Synthesis and Pharmacological Evaluation of 1-Biphenyl-4-yl-3-[4-(substituted phenyl)-piperazin-1-yl]-propan-1-one as Possible Atypical Antipsychotic Agents

Anuj Bahuguna, Mugdha R. Suryawanshi*

Poona College of Pharmacy, Bharti Vidyapeeth Deemed University, Pune – 411038,
Maharashtra, India

Abstract

The present study provides a comprehensive process of synthesizing, structural characterization and pharmacological evaluation of fifteen 1-Biphenyl-4-yl-3-[4-(*substituted phenyl*)-piperazin-1-yl]-propan-1-one analogs. The synthesized compounds had notable inhibitory effects on dopaminergic and serotonergic activity in various behavioral paradigms. Among all synthesised compounds, 3C (1-Biphenyl-4-yl-3-[4-(2-methoxy-phenyl)-piperazin-1-yl]-propan-1-one), 3D (1-Biphenyl-4-yl-3-[4-(3-chloro-phenyl)-piperazin-1-yl]-propan-1-one), 3K (1-Biphenyl-4-yl-3-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-propan-1-one and 3L (1-Biphenyl-4-yl-3-[4-(2,3-dimethyl-phenyl)-piperazin-1-yl]-propan-1-one) exhibited a more favorable atypical antipsychotic profile, characterized by a decreased ability to induce catalepsy.

Keywords: Atypical antipsychotic, 1-Biphenyl-4-yl-3-[4-(*substituted phenyl*)-piperazin-1-yl]-propan-1-one, Pharmacological evaluation, QSAR, similarity study

Introduction

Schizophrenia is a severe mental illness marked by severe reality distortions and changes in perception, cognition, social disengagement, personality, and motor behaviour [1]. Positive symptoms such as delusion, hallucination, and illusion are classified as positive symptoms, whereas negative symptoms such as apathy, low motivation, and alogia are classified as negative symptoms. Following the discovery of traditional antipsychotics, additional neuroleptic drugs with antipsychotic action, such as chlorpromazine and haloperidol, were introduced. By inhibiting dopaminergic transmission in the brain, all of these drugs alleviate schizophrenia's positive symptoms [3]. This non-selective suppression of dopamine induces extrapyramidal symptoms (EPS), such as Parkinsonism and tardive dyskinesia, as a secondary effect of suppressing dopaminergic activity in motor areas of the brain [4].

Other common antipsychotic side effects include hyperprolactemia, sexual abnormalities, malignant neuroleptic syndromes, and cardiac arrhythmias [5]. Clozapine, ziprasidone, and aripiprazole are examples of second-generation or atypical antipsychotics that were developed in the search for new antipsychotic drugs that could treat both types of schizophrenia symptoms and have a broader efficacy. By blocking dopaminergic and serotonergic neurotransmission in the brain, newer atypical antipsychotics were expected to be effective in treating both positive and negative symptoms of schizophrenia [6, 7]. When used long-term, however, many atypical antipsychotics produce side effects such as considerable weight gain, agranulocytosis, blood dyscrasias, and hyperglycemia. [8, 9, 10].

Bifeprunox was submitted with the US Food and Drug Administration in 2007 for its possible atypical antipsychotic action. We chose the bifeprunox scaffold for our investigations because it has better atypical antipsychotic potency than many other drugs from the same category

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**Corresponding Author:*
Dr. Mugdha R. Suryawanshi,
e-mail: mugdha.rs@gmail.com

(**Figure 1**). Several molecular modifications of parent bifeprunox have already been carried out and investigated for their atypical antipsychotic characteristics [11]. We used substituted phenyl piperazine in biphenyl with an acetyl linker since several substituted phenyl piperazines have been found to have anti-dopaminergic activity and lower induction of EPS [12, 13]. Furthermore, biphenyl has been revealed to exhibit anti-inflammatory [14], nitric oxide synthase inhibitory [15], anti-diabetic [16], and fungicidal activity [17] biological properties. As a result, we thought it would be interesting to test a new 1-Biphenyl-4-yl-3-chloro-propan-1-one for anti-dopaminergic and anti-serotonergic activities as well as catalepsy studies.

