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ORIGINAL ARTICLE

Development of novel (1-*H*) benzimidazole bearing pyrimidine-trione based MAO-A inhibitors: Synthesis, docking studies and antidepressant activity

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Abstract The synthesis of some novel (1-*H*) benzimidazole bearing pyrimidine-trione based MAO-A inhibitors were achieved by the reaction between 2*E*)-1-(1*H*-benzimidazol-2-yl)-3-phenyl-prop-2-en-1-ones(**4a–f**) and barbituric acid in the presence of a catalytic amount of acetic acid medium. All the final structures were assigned on the basis of IR, ^{1}HNMR and mass spectra analyses. All the synthesized derivatives showed good antidepressant activity when compared to the standard clomipiramine at a dose level of 20 mg/kg. The compound (**5d**) 5-{(2*E*)-1-(1*H*-benzimidazol-2-yl)-3-[4-(dimethylamino)phenyl] prop-2-en-1-ylidene} pyrimidine-2, 4, 6(1*H*,3*H*,5*H*)-trione significantly reduced the duration of immobility times at 50 mg/kg^{-1} dose level when compared to the standard drug. Molecular docking studies revealed the need for an extra hydrophobic interaction in the titled scaffold for acquiring the promising experimental values. It has been concluded that the computational values obtained after the docking calculation are in good agreement with the experimental values.

1. Introduction

The physiological reasons for depression and manic depressive conditions have not been completely established, but some facts suggested that depressive conditions may be caused by a lack of noradrenaline and serotonin. The majority of the synthetic drugs used in the treatment of such illnesses act by affecting the system of biogenic amines of the brain, thus leading to the action of a mechanism that is capable of increasing their concentration in the respective parts of the brain. Monoamine oxidase is a complex enzymatic system in the CNS particularly

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catalyses deamination or inactivation of biogenic amines. MAO inhibitors increase the intracellular concentration of endogenous amines by inhibiting their deamination, which seems to be the cause of their antidepressant action. In mammals MAO exist in two forms MAO-A and MAO-B which are dimeric in their membrane bound forms. Those agents that can inhibit the above system can produce beneficial change in the condition of the central nervous system. Particularly MAO-A inhibitors have been employed in the treatment of depression, anxiety and mental disorders (Pacher and Keckemeti, 2004; Pacher et al., 2001; Rudorfer and Potter, 1989) while MAO-B inhibitors could be used in the treatment of Parkinson's disease and Alzheimer's disease (Wouters, 1998; Carreiras and Marco, 2004).

Benzimidazoles are considered as the most promising bicyclic heteroaromatic nucleus in the field of medicinal chemistry. 1-*H*-benzimidazol-2-yl-(3-phenylprop)-2-en-1-ones were already proved as important key intermediates for the synthesis of medicinally important derivatives with a pharmacological profile such as anticancer, antitubercular and anti microbial properties (Shaharyar et al., 2009, 2010; Srivastava et al., 2010; Reddy and Reddy, 2010). Barbituric acid and their 5,5-disubstituted derivatives were extensively used in the class of hypnotics-sedatives. Their pharmacological action mainly constituted the introduction of dialkyl lipophilic groups in the 5th position of the activated methylene group. Various barbitone derivative condensations with carbonyl compounds possess different pharmacological profiles such as antimicrobial, selective cell adhesion inhibitors, antioxidant and DNA cleavage activities that have been already reported (Shulman and Laycock, 1967; Sangani et al., 2006; Harriman et al., 2008; Biradar et al., 2010).

Previously 2-substituted benzimidazole and barbituric acid exhibited their CNS depressant activity in experimental animal models (Misra et al., 1984; Shulman and Laycock, 1967). It was envisaged that the above two pharmacophores if linked together by means of a carbon-carbon double bond would exhibit novel molecular templates with a promising CNS depressant activity. Our research focused on the discovery of new MAO-A inhibitors from the above mentioned pharmacophores which would be used in the management of depression. A molecular docking study was performed for the prediction of the binding model of the final derivatives in the target of MAO-A enzyme. The synthetic strategy for the final derivatives involved in the reaction between activated methylene group present in the barbituric acid with the α, β-unsaturated ketone of benzimidazole derivatives in the presence of a catalytic amount of acetic acid produced an exocyclic olefinic linkage. The scheme of the present study is outlined in Fig. 1.

