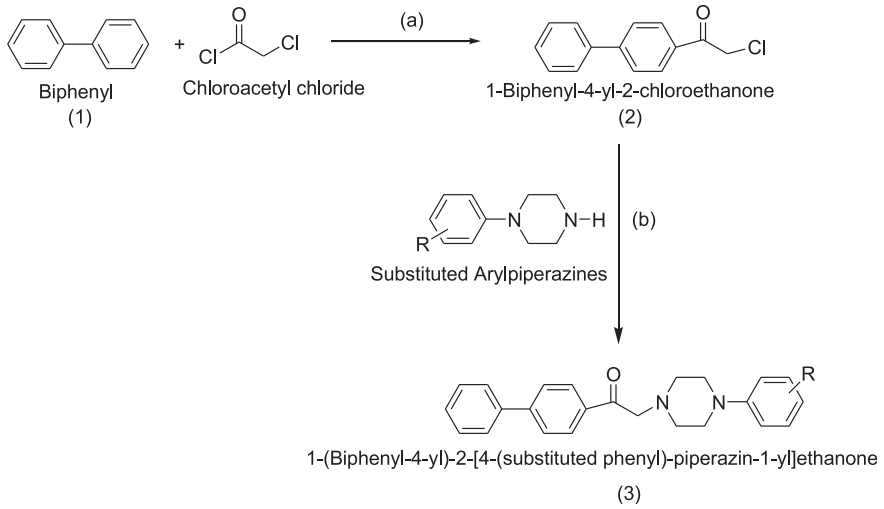


Fig. 1. Planned modification and newly designed antipsychotic molecule.

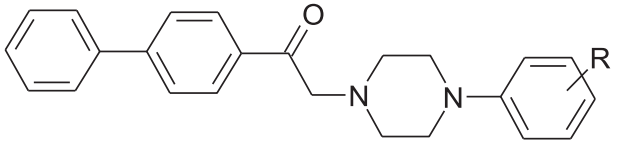


Scheme 1. (a) CS_2, $AlCl_3$, reflux 1 h; (b) DMF, K_2CO_3, heat 60 °C (4–6 h).

and methoxy (**3j**) at *para* position barely increased the anti-dopaminergic activity. As far as di-substituted derivatives are concerned, an appreciable increase in anti-dopaminergic activity was observed in *ortho-meta* di-substituted compounds bearing steric and hydrophobic moieties as in **3k** and **3l**. But in *meta–para* di-halo substituted compounds, remarkably decrease in the anti-dopaminergic activity was observed (**3m**).

In the assessment of anti-serotonergic activity, all derivatives showed increased anti-serotonergic activity except **3b** and **3h** which showed decrease in activity as compared to lead **3n**. Compound **3c** showed good anti-serotonergic activity. In catalepsy induction study on albino mice, it was observed that compound **3c**, **3k** and **3l** showed minimum catalepsy induction but comparatively not less than standard aripiprazole. Among all synthesized compounds, compound **3j** showed high catalepsy induction. Overall from the pharmacological evaluation of synthesized derivatives for antipsychotic activity, the compound 1-(biphenyl-4-yl)-2-[4-(2-methoxyphenyl)-piperazin-1-yl]ethanone (**3c**) and 1-(biphenyl-4-yl)-2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]ethanone (**3k**) showed impressive atypical antipsychotic profile with lower potency for catalepsy induction.

Table 1
Various synthesized compounds with *in vivo* pharmacological data at the dose of 15 mg/kg in male albino mice.



Compd.	R	%Inhibition of climbing behaviour	%Inhibition of head twitches	%Catalepsy induction
3a	2-Cl	38.25	35.21	42.31
3b	2-CH_3	38.54	26.68	35.84
3c	**2-OCH_3**	**53.44**	**61.28**	**29.43**
3d	3-Cl	29.92	32.57	31.84
3e	3-CH_3	33.59	29.61	33.82
3f	3-CF_3	26.38	32.57	31.84
3g	4-Cl	26.36	29.22	35.17
3h	4-F	23.45	24.51	30.48
3i	4-CH_3	33.28	29.83	38.66
3j	4-OCH_3	32.93	36.12	59.28
3k	2,3-diCl	42.83	38.31	28.97
3l	2,3-diCH_3	40.72	35.39	29.87
3m	3,4-diCl	25.71	38.78	30.50
3n	H	31.90	27.98	34.53
Arp		61.10	94.49	26.86

Number of animal used per group $n = 6$, $p < 0.05$. Arp = aripiprazole.
Compound that showed better result among all the synthesized compounds were highlighted in bold.

2.4. Computational studies

2.4.1. Quantitative structure activity relationship study (QSAR)

The QSAR model was generated for antidopaminergic potential. As all the descriptors are not important for specific model generation, and hence to select the optimal set of descriptors, we used systematic variable selection leave one out (LOO) method in stepwise forward manner for the selection of descriptors. The QSAR result for antidopaminergic potential produced highly predictive model that has excellent $r^2 = 0.95$. Further the developed model showed $r^2_{cv} = 0.8971$ and F value 104.5 indicating the model is very well validated and explained. The two best descriptors selected on the basis of importance in biological activity were electron affinity (EA) (eV) and predicted brain/blood partition coefficient (QPlogBB).

