Computer-Aided Design and Analysis of Multifunctional Tetrahydrocannabinol Derivatives Targeting Acetylcholinesterase as Potential Antioxidant Neuroprotectors for Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, oxidative stress, and cholinergic dysfunction. Current therapies offer limited efficacy, highlighting the need for new neuroprotective agents. Tetrahydrocannabinol (**THC**), the main psychoactive component of cannabis, exhibits antioxidant and neuroprotective properties, but its clinical use is restricted due to psychoactivity. To overcome this, a series of structurally modified **THC** derivatives were designed using a computer-aided drug design approach aimed at enhancing drug-likeness and reducing adverse effects. Derivatives were evaluated for pharmacokinetic properties, synthetic accessibility, and antioxidant potential. Molecular docking simulations were used to assess binding interactions with acetylcholinesterase (**AChE**), a key enzyme involved in AD pathology. Among all derivatives, **THC3** and **THC53** emerged as the most promising, demonstrating strong binding to AChE and favorable physicochemical profiles. These findings support their potential as multifunctional agents for AD treatment, combining acetylcholinesterase inhibition with antioxidant neuroprotection. Together, these results highlight the potential of rational drug design in developing new therapies for neurodegenerative diseases.

Keywords: Alzheimer's disease, tetrahydrocannabinol (**THC**), acetylcholinesterase (**AChE**), molecular docking

1. Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder. It is clinically characterized by progressive cognitive impairment, behavioral disturbances, and functional decline resulting from extensive neuronal damage. The pathological hallmarks of AD include the accumulation of amyloid-beta (Aβ) plaques, neurofibrillary tangles, and a marked reduction in acetylcholine levels, primarily due to increased activity of the enzyme acetylcholinesterase (**AChE**). In addition to its role in acetylcholine degradation, **AChE** also contributes to amyloid-beta aggregation, making

it a central target in current therapeutic strategies [1]. Current pharmacological approaches focus predominantly on **AChE** inhibition and attenuation of oxidative damage, while multifunctional agents capable of addressing both processes are increasingly sought after [2].

In this context, tetrahydrocannabinol (**THC**), the principal psychoactive component of cannabis, has emerged as a molecule of interest due to its documented antioxidant and neuroprotective properties. Nevertheless, its potent psychoactivity presents a major barrier to clinical application [3].

This study investigates **THC** derivatives as potential **AChE** inhibitors with enhanced neuroprotective and antioxidant capacity, aiming to identify compounds that retain therapeutic efficacy while minimizing undesirable psychoactive effects, with the ultimate goal of improving treatment outcomes in Alzheimer's disease.

2. Methodology

The design of **THC** derivatives followed the CADMA-Chem approach (*Computer-Assisted Design of Multifunctional Antioxidants*) [4], incorporating functional groups (–OH, $–NH_2$, –SH, –COOH) aimed at improving antioxidant properties and drug-likeness. ADMET properties, toxicity, and synthetic accessibility were evaluated using ADMETlab 3.0 [5]. Quantum chemical calculations were performed in *Gaussian16* at the M06-2X/6-311++G(d,p) level with implicit solvation in water.

Molecular docking simulations were carried out to evaluate the binding affinities and interactions of structurally optimized **THC** derivatives with acetylcholinesterase (**AChE**). Docking was performed in AutoDock 4.2 using the Lamarckian genetic algorithm [6,7], with ligands treated as flexible and the receptor as rigid. The **AChE** structure (PDB ID: 4EY7) [8] was retrieved from the RCSB Protein Data Bank, and all water molecules and co-crystallized ligands were removed in Discovery Studio 4.0. The docking grid was centered at –14.108 × –43.833 × 27.669, with a size of 53 × 53 × 53 and a spacing of 0.375 Å.

3. Results and Discussion

In a previous study [9], 111 **THC** derivatives were designed and classified based on the number of structural substitutions introduced to improve their pharmacological profiles. Using a combination of computational methods – including ADMET predictions and quantum chemical calculations – the compounds were systematically evaluated for their pharmacokinetic properties, toxicity, synthetic accessibility, and antioxidant potential [9]. The initial ADMET screening identified 43 derivatives with favorable drug-likeness, low predicted toxicity, and high synthetic feasibility. These candidates were further refined using systematic exclusion criteria (S_{EC}) and selection based on elimination factors (S^E), which led to the identification of 16 lead compounds with the most balanced profiles (Figure 1).

