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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

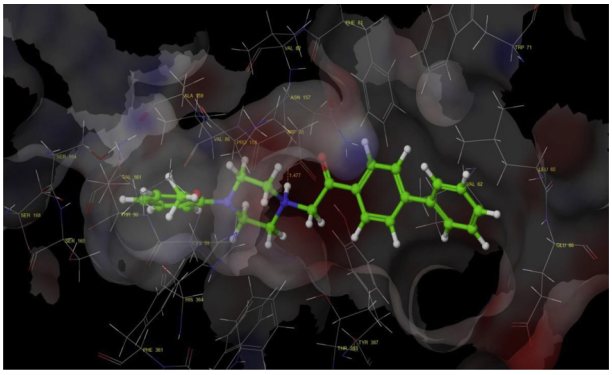

Fig. 2. Glide XP docking of compound **3c** docked in active site of D_2 receptor.

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**)

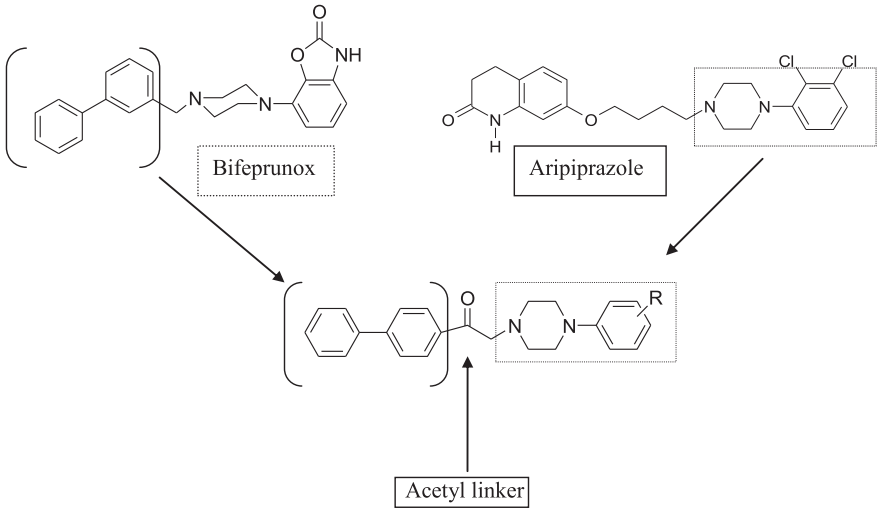

Fig. 1. Planned modification and newly designed antipsychotic molecule.