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Cholinesterase Inhibition Activity and Docking Simulation Study of Coumarin Mannich Base Derivatives

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Abstract

Inhibition of acetylcholinesterase and butyrylcholinesterase (AChE and BuChE) as two major forms of cholinesterases (ChEs) is considered as the common approach for the treatment of Alzheimer's disease (AD). The present study was done to explore the anticholinesterase inhibition property of coumarin Mannich base derivatives. A series of cumarin Manich bases were synthesized (4a-h) through one-pot tri-component reaction in an environmentally friendly condition and evaluated against AChE and BuChE by Ellman's assay. Ligand-protein docking simulation was also performed for the most active compound 4a. Additionally, the criteria of drug likeness of the target compounds was predicted using SwissADME web service. All compounds exhibited weak to moderate inhibitory activity against both AChE and BuChE enzymes. Compound 4a containing p-tolyl piperazin group showed the best activity against AChE (42.4 % at 32 µM), while compound 4g bearing phenylpiperazine moiety was the best BuChE inhibitor (43.9% at 32 µM). Ligand-protein docking simulation also exhibited that the main part of compound 4a in ChE inhibitory activity is amine moiety. Moreover, the prediction of "Lipinski's rule of five" showed that most target compounds can cross the BBB and have properties that would make them likely orally active compounds in humans. This study suggested that the synthesized cumarin Manich bases with some more structural modifications may be considered as a potential compound to target AChE and BuChE.

Keywords: Alzheimer’s disease; Acetylcholinesterase; Butyrylcholinesterse; 4-Hydroxycoumarin; Mannich base.

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Introduction

Alzheimer's disease (AD) is neurodegenerative disorder cusing memory deterioration. Two major pathological cause of AD are the progressive loss of cholinergic neural activity and formation of intra- and extracellular plaques of beta-amyloid (Aβ) causing senile plaques and neurofibrillary tangles of hyperphosphorylated tau protein [1-2]. Acetylcholinesterase (AChE) through acetylcholine (ACh) hydrolysis and cognitive impairment is one of the important factor in alleviation of AD's symptoms [3-5]. AChE inhibitors not only delay the decay of ACh but it also promotes the amyloid-beta fibril formation through its interactions with peripheral anionic site (PAS). In addition, growing evidence suggested that, along with decreased level of ACh in certain brain regions during progression of AD, level of butyrylcholinesterase (BuChE) as other form of cholinesterase increases in the brain of mammals [6-8]. Since BuChE inhibition can raise ACh levels [9-10], dual inhibition of AChE and BuChE can control AD symptoms with no notable side effects [11].

Coumarin has been utilized as a potent anticholinesterase natural based scaffold, due to its ability to bind peripheral binding site of the enzyme [12,13], antioxidant activity [14] and an excellent therapeutic properties in the management of cognition disorders [15-18]. Among the AChE inhibitors belong to coumarin scaffold, AP2238 was the first dual binding site AChE inhibitor [19]. Moreover, amino moiety is the key functional group to improve the activity of the target compounds through interactions with catalytic site of AChE [20].

The Mannich reaction is one of the simple multi-component reactions and versatile green approaches to produce β-amino-carbonyl compounds [21]. Coumarins containing active hydrogen atoms placed between two carbonyl functional groups can reach to Mannich bases in the presence of secondary amines and aldehydes [22].

Hence, in continuation of our previous works on coumarin derivatives [23,24] and based on the important principles of "Green Chemistry" such as one-pot reaction and usage of green solvents [25], we report herein successful preparation, cholinesterase evaluation and in silico studies of a series of novel coumarin Mannich-base derivatives (**4a-h**) for AD therapy (Figure 1).

Materials and Methods

All chemical reagents were commercially. Reactions were monitored by TLC on silica gel. Kofler hot stage

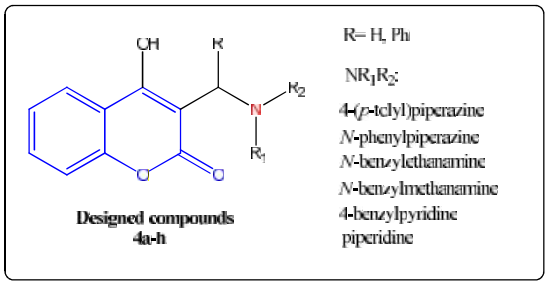

Figure 1. Designed compounds **4a-h**.

was utilized to measure melting points. The IR spectra were acquired using PerkinElmer Spectrum version 10.03.06 (KBr discs). ^{1}H and ^{13}C NMR spectra were recorded on Brucker 500 MHz. The coupling constants (*J*) and chemical shifts (δ) were expressed in Hertz and parts per million, respectively. The CHN elemental analyses were performed using a Rapid Heraeus elemental analyzer and the results were within ±0.5% of the calculated values.

Preparation of Mannich bases of coumarin 4a-h

Mannich bases (**4a-h**) were synthesized according to the method reported before [26, 27]. 4-hydroxycoumarin (1 mmol) in EtOH (5 mL) was added dropwise to ethanolic solution of formaldehyde 37% (1 mmol) and appropriate amine (1.2 mmol). The solution was refluxed for 1 hr. After completion of the reaction (monitored by TLC), the reaction was cooled and allowed to stand in a refrigerator for 24 h. The resulting precipitate was filtered off and washed with ethanol. If no precipitation was produced, the resulting mixture was evaporated under vacuo and the crude product was purified by crystallization from ethylacetate/*n*-hexan (50:50) to yield the desired compounds **4a-h** (yields 75-90 %).

4-hydroxy-3-((4-(p-tolyl)piperazin-1-yl)methyl)-2H-chromen-2-one (4a):

White solid; Yield (80%) mp 194-196 °C; IR (KBr, cm^{-1}): 3490 (O-H), 2930 (C-H), 1665 (C=O). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 16.9 (s, 1H, OH), 7.87 (d, 1H, *J* = 7.5 Hz, H_5 coumarin), 7.48 (t, 1H, *J* = 7.5 Hz, H_7 coumarin), 7.27-7.22 (m, 2H, $H_{6,8}$ coumarin), 7.09 (d, 2H, *J* = 8.0 Hz, Phenyl), 6.85 (d, 2H, *J* = 8.0 Hz, phenyl), 4.06 (s, 2H, CH_2), 2.87-3.60 (m, 8H, piperazine), 2.28 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 173.5, 164.8, 153.5, 147.2, 130.9, 130.3, 129.4, 123.8, 122.6, 120.0, 116.6, 115.9, 88.7, 54.0, 51.1, 47.3, 20.0. Anal. Calcd for: $C_{21}H_{22}N_2O_3$ (350.42): C, 71.98; H, 6.33; N, 7.99. Found: C, 71.65; H, 5.97; N, 7.83.