IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

RECENT UPDATES IN CHEMISTRY OF ALZHEIMER'S SYNTHETIC MOLECULES: A NOVEL INSIGHT INTO THE DRUG DISCOVERY

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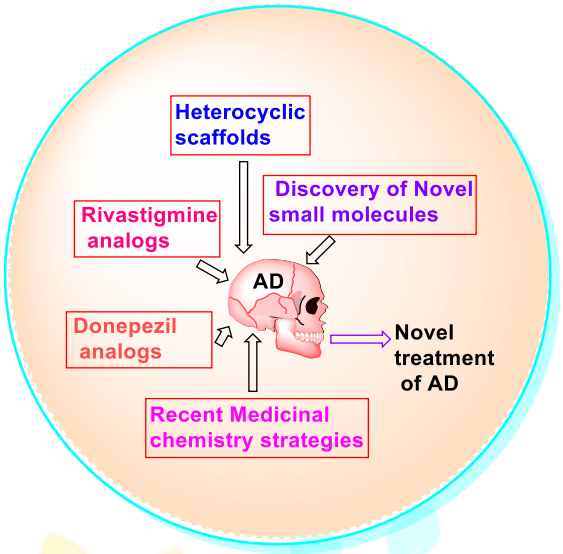
Abstract

Alzheimer's disease (AD) is an ageing disorder characterized by cognitive impairment and memory deficits or dementia. Despite extensive research, effective treatments for AD are still lacking. However, recent strides in synthetic chemistry have opened new avenues for the design and development of small molecules targeting the key pathological features of AD. This comprehensive scientific review highlights the latest advancements in the chemistry of synthetic molecules for AD therapy, with a primary focus on their potential impact in combating the disease. Additionally, researchers have been investigating hybrid molecules capable of targeting multiple biological pathways simultaneously. Moreover, various synthetic approaches were attempted to conjugate two distinct synthons effectively. In the field of medicinal chemistry, heterocyclic scaffolds have been applied to create novel AChE and BuChE inhibitors for AD treatment. A thorough SAR has been established to guide the discovery of new AD medications. Meanwhile, the recent medicinal chemistry strategies were used to designed novel molecules such as, structure-based drug design, molecular hybridization etc. These methodologies were utilized in the scaffold of rivastigmine and donepezil drug and researchers identified novel small molecules with potential activity for AD therapy. In recent research, scientists developed a novel compound with bifunctional groups targeting the τ-protein, which can lead to nerve cell damage and death.

Keywords; Alzheimer's disease, Heterocyclic scaffolds, scaffold hopping, Rivastigmine, Donepezil, AChE and BuChE, SAR.



Introduction

1.1 Overview of Alzheimer's disease

Alzheimer's disease (AD) stands as one of the most pressing and complex challenges of our time casting a shadow over the lives of millions worldwide. This devastating neurodegenerative disorder has a profound impact on individuals, families, and societies, robbing its victims of their memories, cognitive abilities, and ultimately their independence. First described by Dr. Alois Alzheimer over a century ago, the disease has since emerged as a major public health concern, with an increasing prevalence in an aging global population.[1]

The hallmark of Alzheimer's disease is the progressive deterioration of cognitive functions, particularly memory, language, and reasoning abilities. This cognitive decline is accompanied by the accumulation of abnormal protein aggregates, including β-amyloid plaques and tau tangles, in the brains of affected individuals. While significant advances have been made in understanding the pathological underpinnings of AD, there remain many mysteries surrounding its Etiology, diagnosis, and treatment.[2]

In this review article, we aim to provide a comprehensive overview of Chemistry of Alzheimer's synthetic small molecule with their potential activities. By synthesizing the latest research findings and drawing from seminal studies, we seek to shed light on the multifaceted nature of AD, its impact on individuals and societies, and we discussed the major advancements in the medicinal chemistry to designed several potential molecules to diagnose and for the treatment of AD.[3]

1.2 Causes and risk factors associated with Alzheimer's Disease

An increasing age, inherited variables, head injuries, vascular illnesses, infections, and environmental factors (heavy metals, trace metals, and others) have all been identified as risk factors for AD showed in the (**Figure 1**). It is currently unclear what causes the pathological alterations in Alzheimer's disease. However, the main causes of AD are thought to be two of the many hypotheses that have been put forth: some claim that cholinergic dysfunction is an important risk factor for AD, while others believe that changes in the production and processing of amyloid -protein are the primary initiating factors.[4]

