3. AIMS AND OBJECTIVES

Alzheimer's disease (AD) is a neurodegenerative disease predominantly impacts the elderly people lead to cognitive decline[1]. The escalating prevalence of this condition necessitates the discovery of efficient treatments and preventive strategies[2]. To tackle the multifaceted nature of AD, worldwide researchers are primarily focusing on the development of multi-target drug (MTD) having ability to target multiple aspects of the disease[3].

AD involves multiple factors like a decrease in acetylcholine levels, the aggregation of beta-amyloid, plaques, tau hyperphosphorylation, oxidative stress, increase level of MAO enzymes and imbalances in biometals[4]. Targeting a single factor may not adequately address the intricate nature of the disease. Instead, MTDLs with balanced affinities for multiple targets have the potential to offer more significant therapeutic benefits[5]. Currently marketed cholinesterase inhibitors are only mainstay of AD treatment, providing symptomatic relief having potential to only temporary benefits[6]. Recent research has focused on identifying new targets for AD treatment, including development of Aβ aggregation inhibitors, MAO inhibitors and antioxidants. However, addressing AD's multifactorial pathology requires a comprehensive approach[7]. Thus, design of cholinesterase inhibitors with additional activities, such as Aβ aggregation inhibition, MAO inhibition and antioxidant properties, has gained attention. These MTDLs aim to provide a synergistic effect by targeting multiple aspects of the AD. By using combined efforts wherein inhibition of cholinesterase, Aβ aggregation, MAO and having antioxidant activity would prove to be effective strategy to slow down the progression of AD and mitigate its multifaceted pathology. Thus, development of such a compound having ability to target simultaneously multiple therapeutic target will offer enhanced efficacy or compared to monotarget.

As per literature review, 8-hydroxyquinolin (8-HQ) is an organic compound that belongs to the class of heterocyclic aromatic compounds. It consists of a quinoline ring fused with a hydroxyl group (-OH) attached at the 8th position[8]. 8-HQ **(I)** is a derivative of quinoline and possesses its own distinct biological activities. It is well-known for its metal chelating properties. It can bind to metal ions, such as iron, copper, and zinc, forming stable complexes[9]. 8-HQ and its metal complexes have shown neuroprotective properties[10]. 8-HQ can chelate excess metal ions in the brain, which are implicated in neurodegenerative diseases like Alzheimer's and Parkinson's[11]. By reducing metal-induced oxidative stress and inhibiting protein aggregation, 8-HQ derivatives have potential therapeutic applications in

neurodegenerative disorders. In recent years, many 8-HQ and quinoline based hybrids e,g tacrine-8-hydroxyquinolin hybrid, Donepezil+Propargylamine+8-Hydroxyquinoline trihybrid and clioquinol-moracin hybrid[12–14].