From the QSAR study, the statistically significant equation derived was,

$$\mathrm{BA} = 4.9879(\pm 0.2612) + 0.2968(\pm 0.0749)\ \mathrm{QPlogBB} - 4.2743(\pm 0.3363)\ \mathrm{EA(eV)}.$$

$$N = \text{number of compounds} = 14,\ r^2 = 0.95;\ s = 0.0248;\ F = 104.5;\ r^2_{cv} = 0.8971.$$

From the equation it was observed that, electron affinity (EA) correlated negatively with biological activity, however contributed more than QPlogBB towards biological activity. Relatively greater activity in compounds **3b**, **3c**, **3i** and **3l** (groups- 2-CH_3, 2-OCH_3, 4-CH_3, 2,3-diCH_3 respectively) can be attributed to lower EA of these compounds since these are having electron releasing groups and thus increase electron availability in phenyl ring. On the contrary the electron affinity in the compounds **3f**, **3h** and **3m** (groups – 3-CF_3, 4-F, 3,4-diCl) is more and resulted into relatively diminished activity. The second parameter QPlogBB contributed relatively less in the above QSAR but positively correlated with biological activity

Table 2
LIC = experimental %inhibition of climbing behavior, PIC = predicted %inhibition of climbing behaviour. EA = electron affinity, QPlogBB = predicted brain/blood partition coefficient.

Compound	R	LIC	PIC	Residual	EA (eV)	QPlogBB
3a	2-Cl	1.5828	1. 6020	−0.0192	0.804	0.475
3b	2-CH_3	1.5860	1.5900	−0.0040	0.799	0.344
3c	2-OCH_3	1.7279	1.6900	0.0379	0.771	0.274
3d	3-Cl	1.4760	1.4930	−0.0170	0.853	0.495
3e	3-CH_3	1.5263	1.4950	0.0313	0.822	0.316
3f	3-CF_3	1.4213	1.4000	0.0213	0.886	0.597
3g	4-Cl	1.4210	1.4410	−0.0200	0.853	0.524
3h	4-F	1.3702	1.3720	−0.0018	0.863	0.468
3i	4-CH_3	1.5223	1.5440	−0.0217	0.82	0.346
3j	4-OCH_3	1.5176	1.5340	−0.0164	0.823	0.286
3k	2,3-diCl	1.6318	1.6570	−0.0252	0.852	0.619
3l	2,3-diCH_3	1.6099	1.6160	−0.0061	0.81	0.341
3m	3,4-diCl	1.4101	1.3730	0.0371	0.874	0.632
3n	H	1.5039	1.5000	0.0039	0.826	0.356

(data for EA and QPlogBB is shown in Table 2). The blood–brain barrier (BBB) permeability is an important absorption, distribution, metabolism and excretion (ADME) property and crossing the blood–brain barrier is a compulsory step for drug distribution. Several drug targets are located in the central nervous system (CNS) within the brain. The blood–brain barrier is a distinctive membranous barrier that tightly isolates the brain from the circulating blood [19]. Thus, the blood–brain partition coefficient (logBB) is a determining factor for the efficacy of central nervous system-acting drugs. However various physiochemical properties involved in QPlogBB permeation are logP, molecular weight, molecular volume and molecular surface area and so QPlogBB is a contribution of multi molecular and physical properties of the molecules. As the molecular and physical property of the derivatives vary according to structural diversity, it is very difficult to interpret it at molecular level. This QSAR study supports the postulation of design and the results from the behavioural models obtained. The graph for actual activity verses predicted is shown in Fig. 3.

2.4.2. Similarity study

Further the descriptor based similarity study was performed between the synthesized compounds and standard antipsychotic drugs for blood brain barrier permeation analysis. The chemical similarity study is helpful to compare the biological similarity between the set of test and probe molecules. To cross the blood brain barrier (BBB) and exhibit the central nervous system activity the antipsychotic agents should possess the fundamental physicochemical features. Various physiochemical properties involved in BBB permeation are logP, molecular weight, molecular volume and molecular surface area. Here we used Schrodinger suite 2009 to carry out the similarity study between synthesized compounds in test set and four standard drugs (aripiprazole, paliperidone, ketanserin and sertindole) in probe set by using Tanimoto association coefficient (Table 3). The physiochemical properties of compounds **3c**, **3f**, **3j**, **3k** and **3m** showed good similarity with aripiprazole, ketanserin, paliperidone and sertindole; and compounds **3h** and **3n** showed less similarity. Interestingly the compounds **3c** and **3k** which showed high physiochemical similarity with all the probe molecules than other test molecules, also showed good antipsychotic potential.

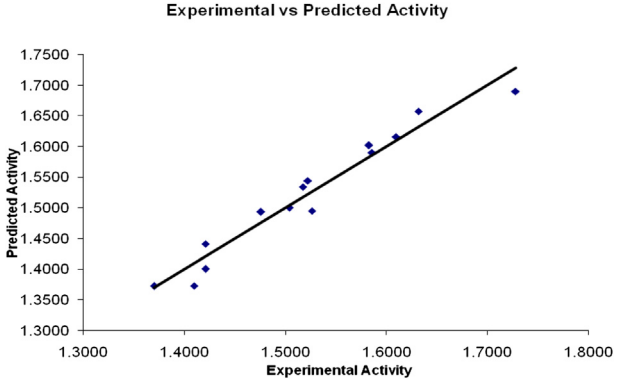


Fig. 3. Correlation graph between LIC (experimental) and PIC (predicted) of the synthesized compounds.