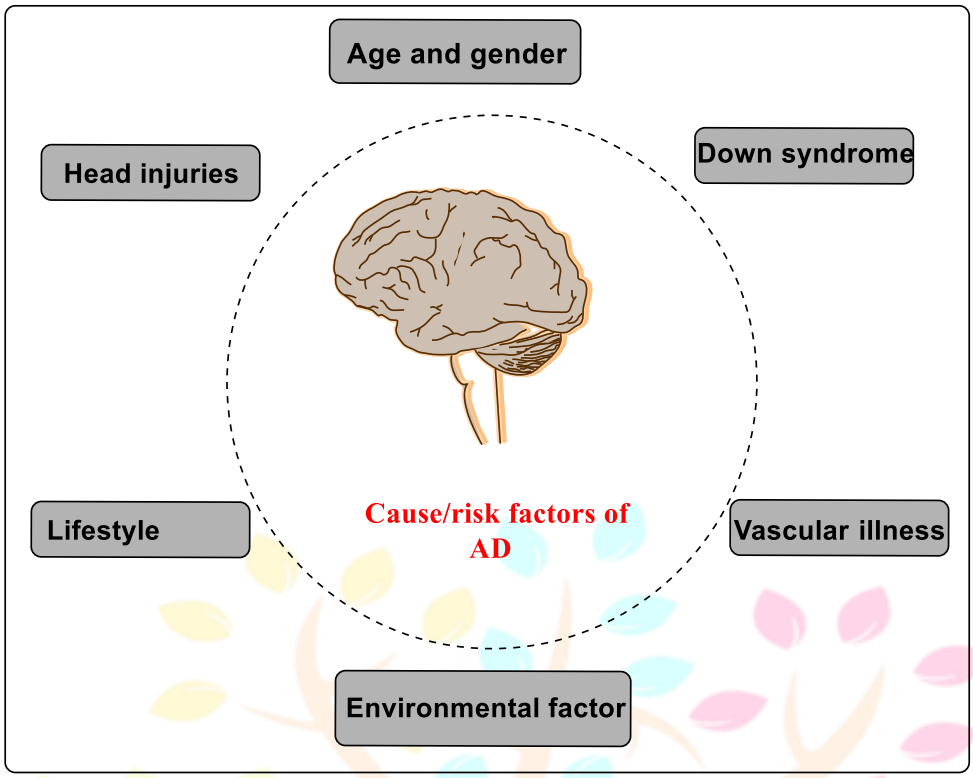


Figure 1: Risk factors associated with AD

1.3 Synthetic Small molecules: A Versatile Toolset for Alzheimer's Research

Synthetic small molecules have emerged as a versatile toolset in the investigation of Alzheimer's disease due to their ability to modulate specific biological processes and molecular targets. Through rational design and high-throughput screening, researchers have generated a diverse array of compounds that can selectively interact with key proteins involved in AD pathology, including β-amyloid, tau, and acetylcholine esterase.[5] Recent studies utilizing small molecules targeting intracellular tau phosphorylation have unveiled mechanisms of tau-mediated neurodegeneration. These findings highlight the significance of synthetic compounds in uncovering the intricate molecular cascades that contribute to cognitive decline.[6] Furthermore, the modulatory effects of synthetic small molecules on cellular processes have opened doors to innovative drug discovery approaches, including repurposing existing compounds for AD treatment.[7]

Wang et al. described a comprehensive and critical evaluation of small compounds being investigated as a lead candidate for developing medicines against tauopathy in Alzheimer's disease. And They have explained various therapeutic small compounds being studied to minimize tau pathology in Alzheimer's disease. Tau post-modification modulators, aggregation inhibitors, and degradation promoters are among the compounds in this class. Most of them are now in preclinical stages, with only fourteen compounds entering clinical trials: LMTM, Rember TM, curcumin, BPN14770, cilostazol, nilotinib, minocycline, lithium, tideglusib, saracatinib, sodium selenate, salsalate, and rapamycin.[8]

2. Statistical data of clinical trial small molecules as potential Anti-Alzheimer's agents from 2019 to 2023

We described a statistical overview of clinical trial agents which were investigated as potential anti-Alzheimer's agents. Over the span of four years, there has been a progressive escalation in the number of drug discovery compounds and subsequent clinical trials focused on Alzheimer's disease. As of January 1, 2023, a total of 187 trials were investigating 141 distinct treatments for Alzheimer's disease. Among these, Phase 3 trials comprised 36 agents in 55 trials, Phase 2 trials involved 87 agents in 99 trials, and Phase 1 trials encompassed 31 agents in 33 trials. Disease-modifying therapies constituted the majority, accounting for 79% of the drugs under investigation, with 28% being repurposed agents. Meeting the participant requirements for all ongoing Phase 1, 2, and 3 trials would necessitate the involvement of 57,465 individuals. In the year of 2023 there were maximum number of agents tried in clinical trial. However, only 36/187 agents were reached in the Phase 3 clinical trial and shown in the bar graph figure 2. Secondly, there are 36 agents in 55 trials in Phase 3. DMTs (disease modifying therapies) account for 67% (N = 24) of medicines in Phase 3 studies, comprising 9 (25% of Phase 3 agents) biologics and 15 (42%). Five (14% of Phase 3 drugs) are potential cognitive enhancers, and seven (19%) of the medications address neuropsychiatric symptoms of Alzheimer's disease which were shown in pie chart figure 3. The trajectory of this advancement is characterized by a day-by-day augmentation in both the array of novel therapeutic agents and the concurrent expansion of clinical trial initiatives.[9] This evolving

landscape is indicative of a robust and ongoing effort within the scientific community to propel the exploration and development of interventions for Alzheimer's disease, thereby reflecting a dynamic pursuit of therapeutic breakthroughs and potential medical solutions for this ailment. Disease modification trials included 96 agents, of which 38 targeted amyloids, with 18 being small molecules and 20 monoclonal antibodies. Additionally, 18% of agents targeted tau, combining small molecules and biologics.[10]

