PREFACE

Alzheimer's disease (AD) stands as a formidable challenge in contemporary healthcare, exacting a toll that extends beyond the afflicted individuals themselves to touch the lives of their families and communities. It is a neurodegenerative disorder characterized by a relentless progression of cognitive decline, memory impairment, and behavioral alterations. The underlying pathology of AD is marked by the aggregation of amyloid-beta (Aβ) plaques and tau tangles within the intricate web of neural circuits. These insidious protein accumulations wreak havoc on neuronal function, precipitating a cascade of events that disrupts inter-neuronal communication, fuels inflammation, and ignites oxidative stress. The ultimate consequence is a widespread atrophy of the brain, particularly affecting regions crucial for memory and cognition, such as the hippocampus.

In the enigmatic world of AD, the aggregation of specific proteins, namely Aβ and tau, assumes a pivotal role in the pathogenesis. Aβ proteins aggregate extracellularly into the dreaded amyloid plaques, while tau proteins intertwine into intracellular neurofibrillary tangles. These proteinaceous aberrations inflict extensive damage on the delicate machinery of neurons, compromising their function, sowing the seeds of inflammation, and ultimately sealing their fate. Thus, the aggregation of these protein culprits represents a decisive turning point in the relentless march of AD. In the realm of medicinal chemistry, α-ketoamides and their derivatives have emerged as compelling contenders, boasting remarkable inhibitory prowess against a spectrum of enzymes, with a keen focus on proteases. These molecules, characterized by their dual electrophilic and nucleophilic attributes, have garnered widespread attention for their potential therapeutic applications across diverse ailments. It is within this context that the following thesis unfolds.

My journey through the corridors of academia has led me to embark on a profound exploration of novel α-ketoamides and their derivatives as modulators of protein aggregation in AD. The

pages that follow document the culmination of years of rigorous research, investigation, and discovery. The work encapsulated herein is divided into four comprehensive studies, each a distinctive facet of the overarching endeavor to unlock the mysteries of AD and advance therapeutic interventions.

Study I (**Chapter 3**) unveils the synthesis of N-benzyl-4-(4-chlorophenyl)-2-oxobutanamide, a compound whose three-dimensional structure was unveiled through X-ray diffraction and optimized using DFT calculations. Spectroscopic validations via FTIR and NMR, along with meticulous theoretical analyses, cast a revealing light on its properties. The profound significance of this compound lies in its capacity to modulate $A\beta_{42}$ aggregation without imposing cellular toxicity, thereby signaling the potential of α-ketoamides as a scaffold for Aβ aggregation modulation.

In Study II (**Chapter 4**), we embark on the synthesis and characterization of twenty-eight piperazine and piperidine-based ketoamide derivatives of high purity. These compounds underwent rigorous evaluation for their ability to modulate Aβ aggregation, with most exhibiting inhibition or delay of Aβ fibril formation. Compound BD23 emerges as a promising lead, distinguished by its solubility, blood-brain barrier permeability, and potent inhibition of tau aggregation in vitro. In vivo studies in an Aβ-induced cognitive impairment mouse model further underline BD23's potential in ameliorating cognitive deficits. Molecular docking and dynamics simulations reinforce the favorable interaction of BD23 with Aβ and tau structures.

Study III (**Chapter 5**) delves deeper into the world of ketoamide derivatives, introducing indole and piperidine-based compounds. A total of twenty-four molecules were synthesized and characterized, displaying significant promise in modulating Aβ aggregation. Compound MD08 emerges as another notable contender, with desirable properties such as solubility, blood-brain barrier permeability, and potent inhibition of tau aggregation. In vivo studies confirm MD08's effectiveness in enhancing cognitive function, while molecular simulations provide insights

into its interactions with Aβ and tau structures.

Study IV (**Chapter 6**) employs an innovative AI-assisted ligand-based virtual screening tool, PyRMD, to explore a vast library of twelve million compounds from the ZINC database. The virtual screening process, coupled with rigorous filtering and prioritization, yields a selection of potential tau aggregation inhibitors. The top candidates, identified through molecular dynamics simulations and MMPBSA binding free energy calculations, represent promising avenues for further exploration in the quest to combat AD.

In conclusion, this thesis signifies a pioneering effort in the pursuit of novel α-ketoamides derivatives as dual Aβ and tau aggregation inhibitors, addressing the primary pathologies underlying AD. Our synthesis endeavors have yielded compounds of substantial yield and high purity, marked by potent activity against both Aβ and tau aggregation. In vivo studies utilizing an Aβ-induced cognitive impairment mouse model validate the potential of lead molecules BD23 and MD08 to mitigate cognitive deficits. Moreover, an innovative AI-assisted virtual screening initiative has unearthed a trove of potential tau aggregation inhibitors, offering a glimpse into the future of AD therapeutics.

This research work represents not only a significant contribution to the field of neurodegenerative disease research but also a testament to the relentless pursuit of knowledge and solutions that drive scientific inquiry. I extend my heartfelt appreciation to my mentors, colleagues, and supporters who have accompanied me on this intellectual journey. May the insights and discoveries contained within these pages inspire further exploration, ignite new avenues of research, and ultimately contribute to the global effort to combat AD and related neurodegenerative conditions.

Date: 23-10-2023

Place: Varanasi

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