Ind. J. Pharm. Edu. Res., 2025; 59(3s):s1090-s1100.
https://www.ijper.org

Original Article

Synthesis, Characterisation and Evaluation of Benzimidazoles Containing Biphenylcarbonylpiperazine at C-2 Position for Antipsychotic Activity

Rani S. Kankate[1,*], Zenish J. Jain[1], Shantanu S. Ghodke[1], Paraag S. Gide[2], Kaustubh S. Patil[1], Smita P. Kakad[1], Sunita N. Surse[1]

[1]Department of Pharmaceutical Chemistry, MET's Institute of Pharmacy, Bhujbal Knowledge City, Nashik, Maharashtra, INDIA.
[2]Department of Pharmaceutics, HSNCB's Dr. L. H. Hiranandani College of Pharmacy, CHM Campus, Ulhasnagar, Maharashtra, INDIA.

ABSTRACT

Aim/Background: The development of antipsychotic medications with a better clinical profile and fewer neurological side effects is still necessary. Since it is widely known that a dopamine D2 opposing component is required for antipsychotic efficaciousness, the majority of modern pharmacological treatments under investigation are based on the development of medications that partially or entirely interfere with dopamine D2-like receptors. Compounds that selectively block a subtype of dopamine D2-like receptors or those that bind to particular serotonin receptor subtypes in addition to dopamine D2 receptors may be able to produce an atypical antipsychotic profile. **Materials and Methods:** In present research work, 14 derivatives of 2-[N4-(4'-phenylbenzoyl)piperazin-1-yl-alkyl]-1H-alkyl/aryl/5-alkyl/chloro/5,6-dichloro-benzo(d) imidazoles were synthesized successfully and confirmed with the spectral characterization by IR, ^{1}H-NMR, ^{13}C-NMR and Mass. **Results:** All 14 synthesized derivatives were evaluated for antipsychotic potential. Catalepsy model was used because it is also a type of negative symptom of schizophrenia. Thus, all the compounds successfully reversed to varying extent, the haloperidol induced cataleptic effect in female mice. **Conclusion:** It was found from the activity profile of the 14 compounds that the synthesized compounds effectively decreased the catalepsy caused by Haloperidol. With respect to this, compounds BPB02, BPB03, BPB05, BPB08, BPB09, BPB12 were found to be more effective.

Keywords: Antipsychotic, Benzimidazole, Biphenyl, Piperazine, Schizophrenia.

Correspondence:
Dr. Rani S. Kankate
Assistant Professor, Department of Pharmaceutical Chemistry, MET's Institute of Pharmacy, Bhujbal Knowledge City, Nashik-422003, Maharashtra, INDIA.
Email: ranipharmacy@gmail.com
ORCID: 0000-0002-7569-0777

Received: 18-11-2024;
Revised: 09-01-2025;
Accepted: 28-04-2025.

INTRODUCTION

Several conventional antipsychotics, primarily arylpiperazines, have been produced following the discovery of chlorpromazine in the early 1950s.[1] Antipsychotic medications have been extensively utilized and demonstrated to be efficacious in managing the positive symptoms of schizophrenia and similar psychoses, as well as in preventing relapses of psychosis.[2] However, these medications have notable disadvantages, such as the presence of persistent symptoms in 25-60% of patients (known as treatment refractory or partial responders), only moderate improvement of negative and cognitive symptoms and a variety of side effects, both immediate (such as extrapyramidal symptoms) and long-term (such as tardive dyskinesia). The term 'atypical' was initially used to describe clozapine due to its unique properties that were found to be different from the conventional or typical Neuroleptics.[3] The term 'atypical' was subsequently adopted to encompass the shared features of more recently developed antipsychotic drugs, which include: (a) the lack of hyperprolactinemia; (b) superior effectiveness in treating positive and negative symptoms as well as symptoms of disorganization; and (c) the absence of tardive dyskinesia or dystonia after long-term administration.[1]

One such drug of arylpiperazine category and still belongs to the atypical class, namely bifeprunox contains aryl+piperazine+biphenyl as the structural moiety (Figure 1).[4,5]

Bifeprunox, a new antipsychotic drug developed by Solvay Pharma, belongs to the third generation of atypical pharmacological agents. It is part of a series of 1-aryl-4-(biarylmethane-ene) piperazines. Bifeprunox has partial agonist properties at DA D2 receptors and partial agonist properties at 5-HT_{1A} receptors. Currently, it is undergoing phase III clinical trials and is anticipated to be released as a treatment for schizophrenia soon. Additionally, it is under consideration for the treatment of bipolar illness.[6] Due to this, there is scope to explore and synthesize more and more

DOI: 10.5530/ijper.20256783

compound's structures. Biphenyl group imparts lipophilicity in a compound and thus imparts good D2 and D4 receptor binding affinity.[7]

In this study, new compounds derived from benzimidazolo piperazinyl carbonyl biphenyl were synthesized. These compounds effectively block D2, D3 and D4 receptors and enhance the release of DA and 5-HT, which are important factors in the mechanism of action of atypical antipsychotic drugs. These compounds have the potential to reduce both positive and negative symptoms of psychosis without causing significant side effects, which could mimic the structure of newer atypical antipsychotic drugs such as Bifeprunox and Pimozide. Along with this, antagonism of D3 and D4 receptors with minimum side effects was also aimed at.

MATERIALS AND METHODS

The chemicals utilized were obtained from Sigma Aldrich and S.D. Fine Chemicals. The compounds were measured in terms of weight and the percentage of the yield was determined, melting point range were taken and are uncorrected. 60-F254 precoated silica gel plates (Merck) were used to perform analytical Thin-Layer Chromatography (TLC). The purpose of this was to determine the identity of the reactants and products during and at the end of the reactions, in order to confirm that the reaction had reached completion. The spots were observed using a UV chamber. The melting point of all the derivatives were determined using Thiel's tube method and remain uncorrected. Infrared spectra were obtained by using a Shimadzu 1000 FTIR spectrometer. The spectra were recorded in the range of 4000-200 cm^{-1} with a resolution of 2.0 and a total of 45 scans were performed. ^{1}H-NMR and ^{13}C-NMR were obtained using a Bruker 500MHz spectrophotometer, with $CDCl_3$ and DMSO used as solvents. The chemical shifts were expressed in parts per million (δ ppm). The mass fragmentations were obtained using an LCMS apparatus equipped with an Atmospheric Pressure Chemical Ionization (APCI) source. The system consisted of a 410 Prostar Binary LC coupled with a 500 MS Ion Trap PDA Detector. Additionally, the mass was also recorded on a 4000Q-TRAP MS/MS System. Haloperidol injection was used as reference drug to study pharmacological activity sold under the brand name 'SERENACE' containing Haloperidol I.P. 5 mg/mL For IV or IM route, Mfg. by: RPG Life Sciences Ltd.

Synthesis of 2-[N^4-(4'-phenylbenzoyl) piperazin-1-yl-alkyl]-1H-alkyl/aryl/5-alkyl/chloro/5,6-dichloro-benzo(d)imidazoles: (Figure 2).

In a two necked round bottom flask 10 g o-Fluoronitrobenzene in dioxane was taken. To this solution 10 g of anhydrous Potassium carbonate was added. Followed by 12 mL of alkylamine was added slowly dropwise through a dropping funnel with stirring under cold condition. The above mixture was refluxed for 3 hr. Subsequently, the mixture was transferred into ice-cold water while being stirred and then subjected to extraction using ether in a separating funnel. The organic layer was isolated and dehydrated using Na_2SO_4. The organic layer of ether was then evaporated using distillation to obtain the liquid product of 2-nitro-N-alkylbenzamine.