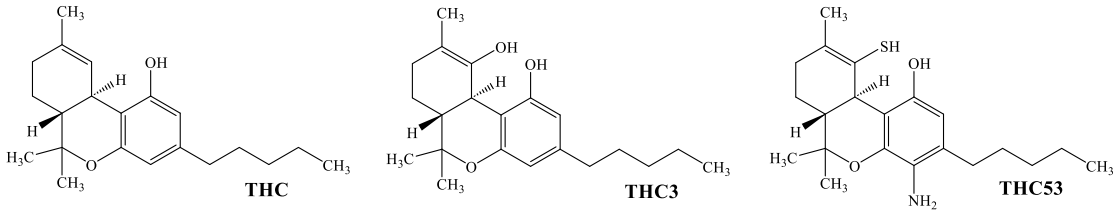

Figure 1. Chemical structures of **THC** and selected **THC** derivatives (**THC3** and **THC53**) exhibiting the most favorable values of the elimination factor (S^E), based on their pharmacokinetic, antioxidant, and synthetic properties.

All compounds were subjected to molecular docking simulations to evaluate their binding affinity toward the active site of the **AChE** enzyme. Among them, **THC3** and **THC53** exhibited the most favorable binding free energy values, with –10.20 kcal/mol and –10.21 kcal/mol, respectively, surpassing the reference compound **THC**, which showed a binding energy of –9.68 kcal/mol (Figure 2). These findings highlight their potential as stable and effective enzyme inhibitors with promising biological activity.

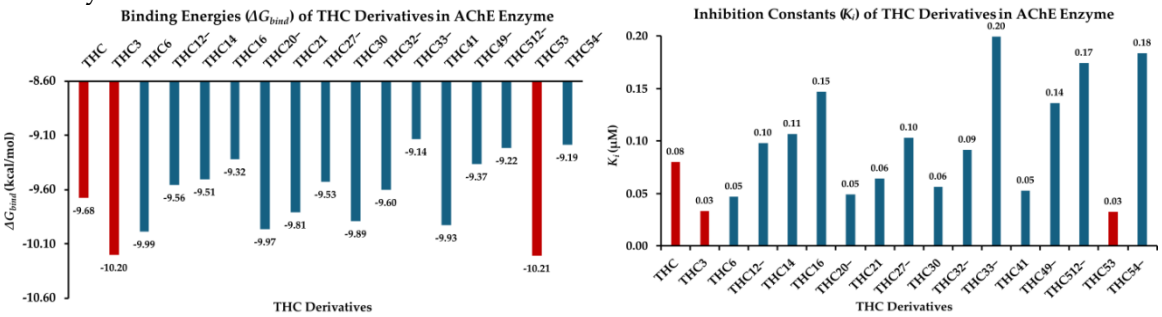

Figure 2. Binding energies (ΔG_{bind}) and inhibition constants (K_i) of **THC** derivatives interacting with the acetylcholinesterase (**AChE**) enzyme. Derivatives with the most favorable binding and inhibition parameters are highlighted in red.

Moreover, quantum chemical parameters such as ionization energy (IE) and electron affinity (EA) indicated a pronounced electron-donating capacity for these derivatives, which is essential for neutralizing reactive oxygen species (ROS) and mitigating oxidative stress [9]. Taken together, these results emphasize the dual nature of **THC3** and **THC53** as multifunctional agents—capable of simultaneously inhibiting acetylcholinesterase and exerting antioxidant neuroprotective effects—making them strong candidates for further investigation in the context of Alzheimer's disease therapy.

4. Conclusions

This study demonstrates the potential of **THC** derivatives as neuroprotective agents acting through a dual mechanism, antioxidant activity and **AChE** inhibition. **THC3** and **THC53** exhibited pronounced electron-donating properties, which are crucial for neutralizing reactive oxygen species and alleviating oxidative stress associated with

neurodegeneration. Additionally, their strong binding affinity toward **AChE** suggests a complementary role in enhancing cholinergic neurotransmission. These results validate the application of computational methods in the identification of multifunctional drug candidates and provide a foundation for further experimental investigation.

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