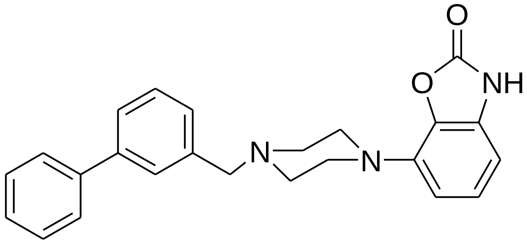

Figure 1. Structure of Bifeprunox

Experimental

Merck pre-coated silica gel F254 plates, thin layer chromatography was used to monitor the reaction's completion. The open capillary method was used to measure the uncorrected melting points of manufactured compounds. The IR spectra of synthetic chemicals was captured in potassium bromide using a Jasco FTIR 4100. For the purpose of recording the 1H-NMR spectra, a Varian Mercury plus300MHz NMR equipment was utilized. Compounds' mass spectra were captured on a 410 Prostar Binary LC using a 500 MS IT PDA detector. Thermo-FLASH Finnigan's EA 1112 underwent an elemental analysis, which is represented by the element's symbol. The theoretical values and the elemental analysis were within 0.4%.

Procedure for synthesis of Biphenyl-4-yl-3-chloro-propan-1-one (2).

A 0.023mol of finely crushed aluminum chloride (anhydrous) and 30mL of CS_2 were added to 0.02mol of biphenyl in a 250mL three-neck flask that was connected to a dropping funnel, a motorized stirrer, and a reflux condenser. Over the course of 20 minutes, 0.02 mol of 3-chloro propionyl chloride was gradually poured from the dropping funnel, starting the mixture's reflux as it was being added. A calcium chloride guard tube was used to seal off the mouths of the condenser and funnel. The reaction was further refluxed for two hours. After cooling, the reaction mixture was carefully poured onto ice that had been smashed up to hold strong hydrochloric acid. After stirring this combination for 15 to 30 minutes, the result was filtered and water washed to get rid of any remaining hydrochloric acid. To remove the remaining biphenyl, washings of petroleum ether was given and the product received recrystallization using a mixture of methanol and water to get pure compound 2.

The practical yield obtained was 4.7g (96.31%).R_f: 0.45. Solvent system- Petroleum ether : Chloroform (2:1).Melting point: 94-95°C.IR [All values in cm^{-1}]: 3062,3038 (C-H aro); 1603 (C=C); 1672 (C=O); 2972,2900 (C-H); 756 (C-Cl). The 1H NMR spectrum of the compound in CDCl3 solvent reveals the following chemical shifts (δ ppm) and corresponding proton multiplicity: 3.46-3.51 (t,2H,CH2- in acyl side chain); 3.92-3.97 (t,2H,CH2 in acyl side chain); 7.47 (d,C2,6 aromatic 2H); 7.68 (d,C2,6' aromatic 2H); 7.71 (m,C3,4,5'; aromatic 3H); 8.04 (d,C3,5 aromatic 2H).

Standardized technique for synthesis of chemical 3A-3N follows:

The reaction flask was filled with a blend of arylpiperazine (0.0026 mol), and K_2CO_3 (0.0026 mol), which was then heated in dimethyl formamide (DMF) for 4-6 hours at 60° C while being stirred. The mixture was added to ice cold water to start the reaction. To obtain the result, this mixture was vacuum-filtered and then water-washed. Chloroform-methanol was used to recrystallize each component.

3A- 1-Biphenyl-4-yl-3-[4-(2-chloro-phenyl)-piperazin-1-yl]-propan-1-one:

Practical yield: 0.7g. (67.30%).R_f: 0.17 (toluene : ethyl acetate (2:0.5).Melting point: 72-74°C.IR [All values in cm^{-1}]: 3064 (C-H aro); 2953, 2876 (C-H ali); 1681 (C=O stretch); 1603 (C=C aro); 763 (C-Cl stretch). ^1H NMR [δ ppm $CDCl_3$]: 2.7-2.8 (t, 4H on $C_{2,6}$ of piperazine ring); 3.28 (t, 4H on $C_{3,5}$ of piperazine ring); 3.03-3.16 (t, 2H of CH_2 of acyl chain); 3.32-3.49 (t, 2H of CH_2 of acyl chain); 6.95-7.40 (m, $C_{3,4,5,6}$ of 2-Cl-phenyl, 4H); 7.45-7.62 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.65-7.83 (m, $C_{2,6,2',6'}$ aromatic 4H); 8.05-8.08 (d, $C_{3,5}$ aromatic 2H).