3. Conclusion

In conclusion, we designed and synthesized a series of fourteen derivatives of 1-(biphenyl-4-yl)-2-[4-(substituted phenyl)-piperazin-1-yl]ethanone and their structures were confirmed by physicochemical and spectral analysis. The strategy chosen for the current study was to combine pharmacophoric key features from biphenyl and aryl piperazine using acetyl linkage to explore atypical antipsychotic profile of the resultant compounds. The pharmacological study revealed that all derivatives possess considerable antidopaminergic and anti-serotonergic activity. Among all synthesized derivatives compound 1-(biphenyl-4-yl)-2-[4-(2-methoxy phenyl)-piperazin-1-yl]ethanone (**3c**) and 1-(biphenyl-4-yl)-2-[4-(2,3-dichlorophenyl)-piperazin-1-yl]ethanone (**3k**) showed im pressive antipsychotic profile with lower potency for catalepsy induction. From the QSAR study of synthesized derivatives, the resulting equation correlated between two variables (QPlogBB positively and EA negatively) and antidopaminergic activity. Further more a descriptor based similarity study was carried out to study blood brain permeation ability of synthesized compounds with standard antipsychotic drugs. From the resultant Tanimoto similarity index, compound **3c** and **3k** showed good similarity with the standard atypical antipsychotic drugs and also found to have good antipsychotic potential.

4. Experimental

4.1. Docking study

Various substitutions were made on aryl part of aryl piperazine considering the unsubstituted compound **3n** as lead. We used the homology model of human dopamine D_2 receptor, previously reported by us [18], for the docking study of designed molecules.

Table 3
Tanimoto similarity study of synthesized compounds with respect to standard drugs.

Compound	Aripiprazole	Ketanserin	Paliperidone	Sertindole
3a	0.3243	0.2505	0.2872	0.5018
3b	0.3098	0.4243	0.2635	0.4615
3c	0.7291	0.5564	0.6332	0.6373
3d	0.4418	0.3618	0.3854	0.5882
3e	0.5424	0.3939	0.4708	0.5829
3f	0.6421	0.4542	0.6577	0.8724
3g	0.4359	0.5124	0.3805	0.5952
3h	0.1262	0.1738	0.1138	0.1669
3i	0.5421	0.3942	0.4705	0.5866
3j	0.7428	0.6102	0.6361	0.6088
3k	0.6850	0.4082	0.6348	0.9029
3l	0.6284	0.3864	0.5726	0.7541
3m	0.6908	0.4155	0.6614	0.9710
3n	0.0574	0.2765	0.0464	0.0000

Docking studies were performed using Glide module from Schrödinger suit 2009 [20]. As it performs grid-based ligand docking, grid was generated with the help of receptor grid generation tool of Glide by keeping all parameters at standard. The structures of molecules were generated within MAESTRO and exhaustive conformational search was carried out using OPLS_2005 force field. These structures then XP docked on the receptor grid for binding evaluation study by keeping all parameters to their standard value.

4.2. Synthesis

Completion of reaction was monitored by thin layer chromatography on Merck pre coated silica gel F_{254} plates. The melting points of synthesized compounds were checked on Veego VMP – D digital melting point apparatus by open capillary method and are uncorrected. The IR spectra of synthesized compounds were recorded on Jasco FTIR 4100 in potassium bromide. The ^{1}H NMR, ^{13}C NMR and ^{13}C DEPT-135 spectra were recorded in $CDCl_3$ using NMR Varian Mercury plus 300 MHz using tetra methyl silane (TMS) as internal standard. The mass spectra of compounds were recorded on 410 Prostar Binary LC with 500 MS IT PDA detector. Elemental analysis was performed on FLASH EA 1112, Thermo-Finnigan and indicated with the element symbol. The elemental analyses were within ±0.4% of the theoretical values.

4.2.1. Synthesis of 1-biphenyl-4-yl-2-chloroethanone (**2**)

In a 250 mL three neck flask (attached with reflux condenser and dropping funnel on a mechanical stirrer) 0.02 mol of biphenyl, 0.023 mol of finely powdered anhydrous $AlCl_3$, and 30 mL of carbon disulphide (CS_2) was placed for stirring. From the dropping funnel 0.02 mol of chloroacetyl chloride was added drop wise over a period of 20 min and reflux of mixture was started while adding. The mouth of both condenser and funnel was closed with calcium chloride guard tube. After addition of CS_2 the reaction was continued for 1 h with reflux. The reaction mixture was cooled and poured slowly on crushed ice containing concentrated hydrochloric acid. This mixture was stirred for 15 min and the product was filtered and washed with water to remove traces of hydrochloric acid. Washing of petroleum ether was given to final product in order to remove any remaining biphenyl and finally recrystallised by ethanol water to get pure compound **2**.

Yield: 91%. Mp: 127–128 °C. Molecular formula: $C_{14}H_{11}ClO$ (230). Elemental analysis: Calcd. C, 72.89; H, 4.81; O, 6.94.; found: C, 72.84; H, 4.80; O, 6.96. IR (cm^{-1}): 3046, 2943, 1691, 1601, ^{1}H NMR (δ ppm $CDCl_3$): 4.75 (s, 2H, CH_2– in acyl side chain); 7.63–7.65 (d, $C_{2,6}$ aromatic, J = 6.9, 2H); 7.71–7.74 (d, $C_{2',6'}$ aromatic, J = 8.4, 2H); 7.45–7.55 (m, $C_{3',4',5'}$; aromatic 3H); 8.03–8.06 (d, $C_{3,5}$ aromatic, J = 8.4, 2H).