To the synthesized, 10 mL of 2-nitro-N-alkylbenzamine in RBF with reflux condenser were introduced 32 g of powdered tin and 70 mL of conc. HCl slowly with care. The mixture was refluxed for 20 min on gentle flame until reaction just started. After 20 min, most tin was reacted and a clear solution was obtained. The reaction mixture was allowed to cool somewhat and the liquid was decanted in a beaker. The residual tin was washed by decantation with 10 mL of water and the washings were added to the contents of the beaker. Liquid ammonia was used to make the solution just alkaline to litmus paper. At this point, the hydrated tin oxide precipitated out. The precipitated hydrated tin oxide solution was digested on a steam bath for 20 min. The solution was then stirred well, filtered and washed with hot water. The cake was transferred to the beaker, heated with 150 mL water to ensure extraction of product and refiltered. The filtrate obtained and the above washings were combined and concentrated until volume reduced significantly. The liquid was acidified to litmus with glacial acetic acid and evaporated on water bath until crystal commenced to separate. Then remaining solution was cooled in ice, crystals were filtered at pump and dried to get N^1-alkyl benzene-1,2-diamine.

2 g of substituted/unsubstituted N^1-alkyl benzene-1,2-diamine and 4 g of chloro acid were transferred to a round bottom flask. To it 6-10 mL of HCl and 3-5 mL of water was added and was refluxed for 6 hr. Following the completion of the reaction, the solution was rinsed with ether using a separating funnel. The solution was added to ice-cold water while stirring and then made alkaline by adding strong Ammonia solution until a precipitate formed. The solid precipitate mentioned earlier was subjected to filtration and subsequently dried to get 5/6-substituted-{2-(chloroalkyl)-1-alkyl-1H-benzo(d)imidazoles (B01-B14). Recrystallisation was done with ethanol.

Simultaneously, Biphenyl-4-carbonyl piperazine/N^1-(4'-phenylbenzoyl)-1H-piperazine (A) was synthesized. 8 g Biphenylcarbonylchloride and 4 g anhydrous Piperazine in DMF was taken in RBF. A total of 23.01 g K_2CO_3 was introduced into the reaction mixture and was stirred for 8 h at a temperature of 80°C. After the reaction is completed, water was introduced to the mixture and the product was extracted by shaking the mixture with DCM in a separating funnel. The layer of dichloromethane was washed consecutively with water and then dried using Na_2SO_4.

The final compound 2-[N^4-(4'-phenyl benzoyl) piperazin-1-yl-alkyl]-1H-alkyl/aryl/5-alkyl/chloro/5,6-dichloro benzo(d)imidazoles (BPB01-BPB14) was synthesized by preparing a solution of 0.3 g of 2-chloroalkyl substituted with or without N-substitution and also with or without 5 and/

or 6-substituted benzimidazole analogues and Biphenyl-4-carbonyl piperazine/N[1]-(4'-phenylbenzoyl)-1H-piperazine in N, N-dimethylformamide was placed in RBF in presence of K_2CO_3 and stirred at 80°C. After the reaction completed, water was introduced to the mixture and the product was separated by agitating it with DCM in a separating funnel. The DCM was washed consecutively with water and then dried using Na_2SO_4. The solvent evaporated, resulting in the formation of the product. Purified using chloroform by recrystallization. The completion of all the reactions was observed using TLC. Detailed description of characteristics of 14 compounds is mentioned in Table 1.[8-14]

Acute Toxicity Studies

The synthesized analogues were examined for acute toxicity (LD_{50}) in albino female mice using the process described by Smith[15] which compliance with the established protocols of the Animal Ethics Committee. The doses administered were 55 mg/kg, 175 mg/kg, 550 mg/kg, 1750 mg/kg and 2000 mg/kg. The synthesized analogues were orally administered to one group of animals, whereas the same volume of normal saline was administered to another group of animals. Each group consisted of five mice and the doses were administered in graduated amounts. Throughout the investigation, the animals had unrestricted access to water and food. After 48 hr of administering the medicine, the percentage of deaths was observed in each group. The LD_{50} value was derived by graphing the graph of dose vs percentage of death. The ED_{50} was estimated based on the obtained LD_{50} value. The ED_{50} value is estimated as $1/10^{th}$ of that of the LD_{50} value according to the Smite Method.[15]

Animals

The study utilized female Swiss albino mice weighing between 25 and 30 g. The animals were kept in colony cages and maintained under standard environmental conditions, including a temperature of 25±2°C, a 12-hr light and 12-hr dark cycle and a relative humidity of 45-55%. They had unrestricted access to food and water. There was no deprivation of food or drink overnight or during the trial. The trials were conducted exclusively during the light period, which spanned from 10:00 to 16:00 hr. The study protocol was approved by the Institutional Animal Ethical Committee. The animals were purchased from Haffkin's Institute located in Parel, Mumbai.

Catalepsy

Catalepsy was generated in a group of five female Swiss albino mice by administering haloperidol (1.0 mg/kg, i.p., Brand name: 'Serenace', 5 mg/mL I.V. ampoule). The level of catalepsy was measured at 30, 60, 90, 120 and 240 min using a standard bar test. The duration of catalepsy was quantified by monitoring the length of time (in seconds) during which the mouse maintained a fixed posture using both front limbs fully extended and supported on a wooden object measuring 4 cm in height and 1.0 cm in diameter. The catalepsy endpoint was defined as the moment when either both front paws were lifted from the bar or the animal exhibited exploratory movement with its head. The severity of the cataleptic behavior was assessed using a scoring system. A score of 1 was given if the animal sustained the imposed position for a minimum of 20 sec. An additional point was provided for every additional 20 sec. Data was collected and documented within a time limit of 1100 sec. The animals were returned to their own individual home cages during the intervals between determinations. The observations were conducted in a tranquil room with a temperature ranging from 23-25°C, specifically between 10.00 and 16.00 hr. The animals in the experimental group were given the test drug at either a dose of 88 mg/kg or 8 mg/kg, which is the ED_{50} value. This was done 30 min after administering haloperidol. The rest of the protocol for evaluating catalepsy remained unchanged as described previously. The data presented expressed as the mean value plus or minus the Standard Error of the Mean (±SEM). The data underwent analysis using one-way ANOVA, specifically with Graphpad Instat Version 3 software. A significance level of less than 0.05 was deemed significant.[16]

RESULTS

Spectral analysis

A. N1-(4'-phenylbenzoyl)-1H-piperazine

Yield: 78%; M.P.:254-256°C; R_f: 0.862; IR ν_{max}(cm^{-1}): 1541(Ar. C=C), 1716(C=O), 3028(C-H Chromophore), 1430(-CH_2), 868(Ar.1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.22-8.01(m, 9H), 2.85-3.35(m, 8H), 2.07(s, 1H); ^{13}C-NMR(δc ppm, DMSO-d6): 45.8-50.2 (d, 4C, -CH_2 of piperazine), 129.3-134.1 (m, 12C, aromatic), 150.1 (s, 1C, -C=O); ESI-MS(m/z): 266.14, 223.01, 181.13, 153.07, 77.09.

B01. 2-(chloromethyl)-1H-benzo[d]imidazole

Yield: 81%; M.P.:145-148°C; R_f: 0.531; IR ν_{max}(cm^{-1}): 1301/2214(Ar.C-N), 2981(C-H Chromophore), 1502(-CH_2), ^{1}H-NMR(δ ppm): 7.26-7.77(m, 4H), 5.12(s, 1H of NH), 4.67(s, 2H of CH_2); ^{13}C-NMR(δc ppm, DMSO-d6): 40.9 (s, 1C, -CH_2), 118.5-137.0 (m, 6C, aromatic), 141.3 (s, 1C, -CN of benzimidazole); ESI-MS(m/z): 166.03, 117.04, 90.03, 52.14.

B02. 2-(2-chloroethyl)-1H-benzo[d]imidazole

Yield: 73%; M.P.:135-137°C; R_f: 0.274; IR ν_{max}(cm^{-1}): 1290/2224(Ar.C-N), 2967(C-H Chromophore), 1499(-CH_2), ^{1}H-NMR(δ ppm): 7.34-7.68(m, 4H), 5.01(s, 1H of NH), 3.71(s, 2H of CH_2), 2.83(s, 2H of CH_2); ^{13}C-NMR(δc ppm, DMSO-d6): 33.6 (s, 1C, -CH_2), 41.9 (s, 1C, -CH_2), 116.5-138.3 (m, 6C, aromatic), 147.6 (s, 1C, -CN of benzimidazole); ESI-MS(m/z): 180.03, 145.07, 117.04, 90.03, 77.03.