3B- 1-Biphenyl-4-yl-3-(4-o-tolyl-piperazin-1-yl)-propan-1-one:

Practical yield: 0.65g. (65%).R_f: 0.54 (toluene : ethyl acetate 2:0.5).Melting point: 78-80°C.IR [All values in cm^{-1}]: 3018 (C-H aro); 2952, 2876, 2841 (C-H ali); 1680 (C=O); 1601 (C=C aro).^1H NMR: 2.31 (s, 3H, CH_3 group on phenyl ring); 2.82 (t, 4H on $C_{2,6}$ of piperazine ring); 3.03 (t, 4H on $C_{3,5}$ of piperazine ring); 3.05-3.08 (t, 2H of CH_2 of acyl chain); 3.36-3.41 (t, 2H of CH_2 of acyl chain); 7.06-7.38 (m, $C_{3,4,5,6}$ of o-tolyl, 4H); 7.40-7.51 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.62-7.72 (m, $C_{2,6,2',6'}$ aromatic 4H); 8.05-8.08 (d, $C_{3,5}$ aromatic 2H).

3C- 1-Biphenyl-4-yl-3-[4-(2-methoxy-phenyl)-piperazin-1-yl]-propan-1-one:

Practical yield: 0.55g. (53%).R_f: 0.6. (toluene : ethyl acetate 2:0.5).Melting point: 92-94°C.IR [All values in cm^{-1}]: 3059 (C-H aro); 2991, 2938, 2836 (C-H ali); 1670 (C=O); 1602 (C=C aro).^1H NMR [δ ppm $CDCl_3$]: 3.73 (s, 3H, OCH_3 group on phenyl ring); 2.59 (t, 4H on $C_{2,6}$ of piperazine ring); 3.45 (t, 4H on $C_{3,5}$ of piperazine ring); 2.51 (t, 2H of CH_2 of acyl chain); 2.65(t, 2H of CH_2 acyl chain); 6.48-6.64 (m, $C_{3,4,5,6}$ of phenyl to piperazine, 4H); 7.22-7.36 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.48-7.58 (m, $C_{2,6,2',6'}$ aromatic 4H); 7.95-8.01 (d, $C_{3,5}$ aromatic 2H).

3D- 1-Biphenyl-4-yl-3-[4-(3-chloro-phenyl)-piperazin-1-yl]-propan-1-one:

Practical yield: 0.65g. (63%).R_f: 0.48. (toluene : ethyl acetate 2:0.5).Melting point: 96-98°C.IR [All values in cm^{-1}]: 3029 (C-H aro); 2974, 2937, 2843 (C-H ali); 1669 (C=O); 1603 (C=C); 764 (C-Cl stretching).^1H NMR: 2.74-2.82 (t, 4H on $C_{2,6}$ of piperazine ring); 3.58 (t, 4H on $C_{3,5}$ of piperazine ring); 2.61 (t, 2H of CH_2 of acyl chain); 2.76(t, 2H of CH_2 of acyl chain); 7.22-7.40 (m, $C_{2,4,5,6}$ of 3Cl-phenyl, 4H); 7.48-7.54(m, $C_{3', 4', 5'}$ aromatic 3H); 7.60-7.71 (m, $C_{2,6,2',6'}$ aromatic 4H); 7.95-8.01 (d, $C_{3,5}$ aromatic 2H).

3E- 1-Biphenyl-4-yl-3-(4-m-tolyl-piperazin-1-yl)-propan-1-one:

Practical yield: 0.61g. (61%).R_f: 0.52 (toluene : ethyl acetate 2:0.5).Melting point: 82°C.IR [All values in cm^{-1}]: 3057 (C-H aro); 2953, 2937, 2839 (C-H ali); 1669 (C=O);1603 (C=C). ^1H NMR: 2.36 (s, 3H, CH_3 group on phenyl ring); 2.56-2.68 (t, 4H on $C_{2,6}$ of piperazine ring); 3.45 (t, 4H on $C_{3,5}$ of piperazine ring); 2.61 (t, 2H of CH_2 of acyl chain); 2.70 (t, 2H of CH_2 of acyl chain); 6.47-6.61 (m, $C_{2,4,6}$ of 4-tolyl, 3H); 7.06-7.11 (t, C_5 of 4-tolyl, 1H); 7.22-7.32 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.48-7.56 (m, $C_{2,6,2',6'}$ aromatic 4H); 7.95-8.01 (d, $C_{3,5}$ aromatic 2H).

