Egyptian Journal of Basic and Applied Sciences xxx (2017) xxx–xxx

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Contents lists available at ScienceDirect

Egyptian Journal of Basic and Applied Sciences

journal homepage: www.elsevier.com/locate/ejbas

Full Length Article

Design, synthesis, spectroscopic characterization and anti-psychotic investigation of some novel Azo dye/Schiff base/Chalcone derivatives

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ARTICLE INFO

Article history:
Received 26 December 2016
Received in revised form 7 October 2017
Accepted 10 October 2017
Available online xxxx

Keywords:
Design
MVD
Catalepsy
Antipsychotic agent
X-ray crystallography

ABSTRACT

The purpose of the study is to design, synthesise and assess the antipsychotic activity of a set of the novel (5-(10-(3-*N*, *N*-Dimethylamino) propyl)-10*H*-phenothiazine-3-yl)-1,3,4-thiadiazo-2-yl) Azodye/Schiff base/Chalcone derivatives. The newly synthesised compound structure was characterised by FT-IR, ^{1}H NMR, Mass spectroscopy and elemental analysis. Each compound has been shown an excellent anti-psychotic activity in a haloperidol-induced catalepsy metallic bar test. The results found are firmly similar to docking study. Among the synthesised derivatives, compound 2-Amino-6-(3-hydroxy-4-methyl phenyl) pyrimidine-4-yl) (7-chloro-10-(3-(*N*, *N*-dimethylamino) propyl)-10*H*-phenothiazine-3-yl) methanone (**GC8**) exhibiting high potency of catalepsy induction. Therefore, the derivative of GC8 has been considered that a potent anti-psychotic agent among the synthesised compounds.
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1. Introduction

Dopamine receptors are responsible for several functions such as fine motor control, emotion, learning, cognition, pleasure, sensation, motivation, memory and modulation of neuroendocrine behaviour, movements etc., [1]. Some changes in the role of dopaminergic receptor actions are generated many diseases like parkinsonism, psychomotor, schizophrenia, neurodegeneration, drug abuse, delusions and hallucinations etc., [2]. These receptors are mainly divided into D1-5. They belong to the class of G-protein-coupled-receptors [3,4]. Here, D1 and D5 receptors are known as D1 family associates, whereas D2, D3 and D4 receptors are known as D2 family associates [5]. Both families coupled with G-protein and retard the adenylyl cyclase [6,7]. With the knowledge of some evidence state that the possibility of the existence of D6 and D7 dopamine receptors, but such a type of receptor has not been sturdily documented. Generally, these receptors bind to the plasma membrane as a homodimer, heterodimers or higher-order oligomers etc., [8]. It has been targeted for different psychotic illnesses and also be considered in some non-psychotic disorders [9]. Drugs used to treat the psychotic problem are known as antipsychotic agents (or neuroleptic) is majorly classified into two types. Earlier antipsychotic drugs are called as typical or classical antipsychotic agents, whereas; currently available drugs are recognised as a second generation or atypical antipsychotic agents. Both the type of the antipsychotic agent is having a tendency to obstruct receptors in brain's dopamine pathways [10]. Most of the antipsychotic agents are having substantial side effects, such as dysphoria, parkinsonism, tardive dyskinesia, galactorrhea, sedation, irritability, hyperprolactinaemia, sexual functioning disorder and symptoms of ADHD, depression, narcolepsy, anxiety, improved appetite, obesity threat, paranoia, aggression, psychomotor agitation, diabetes mellitus (Type 2), akathisia, extrapyramidal symptoms and menstrual trouble [11]. Therefore, identification of a novel antagonist of dopamine receptor is needed to treat nervous diseases effectively. In recent years, there has been an immense awareness among the scientists toward the design of new drugs, which consumes less time, highly potent and lower cost to prepare an effective drug molecule against various health problems. Rapid and high throughput method of drug discovery is an only way to improve the therapeutic value of drugs in the animal model. Molecular docking is a one among the method to measure the biological activity of the proposed molecule with the targeted receptor rapidly using Molegro Virtual Docker (MVD). With the support of MVD, we found a bunch of novel compounds known as potent dopamine pathway inhibitors and bearing least side effect due to the presence of trusted thiadiazole and phenothiazine nucleus as part of the molecular structure. This study stated that easy way for the synthesis of novel Azo dye/Schiff bases/Chalcone

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https://doi.org/10.1016/j.ejbas.2017.10.003
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Please cite this article in press as: Gopi C et al. Design, synthesis, spectroscopic characterization and anti-psychotic investigation of some novel Azo dye/Schiff base/Chalcone derivatives. Egyp. Jour. Bas. App. Sci. (2017), https://doi.org/10.1016/j.ejbas.2017.10.003

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derivatives and their antipsychotic activity by using virtual docking and a metallic bar test. The synthesised compound structure was characterised by FT-IR, ^{1}H NMR, mass spectroscopy and elemental analysis.