B03. 2-(chloromethyl)-1-methyl-1 H-benzo[d]imidazole

Yield: 75%; M.P.:180-182°C; R_f: 0.317; IR ν_{max}(cm^{-1}): 1320/2233(Ar.C-N), 2997(C-H Chromophore), 1541(-CH_2), ^{1}H-NMR(δ ppm): 7.21-7.80(m, 4H), 4.64(s, 2H of CH_2), 3.63(s, 3H of CH_3); ^{13}C-NMR(δc ppm, DMSO-d6): 31.5 (s, 1C, -CH_3), 35.4 (s, 1C, -CH_2), 115.5-134.3 (m, 6C, aromatic), 139.3 (s, 1C, -CN of benzimidazole); ESI-MS(m/z): 180.10, 145.07, 131.06, 117.06, 76.11.

B04. 2-(chloromethyl)-1-ethyl-1H-benzo[d]imidazole

Yield: 69%; M.P.:178-180°C; R_f: 0.350; IR ν_{max}(cm^{-1}): 1299/2201(Ar.C-N), 2979(C-H Chromophore), 1503(-CH_2), ^{1}H-NMR(δ ppm): 7.26-7.76(m, 4H), 4.84(s, 2H of CH_2), 3.77(q, 2H of CH_2), 1.51(t, 3H of CH_3); ^{13}C-NMR(δc ppm, DMSO-d6): 16.2 (s, 1C, -CH_2), 33.1 (s, 1C, -CH_3), 35.7 (s, 1C, -CH_2), 114.3-138.9 (m, 6C, aromatic), 148.3 (s, 1C, -CN of benzimidazole); ESI-MS(m/z): 194.03, 159.09, 131.06, 90.03, 77.03, 41.02.

B05. 2-(chloromethyl)-1-propyl-1 H-benzo[d]imidazole

Yield: 82%; M.P.:184-186°C; R_f: 0.375; IR ν_{max}(cm^{-1}): 1339/2251(Ar.C-N), 2988(C-H Chromophore), 1546(-CH_2), ^{1}H-NMR(δ ppm): 7.19-7.57(m, 4H), 4.61(s, 2H of CH_2), 3.73(t, 2H of CH_2), 1.81(m, 2H of CH_2), 1.02 (t, 2H of CH_3); ^{13}C-NMR(δc ppm, DMSO-d6): 11.5 (s, 1C, -CH_3), 26.4 (s, 1C, -CH_2), 37.4 (s, 1C, -CH_2), 49.3 (s, 1C, -CH_2), 117.2-136.7 (m, 6C, aromatic), 147.7 (s, 1C, -CN of benzimidazole); ESI-MS(m/z):208.03, 165.022, 116.03, 65.01, 52.03.

B06. 1-butyl-2-(chloromethyl)-1H-benzo[d]imidazole

Yield: 70%; M.P.:180-183°C; R_f: 0.387; IR ν_{max}(cm^{-1}): 1302/2241(Ar.C-N), 3021(C-H Chromophore), 1522(-CH_2), ^{1}H-NMR(δ ppm): 7.08-7.61(m, 4H), 4.55(s, 2H of CH_2), 3.34(t, 2H of CH_2), 1.77(m, 2H of CH_2), 1.37(m, 2H of CH_2), 0.96 (t, 2H of CH_3); ^{13}C-NMR(δc ppm, DMSO-d6): 13.8 (s, 1C, -CH_3), 20.2 (s, 1C, -CH_2), 33.1 (s, 1C, -CH_2), 37.8 (s, 1C, -CH_2), 47.6 (s, 1C, -CH_2), 114.9-140.1 (m, 6C, aromatic), 146.5 (s, 1C, -CN of benzimidazole); ESI-MS(m/z): 222.03, 193.05, 165.02, 90.03, 74.98.

B07. 2-(chloromethyl)-5-methyl-1 H-benzo[d]imidazole

Yield: 71%; M.P.:139-142°C; R_f: 0.375; IR ν_{max}(cm^{-1}): 1345/2221(Ar.C-N), 3001(C-H Chromophore), 1532(-CH_2), ^{1}H-NMR(δ ppm): 7.06-7.57(m, 3H), 5.12(s, 1H of NH), 4.64(s, 2H of CH_2), 2.35(s, 3H of -CH_3); ^{13}C-NMR(δc ppm, DMSO-d6): 24.3 (s, 1C, -CH_3), 41.9 (s, 1C, -CH_2), 115.5-132.7 (m, 6C, aromatic), 139.7 (s, 1C, -CN of benzimidazole); ESI-MS(m/z): 180.1, 131.06, 119.05, 90.04, 77.03.

B08. 2-(2-chloroethyl)-5-methyl-1H-benzo[d]imidazole

Yield: 67%; M.P.:79-82°C; R_f: 0.454; IR ν_{max}(cm^{-1}): 1330/2276(Ar.C-N), 3010(C-H Chromophore), 1522(-CH_2), ^{1}H-NMR(δ ppm): 7.40-7.56(m, 3H), 5.07(s, 1H of NH), 3.97(t, 2H of CH_2), 2.83(t, 3H of -CH_3), 2.37(s, 3H, of -CH_3); ^{13}C-NMR(δc ppm, DMSO-d6): 26.1 (s, 1C, -CH_3), 33.2(s, 1C, -CH_2), 40.04 (s, 1C, -CH_2), 116.1-135.9 (m, 6C, aromatic), 151.8 (s, 1C, -CN of benzimidazole); ESI-MS(m/z): 180.1, 131.06, 119.05, 90.04, 77.03.

B09. 5-chloro-2-(chloromethyl)-1H-benzo[d]imidazole

Yield: 63%; M.P.:78-82°C; R_f: 0.322; IR ν_{max}(cm^{-1}): 1313/2199(Ar.C-N), 3000(C-H Chromophore), 1510(-CH_2), ^{1}H-NMR(δ ppm): 7.34-7.71(m, 3H), 4.73(s, 1H of NH), 4.44(s, 2H of CH_2); ^{13}C-NMR(δc ppm, DMSO-d6): 45.3 (s, 1C, -CH_2), 116.7-140.3 (m, 6C, aromatic), 140.7 (s, 1C, -CN of benzimidazole); ESI-MS(m/z): 199.99, 151.06, 117.04, 105.04, 53.01.

B10. 5-chloro-2-(2-chloroethyl)-1H-benzo[d]imidazole

Yield: 68%; M.P.:96-100°C; R_f: 0.331; IR ν_{max}(cm^{-1}): 1343/2203(Ar.C-N), 2963(C-H Chromophore), 1523(-CH_2), ^{1}H-NMR(δ ppm): 7.24-7.64(m, 3H), 5.12(s, 1H of NH), 3.71(s, 2H of CH_2), 2.83 (s, 2H of CH_2); ^{13}C-NMR(δc ppm, DMSO-d6): 33.7 (s, 1C, -CH_2),41.3 (s, 1C, -CH_2), 115.8-138.7 (m, 6C, aromatic), 153.1 (s, 1C, -CN of benzimidazole); ESI-MS(m/z): 218.02, 179.03, 151.03, 109.92, 52.03.

B11. 5,6-dichloro-2-(chloromethyl)-1H-benzo[d]imidazole

Yield: 67%; M.P.:148-150°C; R_f: 0.349; IR ν_{max}(cm^{-1}): 1296/2198(Ar.C-N), 3003(C-H Chromophore), 1515(-CH_2), ^{1}H-NMR(δ ppm): 7.65(s, 2H), 4.89(s, 1H of NH), 3.76(s, 2H of CH_2); ^{13}C-NMR(δc ppm, DMSO-d6): 38.4 (s, 1C, -CH_2), 117.2-138.9 (m, 6C, aromatic), 147.2 (s, 1C, -CN of benzimidazole); ESI-MS(m/z): 233.95, 184.96, 119.95, 66.02.

