Multifunctional Tetrahydrocannabinol Derivatives as Potential Antioxidant Neuroprotectors: *In Silico* Targeting of Monoamine Oxidase B and Catechol-O-Methyltransferase in Parkinson's Disease Therapy

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder linked to dopamine depletion. Inhibiting monoamine oxidase B (**MAO-B**) and catechol-O-methyltransferase (**COMT**), key enzymes in dopamine degradation, can enhance dopamine availability. This study explored the inhibitory potential of tetrahydrocannabinol (**THC**) derivatives, known for their antioxidant and neuroprotective properties. Using the CADMA-Chem strategy (*Computer-Assisted Design of Multifunctional Antioxidants, which is based on Chemical properties)*, 111 derivatives were designed, and 16 with favorable ADMET profiles were selected. Molecular docking revealed strong binding affinities of **THC30** and **THC41** to **MAO-B**, and **THC32**$^{-}$ and **THC49**$^{-}$ to **COMT**. These findings suggest that selected **THC** derivatives may serve as promising multifunctional candidates for Parkinson's disease therapy, pending further experimental validation.

Keywords: Parkinson's Disease, tetrahydrocannabinol (**THC**), monoamine oxidase type B (**MAO-B**), catechol-O-methyltransferase (**COMT**), molecular docking

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects 1–2% of the population over the age of 60, making it the second most common neurological condition worldwide. It is characterized by the loss of dopaminergic neurons, resulting in reduced dopamine levels in the striatum and symptoms such as bradykinesia,

rigidity, tremors, and postural instability [1]. Levodopa (L-dopa), a dopamine precursor, remains the gold standard in PD treatment. However, prolonged use often results in motor complications, including fluctuations and dyskinesias [2].

Dopamine metabolism is regulated by two key enzymes: monoamine oxidase B (**MAO-B**), which oxidizes dopamine, and catechol-O-methyltransferase (**COMT**), which methylates levodopa, reducing its availability in the brain. Inhibiting these enzymes can enhance and prolong dopamine availability in the brain [1,2].

Tetrahydrocannabinol (**THC**), the principal psychoactive constituent of *Cannabis sativa*, has attracted considerable attention due to its pronounced antioxidant and neuroprotective activities. However, despite its therapeutic promise, the clinical application of **THC** remains limited, primarily due to its potent psychoactive effects [3].

This study aims to investigate the inhibitory potential of **THC** derivatives against **MAO-B** and **COMT** enzymes, with the broader objective of assessing their ability to modulate dopamine metabolism in the context of Parkinson's disease therapy.

2. Methodology

THC derivatives were designed using the CADMA-Chem approach (*Computer-Assisted Design of Multifunctional Antioxidants*) [4], by introducing polar functional groups to enhance antioxidant potential and pharmacokinetic properties. ADMET profiles, predicted toxicity, and synthetic feasibility were evaluated using ADMETlab [5]. Molecular docking was performed to evaluate the binding affinities of Gaussian16-optimized **THC** derivatives toward **MAO-B** (PDB ID: 2V5Z) [6] and **COMT** (PDB ID: 4PYL) [7]. Docking simulations were conducted in AutoDock 4.2 using the Lamarckian genetic algorithm [8], with flexible ligands and rigid receptors. Before docking, water molecules and co-crystallized ligands were removed in Discovery Studio 4.0. The **MAO-B** grid was centered at 51.886 × 156.453 × 28.559 Å, and the **COMT** grid at –24.482 × 29.543 × 5.845 Å, both using a grid size of 53 × 53 × 53 Å and a spacing of 0.375 Å.

3. Results and Discussion

In a prior study, 111 **THC** derivatives were generated and categorized based on the extent of structural modifications aimed at enhancing their pharmacological properties. Through a combination of computational approaches, including ADMET predictions and quantum chemical analyses, the compounds were assessed for pharmacokinetics, toxicity, synthetic accessibility, and antioxidant activity [9]. Initial screening highlighted 43 candidates with favorable profiles, which were further narrowed down using systematic exclusion criteria (S_{EC}) and elimination factors (S^{E}), resulting in 16 lead compounds with optimal overall characteristics (Figure 1).

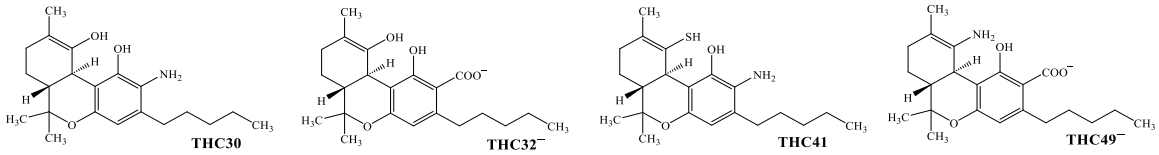

Figure 1. Chemical structures of representative acid-base forms of **THC** derivatives (**THC30**, **THC41**, **THC32⁻**, and **THC49⁻**), exhibiting the most favorable elimination factor (S^E) values and selected based on their pharmacokinetic, antioxidant, and synthetic properties.