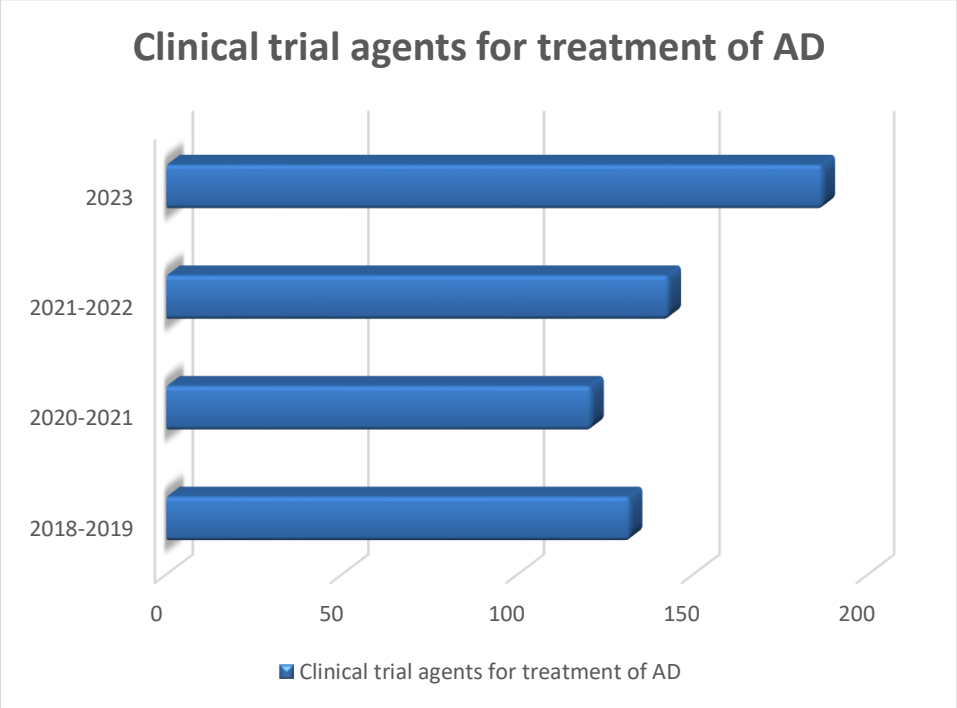


Figure 2: Clinical trial agents for treatment of Alzheimer's disease

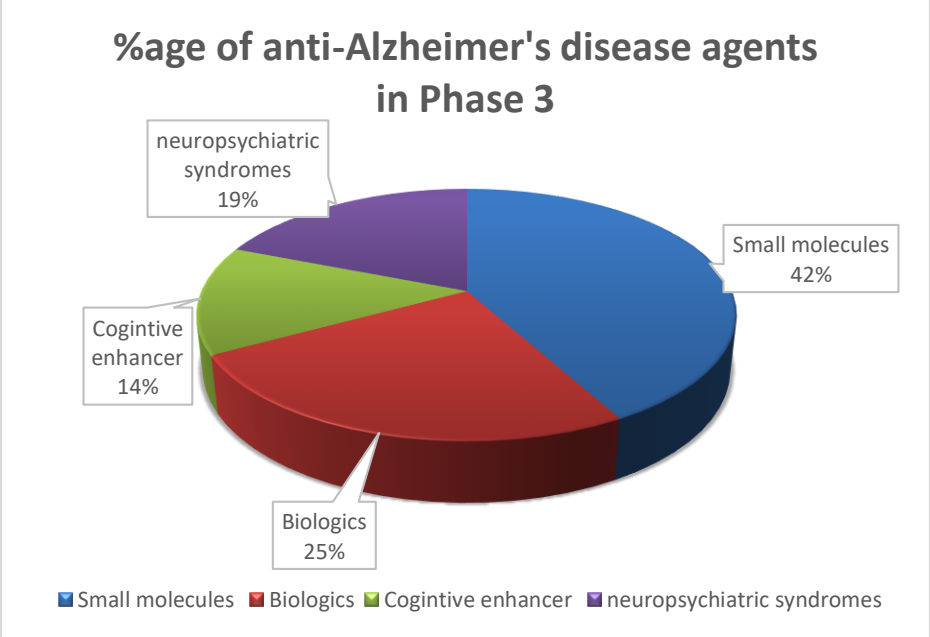


Figure 3: Mechanisms of agents in Phase 3 clinical trial.

3. Recent advancements in the chemistry of Heterocyclic scaffolds as potential Anti-Alzheimer's agents.

Heterocyclic scaffolds encompass multifaceted implications within the framework of drug design and development. These heterocycles have exhibited an evolving role as fundamental frameworks in the creation of numerous synthetic derivatives possessing potent anti-Alzheimer's potential. Given the limited availability of efficacious drugs targeting Alzheimer's disease in the market, there is a pressing demand for the identification, design, and development of novel anti-Alzheimer's agents to address the intricate clinical manifestations associated with this condition. The primary objective of this is to comprehensively encapsulate recent strides in the medicinal chemistry of compounds based on heterocyclic structures, focusing on their potential for combating Alzheimer's disease. This objective entails three key aspects:

a. The comprehensive depiction of literature reports encompassing the anti-Alzheimer's potential of derivatives rooted in heterocyclic moieties.

b. Illumination of contemporary breakthroughs in the medicinal chemistry of heterocyclic compounds, emphasizing their therapeutic promise against Alzheimer's disease.

c. Synthesis of a comprehensive correlation between the structure-activity relationship (SAR) and pharmacological responses, encompassing in silico investigations and mechanistic studies to offer insights into the strategic design and development of lead molecules with desired properties.

In essence, this endeavors to provide a holistic overview of the recent advancements in harnessing the potential of heterocyclic compounds as a foundation for the next generation of anti-Alzheimer's drugs, thereby contributing to the advancement of therapeutic interventions for this complex disorder.[1] In the realm of heterocyclic chemistry, notable advancements have been achieved in the development of heterocyclic derivatives, including but not limited to imidazole, oxadiazole, triazole, pyrazole, and pyrazoline moieties, as potential agents with anti-Alzheimer's properties. These recent developments represent a significant stride in the field, highlighting the strategic utilization of diverse heterocyclic frameworks to engineer compounds possessing therapeutic potential against Alzheimer's disease.[11]

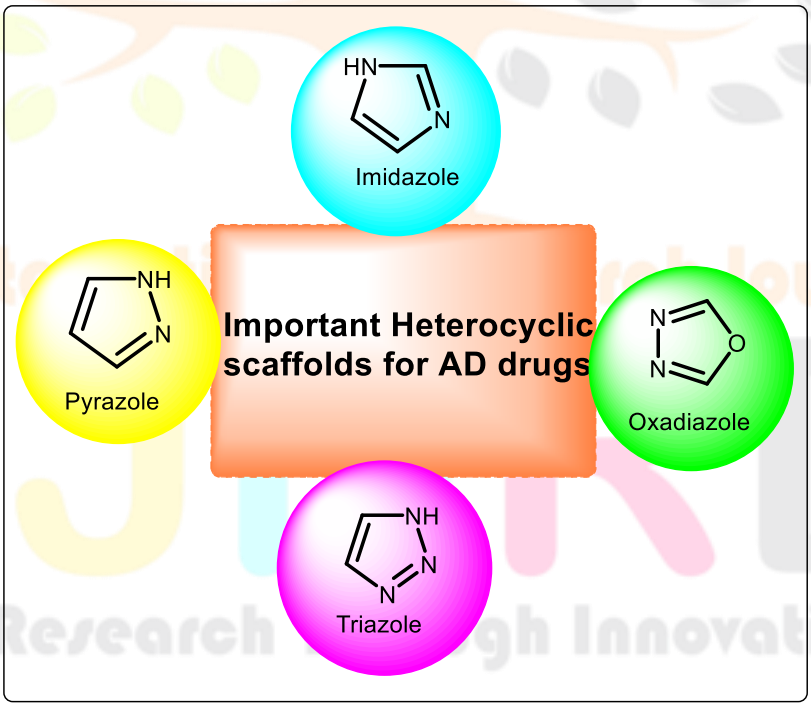


Figure 4: Heterocyclic scaffolds for the discovery of Anti- Alzheimer's drugs

3.1 Imidazole Derivatives

The imidazole core moiety plays a pivotal role in modulating cholinesterase activity. Imidazole-based cholinesterase inhibitors have demonstrated remarkable efficacy in addressing neurodegenerative conditions such as Alzheimer's and Parkinson's diseases. The

distinctive structural attributes of imidazole compounds substantially influence their inhibitory potential; however, minor variations in the activity of reported analogs are attributed to the diversity in substituent nature and positions on aromatic rings.[12]

Substituents with reduced steric bulk attached to the imidazole ring notably enhance the inhibitory capabilities against both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) in comparison to larger groups. The inhibitory efficiencies of AChE and BChE are influenced by the magnitude of substitution. Electron withdrawing groups (e.g., $–CF_3$, –Cl, $–NO_2$, –COOH) augment enzymatic activity, whereas electron-donating groups (e.g., $–CH_3$, $–OCH_3$) exhibit inhibitory effects.In view of these findings, the development of new imidazole derivatives holds promising potential for the creation of innovative and economical anticholinesterase drugs.