B12. 5,6-dichloro-2-(2-chloroethyl)-1H-benzo[d]imidazole

Yield: 73%; M.P.:135-140°C; R_f: 0.367; IR ν_{max}(cm^{-1}): 1300/2247(Ar.C-N), 3017(C-H Chromophore), 1530(-CH_2), ^{1}H-NMR(δ ppm): 7.50(s, 2H), 4.56(s, 1H of NH), 3.71(t, 2H of CH_2), 2.84(t, 2H of CH_2); ^{13}C-NMR(δc ppm, DMSO-d6): 30.2 (s, 1C, -CH_2), 41.5 (s, 1C, -CH_2), 116.7-138.4 (m, 6C, aromatic), 149.9 (s, 1C, -CN of benzimidazole); ESI-MS(m/z): 247.97, 184.94, 151.03, 117.04, 76.03.

B13. 2-(chloromethyl)-1-phenyl-1 H-benzo[d]imidazole

Yield: 66%; M.P.:83-85°C; R_f: 0.356; IR ν_{max}(cm^{-1}): 1278/2203(Ar.C-N), 3004(C-H Chromophore), 1520(-CH_2), ^{1}H-NMR(δ ppm): 7.22-7.62(m, 9H), 4.62(s, 2H of CH_2); ^{13}C-NMR(δc ppm, DMSO-d6): 35.3 (s, 1C, -CH_2), 116.9-138.9 (m, 12C, aromatic), 141.9 (s, 1C, -CN of benzimidazole); ESI-MS(m/z): 242.06, 207.09, 131.06, 77.03.

B14. 2-(2-chloroethyl)-1-phenyl-1H-benzo[d]imidazole

Yield: 74%; M.P.:45-50°C; R_f: 0.298; IR ν_{max}(cm^{-1}): 1364/2242(Ar.C-N), 2996(C-H Chromophore), 1555(-CH_2), ^{1}H-NMR(δ ppm): 7.08-7.57(m, 9H), 3.24(s, 2H of CH_2), 2.84(s, 2H of CH_2); ^{13}C-NMR(δc ppm, DMSO-d6): 27.5 (s, 1C, -CH_2), 42.9 (s, 1C, -CH_2), 113.7-135.9 (m, 12C, aromatic), 145.7 (s, 1C, -CN of benzimidazole); ESI-MS(m/z): 256.08, 207.09, 193.07, 117.04, 76.03.

BPB01. 2-[N⁴-(4'-phenylbenzoyl)piperazin-1-yl-methyl]-1H-benzo(d)imidazole

Yield: 50%; M.P.:114-116°C; R_f: 0.835; IR ν_{max}(cm^{-1}): 1327/1290/2267(Ar.C-N), 1716(C=O), 748/700(C-H), 3030(C-H Chromophore), 1456(-CH_2), 856(Ar.1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.28-7.7(m, 13H), 3.993(s,2H), 3.5-3.95(m, 8H), 1.643(s, 3H); ^{13}C-NMR(δc ppm, DMSO-d6): 48.1-52.3 (d, 4C, -CH_2 of piperazine), 55.3 (s, 1C, -CH_2), 115.3-138.8 (m, 18C,

Table 1: Detailed representation of characteristics of 14 final compounds that were synthesized.

Code	R_1	R_2	R_3	n	Colour	Molecular Formula	Molecular Weight
B01	H	H	H	1	Dark yellow	$C_8H_7N_2Cl$	166.03
B02	H	H	H	2	White	$C_9H_9N_2Cl$	180.63
B03	Methyl	H	H	1	White	$C_9H_9N_2Cl$	180.05
B04	Ethyl	H	H	1	White	$C_{10}H_{11}N_2Cl$	194.06
B05	n-Propyl	H	H	1	White	$C_{11}H_{13}N_2Cl$	208.08
B06	n-Butyl	H	H	1	White	$C_{12}H_{15}N_2Cl$	222.09
B07	H	-CH_3	H	1	Brown	$C_9H_9N_2Cl$	180.05
B08	H	-CH_3	H	2	Brown	$C_{10}H_{11}N_2Cl$	194.06
B09	H	-Cl	H	1	Light brown	$C_8H_6N_2Cl_2$	199.99
B10	H	-Cl	H	2	Brown	$C_9H_8N_2Cl_2$	214.01
B11	H	-Cl	-Cl	1	Orangish brown	$C_8H_5N_2Cl_3$	233.95
B12	H	-Cl	-Cl	2	Cream	$C_9H_7N_2Cl_3$	247.97
B13	Phenyl	H	H	1	Reddish pink	$C_{14}H_{11}N_2Cl$	242.06
B14	Phenyl	H	H	2	Reddish black	$C_{15}H_{13}N_2Cl$	256.73
BPB01	H	H	H	1	Brown	$C_{25}H_{24}N_4O$	396.48
BPB02	H	H	H	2	Yellowish brown	$C_{26}H_{26}N_4O$	410.51
BPB03	Methyl	H	H	1	Cream	$C_{26}H_{26}N_4O$	410.51
BPB04	Ethyl	H	H	1	White	$C_{27}H_{24}N_4O$	424.54
BPB05	n-Propyl	H	H	1	White	$C_{28}H_{24}N_4O$	438.56
BPB06	n-Butyl	H	H	1	White	$C_{29}H_{24}N_4O$	452.59
BPB07	H	-CH_3	H	1	White	$C_{26}H_{24}N_4O$	410.51
BPB08	H	-CH_3	H	2	Light yellow	$C_{27}H_{24}N_4O$	424.54
BPB09	H	-Cl	H	1	Faint yellow	$C_{25}H_{24}ClN_4O$	430.93
BPB10	H	-Cl	H	2	Faint brown	$C_{26}H_{24}ClN_4O$	444.17
BPB11	H	-Cl	-Cl	1	Faint brown	$C_{25}H_{24}Cl_2N_4O$	465.37
BPB12	H	-Cl	-Cl	2	Brownish cream	$C_{26}H_{24}Cl_2N_4O$	479.4
BPB13	Phenyl	H	H	1	Brownish cream	$C_{31}H_{24}N_4O$	472.58
BPB14	Phenyl	H	H	2	Brownish cream	$C_{32}H_{24}N_4O$	486.61

R_1, R_2, R_3 are the different substitutions present on the compound, n is the number of carbon.

aromatic), 141.3 (s, 1C, -CN of benzimidazole), 168.9 (s, 1C, -C=O); ESI-MS(m/z): 396.20, 320.16, 306.18, 227.13, 146.08, 145.06, 118.05, 101.2, 83.1, 78.9.

BPB02. 2-[N4-(4'-phenylbenzoyl) piperazin-1-yl-ethyl]-1H-benzo(d)imidazole

Yield: 51.66%; M.P.: 220-224°C; R_f: 0.753; IR ν_{max}(cm^{-1}):1358/1290/1248(Ar.C-N), 1617(C=O), 743/694(C-H), 3021(C-H Chromophore), 1468/1455(-CH_2), 856(Ar.1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.26-7.7(m, 13H), 3.63(s, 2H), 2.69-3.3(m, 8H), 2.66(s, 3H); ^{13}C-NMR(δc ppm, DMSO-d6): 27.9 (s, 1C, -CH_2) 46.3-51.6 (d, 4C, -CH_2 of piperazine), 56.0 (s, 1C, -CH_2), 119.2-141.4 (m, 18C, aromatic), 141.3 (s, 1C, -CN of benzimidazole), 166.7 (s, 1C, -C=O); ESI-MS m/z: 410.21, 334.18, 320, 244.17, 146.08, 118.05, 101.2, 83.1.

BPB03. 1-methyl-2-[N4-(4'-phenylbenzoyl)piperazin-1-yl-methyl]-1H-benzo(d)imidazole

Yield: 42%; M.P.: 242-245°C, IR ν_{max}(cm^{-1}): 1358/1290/1248(Ar.C-N), 1617(C=O), 744/694(C-H), 3022(C-H Chromophore), 1468/1456/1434(-CH_2), 853(Ar.1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.26-7.7(m, 13H), 3.63(s, 2H), 3.3-3.62(m, 8H), 2.66(s, 3H); ^{13}C-NMR(δc ppm, DMSO-d6): 32.0 (s, 1C, -CH_3), 40.2 (s, 1C, -CH_2), 49.1-51.9 (d, 4C, -CH_2 of piperazine), 116.3-137.5 (m, 18C, aromatic), 148.1 (s, 1C, -CN of benzimidazole), 169.1 (s, 1C, -C=O); ESI-MS m/z: 410.21, 189.13, 238.12, 132.07, 181.4, 152.