4.2.2. General procedure for syntheses of compound **3a**–**3n**

A mixture of **2** (0.0026 mol), aryl piperazine (0.0026 mol) and anhydrous potassium carbonate (0.0026 mol) was added to reaction flask and heated in DMF for 4–6 h with stirring at 60 °C. The reaction was carried out by pouring the mixture in ice cold water. This mixture was filtered under vacuum and the product was washed with water. All the compounds were recrystallised from ethanol–water system.

4.2.3. 1-(Biphenyl-4-yl)-2-[4-(2-chlorophenyl)-piperazin-1-yl] ethanone (**3a**)

Yield: 83%. mp: 100–102 °C. Elemental analysis: Calcd. C, 73.74; H, 5.93; N, 7.17; O, 4.09.; found: C, 73.81; H, 5.91; N, 7.15; O, 4.10. IR (cm^{-1}): 3064, 2942, 2827, 1682, 1603, 793. ^{1}H NMR (δ ppm $CDCl_3$): 2.7–2.82 (t, 4H, $-CH_2-N-(CH_2)_2$, J = 4.5); 3.2–3.3 (t, 4H, ArN–$(CH_2)_2$, J = 4.6); 3.9 (s, 2H, $-CH_2$); 6.5–8.11 (m, 13H, ArH). MS (ESI): m/z 391.15 (M^+ H). ^{13}C NMR (δ ppm $CDCl_3$): 49.3 (ArN–CH_2–, ArN–CH_2– of pyrazine); 52.61 (N–CH_2–, N–CH_2– of pyrazine at aliphatic site), 65.50 (aliphatic –CH_2–); 114.61, 119.58, 123.47, 127.73 (5C), 127.61, 129.10 (4C), 129.68, 134.63, 138.80, 146.80, 150.72(Aromatic C); 195.80 (–C=O).

4.2.4. 1-(Biphenyl-4-yl)-2-(4-o-tolylpiperazin-1-yl)ethanone (**3b**)

Yield: 64%. mp: 100–101 °C. Elemental analysis: Calcd. C, 81.05; H, 7.07; N, 7.56; O, 4.32.; found: C, 81.09; H, 7.06; N, 7.58; O, 4.31. IR (cm^{-1}): 3060, 2949, 2821, 1684, 1601. ^{1}H NMR (δ ppm $CDCl_3$): 2.34 (s, 3H, Ar–CH_3); 2.71–2.8 (t, 4H, $-CH_2-N-(CH_2)_2$, J = 4.9); 3.28–3.32 (t, 4H, ArN–$(CH_2)_2$, J = 5.2); 3.87 (s, 2H, $-CH_2$); 6.69–8.1 (m 13H ArH). ^{13}C NMR (δ ppm $CDCl_3$): 14.27 (Ar–CH_3); 50.04 (ArN–CH_2–, ArN–CH_2– of pyrazine); 52.94 (N–CH_2–, N–CH_2– of pyrazine at aliphatic site), 64.62 (aliphatic –CH_2–); 113.28, 117.05, 120.75, 123.67, 125.58, 127.45 (5C), 128.43, 128.34 (4C), 134.76, 138.79, 146.24, 149.26 (Aromatic C); 195.40 (–C=O).

4.2.5. 1-(Biphenyl-4-yl)-2-[4-(2-methoxyphenyl)-piperazin-1-yl] ethanone (**3c**)

Yield: 74%. mp: 78–80 °C. Elemental analysis: Calcd. C, 77.69; H, 6.78; N, 7.25; O, 8.28.; found: C, 77.72; H, 6.77; N, 7.28; O, 8.25. IR (cm^{-1}): 3060, 2938, 2818, 1681, 1601. ^{1}H NMR (δ ppm $CDCl_3$): 2.7–2.8 (t, 4H, $-CH_2-N-(CH_2)_2$, J = 5.3); 3.28–3.33 (t, 4H, ArN–$(CH_2)_2$, J = 5.2); 3.87 (s, 3H, $-OCH_3$); 3.91 (s, 2H, $-CH_2$); 6.72–8.11 (m, 13H, ArH). ^{13}C NMR (δ ppm $CDCl_3$): 49.94 (ArN–CH_2–, ArN–CH_2– of pyrazine); 53.36 (N–CH_2–, N–CH_2– of pyrazine at aliphatic site); 54.90 (Ar–O–CH_3); 64.54 (aliphatic –CH_2–); 113.73, 115.27, 119.62, 120.43, 127.20 (5C), 129.16 (4C), 134.65, 138.90, 142.38, 143.82, 145.92 (Aromatic C); 195.67 (–C=O).

4.2.6. 1-(Biphenyl-4-yl)-2-[4-(3-chlorophenyl)-piperazin-1-yl] ethanone (**3d**)

Yield: 83%. mp: 136–138 °C. Elemental analysis: Calcd. C, 73.74; H, 5.93; N, 7.17; O, 4.09.; found: C, 73.68; H, 5.91; N, 7.15; O, 4.10. IR (cm^{-1}): 3031, 2972, 2911, 2842, 1686, 1598, 767. ^{1}H NMR (δ ppm $CDCl_3$): 2.7–2.8 (t, 4H, $-CH_2-N-(CH_2)_2$, J = 4.6); 3.28 (t, 4H, ArN–$(CH_2)_2$, J = 5.1); 3.91 (s, 2H, $-CH_2$); 7.12–8.11 (m, 13H, ArH). ^{13}C NMR (δ ppm $CDCl_3$): 50.13 (ArN–CH_2–, ArN–CH_2– of pyrazine); 52.62 (N–CH_2–, N–CH_2– of pyrazine at aliphatic site), 64.51 (aliphatic –CH_2–); 112.34, 114.73, 122.43, 127.31 (5C), 128.54 (4C), 129.72, 134.33, 134.58, 139.86, 145.92, 149.42 (Aromatic C); 195.78 (–C=O).