3F- 1 -Biphenyl-4-yl-3-[4-(3-trifluromethyl-phenyl)-piperazin-1-yl]-propan-1-one:

Practical yield: 0.82g. (73%).R_f: 0.58. (toluene : ethyl acetate : 2:0.5).Melting point: 91-92°C.IR [All values in cm^{-1}]: 3031 (C-H aro); 2955, 2938, 2879, 2841 (C-H ali); 1669 (C=O); 1604 (C=C aro); 1357 (C-F).^1H NMR [δ ppm $CDCl_3$]: 2.59-2.70 (t, 4H on $C_{2,6}$ of piperazine ring); 3.40-3.48 (t, 4H on $C_{3,5}$ of piperazine ring); 2.63 (t, 2H of CH_2

of acyl chain); 2.74 (t, 2H CH_2 of acyl chain); 6.59-6.84 (m, 3H, $C_{2,4,6}$ of trifuromethyl phenyl); 7.01-7.12 (t, 1H, C_5 of trifluromethyl phenyl); 7.22-7.32 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.61-7.72 (m, $C_{2,6,2',6'}$ aromatic 4H); 7.90-8.1 (d, $C_{3,5}$ aromatic 2H).

3G- 1-Biphenyl-4-yl-3-[4-(4-chloro-phenyl)-piperazin-1-yl]-propan-1-one:

Practical yield: 0.75g. (72%).R_f: 0.63. (toluene : ethyl acetate 2:0.5). Melting point: 101-102°C.IR [All values in cm^{-1}]: The infrared spectrum of the compound exhibits characteristic absorption peaks at 3034 cm^-1, corresponding to C-H aromatic stretching vibrations. Additionally, peaks at 2949 cm^-1 and 2840 cm^-1 are observed, which can be attributed to C-H aliphatic stretching vibrations. Another prominent peak is shown at 1671 cm^-1, indicating C=O stretching vibrations. Furthermore, a peak at 1602 cm^-1 is observed, corresponding to C=C aromatic stretching vibrations. Lastly, a peak at 761 cm^-1 is observed, indicating C-Cl stretching vibrations.^{1}H NMR [δ ppm $CDCl_3$]: 2.61-2.70 (t, 4H on $C_{2,6}$ of piperazine ring); 3.39-3.47 (t, 4H on $C_{3,5}$ of piperazine ring); 2.63 (t, 2H of CH_2 of acyl chain); 2.76 (t, 2H of CH_2 of acyl chain); 6.58-6.71 (d, 2H, $C_{2,6}$ on chloro-phenyl); 7.09-7.16 (d, 2H, $C_{3,5}$ on chloro-phenyl); 7.22-7.35 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.61-7.75 (m, $C_{2,6,2',6'}$ aromatic 4H); 7.95-8.1 (d, $C_{3,5}$ aromatic 2H).

3H- 1-Biphenyl-4-yl-3-[4-(4-fluro-phenyl)-piperazin-1-yl]-propan-1-one:

Practical yield: 0.64g. (64%).R_f: 0.18 (toluene : ethyl acetate 2:0.5).Melting point: 98-100°C.IR [All values in cm^{-1}]: 3032 (C-H aro); 2945, 2884, 2844 (C-H ali); 1671 (C=O); 1602 (C=C aro). ^{1}H NMR: 2.74 (t, 4H on $C_{2,6}$ of piperazine ring); 3.16 (t, 4H on $C_{3,5}$ of piperazine ring); 3.16-3.19 (t, 2H of CH_2 of acyl chain); 3.29-3.34 (t, 2H of CH_2 of acyl chain); 6.89-7.40 (m, 4H aromatic on fluro-phenyl ring); 7.43-7.5 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.62-7.71 (m, $C_{2,6,2',6'}$ aromatic 4H); 8.04-8.07 (d, $C_{3,5}$ aromatic 2H).

3I- 1-Biphenyl-4-yl-3-(4-p-tolyl-piperazin-1-yl)-propan-1-one:

Practical yield: 0.75g. (75%).R_f: 0.41 (toluene : ethyl acetate 2:0.5).Melting point: 87-88°C.IR [All values in cm^{-1}]: 3032 (C-H aro); 2973, 2941, 2839 (C-H ali); 1671 (C=O); 1602 (C=C aro).

^{1}H NMR: 2.41 (s, 3H, CH_3 group on phenyl ring); 2.61-2.68 (t, 4H on $C_{2,6}$ of piperazine ring); 3.48 (t, 4H on $C_{3,5}$ of piperazine ring); 2.62 (t, 2H of CH_2 of acyl chain); 2.71 (t, 2H of CH_2 of acyl chain) 6.47-6.78 (m, $C_{2,3,5,6}$ of 4-tolyl, 4H); 7.27-7.42 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.6-7.7 (m, $C_{2,6,2',6'}$ aromatic 4H); 8.01-8.11 (d, $C_{3,5}$ aromatic 2H).