BPB04. 1-ethyl-2-[N^4-(4'-phenylbenzoyl)piperazin-1-yl-methyl]-1H-benzo(d)imidazole

Yield: 53.33 %; M.P.:247-250°C; IR ν_{max}(cm^{-1}): 1358/1290/2267(Ar.C-N), 1617(C=O), 744/694(C-H), 3022(C-H Chromophore), 1471/1456/1445/1436(-CH_2), 853(Ar.1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.26-7.7(m, 12H), 3.77(s, 2H), 3.3(m, 8H), 2.66(s, 3H); ^{13}C-NMR(δc ppm, DMSO-d6): 16.2 (s, 1C, -CH_3), 35.8 (s, 1C, -CH_2), 39.1 (s, 1C, -CH_2 of -C-N), 48.0-52.4 (d, 4C, -CH_2 of piperazine), 127.7-148.5 (m, 18C, aromatic), 150.5 (s, 1C, -CN of benzimidazole), 167.3 (s, 1C, -C=O); ESI-MS m/z: 424.23, 202.13, 224.11, 146.08, 152, 130, 104, 77.

BPB05. 1-propyl-2-[N4-(4'-phenylbenzoyl)piperazin-1-yl-methyl]-1H-benzo(d)imidazole

Yield: 51.66%; M.P.:255-260°C; IR ν_{max}(cm^{-1}): 1369/1359/1291(Ar.C-N), 1617(C=O), 743/694(C-H), 3026(C-H Chromophore), 1456/1468/1445/1435(-CH_2), 853(Ar.1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.26-7.7(m, 12H), 3.73(s, 2H), 1.81(t, 3H), 3.3(m, 8H), 2.66(s, 3H); ^{13}C-NMR(δc ppm, DMSO-d6): 11.5 (s, 1C, -CH_3), 26.4 (s, 1C, -CH_2), 38.1-40.5 (d, 2C, -CH_2 of -C-N), 47.4-51.0 (d, 4C, -CH_2 of piperazine), 115.9-138.1 (m, 18C, aromatic), 148.5 (s, 1C, -CN of benzimidazole), 168.3 (s, 1C, -C=O); ESI-MS m/z: 438.24, 233.19, 224.11, 160.1, 181.4, 152, 104, 77.

BPB06. 1-butyl-2-[N4-(4'-phenylbenzoyl)piperazin-1-yl-methyl]-1H-benzo(d)imidazole

Yield: 53.33%; M.P.:250-255°C; IR ν_{max}(cm^{-1}): 1359/1291(Ar. C-N), 1617(C=O), 744/694(C-H), 3026(C-H Chromophore), 1456/1445/1436(-CH_2), 853(Ar. 1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.26-7.7(m, 12H), 1.77(s, 3H), 3.3(m, 8H), 2.66(s, 3H); ^{13}C-NMR(δc ppm, DMSO-d6): 13.8 (s, 1C, -CH_3), 20.2 (s, 1C, -CH_2), 31.3 (s, 1C, -CH_2), 38.2 (s, 1C, -CH_2 of -C-N), 48.9-52.3 (d, 4C, -CH_2 of piperazine), 57.2 (s, 1C, -CH_2), 121.1-144.1 (m, 18C, aromatic), 146.2 (s, 1C, -CN of benzimidazole), 159.9 (s, 1C, -C=O); ESI-MS m/z: 452.26, 231.17, 224.11, 174.12, 181.4, 152, 104, 77.

BPB07. 5-methyl-2-[N4-(4'-phenylbenzoyl)piperazin-1-yl-methyl]-1H-benzo(d)imidazole

Yield: 70%; M.P.:212-215°C; IR ν_{max}(cm^{-1}): 1359/1291(Ar.C-N), 1617(C=O),743/694(C-H), 3026(C-H Chromophore),1445/1455(-CH_2), 853(ar. 1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.28-7.7(m, 12H), 3.95(s, 2H), 3.6-3.9(m, 8H), 2.542(Broad s, 1H), 2.253(s.3H); ^{13}C-NMR(δc ppm, DMSO-d6): 24.3 (s, 1C, -CH_3), 48.0-52.1 (d, 4C, -CH_2 of piperazine), 55.5 (s, 1C, -CH_2), 115.4-139.4 (m, 18C, aromatic), 142.5 (s, 1C, -CN of benzimidazole), 160.9 (s, 1C, -C=O); ESI-MS m/z: 410.21, 320.16, 306.18, 244.17, 160.1,145.06, 128.2, 119, 101, 83.1, 78.9.

BPB08. 5-methyl-2-[N4-(4'-phenylbenzoyl) piperazin-1-yl-ethyl]-1H-benzo(d)imidazole

Yield: 50%; M.P.:230-234°C; IR ν_{max}(cm^{-1}): 1369/1359/1291(Ar.C-N), 1617(C=O), 743/694(C-H), 3026(C-H Chromophore), 1455/1468/1445(-CH_2), 853(Ar.1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.26-7.7(m, 12H), 3.6-3.9(m, 8H), 2.542(Broad s, 1H), 2.253(s.3H); ^{13}C-NMR(δc ppm, DMSO-d6): 22.2 (s, 1C, -CH_3), 28.1 (s, 1C, -CH_2) 48.3-50.7 (d, 4C, -CH_2 of piperazine), 55.0 (s, 1C, -CH_2), 116.2-140.5 (m, 18C, aromatic), 151.0 (s, 1C, -CN of benzimidazole), 164.8 (s, 1C, -C=O); ESI-MS m/z: 424.23, 334.18, 317.4, 258.18, 177.2,159.2, 145,128.2, 119, 101.2, 83.1, 78.9.

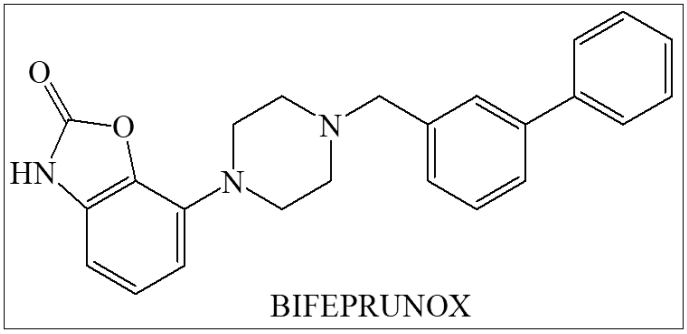

Figure 1: Structure of Bifeprunox.

BPB09. 5-chloro-2-[N4-(4'-phenylbenzoyl)piperazin-1-yl-methyl]-1H-benzo(d)imidazole

Yield: 51.66%; M.P.:120-125°C; IR ν_{max}(cm^{-1}): 1385/1357/1324/1290(Ar.C-N), 1618(C=O), 743/693(C-H), 2927-3128(C-H Chromophore), 1454-1433(-CH_2), 852(Ar.1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.26-7.7(m, 12H), 2.66(s, 3H), 3.3(m, 8H); ^{13}C-NMR(δc ppm, DMSO-d6): 46.2-49.5 (d, 4C, -CH_2 of piperazine), 52.1 (s, 1C, -CH_2), 116.3-140.8 (m, 18C, aromatic), 144.2 (s, 1C, -CN of benzimidazole), 163.7 (s, 1C, -C=O); ESI-MS m/z: 430.16, 320.16, 306.18, 177.2, 145, 128, 119, 101.2, 83.1, 78.9.

BPB10. 5-chloro-2-[N4-(4'-phenylbenzoyl) piperazin-1-yl-ethyl]-1H-benzo(d)imidazole

Yield: 51.66%; M.P.:215-220°C; IR ν_{max}(cm^{-1}): 1359/1291/1248(Ar.C-N), 1617(C=O), 743/694(C-H), 3025/3019/2963(C-H Chromophore), 1468/1455/1445/1434(-CH_2), 853(Ar.1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.26-7.7(m, 12H), 2.66(s, 3H), 3.3(m, 8H); ^{13}C-NMR(δc ppm, DMSO-d6): 23.1 (s, 1C, -CH_2), 30.7 (s, 1C, -CH_2), 48.3-52.0 (d, 4C, -CH_2 of piperazine), 118.7-140.9 (m, 18C, aromatic), 143.3 (s, 1C, -CN of benzimidazole), 151.7 (s, 1C, -C=O); ESI-MS m/z: 447.5, 335.3, 317.4,274.4,177.2, 159.2, 145, 128.2, 119, 101.2, 83. 1, 78.9.