4.2.7. 1-(Biphenyl-4-yl)-2-(4-m-tolyl-piperazin-1-yl)ethanone (**3e**)

Yield: 84%. mp: 130–132 °C. Elemental analysis: Calcd. C, 81.05; H, 7.07; N, 7.56; O, 4.32.; found: C, 81.12; H, 7.08; N, 7.54; O, 4.33. IR (cm^{-1}): 3060, 3034, 2965, 2828, 1689, 1601. ^{1}H NMR (δ ppm $CDCl_3$): 2.31 (s, 3H, Ar–CH_3); 2.7–2.8 (t, 4H, $-CH_2-N-(CH_2)_2$, J = 4.8); 3.26–3.29 (t, 4H, ArN–$(CH_2)_2$, J = 4.7); 3.91 (s, 2H, $-CH_2$); 6.66–8.11 (m, 13H, ArH). MS (ESI): m/z 371.2 (M^+ H). ^{13}C NMR (δ ppm $CDCl_3$): 21.75 (Ar–CH_3); 49.15 (ArN–CH_2–, ArN–CH_2– of pyrazine); 53.61 (N–CH_2–, N–CH_2– of pyrazine at aliphatic site), 64.50 (aliphatic –CH_2–); 113.31, 117.05, 120.75, 127.26 (5C), 128.76, 128.96 (4C), 134.71, 138.81, 139.84, 146.04, 151.32 (Aromatic C); 195.87 (–C=O). DEPT-135 ($CDCl_3$): CH_2 negative peaks: 49.16 (2C), 53.62 (2C), 64.54; CH and CH_3 Positive peaks: 21.75, 113.30, 117.04, 120.74, 127.25 (5C), 128.76 and 128.96 (4C).

4.2.8. 1-(Biphenyl-4-yl)-2-[4-(3-trifluromethylphenyl)-piperazin-1-yl]ethanone (**3f**)

Yield: 82%. mp: 130–135 °C. Elemental analysis: Calcd. C, 70.74; H, 5.46; N, 6.60; O, 3.77.; found: C, 70.81; H, 5.45; N, 6.62; O, 3.76. IR (cm^{-1}): 3088, 2993, 2954, 2840, 1691, 1604. ^{1}H NMR (δ ppm $CDCl_3$): 2.79–2.83 (t, 4H, $-CH_2-N-(CH_2)_2$, J = 4.5); 3.31–3.34 (t, 4H, ArN–$(CH_2)_2$, J = 4.6); 3.922 (s, 2H, $-CH_2$); 7.06–8.1 (m, 13H, ArH). MS

(ESI):*m/z* 425.2 (M^+ H). ^{13}C NMR (δ ppm $CDCl_3$): 49.73 (ArN–$\underline{C}H_2$–, ArN–$\underline{C}H_2$– of pyrazine); 52.53 (N–$\underline{C}H_2$–, N–$\underline{C}H_2$– of pyrazine at aliphatic site), 64.63 (aliphatic –$\underline{C}H_2$–); 121.26 (Ar–$\underline{C}F_3$); 108.10, 116.79, 122.26, 127.54 (5C), 128.81, 129.36 (4C), 131.15, 134.56, 139.69, 146.12, 150.10 (Aromatic $\underline{C}$); 195.56 (–$\underline{C}$=O).

4.2.9. 1-(Biphenyl-4-yl)-2-[4-(4-chlorophenyl)-piperazin-1-yl] ethanone (**3g**)

Yield: 79%. mp: 168–170 °C. Elemental analysis: Calcd. C, 73.74; H, 5.93; N, 7.17; O, 4.09.; found: C, 73.69; H, 5.91; N, 7.15; O, 4.08. IR (cm^{-1}): 3088, 3034, 2966, 2839, 1689, 1599, 758. ^{1}H NMR (δ ppm $CDCl_3$): 2.81–2.83 (t, 4H, –CH_2–N–($\underline{C}H_2$)$_2$, J = 4.9); 3.24–3.27 (t, 4H, ArN–($\underline{C}H_2$)$_2$, J = 4.8); 3.93 (s, 2H, –$\underline{C}H_2$); 6.84–8.1 (m, 13H, Ar$\underline{H}$). ^{13}C NMR (δ ppm $CDCl_3$): 49.68 (ArN–$\underline{C}H_2$–, ArN–$\underline{C}H_2$– of pyrazine); 53.49 (N–$\underline{C}H_2$–, N–$\underline{C}H_2$– of pyrazine at aliphatic site), 64.47 (aliphatic –$\underline{C}H_2$–); 114.68 (2C), 119.70 (2C), 127.42 (5C), 129.17 (4C), 134.69, 139.82, 146.06, 146.89, 147.68 (Aromatic $\underline{C}$); 195.77 (–$\underline{C}$=O).