3J- 1-Biphenyl-4-yl-3-[4-(4-methoxy-phenyl)-piperazin-1-yl]-propan-1-one:

Practical yield: 0.52g. (50%).R_f: 0.11 (toluene : ethyl acetate 2:0.5).Melting point: 105-106°C.IR [All values in cm^{-1}]: 3062 (C-H aro); 2991, 2934, 2836 (C-H ali); 1670 (C=O); 1602 (C=C). ^{1}H NMR [δ ppm $CDCl_3$]: 3.73 (s, 3H, OCH_3 group on phenyl ring); 2.61-2.68 (t, 4H on $C_{2,6}$ of piperazine ring); 3.41 (t, 4H on $C_{3,5}$ of piperazine ring); 2.58 (t, 2H of CH_2 of acyl chain); 2.71 (t, 2H of CH_2 of acyl chain); 6.52-6.76 (m, $C_{2,3,5,6}$ of phenyl to piperazine, 4H); 7.32-7.46 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.58-7.71 (m, $C_{2,6,2',6'}$ aromatic 4H); 8.01-8.13 (d, $C_{3,5}$ aromatic 2H).

3K- 1-Biphenyl-4-yl-3-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-propan-1-one:

Practical yield: 0.64g. (57%).R_f: 0.56. (toluene : ethyl acetate 2:0.5).Melting point: 86-88°C.IR [All values in cm^{-1}]: 3062, 3038 (C-H aro); 2972, 2900 (C-H ali); 1672 (C=O aro); 1603 (C=C); 787, 756 (C-Cl stretching).^{1}H NMR [δ ppm $CDCl_3$]: 2.58-

2.65 (t, 4H on $C_{2,6}$ of piperazine ring); 3.48 (t, 4H on $C_{3,5}$ of piperazine ring); 2.64 (t, 2H of CH_2 of acyl chain); 2.75 (t, 2H of CH_2 of acyl chain); 6.55-6.90 (m, $C_{,4,5,6}$ of phenyl to piperazine, 3H); 7.28-7.37 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.48-7.56 (m, $C_{2,6,2',6'}$ aromatic 4H); 7.95-8.01 (d, $C_{3,5}$ aromatic 2H).

3L- 1-Biphenyl-4-yl-3-[4-(2,3-dimethyl-phenyl)-piperazin-1-yl]-propan-1-one:

Practical yield: 0.68g. (67%).R_f: 0.31 (toluene : ethyl acetate 2:0.5).Melting point: 82-83°C.IR [All values in cm^{-1}]: 3073 (C-H aro); 2958, 2944, 2817 (C-H ali); 1675 (C=O); 1602 (C=C). ^{1}H NMR: 2.22-2.26 (m, 6H, CH_3 groups on phenyl ring); 2.77 (t, 4H on $C_{2,6}$ of piperazine ring); 2.97 (t, 4H on $C_{3,5}$ of piperazine ring); 3.00-3.05 (t, 2H of CH_2 of acyl chain); 3.31-3.35 (t, 2H of CH_2 of acyl chain) 6.90-7.05 (m, $C_{4,5,6}$ of 2,3 dimethyl phenyl ring, 3H); 7.45-7.50 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.62-7.71 (m, $C_{2,6,2',6'}$ aromatic 4H); 8.05-8.08 (d, $C_{3,5}$ aromatic 2H). MS (ESI):m/z 399.5 (M+ H$^+$), 400.5 (M+2), 402.5 (M+4).

3M- 1-Biphenyl-4-yl-3-[4-(3,4-dichloro-phenyl)-piperazin-1-yl]-propan-1-one:

Practical yield: 0.69g. (61%).R_f: 0.36 (toluene : ethyl acetate 2:0.5).Melting point: 90-92°C.IR [All values in cm^{-1}]: 3032 (C-H); 2938, 2848 (C-H); 1676 (C=O); 1601 (C=C); 764 (C-Cl).^{1}H NMR: 2.73 (t, 4H on $C_{2,6}$ of piperazine ring); 2.98 (t, 4H on $C_{3,5}$ of piperazine ring); 3.01-3.22 (t, 2H of CH_2 of acyl chain); 3.29-3.33 (t, 2H of CH_2 of acyl chain); 6.72-6.96 (m, $C_{2,5,6}$ of phenyl to piperazine, 3H); 7.25-7.38 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.40-7.62 (m, $C_{2,6,2',6'}$ aromatic 4H); 8.04-8.06 (d, $C_{3,5}$ aromatic 2H). MS (ESI):m/z 439.1 (M+ H$^+$), 440.1 (M+2), 442.1 (M+4).