Yoon et al. synthesized new compounds featuring a benzimidazole core and tested their effectiveness as inhibitors of AChE and BChE. Several of these compounds showed strong AChE inhibition, with four benzimidazoles having IC_{50} values below 10 mM. Compound which contained a nitro group ($-NO_2$), displayed the highest inhibition, with IC_{50} values of 5.12 mM for AChE and 8.63 mM for BChE. The study revealed that modifying substituents at the 2nd position of the benzimidazole core and the 4th position of the aryl ring could yield promising analogs with potent ChE inhibition. Notably, compounds containing electron-withdrawing groups (EWGs) at the 4th position of the phenyl ring showed enhanced activity.

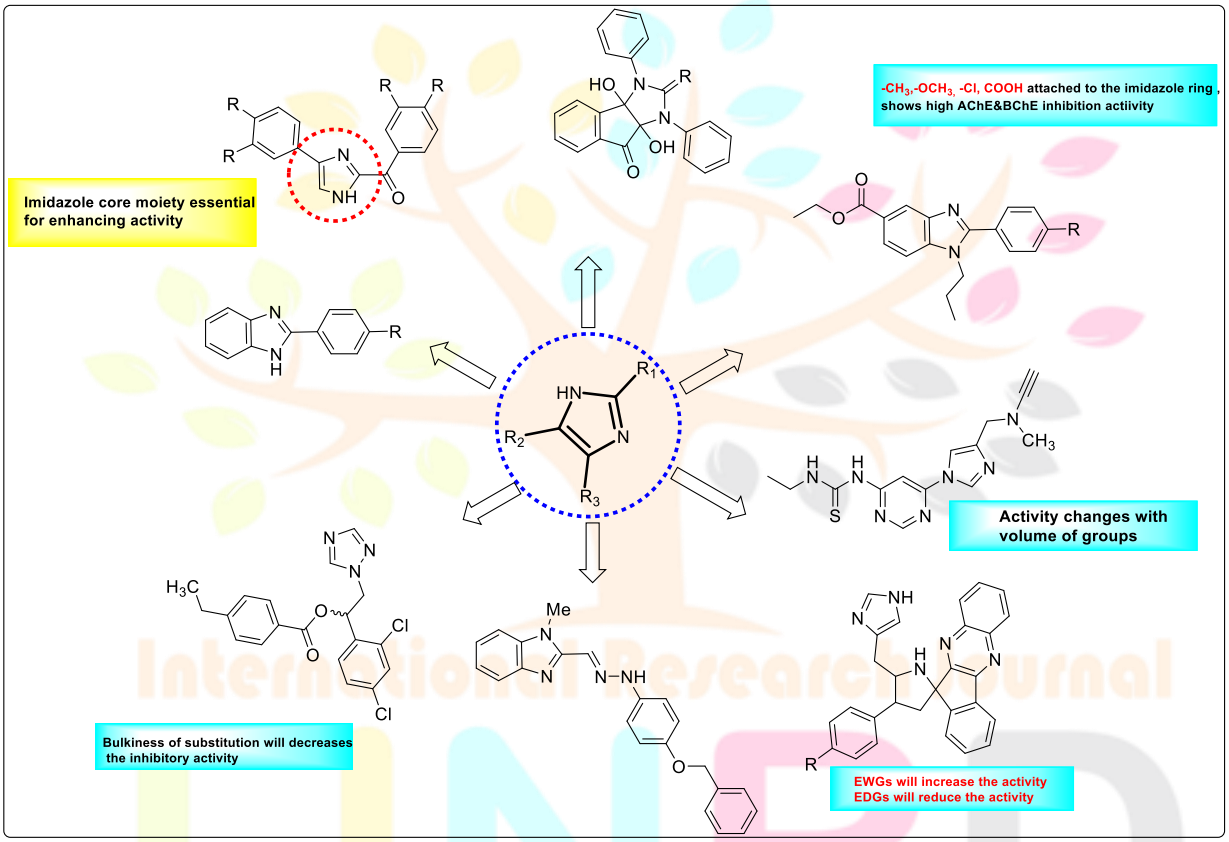


Figure 5: SAR analysis of substituted imidazole

The study aimed to assess the MT-stabilizing activity of test compounds in QBI-293 cells. This was done by observing the increase in acetylated α-tubulin (AcTub), a recognized marker of stable microtubules. The compounds were compared to known MT-stabilizing imidazoles and triazolo pyrimidines. Additionally, the impact of compound treatment on total α-tubulin was examined due to the degradation effect observed in certain imidazoles. The evaluation of compound effects on COX and 5-LOX-derived eicosanoid biosynthesis was conducted using a modified RBL-1 cell assay, suitable for assessing both COX-derived prostaglandins and 5-LOX-derived leukotrienes generated in the presence or absence of the test compounds.[13]

3.2 Oxadiazole Derivatives

A new series of chiral coumarin/1,2,4-oxadiazole hybrid compounds were synthesized and assessed for their inhibitory activity against cholinesterase's (ChE). Enantiomers 57 and 58 demonstrated strong inhibitory activity against BChE, with IC_{50} values of 8.17 and 9.56 mM, respectively, exhibiting selectivity for BChE over AChE by 9.49- and 7.58-fold. These compounds have the potential to serve as a molecular template for developing multifunctional anti-Alzheimer's disease (AD) drugs. Another set of hybrids, incorporating a 2-aminopyrimidine (2-AP) unit linked to substituted 1,3,4-oxadiazoles, were also evaluated. Compound 59, featuring a phenyl ring at the 5th position of the 1,3,4-oxadiazole core, displayed notable AChE inhibitory activity (IC_{50} = 5.69 mM). Compound 60, with a 3,4,5-

trimethoxyphenyl group, showed significant AChE inhibitory potential (IC_{50} = 5.91 mM). Compound 61, containing a naphthyl ring, exhibited the most potent AChE inhibitory activity (IC_{50} = 6.52 mM) attributed to its enhanced lipophilicity, potentially facilitating interactions with AChE's active site residues. The study suggests that N-(pyrimidin-2-yl)-1,3,4-oxadiazole derivatives hold promise as potential scaffolds for dementia treatment, with compound being a noteworthy candidate for further investigation.[14]