Table 2: Effect of synthesized compounds on catalepsy in mice.

Group	Treatment (Dose in mg/kg)	Score (Mean±S.E.M.)				
		30 min	60 min	90 min	120 min	240 min
1	Haloperidol (1 mg/kg)	12.4±0.9274	43.4±2.182	35.4±1.077	23.6±1.600	5.8±0.5831
2	BPB01 (88 mg/kg)	10.2±0.8602	23.2±1.068	10±0.7071	7.2±0.8602	1.6±0.2449
3	BPB02 (88 mg/kg)	9.4±1.077	12.6±0.7071	19.2±1.068	10.2±0.8602	2.2±0.4899
4	BPB03 (8 mg/kg)	8.2±1.114	10±1.068	14±1.703	15.4±0.6782	2±0.000
5	BPB04 (8 mg/kg)	7.8±0.3734	18.2±0.8602	20±0.5477	10.4±0.8718	2±0.000
6	BPB05 (8 mg/kg)	7.6±1.030	7.4±0.5099	6.8±1.068	3.4±0.2449	2±0.000
7	BPB06 (8mg/kg)	7.2±0.3742	12.4±0.8602	13.2±1.241	10±0.8367	1.6±0.6000
8	BPB07 (88 mg/kg)	8.8±0.8000	20.2±0.3742	17 ±1.304	11.8±1.319	2±0.5477
9	BPB08 (88 mg/kg)	4.8±0.3742	7.2±0.3742	7.2±0.8602	4.4±0.8124	1.6±0.2449
10	BPB09 (88 mg/kg)	5±0.3162	5.8±0.3742	3.2±0.2000	2.6±0.2449	1±0.000
11	BPB10 (88 mg/kg)	9±1.517	12.6±0.5099	13.4±0.8124	10.2±1.393	1.4±0.2449
12	BPB11 (88 mg/kg)	8±0.7071	12.4±0.5099	9.6±1.166	8.4±1.288	2.2±0.3742
13	BPB12 (88 mg/kg)	4.4±0.2449	6±0.6325	5.2±0.8602	3.4±0.5099	1±0.000
14	BPB13 (88 mg/kg)	6.2±0.6633	9±1.000	5.6±0.2449	3.2±0.2000	1.6±0.4000
15	BPB14 (88 mg/kg)	8.4±0.2449	21±0.000	20.2±0.3742	6.2±0.5831	1.8±0.3742

Scores=time recorded for mice when both front paws were removed from the bar or if the animal moved its head in an exploratory manner expressed as Mean±S.E.M. A *p* value of <0.05 was considered significant. Dose was determined in terms of ED_{50} determined from acute toxicity studies. (*n*=5).

BPB11. 5,6-dichloro-2-[N4-(4'-phenylbenzoyl) piperazin-1-yl-methyl]-1H-benzo(d)imidazole

Yield: 49.09%; M.P.:210-212°C; IR ν_{max}(cm^{-1}): 1358/1291(Ar.C-N), 1617(C=O), 743/694(C-H), 3019(C-H Chromophore), 1468/1455/1445/1434(-CH_2), 853(Ar.1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.26-7.7(m, 12H), 2.66(s, 3H), 3.3(m, 8H); ^{13}C-NMR(δc ppm, DMSO-d6): 48.1-50.3 (d, 4C, -CH_2 of piperazine), 54.1 (s, 1C, -CH_2), 127.3-147.8 (m, 18C, aromatic), 149.3 (s, 1C, -CN of benzimidazole), 167.6 (s, 1C, -C=O); ESI-MS m/z: 464.12, 320.16, 306.18, 298.08, 177.2, 214.01, 145, 128.2, 119, 101.2, 83.1, 78.9.

BPB12. 5,6-dichloro-2-[N4-(4'-phenylbenzoyl) piperazin-1-yl-ethyl]-1H-benzo(d)imidazole

Yield: 68.33%; M.P.:180-181°C; IR ν_{max}(cm^{-1}): 1359/1291(Ar.C-N), 1617(C=O), 743/694(C-H), 3019(C-H Chromophore), 1468/1455/1445/1434(-CH_2), 853(Ar.1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.26-7.7(m, 12H), 2.69(s, 3H), 3.3(m, 8H); ^{13}C-NMR(δc ppm, DMSO-d6): 29.1 (s, 1C, -CH_2), 36.3 (s, 1C, -CH_2), 48.0-52.5 (d, 4C, -CH_2 of piperazine), 117.2-138.4 (m, 18C, aromatic), 139.3 (s, 1C, -CN of benzimidazole), 159.0 (s, 1C, -C=O); ESI-MS m/z: 478.13, 334.18, 317.4, 312.19, 177.2, 159.2,145, 128.2, 119, 101.2, 83.1, 78.9.

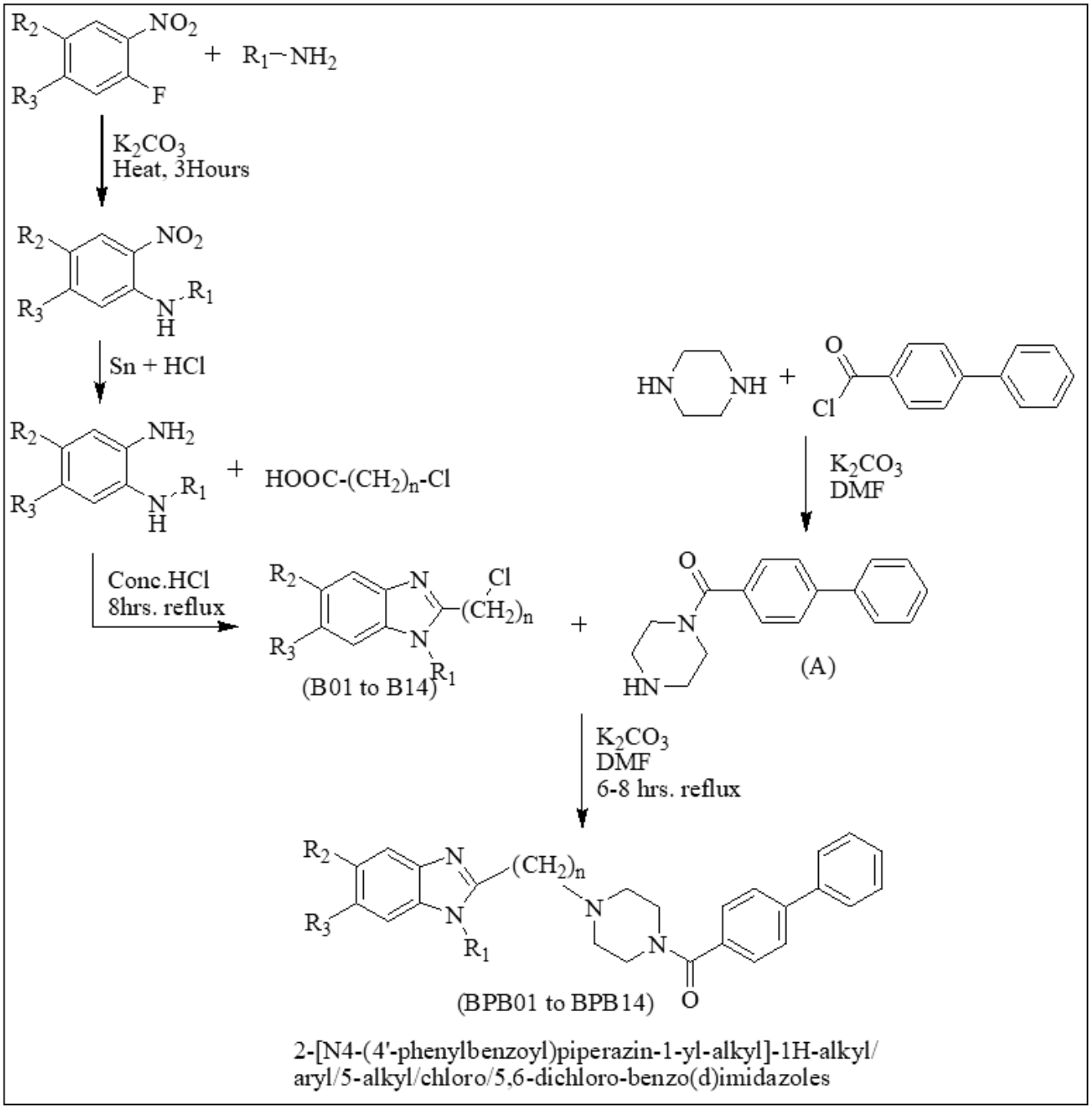

Figure 2: Scheme of synthesis of 2-[N4-(4'-phenylbenzoyl)piperazin-1-yl-alkyl]-1H-alkyl/aryl/5-alkyl/chloro/5,6-dichloro-benzo(d)imidazoles.

