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Exploring dimethoxy naphthalenyl methoxyphenyl quinazolinyl amine as a PDE10A inhibitor: In-silico studies, synthesis and binding interactions with serum albumin

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ABSTRACT

Phosphodiesterase 10A (PDE10A) inhibitors stand out as key players in the quest for effective treatments against neurological disorders. Among them, Papaverine has gained attention for its ability to activate striatal output, hinting at potential antipsychotic properties. A thorough computational analysis of 28 alkoxy quinazoline derivatives derived from Papaverine led to the discovery of Dimethoxynaphthalenyl methoxyphenyl quinazolinyl amine (QPhN), addressing its exceptional docking score (-27.71) and binding energy (−44 kJ/mol). The main contributors of this binding were Gln716 and Phe719. Absorption, Distribution, Metabolism, Excretion (ADME) and Toxicity analysis predicted its drug likeness, bioavailability and highest CNS scoring (0.0409). Notably, its synthesis involved two-step process, first cyclic addition of dimethoxy quinazolinyl chloride and dioxaborolanyl phenol took place along with alkylation with bromomethyl naphthalene. To better understand the ADME profile of QPhN, its interaction with serum albumin (SA) was analyzed with the help of Photo physical studies. Fluorescence emission of SA was quenched to reveal the subtle shifts (distinct red shift of around 20 nm) in the protein's microenvironment. Through static quenching analysis, a binding constant value in the range ($K = 10^4$ M^{-1}) underscored the prevalence of non-covalent interactions between QPhN and SA with involvement of one binding site. Additionally, the interaction between QPhN and SA was enthalpically and entropically compelled to sub domain IIA with ΔH (−72.2 kJ/mol), ΔS (−210.37 J mol^{-1} K^{-1}) and ΔG (−9.62 kJ/mol) values. The binding represents weak perturbation (1–3 %) of α-helix content of SA with increasing concentration of QPhN. The study highlighted the importance of QPhN as a promising marker for PDE10A.

1. Introduction

Cyclic nucleotide Phosphodiesterase (PDE) is a family of eleven enzymes involved in the regulation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). To regulate the levels of cAMP and cGMP, PDEs hydrolyze cyclic nucleotide into their respective nucleotide monophosphates. PDE 1,2,3,10 and 11 act as dual substrate enzyme while PDE 4,7 and 8 are involved in the hydrolysis of cAMP only and PDE 5,6 and 9 are involved in the breaking of cGMP only [1,2]. Some PDEs are further divided into subtypes like PDE1A/B/C, PDE3A/B, PDE4A/B/C/D, PDE8A/B and PDE10A each corresponding to a distinct gene. In comparison with other isozymes, PDE10A protein consists of higher homology and is restricted to mammals only. It is mainly expressed in striatum (a part of basal ganglia), cerebellum and nucleus accumbens [3–5]. Recent studies have proved that it is mainly expressed in rat brain mimicking human brain also [6,7]. The two variants of PDE10A namely, PDE10A1 and PDE10A2 exist out of which A2 variant is prevalent in human brain than A1 variant. Its higher expression in striatal region makes it a lead target for neuroscience diseases [8,9]. Hence, its inhibition with suitable inhibitor becomes a necessary condition to treat neurological diseases.

The first approval of a PDE10A inhibitor- Papaverine **(1)** (as shown in scheme 1) was done by Suiciak et al., in 2006 which showed excellent potency (36 nM). Papaverine inhibited PDE10A showcased increase in the phosphorylation of cAMP and cGMP levels in striatal region and brain-derived neurotropic factor in a Huntington's disease mouse model [10]. Despite having these advantageous properties, Papaverine showed rapid metabolism, shorter half-lives and low blood–brain barrier (BBB)

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