2. Materials and method

2.1. Molecular docking

Virtual screening has been playing an important role in drug discovery processes which deal with a quick search of chemical structures likely to have more chemical binding to the drug target (protein or enzyme) from large libraries. MVD is a powerful docking tool used to detect the binding ability lies between the ligand and receptor. Before we start the docking process, the human dopamine D2 receptor template was collected from the protein bank as mentioned in Fig. 1. A setup of 26 different ligands was built in ChemDraw (Table 1), and the 2D structure was converted to the 3D structure using molegro virtual software [12]. The best 3D structure of ligand was selected from energy minimization through molecular objective functions and modeller score in MVD [13,14]. The properties of each ligand such as absorption, distribution, metabolism and excretion were also studied. The best conformation was selected and used to predict the strength of the bond between the receptor and ligand. The result reveals that around 10 compounds (Table 2) out of 26 are capable of making a perfect binding to the active site of the receptor amino acid. It also helped us to find out the order of prioritising molecules to synthesise from the bunch of the molecule based on moledock score, rerank score and hydrogen bond binding energy with DA. The docking study pathway was presented in Fig. 2.

2.2. Chemistry

The raw materials and solvents were purchased from Ranbaxy, Sigma-Alrich, Ranchem companies. The melting points of prepared analogues were recorded in open capillary tube method on an Electrothermal 9100 melting point apparatus and are uncorrected. Functional group of synthesised compound was confirmed by using Fourier transform infrared spectroscopy (FT-IR) between the ranges from 4000 cm^{-1} to 400 cm^{-1}. The number of proton present in the analogues was recorded on the Bruker ^{1}H NMR spectroscopy from chemical shift (δ) and the molecular mass of the compound was analysed by the Shimadzu mass spectroscopy. The element analysis was performed on Perkin Elmer 2400 CHN elemental analyser.

2.2.1. Synthesis of 4-(Phenylamino)benzoic acid (Scheme-I)

Aniline (0.1 mol, 9.3 ml), para chloro benzoic acid (0.1 mol, 15.6 g), potassium carbonate (0.01 mol, 1.38 g) and 0.63 g of copper wire were dissolved in 30 ml of *N, N*-dimethylformamide (DMF) contained round bottom flask of about 250 ml capacity. The mixture was allowed to agitate for 30 min at 20–25 °C. The flask was fitted with a reflux condenser and heated at 80 °C for 4 h with occasional shaking. The crude 4-(Phenylamino) benzoic acid was filtered, washed with little cold water and crystallized from ethanol.

2.2.2. Synthesis of 10H-Phenothiazine 3-carboxylic acid

An ethanolic solution of 4-(Phenylamino) benzoic acid (0.01 mol, 2.13 g) was added dropwise to a mixture of sulphur (0.01 mol, 0.32 g) and iodine (0.01 mol, 1.26 g). Shake the mixture until it became a solution. Placed the solution in a round bottom flask of about 250 capacities and fitted with the reflux condenser. The mixture was subjected to reflux on a water bath around 3 h with occasional shaking. The crude 10*H*-Phenothiazine 3-carboxylic acid was separated with a vacuum pump, washed with a small portion of cold water and re-crystallized from ethanol.

2.2.3. Synthesis of 5-(10-(3-(N,N-Dimethylamino)propyl-10H-phenothiazine-3-yl)-1,3,4-thiadiazole-2-amine

10*H*-Phenothiazine 3-carboxylic acid (0.01 mol, 2.43 g) and thiosemicarbazide (0.01 mol, 0.75 g) were dissolved in 60 ml of phosphorus oxychloride with the stirring duration of 10 min. The contents were placed in a distillation flask fitted with the reflux condenser. The flask was heated on a water bath for around 4 h. The reflux was detached from reflux condenser and added dropwise 3-Chloro-*N, N*-dimethyl propanamine (0.01 mol, 1.21 ml), sodium hydride (0.01 mol, 0.24 g) in DMF. Again, the reaction mixture was warmed for 3 h in a water bath. The hot solution was cooled to room temperature and separated crude product was

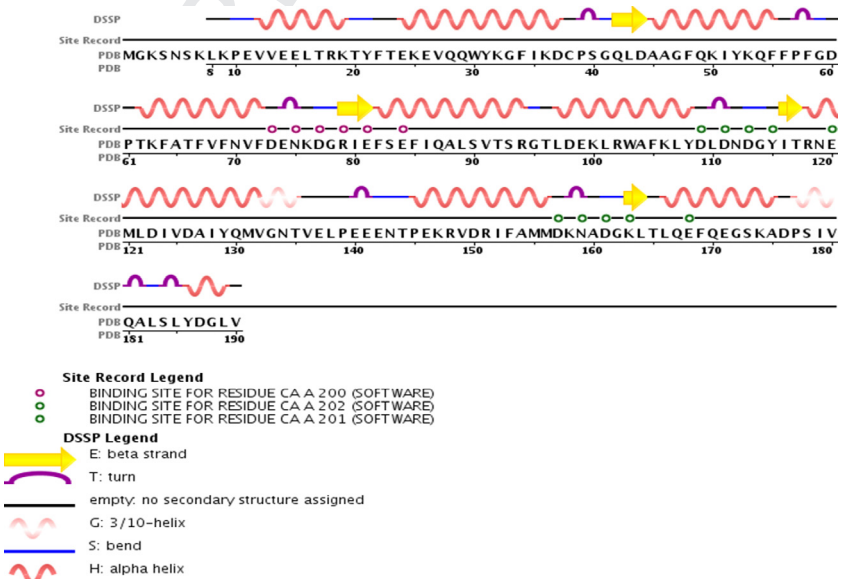

Fig. 1. Dopamine D2 Receptor (DA) pdb format structure from protein data bank.

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