3N- 1-Biphenyl-4-yl-3-(4-phenyl-piperazin-1-yl)-propan-1-one:

Practical yield: 0.70g. (74%).R_f: 0.48 (toluene : ethyl acetate 2:0.5).Melting point: 99-100°C.IR [All values in cm^{-1}]: 3058, 3036 (C-H aro); 2944, 2884, 2845 (C-H ali); 1671 (C=O); 1602 (C=C).^{1}H NMR: 2.56-2.64 (t, 4H on $C_{2, 6}$ of piperazine ring); 3.44-3.51 (t, 4H on $C_{3, 5}$ of piperazine ring); 2.61 (t, 2H of CH_2 of acyl chain); 2.74 (t, 2H of CH_2 of acyl chain); 6.59 (d, aromatic 2H on $C_{2, 6}$ of phenyl ring to piperazine); 6.64-6.71 (t, aromatic 1H on C_4 of phenyl ring to piperazine); 7.04-7.17 (t, aromatic 2H on $C_{3, 5}$ of phenyl ring to piperazine); 7.23-7.31 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.42-7.56 (d, $C_{2, 6}$, aromatic 2H); 7.70-7.76 (d, $C_{2', 6'}$, aromatic 2H); 7.95-8.1 (d, $C_{3,5}$ aromatic 2H).

3O- 1-Biphenyl-4-yl-3-(4-methylpiperazin-1-yl)propan-1-one:

Practical yield: 0.40g. (50%).R_f: 0.38 (toluene : ethyl acetate 2:0.5).Melting point: 110-111°C.IR [All values in cm^{-1}]: 3051, 3031 (C-H aro); 2967, 2943, 2838 (C-H ali); 1675 (C=O); 1602 (C=C aro).^{1}H NMR: 2.27 (s, 3H of CH3 gp of piperazine ring); 2.48-2.56 (t, 8H on $C_{2,3,5, 6}$ of piperazine ring); 2.61 (t, 2H of CH_2 of acyl chain); 2.72 (t, 2H of CH_2 of acyl chain); 7.43-7.51 (m, $C_{3', 4', 5'}$ aromatic 3H); 7.62-7.64 (d, $C_{2, 6}$, aromatic 2H); 7.68-7.70 (d, $C_{2', 6'}$, aromatic 2H); 7.95-8.01 (d, $C_{3,5}$ aromatic 2H).

Pharmacology

Experimental groups

In order to carry out the experiment, male Albino mice weighing between 20 and 25 grams each were acquired from the Serum Institute of India in Pune. The animals were fed with regular food pellets and kept in a proper habitat (22°C). Three groups of six mice each were created as the control, test, and standard groups for the experiment. For injection, all doses were dissolved in water and calculated based on body weight (WFI). Unless otherwise noted, administration was done via intra peritoneal route. The experimental study's standard drug was aripiprazole. All animal tests were approved by the Poona College of Pharmacy's institutional animal ethical committee.

Inhibition of apomorphine induced climbing behavior

The apomorphine induced climbing behaviour of animals under study was evaluated as per reported method [18]. This served as a possible prototype for monitoring mice climbing behavior.

Antagonism of 5-HTP induced head twitches

The antagonism of 5-HTP induced head twitches behaviour of animals under study was evaluated as per reported method [19].

Haloperidol induced catalepsy

The haloperidol induced catalepsy was monitored as per the reported protocol. [20]. The researchers employed a conventional bar test to assess the extent of haloperidol-induced catalepsy. Measurements were taken at 30-minute intervals up to 120 minutes, and thereafter at 240 minutes. The duration of catalepsy was assessed by observing the length of time during which the mouse maintained a prescribed posture, wherein both of its front limbs were extended and supported by a wooden bar measuring 4 cm in height and 1 cm in diameter. Catalepsy ceased when either the animal's front paws were released from the bar or when the animal exhibited exploring movements with its head.

Statistical analysis

The statistical significance of the animal groups was evaluated using a one-way ANOVA method. The statistical analysis employed Dunnet's t-test to evaluate the importance of intergroup differences or post hoc comparisons.