Evaluated were hybrids comprising substituted 5-phenyl-1,3,4-oxadiazoles and N-benzylpiperidine, targeting Alzheimer's disease. The assessed compounds exhibited varying degrees of enzyme inhibition against hAChE and hBChE, ranging from moderate to highly effective. The outcomes of in vitro tests substantiated these findings, underscoring that elongating the molecular chain and strategically placing the 1,3,4-oxadiazole unit between the N-benzylpiperazine core and the terminal phenyl group could significantly enhance their inhibitory efficacy against the target enzymes. To summarize, these findings collectively highlight compound 64 as a promising contender for potential application in AD therapy.[15] Shrivastava et al. (2019) developed a new hybrid with a 1,3,4-oxadiazole nucleus that is linked to 4-aminopyridine, and they assessed it for its potential antioxidant and AChE inhibitory properties.[16]

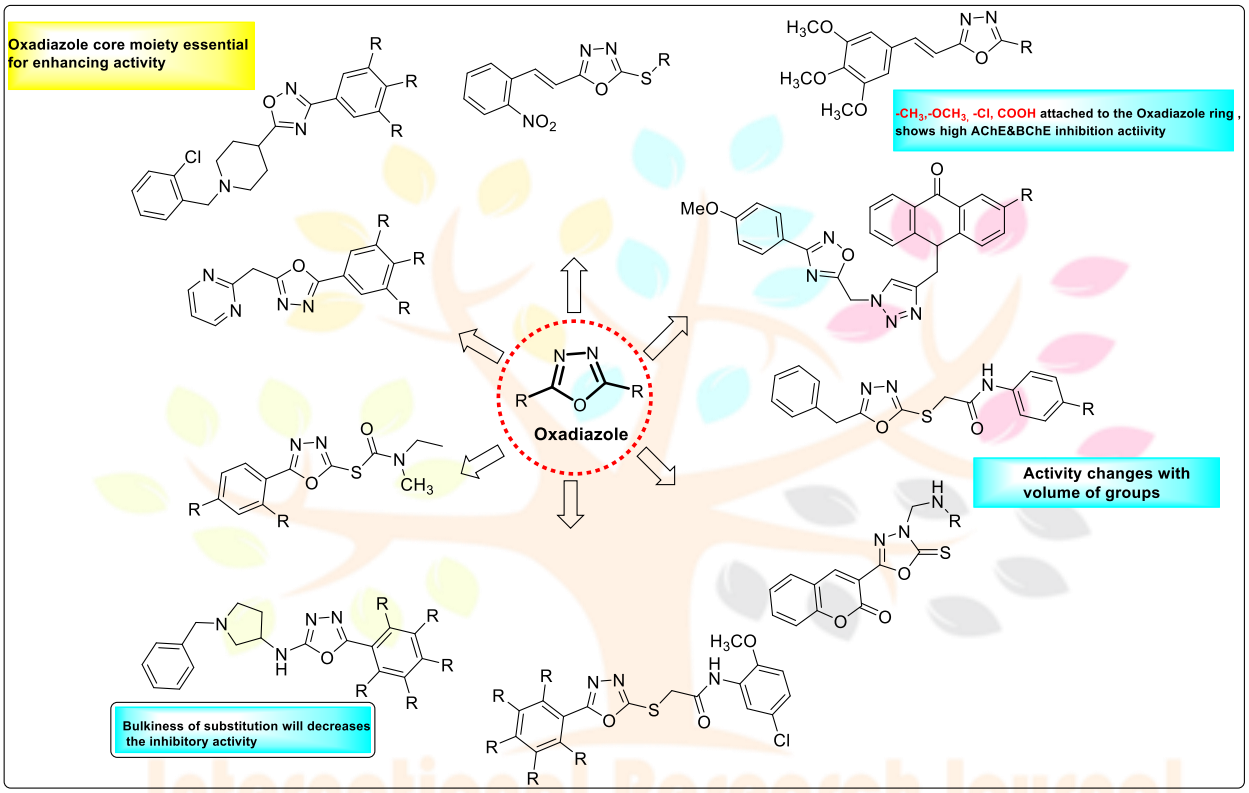


Figure 6: SAR analysis of substituted oxadiazole

3.3 Triazole Derivatives

A new group of compounds called 1,2,3-triazole-genipin analogues was developed, synthesized, and tested for their potential to protect nerve cells (neuroprotective activity) and their ability to inhibit enzymes known as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). These enzymes are implicated in the breakdown of important neurotransmitters in the brain. The genipin analogues that had bromomethyl and diphenyl hydroxy-triazole structures displayed properties that could protect nerve cells from damage caused by a toxic substance called H_2O_2. Additionally, these analogues showed strong inhibitory effects on BuChE in laboratory tests, with IC_{50} values of 31.77 and 54.33 µM, respectively. For comparison, a known reference compound, galantamine, had an IC_{50} value of 34.05 µM for the same enzyme. Molecular docking studies, which simulate how molecules interact, indicated that these genipin analogues have a favorable binding energy and form interactions with specific amino acids of BuChE through processes like hydrogen bonding and hydrophobic interactions. Overall, these 1,2,3-triazole-genipin analogues hold potential as promising starting points for the development of drugs to combat Alzheimer's disease.[17] Methylindolinone-1,2,3-triazole derivatives were synthesized and evaluated for their ability to inhibit cholinesterase enzymes (ChE) in laboratory tests. While most of the newly synthesized compounds demonstrated weak inhibitory effects on acetylcholinesterase (AChE), they exhibited moderate to strong inhibition against butyrylcholinesterase (BChE). The compound numbered 148 displayed notable BChE inhibitory activity, with an IC_{50} value of 4.78 mM, surpassing the activity of donepezil (with an IC_{50} value of 5.19 mM). Through molecular docking analysis, compound 148 was observed to effectively bind to both the peripheral and catalytic sites of the BChE enzyme simultaneously.[18]