4.2.10. 1-(Biphenyl-4-yl)-2-[4-(4-flurophenyl)-piperazin-1-yl] ethanone (**3h**)

Yield: 81%. mp: 165–170 °C. Elemental analysis: Calcd. C, 76.98; H, 6.19; N, 7.48; O, 4.27.; found: C, 77.02; H, 6.20; N, 7.46; O, 4.28. IR (cm^{-1}): 3063, 2965, 2928, 2835, 1687, 1600. ^{1}H NMR (δ ppm $CDCl_3$): 2.78–2.81 (t, 4H, –CH_2–N–($\underline{C}H_2$)$_2$, J = 5.2); 3.19–3.22 (t, 4H, ArN–($\underline{C}H_2$)$_2$, J = 5.3); 3.91 (s, 2H, –$\underline{C}H_2$); 6.86–8.11 (m, 13H, Ar$\underline{H}$). MS (ESI): *m/z* 375.2 (M^+ H). ^{13}C NMR (δ ppm $CDCl_3$): 50.08 (ArN–$\underline{C}H_2$–, ArN–$\underline{C}H_2$– of pyrazine); 53.54 (N–$\underline{C}H_2$–, N–$\underline{C}H_2$– of pyrazine at aliphatic site), 64.43 (aliphatic –$\underline{C}H_2$–); 115.61 (2C), 117.97 (2C), 127.26 (5C), 128.97 (4C), 134.69, 139.82, 146.06, 147.92, 156.29 (Aromatic $\underline{C}$); 195.81 (–$\underline{C}$=O). DEPT-135 ($CDCl_3$): $\underline{C}H_2$ negative peaks: 50.08 (2C), 53.55 (2C), 64.45; $\underline{C}H$ and $\underline{C}H_3$ Positive peaks: 115.60 (2C), 117.89 (2C), 127.22 (5C), and 128.97 (4C).

4.2.11. 1-(Biphenyl-4-yl)-2-(4-p-tolyl-piperazin-1-yl)ethanone (**3i**)

Yield: 62%. mp: 148–150 °C. Elemental analysis: Calcd. C, 81.05; H, 7.07; N, 7.56; O, 4.32.; found: C, 80.99; H, 7.09; N, 7.58; O, 4.30. IR (cm^{-1}): 3044, 2964, 2836, 1687, 1605. ^{1}H NMR (δ ppm $CDCl_3$): 2.32 (s, 3H, Ar–$\underline{C}H_3$); 2.7–2.8 (t, 4H, –CH_2–N–($\underline{C}H_2$)$_2$, J = 5.4); 3.25–3.29 (t, 4H, ArN–($\underline{C}H_2$)$_2$, J = 5.4); 3.9 (s, 2H, –$\underline{C}H_2$); 6.7–8.11 (m, 13H, Ar$\underline{H}$). ^{13}C NMR (δ ppm $CDCl_3$): 22.16 (Ar–$\underline{C}H_3$); 49.82 (ArN–$\underline{C}H_2$–, ArN–$\underline{C}H_2$– of pyrazine); 52.92 (N–$\underline{C}H_2$–, N–$\underline{C}H_2$– of pyrazine at aliphatic site), 64.73 (aliphatic –$\underline{C}H_2$–); 113.98(2C), 126.82, 127.69 (5C), 129.21 (4C), 130.32 (2C), 134.73, 139.64, 146.23, 147.24 (Aromatic $\underline{C}$); 195.54 (–$\underline{C}$=O).

4.2.12. 1-(Biphenyl-4-yl)-2-[4-(4-methoxyphenyl)-piperazin-1-yl] ethanone (**3j**)

Yield: 63%. mp: 150–152 °C. Elemental analysis: Calcd. C, 77.69; H, 6.78; N, 7.25; O, 8.28.; found: C, 77.74; H, 6.75; N, 7.28; O, 8.30. IR (cm^{-1}): 3033, 3000, 2947, 2834, 1684, 1601. ^{1}H NMR (δ ppm $CDCl_3$): 2.7–2.8 (t, 4H, –CH_2–N–($\underline{C}H_2$)$_2$, J = 5.1); 3.26–3.3 (t, 4H, ArN–($\underline{C}H_2$)$_2$, J = 5.2); 3.83 (s, 3H, –O$\underline{C}H_3$); 3.88 (s, 2H, –$\underline{C}H_2$); 6.72–8.1 (m, 13H, Ar$\underline{H}$). ^{13}C NMR (δ ppm $CDCl_3$): 55.66 (Ar–O–$\underline{C}H_3$); 49.73 (ArN–$\underline{C}H_2$–, ArN–$\underline{C}H_2$– of pyrazine); 52.86 (N–$\underline{C}H_2$–, N–$\underline{C}H_2$– of pyrazine at aliphatic site), 64.53 (aliphatic –$\underline{C}H_2$–); 114.96(2C), 115.10(2C), 127.48 (5C), 129.24 (4C), 134.46, 139.45, 146.18, 147.83, 148.28 (Aromatic $\underline{C}$); 195.69 (–$\underline{C}$=O).