2. Materials and methods

2.1. Chemistry

All the solvents and chemicals were purchased from MERCK, Nice chemicals and SD Fine Chemicals. Melting points were determined by using melting point apparatus MP-DS TID 2000 V and the values were uncorrected. Reactions were monitored by thin layer chromatography (TLC-methanol:acetone-6:4) on pre coated silica gel G plates using iodine vapour as visualizing agent. IR spectra were recorded on JASCO FT/IR-140 spectrophotometer by using KBr pellets technique. PMR spectra were recorded using BRUCKER FT-NMR-500 MHz spectrophotometer by using DMSO as solvent and TMS as internal standard. The chemical shift was expressed in δ ppm. Mass spectra were recorded on a JEOL GCmate mass spectrometer.

*2.1.1. Synthesis of 2(α-hydroxyethyl) benzimidazole (**2a**)*

O-Phenylenediamine (0.25 mol) was mixed with lactic acid (0.36 mol) in a RBF and refluxed for 3 h. The reaction mixture was cooled and added with 10% NaOH until basicity to litmus paper. The crude pink coloured product obtained was dissolved in 400 ml of boiling water. To this add 2 g of decolourising carbon and heated for 15 min. The mixture was filtered rapidly at the pump through a preheated Buchner funnel. The product obtained was further filtered and washed with 25 ml cold water and dried at 100 °C.

*2.1.2. Synthesis of 2-acetyl benzimidazole (**3a**)*

A solution of 2-(α-hydroxy) ethyl benzimidazole **2a** (0.01 mol) in dil. H_2SO_4 (5%, 40 ml) was added drop wise to the solution of $K_2Cr_2O_7$ (0.15 mol) in H_2SO_4 (25%, 80 ml) with constant stirring at room temperature over a period of 20 min. Further the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was neutralized with aqueous NH_3 solution (1:1) and resultant orange solid was filtered, washed with water, dried and recrystallized from ethyl acetate.

*2.1.3. Synthesis of (2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-one (**4a–f**)*

2-Acetyl benzimidazole (0.01 mol) and appropriately substituted aromatic aldehydes (0.012 mol) were mixed in ethanol (20 ml) containing 10% aq. KOH (8 ml) and magnetically stirred the solution constantly at room temperature for 10 h. The whole mixture transferred into 100 ml ice cold water and acidified with dil. HCl. The solid formed was filtered, washed, dried and recrystallized from absolute ethanol.

*2.1.4. Synthesis of 5-[(2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-ylidene] pyrimidine-2,4,6 (1H,3H,5H)-triones (**5a–f**)*

To a solution of (**4a–f**) (0.01 mol) in 7 ml acetic acid, barbituric acid (0.01 mol) was added with constant stirring. The reaction mixture was then refluxed for 7 h with occasional stirring. The reaction progress was monitored by TLC (methanol:acetone, 6:4). The resultant contents were poured into crushed ice. The crude product was filtered, washed with water, dried and recrystallized from methanol. The physical characterizations of all the synthesized derivatives are summarized in Table 1.

*2.1.4.1. 5-[(2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-] pyrimidine-2,4,6 (1H,3H,5H)-trione (**5a**).* FTIR (KBr, V_{max} cm^{-1})**:** 3230 (NHstr), 1693 (C═O), 1587 (C═N). ^{1}HNMR (DMSO-d_6), δppm 9.1 (1*H*, s, NH benzimidazole), 8.0–8.4 (2*H*, s, pyrimidine NH) 6.4–8.1 (11*H*, m, 9ArH, 2CH═CH). M.S: m/z = 359.21 ($M^+ + 1$).

*2.1.4.2. 5-[(2E)-1-(1H-benzimidazol-2-yl)-3-(4-chlorophenyl) prop-2-en-1-ylidene] pyrimidine-2,4,6 (1H,3H,5H)-trione (**5b**).* FT-IR (KBr, V_{max} cm^{-1})**:** 3232 (NHstr), 1678 (C═O), 1581 (C═N), 771 (Ar-Cl). ^{1}HNMR (DMSO-d_6), δppm:8.9 (1*H*, s,