Triazole derivatives exhibit strong inhibitory effects on both AChE and BChE, influenced by the electronic characteristics and positions of substituents linked to the 1,2,3-triazole ring. Smaller groups attached to the triazole ring demonstrate higher inhibitory activity against

AChE and BChE compared to larger groups. Electron-withdrawing groups (e.g., –F, –Cl, –Br, –CN, –OH) can enhance activity depending on their positions, while electron-donating groups (e.g., $–CH_3$, $–OCH_3$, Et, n-Bu) can decrease activity. These analogues display favorable ChE inhibitory effects with minimal risk of adverse effects. Further modifications in the core structure offer potential for designing even more potent compounds within this category.[19]

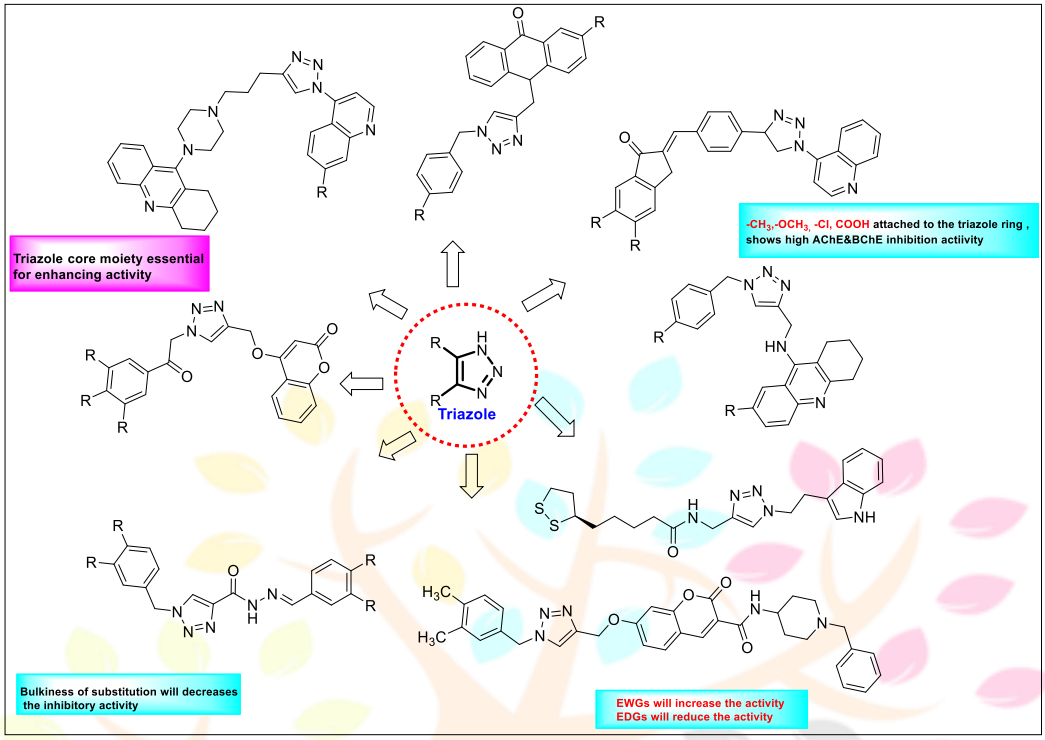


Figure 6: SAR analysis of Triazole heterocyclic derivatives for AD

3.4 Pyrazole Derivatives

The diverse applications of pyrazoles within the realm of pharmaceuticals have spurred significant advancements in the methods for synthesizing pyrazoles. Over the past decade, numerous comprehensive and efficient methodologies, incorporating transition-metal catalysts, photo redox reactions, one-pot multicomponent processes, novel reactants, and innovative reaction mechanisms, have yielded substantial progress in the synthesis and modification of pyrazole derivatives. This review provides a concise overview of these recent developments and underscores the potential utility of pyrazole frameworks in the advancement of pharmaceuticals aimed at treating Alzheimer's disease (AD) and Parkinson's disease (PD), both prominent chronic neurodegenerative conditions. The diverse range of pyrazole compounds discussed herein exhibits promise as prospective candidates for the creation of innovative neurodegenerative therapeutic agents.