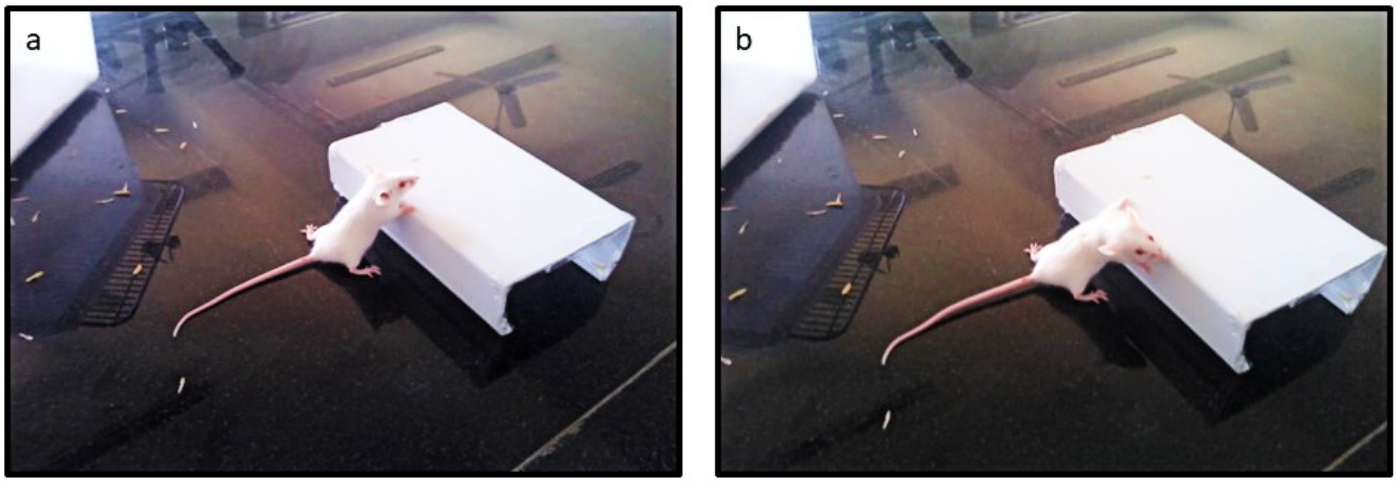

Figure 3: Movement of mice head during screening of antipsychotic activity.

BPB13.1-phenyl-2-[N4-(4'-phenylbenzoyl)piperazin-1-yl-methyl]-1H-benzo(d)imidazole

Yield: 50%; M.P.: 175-177°C; IR ν_{max}(cm^{-1}): 1358/1327/1286(Ar.C-N), 1616(C=O), 693/742(C-H), 3027(C-H Chromophore), 1495/1430/1455(-CH_2), 846(Ar.1,4 disubstitution); ^{1}H-NMR(δ ppm): 7.26-7.7(m, 15H), 2.69(s, 3H), 3.3(m, 8H), 3.5-3.95(m, 8H); ^{13}C-NMR(δc ppm, DMSO-d6): 45.1-49.1 (d, 4C, -CH_2 of piperazine), 52.9 (s, 1C, -CH_2), 115.4-138.8 (m, 24C, aromatic), 141.5 (s, 1C, -CN of benzimidazole), 161.6 (s, 1C, -C=O); ESI-MS m/z: 475, 250, 222, 195.3, 181.4, 152, 130, 104, 77.

BPB14. 1-phenyl-2-[N4-(4'-phenylbenzoyl) piperazin-1-yl-ethyl]-1H-benzo(d)imidazole:

Yield: 68.33%; M.P.:220-222°C; IR ν_{max}(cm^{-1}): 1359/1285/(Ar.C-N), 1614(C=O), 691/742(C-H), 3019(C-H Chromophore), 1459/1432(-CH_2), 847(Ar.1,4 disubstitution); ^{1}H- (δ ppm): 7.26-7.7(m, 15H), 2.69(s, 3H), 3.3(m, 8H), 3.5-3.95(m, 8H), ^{13}C-NMR(δc ppm, DMSO-d6): 21.3 (s, 1C, -CH_2) 47.2-52.5 (d, 4C, -CH_2 of piperazine), 57.0 (s, 1C, -CH_2), 114.7-136.4 (m, 24C, aromatic), 143.5 (s, 1C, -CN of benzimidazole), 167.9 (s, 1C, -C=O); ESI-MS m/z: 486.24, 265.16, 222, 195.3, 181.4, 152, 130,104, 77.

Pharmacological Screening of Compounds

Acute toxicity studies (OECD guidelines, 2000)

The acute toxicity test was performed for two representative compounds out of the 14 synthesized compounds, to ascertain the LD_{50} values as per OECD guidelines. The experimental dose was chosen within the range of the minimal effective dose and the maximum non-lethal dose. A total of 30 Swiss Albino Mice were required for this study.

Screening of Antipsychotic Activity

Catalepsy is a type of negative symptom of schizophrenia which was used as a model for testing of activity of all 14 synthesized compounds. Swiss albino female mice were used and test was carried out using propylene glycol (0.3 mL, i.p.) as a suitable vehicle for dilution and as a control. All the compounds suitably reduced the cataleptic score (Table 2) of standard (haloperidol) indicating their effectiveness in treatment of schizophrenia. The score represents the time measured for mice when they had both front paws withdrawn from the bar or when the animal moved its head in an exploratory manner. The score is expressed as the Mean±S.E.M. as shown in the Figure 3.

DISCUSSION

To confirm the synthesis of intermediate compounds as well as the final derivatives, spectral analysis was performed using methods such as IR, NMR and MS. In the IR spectrum of the intermediate A the peak for -C=O can be observed at 1716 and the -C=C- is seen at 1541. In case of the ^{1}H NMR spectra the 8 protons of -CH_2- of piperazine, 9 aromatic protons and 1 proton from the piperazine NH are present at 2.85-3.35, 7.22-8.01 and 2.07 ppm respectively, the ^{13}C NMR showed the 4C of piperazine at the 45.8-50.2 ppm, the multiplate of aromatic carbons were recorded at 129.3-134.1 ppm and the carbonyl C was found at 150.1 ppm. Molecular ion peak was found to be at 266 in MS spectra. Further for intermediates of substituted benzimidazoles B01 to B14 the molecular ion peaks were observed at required values in the MS, IR peaks were identified at ranges such as 2300-2200 cm^{-1} for the aromatic C-N bond and the Sp_2 alkyl groups can be seen between 3000-2900 cm^{-1}. Along with it from ^{1}H NMR interpretation, the aliphatic protons are observed between 2.00 to 4.50 ppm, the single proton of -NH is found in all the intermediates around 5 ppm and the aromatic protons are identified as multiplies between the range 7.00 to 9.00 ppm. In ^{13}C NMR the aromatic C was found between the range 110-130 ppm, the aliphatic C was identified

around 30-45 ppm and the C of C-N was observed around 150 ppm. The final derivatives were also confirmed by spectral methods of analysis. During the interpretation of BPB01 to BPB14 in IR the aromatic C-N bond was identified around values 1350 and 2250 cm^{-1}, the carbonyl group -C=O was found to be present around 1700 cm^{-1}, the ^{1}H NMR showed the exact number of protons in the synthesized compounds, the aliphatic protons were found to be around 2.00-4.80 ppm, while the aromatic protons were observed between the range 7.00-9.00 ppm, in ^{13}C NMR the carbon type and number of carbons were correctly identified. Also, the molecular weights of all the synthesized derivatives were confirmed by Mass Spectrometry.