4.2.13. 1-(Biphenyl-4-yl)-2-[4-(2,3-dichlorophenyl)-piperazin-1-yl] ethanone (**3k**)

Yield: 85%. mp: 155–160 °C. Elemental analysis: Calcd. C, 67.77; H, 5.21; N, 6.59; O, 3.76.; found: C, 67.82; H, 5.20; N, 6.61; O, 3.77. IR (cm^{-1}): 3062, 2946, 2832, 1687, 1581, 769. ^{1}H NMR (δ ppm $CDCl_3$): 2.7–2.8 (t, 4H, –CH_2–N–($\underline{C}H_2$)$_2$, J = 4.5); 3.2–3.5 (t, 4H, ArN–($\underline{C}H_2$)$_2$, J = 4.6); 3.89 (s, 2H, –$\underline{C}H_2$); 6.8–8.11 (m, 12H, Ar$\underline{H}$). MS (ESI): *m/z* 425.1 (M^+ H), 426.1 (M + 2), 427.1 (M + 4). ^{13}C NMR (δ ppm $CDCl_3$): 49.36 (ArN–$\underline{C}H_2$–, ArN–$\underline{C}H_2$– of pyrazine); 52.18 (N–$\underline{C}H_2$–, N–$\underline{C}H_2$– of pyrazine at aliphatic site); 64.58 (aliphatic –$\underline{C}H_2$–); 118.92, 120.75, 121.72, 127.47 (5C), 128.73, 128.87 (4C), 131.48, 134.83, 139.86, 146.12, 151.29 (Aromatic $\underline{C}$); 195.76 (–$\underline{C}$=O).

4.2.14. 1-(Biphenyl-4-yl)-2-[4-(2,3-dimethylphenyl)-piperazin-1-yl]ethanone (**3l**)

Yield: 77%. mp: 108–110 °C. Elemental analysis: Calcd. C, 81.21; H, 7.34; N, 7.29; O, 4.16.; found: C, 81.15; H, 7.31; N, 7.30; O, 4.18. IR (cm^{-1}): 3059, 2941, 2820, 1684, 1597. ^{1}H NMR (δ ppm $CDCl_3$): 2.32–2.4 (m, 6H, Ar–(CH_3)$_2$); 2.7–2.8 (t, 4H, –CH_2–N–($\underline{C}H_2$)$_2$, J = 4.6); 3.28 (t, 4H, ArN–($\underline{C}H_2$)$_2$, J = 4.8); 3.9 (s, 2H, –$\underline{C}H_2$); 6.7–8.11 (m, 12H, Ar$\underline{H}$). MS (ESI): *m/z* 385.2 (M^+ H). ^{13}C NMR (δ ppm $CDCl_3$): 11.30, 16.87 (Ar–$\underline{C}H_3$); 49.86 (ArN–$\underline{C}H_2$–, ArN–$\underline{C}H_2$– of pyrazine); 52.67 (N–$\underline{C}H_2$–, N–$\underline{C}H_2$– of pyrazine at aliphatic site); 64.48 (aliphatic –$\underline{C}H_2$–); 112.32, 119.43, 124.32, 127.89, 127.56 (5C), 128.21 (4C), 133.93, 137.39, 139.32, 146.33, 148.70 (Aromatic $\underline{C}$); 195.45 (–$\underline{C}$=O).

4.2.15. 1-(Biphenyl-4-yl)-2-[4-(3,4-dichlorophenyl)-piperazin-1-yl] ethanone (**3m**)

Yield: 74%. mp: 145–147 °C. Elemental analysis: Calcd. C, 67.77; H, 5.21; N, 6.59; O, 3.76.; found: C, 67.82; H, 5.19; N, 6.60; O, 3.75. IR (cm^{-1}): 3088, 3032, 2965, 2831, 1686, 1601, 762. ^{1}H NMR (δ ppm $CDCl_3$): 2.68–2.8 (t, 4H, –CH_2–N–($\underline{C}H_2$)$_2$, J = 5.1); 3.3 (t, 4H, ArN–($\underline{C}H_2$)$_2$, J = 4.9); 3.89 (s, 2H, –$\underline{C}H_2$); 6.8–8.11 (m, 12H, Ar$\underline{H}$). ^{13}C NMR (δ ppm $CDCl_3$): 49.43 (ArN–$\underline{C}H_2$–, ArN–$\underline{C}H_2$– of pyrazine); 52.57 (N–$\underline{C}H_2$–, N–$\underline{C}H_2$– of pyrazine at aliphatic site); 64.73 (aliphatic –$\underline{C}H_2$–); 112.42, 114.23, 124.58, 148.56, 127.62 (5C), 128.63 (4C), 131.59, 133.82, 134.63, 139.57, 146.12 (Aromatic $\underline{C}$); 195.68 (–$\underline{C}$=O).

4.2.16. 1-(Biphenyl-4-yl)-2-(4-phenyl-piperazin-1-yl)ethanone (**3n**)

Yield: 84%. mp: 180–184 °C. Elemental analysis: Calcd. C, 80.87; H, 6.79; N, 7.86; O, 4.49.; found: C, 80.91; H, 6.81; N, 7.84; O, 4.50. IR (cm^{-1}): 3096, 3060, 2960, 2844, 1686, 1602. ^{1}H NMR (δ ppm $CDCl_3$): 2.78–2.82 (t, 4H, –CH_2–N–($\underline{C}H_2$)$_2$, J = 4.95); 3.28–3.31 (t, 4H, ArN–($\underline{C}H_2$)$_2$, J = 4.9); 3.91 (s, 2H, –$\underline{C}H_2$); 6.93–8.1 (m, 14H, Ar$\underline{H}$). MS (ESI): *m/z* 357.2 (M^+ H). ^{13}C NMR (δ ppm $CDCl_3$): 49.56 (ArN–$\underline{C}H_2$–, ArN–$\underline{C}H_2$– of pyrazine); 53.26 (N–$\underline{C}H_2$–, N–$\underline{C}H_2$– of pyrazine at aliphatic site); 63.73 (aliphatic –$\underline{C}H_2$–); 114.43 (2C), 119.23, 124.58, 127.62 (4C), 128.90 (6C), 133.85, 138.47, 145.83, 148.56 (Aromatic $\underline{C}$); 194.86 (–$\underline{C}$=O).