Results and Discussion

Chemistry

The chemical compounds The compound is named as 1-Biphenyl-4-yl-3-[4-(substituted phenyl)-piperazin-1-yl].As depicted in Scheme 1 (**Figure 2**), the synthesis of -propan-1-one (3A-3O) was accomplished by a two-step process. The Friedel-Crafts acylation reaction was employed to acylate biphenyl (1) using 3-chloropropionyl chloride as the acylating agent. The reaction was conducted in the presence of anhydrous aluminum chloride ($AlCl_3$) as a catalyst and carbon disulfide (CS_2) as the solvent. As a result of this reaction, biphenyl-4-yl-3-chloro-propan-1-one (2) was synthesized. Fifteen molecules of 1-Biphenyl-4-yl-3-[4-(substituted phenyl)-piperazin-1-ylThe synthesis of derivatives of propan-1-one (3A-3O) was carried out by reacting compound 2 with different substituted aryl piperazine moieties along with DMF and potassium carbonate (K_2CO_3). The confirmation of synthesis was carried out by elemental analysis, FTIR, ^{1}H-NMR and mass spectra (ESI). After employing ethanol and water for recrystallization, all of the compounds were recovered in concentrations ranging from 62 to 85 percent.

Here, in synthesized derivatives FTIR spectrum of compound for example 3B showed 3018, 2952 cm^{-1} which represents aromatic and aliphatic C-H stretching respectively, whereas, 1680 cm^{-1} and 1601 cm^{-1} showed carbonyl C=O and aromatic C=C stretching respectively. ^{1}H-NMR showed no presence of NH peak for aryl piperazine and furthermore singlet at 2.31 δ ppm represented presence of aromatic $-CH_3$; 2.82 δ ppm and 3.03 δ ppm showed presence of piperazine protons; triplet at 3.05 δ ppm and 3.36-3.41 represented $–CH_2$- protons and 7.06-8.08 δ ppm range showed aromatic protons. Further for confirmation of molecular weight, Mass spectrum was carried out and it showed M^+ H peak at 385.22 confirming the successful completion of synthesis.

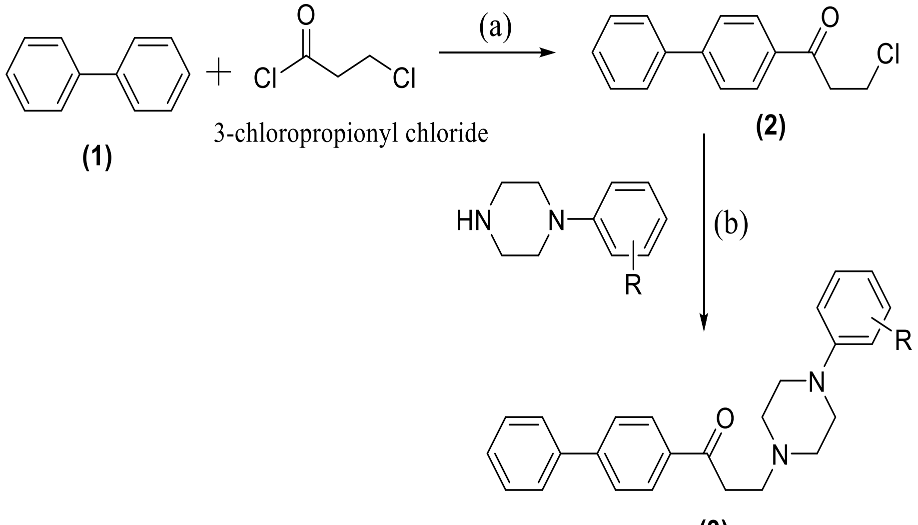

Figure 2. The scheme (a) The reaction was conducted by refluxing a mixture of carbon disulphide and aluminum chloride for a duration of 1 hour. (b) The reaction was carried out by heating a mixture of DMF and K_2CO_3 at 60°C for four to six hours.

Table 1. In-vivo data of the synthetic compounds studied

(Animal used: Albino mice, Dose 30 mg/kg)

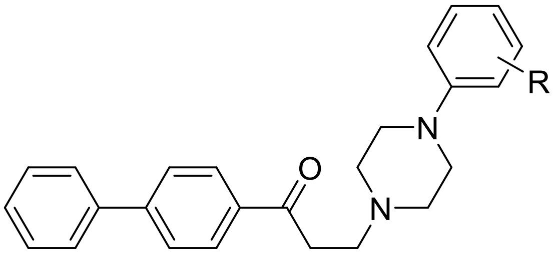

Table 1.