Comparison of antipsychotic activity of synthesized compounds with standard

The activity profile of the 14 compounds showed that the synthesized compounds effectively decreased the catalepsy caused by Haloperidol. With respect to this, compounds BPB02, BPB03, BPB05, BPB08, BPB09, BPB12 had more effective; whereas compounds BPB01, BPB04, BPB07, BPB14 less effective at the said ED50 dose. Remaining compounds BPB06, BPB10, BPB11, BPB13 were found intermediately effective. The activity profile is given in Table 2.

CONCLUSION

The 14 compounds that were synthesized, effectively decreased catalepsy caused by Haloperidol. With respect to this, compounds BPB02, BPB03, BPB05, BPB08, BPB09, BPB12 were more effective; compounds BPB06, BPB10, BPB11, BPB13 had intermediate effect, whereas compounds BPB01, BPB04, BPB07, BPB14 were less effective.

The relationship between the structure and activity of the synthesised compounds has demonstrated that the combination of benzimidazole with piperazinyl carbonyl biphenyl serves as promising lead molecules capable of alleviating both positive and negative symptoms of psychosis. The antipsychotic screening results indicate that compounds with smaller substitutions at the R_1, R_2 and R_3 positions, such as -H, -CH_3 and -Cl, exhibit favourable antipsychotic properties; conversely, larger substitutions at these positions slightly diminish activity.

Keeping in mind the cost constraints and availability of materials, an attempt has been made to synthesize unique parent molecules with greater efficacy and minimization of side effects. Also, the attempt was to synthesis such unique compounds with altogether new structure in the history of antipsychotics which may add on to unique library of antipsychotic drugs. Also, the novel 14 compounds that are synthesized can be used as a basis for synthesizing multiple unique derivatives which may show even higher efficacy and selectivity.

ACKNOWLEDGEMENT

The authors are very thankful to the management of METs Institute of Pharmacy for their constant support and providing all facilities to complete this work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DA: Dopamine; **5-HT:** 5-Hydroxytryptamine receptor; **TLC:** Thin Layer Chromatography; **UV:** Ultraviolet; **FTIR:** Fourier Transform Infrared Spectroscopy; **^{1}H-NMR:** Proton Nuclear Magnetic Resonance; **^{13}C-NMR:** Carbon Nuclear Magnetic Resonance; **$CDCl_3$:** Deuterated Chloroform; **DMSO:** Dimethyl sulfoxide; **LCMS:** Liquid Chromatography-Mass Spectroscopy; **APCI:** Atmospheric Pressure Chemical Ionization; **MS:** Mass Spectroscopy; **I.P.:** Indian Pharmacopoeia; **IV:** Intravenous; **IM:** Intramuscular; **g:** Grams; **mL:** Millilitres; **Na_2SO_4:** Sodium Sulphate; **RBF:** Round Bottom Flask; **HCl:** Hydrochloric Acid; **DMF:** Dimethyl formamide; **K_2CO_3:** Potassium Carbonate; **DCM:** Dichloromethane; **LD_{50}:** Lethal Dose 50; **ED_{50}:** Effective Dose 50; **SEM:** Standard Error of Mean; **ANOVA:** Analysis of Variance; **M.P.:** Melting Point; **OECD:** Organization for Economic Cooperation and Development.

ANIMAL ETHICS APPROVAL

The work is approved by the institution ethics committee.

SUMMARY

To summarize the synthetic work, 14 compounds as per planned were synthesized successfully and confirmed with the spectral characterization by IR, ^{1}H-NMR, ^{13}C-NMR and Mass. Further, various important functional groups were detectable by IR, proton and carbon count matched with ^{1}H-NMR and ^{13}C-NMR spectra respectively and molecular weight were justified by Mass fragmentation pattern. All 14 compounds were evaluated for antipsychotic activity. Catalepsy model was used because it is also a type of negative symptom of schizophrenia. Thus, all the compounds successfully reversed to varying extent, the haloperidol induced cataleptic effect in female mice.

REFERENCES

1. Orzelska-Górka J, Mikulska J, Wiszniewska A, Biała G. New atypical antipsychotics in the treatment of schizophrenia and depression. International journal of molecular sciences. 2022;23(18):10624.
2. Sabe M, Pillinger T, Kaiser S, Chen C, Taipale H, Tanskanen A, *et al.* Half a century of research on antipsychotics and schizophrenia: A scientometric study of hotspots, nodes, bursts and trends. Neuroscience & Biobehavioral Reviews. 2022;136:104608.
3. Chart-Pascual JP, Montero-Torres M, Ortega MA, Mar-Barrutia L, Martinez IZ, Alvarez-Mon M, *et al.* Areas of interest and sentiment analysis towards second generation antipsychotics, lithium and mood stabilizing anticonvulsants: Unsupervised analysis using Twitter. Journal of Affective Disorders. 2024;351:649-60.

4. Rathore A, Asati V, Kashaw SK, Agarwal S, Parwani D, Bhattacharya S, *et al.* The recent development of piperazine and piperidine derivatives as antipsychotic agents. Mini Reviews in Medicinal Chemistry. 2021;21(3):362-79.
5. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. The Lancet. 2009;373(9657):31-41.
6. Kumar RR, Sahu B, Pathania S, Singh PK, Akhtar MJ, Kumar B. Piperazine, a Key Substructure for Antidepressants: Its Role in Developments and Structure-Activity Relationships. ChemMedChem. 2021;16(12):1878-901.
7. Kapur S, Seeman P. Does fast dissociation from the dopamine D2 receptor explain the action of atypical antipsychotics?: A new hypothesis. American Journal of Psychiatry. 2001;158(3):360-9.
8. Gao L, Hao C, Ma R, Chen J, Zhang G, Chen Y. Synthesis and biological evaluation of a new class of multi-target heterocycle piperazine derivatives as potential antipsychotics. RSC advances. 2021;11(28):16931-41.
9. Singh S, Bali A, Peshin T. Synthesis and evaluation of aryl substituted propyl piperazines for potential atypical antipsychotic activity. Medicinal Chemistry. 2021;17(5):429-41.
10. Al-Wasidi AS, Refat MS, Naglah AM, Elhenawy AA. Different potential biological activities of benzimidazole derivatives. Egyptian Journal of Chemistry. 2021;64(5):2631-46.
11. Adhikari A, Bhakta S, Ghosh T. Microwave-assisted synthesis of bioactive heterocycles: An overview. Tetrahedron. 2022;126:133085.
12. Hussain S, Taha M, Rahim F, Hayat S, Zaman K, Iqbal N, *et al.* Synthesis of benzimidazole derivatives as potent inhibitors for α-amylase and their molecular docking study in management of type-II diabetes. Journal of Molecular Structure. 2021; 1232:130029.
13. Singh H, Kumar R, Tiwari P, Singh A. Recent Advances in Synthetic Strategies of Benzimidazole and its Analogs: A Review. Current Organic Chemistry. 2022;26(19):1767-78.
14. BARI DG, SARAVANAN K, AHMAD R. Antipsychotic Evaluation of Novel Series of Aryl Piperazine Congeners. International Journal of Pharmaceutical Research. 2021;13(2).
15. Smith QE. Medicinal Chemistry, vol. 1.
16. Waku I, Magalhaes MS, Alves CO, de Oliveira AR. Haloperidol-induced catalepsy as an animal model for parkinsonism: A systematic review of experimental studies. European Journal of Neuroscience. 2021;53(11):3743-67.

Cite this article: Kankate RS, Jain ZJ, Ghodke SS, Gide PS, Patil KS. Snthesis, Characterisation and Evaluation of Benzimidazoles Containing Biphenylcarbonylpiperazine at C-2 Position for Antipsychotic Activity. Indian J of Pharmaceutical Education and Research. 2025;59(3s):s1090-s1100.