4.3. Pharmacology

4.3.1. Experimental groups

Male albino mice (weight range of 20–25 g) procured from Serum Institute of India, Pune were used for experimental study. The animals were kept in suitable environmental condition (22 ± 2° C with 12 h light/dark cycle) and fed with standard food pellets. For experiment purpose three groups of animals as control, test and standard, each with 6 animals were made. All the doses were calculated on body weight basis and were prepared in water for injection (WFI). Route of administration was i.p. except wherever mentioned. Aripiprazole was used as standard for experimental study. Institutional animal ethical committee, Poona College of pharmacy approved all animal experiments.

4.3.2. Inhibition of apomorphine induced climbing behaviour

Administration of apomorphine to mice results in an unusual climbing behaviour characterized initially by rearing and then full-climbing activity, predominantly mediated by the mesolimbic

dopamine system. On the basis of this test, the relative antipsychotic potential of the synthesized compounds has been determined. Climbing behaviour was assessed in the animals by placing them individually in the cylindrical wire mesh cage (height 18 cm, diameter 14 cm). Five minutes after administration of apomorphine (1.0 mg/kg) (intraperitoneal; i.p), standard or test compound was administered at 15 mg/kg dose by i.p. route. After 10 min climbing behaviour was assessed at 5-min intervals for 30 min. In standard group, animal received aripiprazole at dose of 15 mg/kg [21].

4.3.3. Antagonism of 5-HTP induced head twitches

5-HTP was used as the precursor of serotonin. In mice because of 5-HTP, the characteristic symptom of head-twitches is observed. Antagonism of head twitches induced by 5-HTP in mice indicates anti-serotonergic activity. Each animal in the control group was injected with WFI. After 30 min the animals were injected with carbidopa solution (25 mg/kg) prepared in WFI. It was followed by administration of 5-HTP solution (100 mg/kg, i.v.) after 30 min. The numbers of head twitches were counted for a period of 5 min which was followed by an interval of 5 min before the next count. Head twitches were counted for a period of 1 h. For test compounds each animal was administered at 15 mg/kg dose after 30 min followed by 5-HTP solution and carbidopa. Head twitches were counted similar to control group. In standard group, animal received aripiprazole at dose of 15 mg/kg [22].

4.3.4. Haloperidol induced catalepsy

It has been noticed that catalepsy in rodent is a model predictive of EPS in human. Animals in the control group were administered with haloperidol (1 mg/kg), which was taken as the prototype of typical antipsychotics as result catalepsy was induced in the animals. Assessment of catalepsy was done by placing the forepaws of mice on a horizontal bar (2 mm in diameter) kept at a height of 2.5 cm from the platform with hind paws resting on the platform. The evaluation of haloperidol induced catalepsy was done by recording the time span for which the mice retained their forepaws on the horizontal bar during the observation periods of 5 min. The animals in the test group were administered with test drug instead of haloperidol and the remaining procedure for assessment of catalepsy was same as mentioned above [23].

4.4. Statistical analysis

The data obtained from the above studies was analysed to one way analysis of variance (ANOVA) for determining the significant difference between the groups. The inter group significance or post hoc comparison was analysed using Dunnet's t test. P values <0.05 were considered to be significant. All the values were expressed as percentage inhibition of respective behaviour model relative to control group.

4.5. Computational studies

4.5.1. QSAR Study

In the present study 14 derivatives and their corresponding antipsychotic potential were used for QSAR generation. All the computational studies were performed using maestro, graphical user interface for Schrödinger suite 2009 [24]. The 3D structure of molecules was built using 'build' module within Schrödinger. All the structures were minimized using MacroModel by OPLS_2005 with Powell–Reeves conjugate gradient convergence criterion of 0.05 kcal/mol force field at a maximum of 3500 iteration. An 8 A^0 and 20 A^0 cut-off was applied for both van der Waals interactions and electrostatic energies respectively [25]. Physically significant descriptors and pharmaceutically relevant properties were calculated by using QikProp module within Schrödinger suite [26]. To derive QSAR models, the QikProp calculated descriptors were used as independent variables and the BA as the dependent variable. All the statistical work was done in Strike module [27]. Cross-validated multiple linear regressions (MLR) method of leave one out (LOO) was performed to generate QSAR equation. The QSAR equation for antipsychotic potential was evaluated by cross validated correlation coefficient (r^2_{cv}), standard error of estimation (s), F-test (F) and correlation coefficient (r^2).

4.5.2. Similarity study

In the present study we performed the similarity study of 14 synthesized derivatives (test molecules) along with four standard drugs aripiprazole, sertindole, ketanserin and paliperidone (probe molecules). All the computational studies were performed using MAESTRO, graphical user interface for Schrödinger suite 2009. The 3D structure of molecules was built using 'build' module within Schrödinger. The various physicochemical properties such as log P, molecular weight, solvent accessible surface area and molecular volume were calculated by using QikProp module within Schrödinger suite as these properties of the antipsychotic drugs are responsible to cross BBB. The descriptor-based similarity study was done in Strike module. The similarity study was carried out using tanimoto association coefficient, which gives the similarity values in scale from 0 to 1. The tanimoto distance metric is a normalized measure of the similarity in descriptor space between a test molecule and a probe molecule. Similarities lie between one and zero with a value of one indicating identical molecules and a value of zero indicating completely dissimilar molecules.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2013.12.043. These data include MOL files and InChIKeys of the most important compounds described in this article.

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