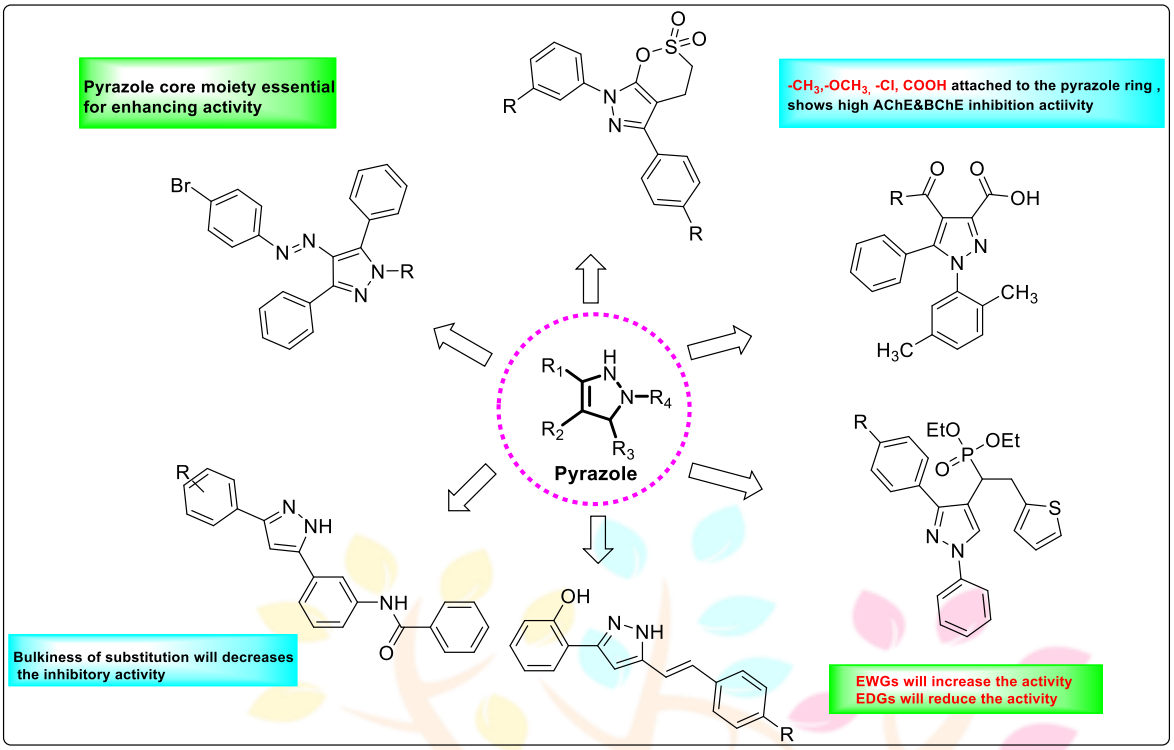


Figure 7: SAR analysis of Pyrazole heterocyclic derivatives for AD

Structure-activity relationship (SAR) investigations were conducted, focusing on the central core and substitution arrangement within the pyrazole scaffold. The observed variations in cholinesterase activity among the examined analogs are attributed to differences in the substitution patterns present in the core structure of the molecule. These structural characteristics significantly influence inhibitory activity, with further variability in analog activity linked to the nature and positions of substituents on aryl rings. Smaller groups attached to the pyrazole ring enhance inhibitory potential against both AChE and BChE compared to bulkier groups. The presence of electron-withdrawing atoms or groups (e.g., –F, –Cl, –Br) heightens activity, while electron-donating groups (EDG) (e.g., $–CH_3$, $–OCH_3$) reduce it. This indicates that electronic and steric factors intrinsic to the inhibitor molecule play a pivotal role in affecting cholinesterase activity.In a study conducted by Shaikh et al. in 2020, new structures involving N-substituted pyrazole-derived α-amino phosphonates were introduced and subjected to evaluation for their potential as anti-cholinesterase (anti-ChE) agents. Notably, two of these analogs, namely compound 8 (with an IC_{50} value of 0.055 mM for AChE inhibition) and compound 9 (with an IC_{50} value of 0.017 mM for AChE inhibition), exhibited robust effectiveness against acetylcholinesterase (AChE). The remaining analogs demonstrated moderate to substantial inhibition of butyrylcholinesterase (BChE), surpassing the performance of widely used drugs like galantamine and rivastigmine. As a result of this investigation, a collection of promising lead compounds emerged, holding significant potential for further advancement as agents targeting Alzheimer's disease.[20]

3.5 Pyrazoline Derivatives

The SAR analysis of pyrazoline derivatives, reveals their significant activity against cholinesterase enzymes. Structural attributes play a pivotal role in inhibition, offering the potential for precise adjustment of analog activity by modifying the nature and positions of substituents on aryl rings. Smaller groups linked to the pyrazoline ring notably enhance inhibitory efficacy against both AChE and BChE in comparison to bulkier groups. Changes in ChE activity correspond with the size of substitution, highlighting the influence of steric and electronic factors in fine-tuning the compound structure.

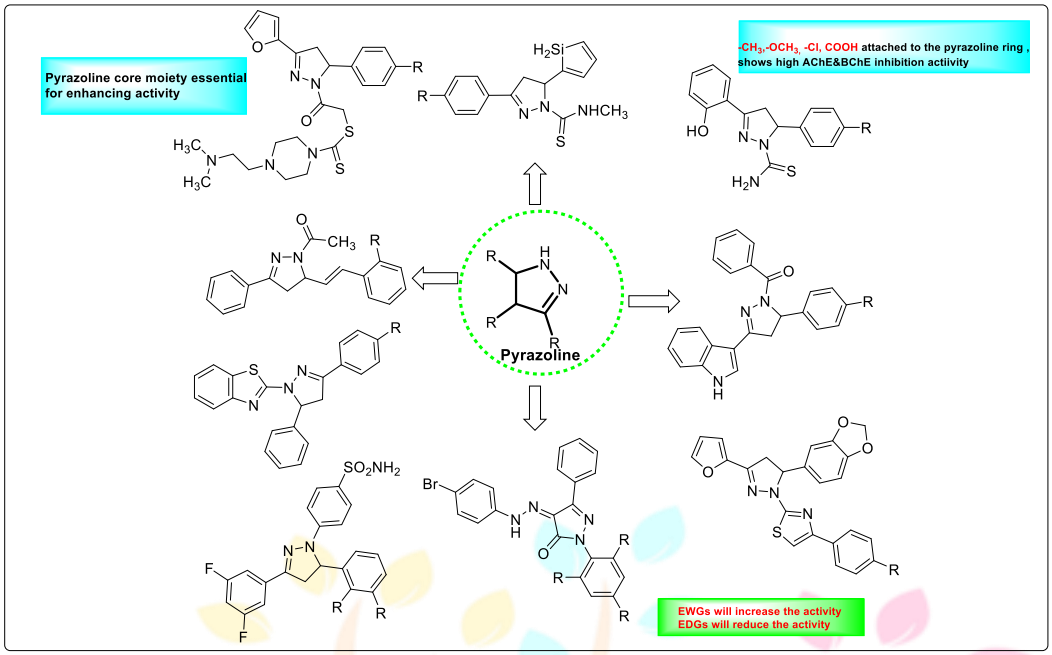


Figure 8: SAR analysis of Pyrazoline heterocyclic derivatives for AD

Electron-withdrawing groups (e.g., –F, –Cl, –Br) demonstrate activity enhancement, while electron-donating groups (e.g., $–CH_3$, $–(CH_3)_2$) reduce it. The described analogs exhibit moderate to substantial ChE inhibitory abilities with minimal risk of adverse effects. Additionally, these analogs are economically viable and straightforward to synthesize in a laboratory setting, rendering them attractive for future commercial development and marketing as cholinesterase-targeting drugs. In a study by Sever et al. conducted in 2020, thiazolyl-pyrazoline analogs were synthesized and subjected to an assessment of their potential to inhibit acetylcholinesterase (AChE). In vitro investigations revealed that all the compounds exhibited significant AChE inhibitory activity, surpassing the potency of the reference drug tacrine.[26] The study involved the synthesis and evaluation of eighteen pyrazoline compounds for their potential to inhibit acetylcholinesterase (AChE) activity in vitro. The interaction between the pyrazolines and the enzyme was investigated through computational simulations. Compound 2B within the series displayed the most significant inhibitory activity against AChE, with an IC_{50} value of 58 nM. Molecular docking analyses highlighted key interactions involving π–π interactions with Trp 286 and Tyr 341 residues. A connection between the HOMO-1 surfaces and AChE inhibition was established. ADMET assays indicated a favorable profile for compound 2B. Based on these findings, the promising compound 2B opens possibilities for exploring analogues to develop new anti-Alzheimer's disease agents.[21]