Compound	R	The percentage of inhibition observed in the climbing behavior	The percentage of inhibition of head twitches	The percentage of catalepsy induction
3A	2-Cl	**54.00**	41.37	46.21
3B	2-CH_3	**58.00**	40.51	42.36
3C	2-OCH_3	**57.14**	**51.61**	38.11
3D	3-Cl	**50.71**	**44.82**	34.40
3E	3-CH_3	49.82	41.30	37.37
3F	3-CF_3	43.40	40.00	**33.91**
3G	4-Cl	42.17	41.37	37.14
3H	4-F	37.53	34.48	36.66
3I	4-CH_3	45.16	40.74	39.74
3J	4-OCH_3	47.25	37.03	60.21
3K	2,3-diCl	46.11	**41.37**	**32.41**
3L	2,3-diCH_3	**51.40**	40.15	36.51
3M	3,4-diCl	39.10	37.00	36.14
3N	H	46.81	31.57	**33.18**
3O	n-methyl piperazine	37.41	30.30	**28.15**
Arp		67.40	94.41	30.81

Number of animals used n= 6, $p<0.05$. Arp = aripiprazole.

Pharmacology

In order to evaluate the potential of synthetic derivatives of antipsychotics, a haloperidol-induced catalepsy paradigm was used in conjunction with the reduction of apomorphine-induced mountaineering behavior and the suppression of 5HTP-induced head pains. Studies on the effects of a variety of various substitutions on the aryl ring were carried out after the starting point of compound 3N served as a guide. This was done after the starting point of compound 3N served as a guide. Every piece of biological information is put through statistical analysis, and the findings are displayed as suppression rates for each behavioral model. (**Table 1**).

The capacity of all drugs to suppress apomorphine-induced mountaineering behaviour was used to test their central antidopaminergic activity. The bioactivity of all substituents diminishes from the ortho to the para position in general. In comparison to lead 3N, the presence of chlorine 3A and methyl 3B on the aryl ring resulted in greater antidopaminergic activity [21]. Apomorphine-induced mountaineering behaviour was considerably reversed when methoxy 3C was substituted at the ortho site. The presence of methyl 3E in the meta position increased antidopaminergic activity marginally, whereas chlorine 3D and trifluoromethyl 3F decreased antidopaminergic activity. The anti-dopaminergic effect was reduced by replacing the p location with the halogens 3G and 3H. A marginal improvement in the inhibitory effect on dopamine receptors was seen when para-position replacements were made with methyl 3I and methoxy 3J. In the realm of di-substituted derivatives, it is worth mentioning that ortho-meta di-substituted molecules encompassing hydrophobic groups and steric features, namely 3L and 3K, exhibited a notable augmentation in their anti-dopaminergic efficacy. This was the case because these molecules possess both steric and hydrophobic groups. However, antidopaminergic activity was shown to be significantly reduced in meta-para di-halo substituted molecules.

The anti-serotonergic activity of all of the derivatives was found to be higher than that of lead 3N, with the sole exception of 3B and 3H, which demonstrated a very modest decrease in activity when compared to lead 3N. The anti-serotonergic action of compound 3C was very significant. In a study on the development of cataplexy in albino mice, compounds 3F, 3K, 3N, and 3O showed the lowest levels of the neurological disorder; nonetheless, their levels were not considerably lower than those of normal aripiprazole [21]. Compound 3J has the highest potential to induce catalepsy out of all of the compounds that have been synthesized. In general, the molecule 3C is (1-Biphenyl-4-yl-3-[4-(2-methoxy-phenyl)-piperazin-1-yl], 3-Biphenyl-4-yl-3-[4-(3-chloro-phenyl)-piperazin-1-yl]), 3D (1-Biphenyl-4-yl-3-[4-(3-chloro-phenyl)-piperazin-1-yl]), exhibited a better atypical antipsychotic profile and was less effective in inducing catalepsy.

Conclusion

In conclusion, the process of synthesizing a range of derivatives of 1-Biphenyl-4-yl-3-[4-(substituted phenyl)-piperazin1-yl]-propan-1-one was conducted and subsequently verified through the utilization of physicochemical and spectral analysis techniques. According to the findings of the pharmacological research, all of the compounds exhibited a significant amount of atypical antipsychotic activity. Among the various synthesized derivatives, compound, 3C (1-Biphenyl-4-yl-3-[4-(2-methoxy-phenyl)-piperazin-1-yl]-propan-1-one) is of particular interest, 3D (1-Biphenyl-4-yl-3-[4-(3-chloro-phenyl)-piperazin-1-yl]-propan-1-one), 3K (1-Biphenyl-4-yl-3-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-propan-1-one and 3L (1-Biphenyl- 4-yl-3-[4-(2,3-dimethyl-phenyl)-piperazin-1-yl]-propan-1-one) displayed an improved atypical antipsychotic profile together with a decreased catalepsy induction.

Conflict of Interest

The authors declare no conflict of interest.

Disclaimer

The views, thoughts and opinions expressed in this review belong solely to the authors, and not necessarily to the author's employer, organization, committee or other group or individual.

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