To further explore their therapeutic relevance, molecular docking simulations were performed to investigate the binding affinity of the selected derivatives toward the active sites of **MAO-B** and **COMT**. Docking analysis showed that **THC30** and **THC41** exhibited strong binding affinities toward **MAO-B** (–10.87 and –10.26 kcal/mol), comparable to **THC** (–11.33 kcal/mol) (Figure 2), while also demonstrating favorable antioxidant properties based on quantum chemical calculations [9].

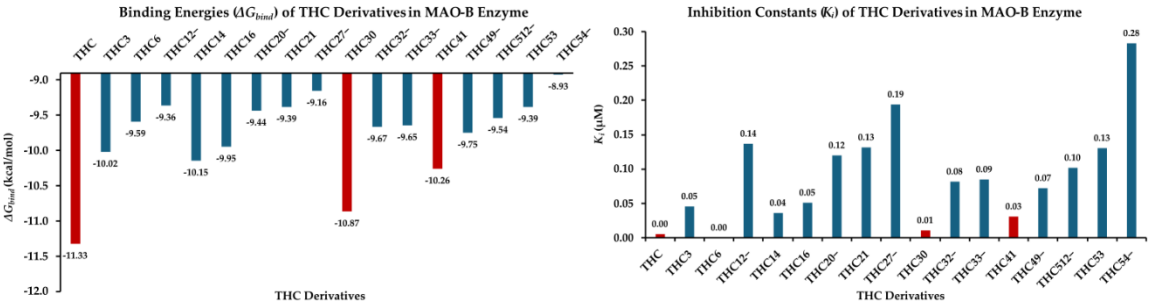

Figure 2. Binding Energies (ΔG_{bind}) and Inhibition Constants (K_i) of **THC** Derivatives Targeting **MAO-B** (top compounds in red)

Among the evaluated derivatives, **THC32⁻** and **THC49⁻** exhibited the strongest binding to **COMT** (–11.97 and –10.38 kcal/mol), significantly outperforming the parent compound **THC** (–7.10 kcal/mol). Their monoanionic forms are further stabilized within the enzyme's active site by the presence of a metal ion, while quantum chemical calculations also revealed pronounced antioxidant potential for both compounds (Figure 3).

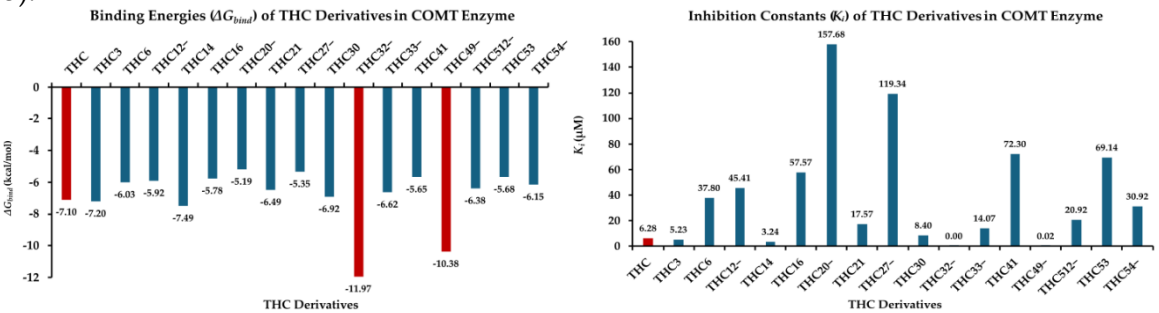

Figure 3. Binding Energies (ΔG_{bind}) and Inhibition Constants (K_i) of **THC** Derivatives Targeting **COMT** (top compounds in red)

4. Conclusions

This study demonstrated the potential of **THC** derivatives as multifunctional neuroprotective agents through computational design and evaluation. ADMET profiling and quantum chemical calculations identified compounds with favorable pharmacokinetics, low predicted toxicity, and strong antioxidant capacity. Docking results revealed that **THC30** and **THC41** bind effectively to **MAO-B**, while **THC32$^-$ and THC49$^-$** show high affinity for **COMT**, with binding comparable to or better than parent **THC**. These findings support the potential of selected derivatives as stable enzyme inhibitors with pronounced antioxidant and neuroprotective effects. Further experimental validation is needed to confirm their therapeutic relevance.

Acknowledgment

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