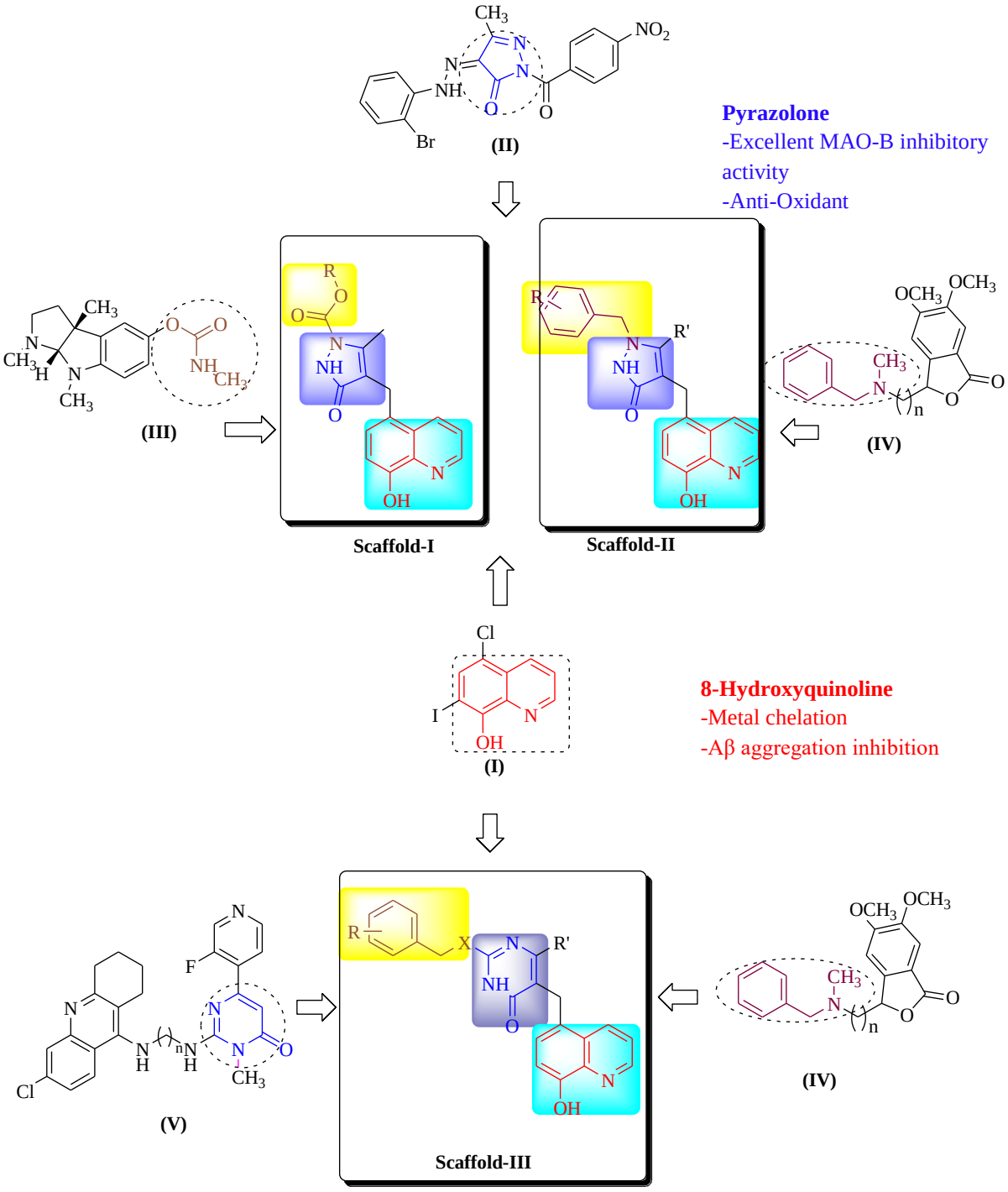

Figure 3.1. Molecular hybridization approach adopted for the development of novel MTDLs as anti-AD agents

Pyrazolone **(II)** is an organic compound characterized by a five-membered ring consisting of three carbon atoms and two nitrogen atoms. Additionally, it contains a ketone

group, with an oxygen atom bonded to one of the carbon atoms[15]. Pyrazolone derivatives have undergone extensive research due to their potential pharmaceutical properties. Certain drugs derived from pyrazolone, such as phenylbutazone and metamizole, are commonly used for their analgesic and anti-inflammatory effects[16]. Apart from their pharmaceutical applications, some pyrazolone derivatives have exhibited additional biological activities. For instance, specific compounds have displayed antioxidant, antimicrobial, antitumor and nueroprotective properties. Moreover, Pyrazole ring system and its analogues pyrazoline, pyrazolone and pyrazolidine was considered as a cyclic hydrazine, which were displayed high affinity towards various enzymes like MAO and cholinesterases[17,18]. The carbamate **(III)** fragment is widely used in pharmaceutical and agrochemical industries due to its ability to form reversible covalent bonds with biological targets[19]. The carbamate moiety act as an enzyme inhibitor by binding covalently to the active site of enzymes, resulting in the inhibition of enzyme activity while amine fragment (**IV**) forms strong cation-π interaction with amino acid residues in the active site of the enzymes[20–22]. Remarkable biological activities associated with the 8-HQ and Pyrazolone nucleus prompted us to fuse these two privileged moiety into a single scaffold with amine and carbamate fragment which could offers multiple favourable activities for the treatment of AD (**Figure 3.1**).

Moreover, pyrimidinone **(II)** emerges as a bioactive heterocyclic compound of considerable interest in the realm of drug development. Its aromatic properties, versatile functional groups, and the potential for substitution at various positions bestow upon pyrimidine a broad spectrum of biological effects. Pyrimidinone derivatives exhibit promising potential in combating a diseases like AD, cancer, inflammation, oxidative stress, and viral infections. In essence, pyrimidinone serves as a pivotal heterocyclic scaffold with multifarious medicinal applications. Its capability to interact with an array of biological targets, alongside the facile synthesis of pyrimidinone derivatives, positions it as an attractive avenue for drug investigation and advancement. The broad spectrum of biological activity of pyrimidinone spurred our interest in to integrate pyrimidinone with 8-HQ **(I)** nucleus in single scaffold with benzyl moiety which could offers multiple favourable activities for the treatment of AD **(Figure 3.1**).

To explore their potential as anti-AD agents and establish a meaningful structure-activity relationship (SAR), the designed scaffolds underwent structural modifications through the incorporation of various substituents. Thus, the main aim was to synthesize the designed

pyrazolone based **(I, II)** and pyrimidinone based **(III)** compounds and assess their anti-AD activities. The details of the experimental work conducted to accomplish the proposed plan are presented in **Chapter 4.**

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