4. Recent Developed Hybrid synthetic compounds as potential Anti-Alzheimer's agent

In recent years, the field of drug discovery has witnessed a growing interest in the development of hybrid synthetic compounds with the potential to serve as effective agents in the fight against Alzheimer's disease (AD). The multifactorial nature of AD, characterized by intricate molecular pathways and complex pathological processes, has driven researchers to explore innovative strategies in drug design. Hybrid compounds, amalgamating distinct molecular moieties or pharmacophores, offer a unique approach to address the multifaceted challenges posed by AD. These novel synthetic constructs hold the promise of simultaneously targeting multiple pathways involved in disease progression, leading to improved therapeutic outcomes. This article reviews the recent advancements in the design and synthesis of hybrid compounds intended as potential anti-Alzheimer's agents, shedding light on their molecular attributes, mechanism of action, and therapeutic potential in the context of combating this debilitating neurodegenerative disorder.

4.1 Hydroxytyrosol-Donepezil Hybrids as Potential Antioxidant and Neuroprotective Agents

Various synthetic methodologies were investigated to efficiently combine two distinct synthons, yielding favorable outcomes. Additionally, a derivative involving nitro-hydroxytyrosol was synthesized, broadening its potential application to encompass other neurodegenerative and inflammatory models. Subsequently, the bioactivity of these compounds was assessed through diverse chemical and biological assays conducted on a human neuroblastoma cell line (SHSY-5Y). Notably, these experiments yielded significant results concerning cell viability and the modulation of cellular redox equilibrium. Across the spectrum, all hybrid compounds demonstrated minimal cell death even at concentrations below 1 μM, establishing their stability and non-toxic nature. Notably, the nitro-hybrid compound showcased exceptional efficacy in diminishing reactive oxygen species (ROS) levels to physiological ranges, indicating its potency in mitigating oxidative stress.[22]

4.2 Hybrid of donepezil chalcone rivastigmine potential multifunctional Anti-Alzheimer's agent.

A series of novel hybrid compounds, resulting from the rational fusion of donepezil, chalone, and rivastigmine, were designed and synthesized. In vitro bioactivity assessments revealed that compound 10c exhibited reversible inhibition of both human acetylcholinesterase (huAChE) and human butyrylcholinesterase (huBuChE), with IC_{50} values of 0.87 μM and 3.3 μM, respectively. Notably, it displayed substantial anti-inflammatory properties by suppressing the production of IL-6 and TNF-α. Additionally, compound 10c effectively hindered self-mediated aggregation of Aβ1-42 (60.6%) and huAChE-mediated induced aggregation of Aβ1-40 (46.2%), highlighting its potential in addressing Alzheimer's disease pathology.

Furthermore, compound 10c demonstrated significant neuroprotective effects against Aβ1-42-induced PC12 cell injury and activated the ubiquitin-proteasome system (UPS) pathway in HT22 cells, leading to the degradation of tau protein and amyloid precursor protein (APP). Remarkably, 10c exhibited robust stability in simulated gastrointestinal fluids and liver microsomes in vitro. Pharmacokinetic analysis in rats following intragastric administration showed rapid absorption and distribution of compound 10c in the brain. PET-CT imaging demonstrated the brain's quick uptake of [11C]10c, with gradual clearance over time. Moreover, at a dosage of 5 mg/kg, compound 10c ameliorated memory impairment induced by scopolamine, indicating its potential for cognitive enhancement. Given these promising findings, further comprehensive investigations are warranted to explore the therapeutic potential and mechanisms of compound 10c.[23]

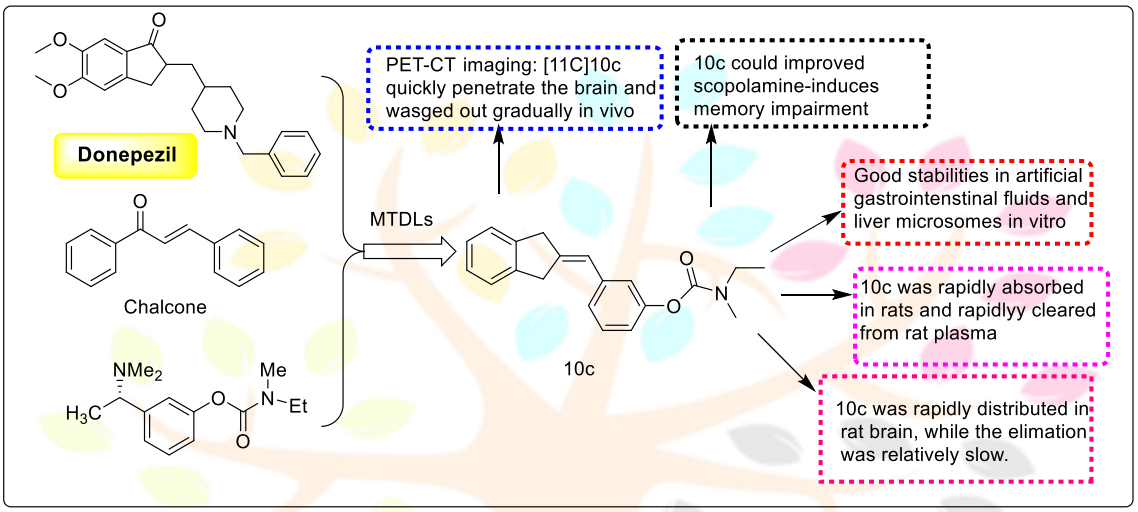


Figure 9: Novel hybrid molecule from Donepezil, chalcone and rivastigmine

5. Recent medicinal chemistry strategies to developed novel molecules as potential Anti-Alzheimer's agents

There are several medicinal chemistry approaches utilized in the discovery of the small molecules against different mechanisms of AD. For instance: AChE inhibitors approved by the Food and Drug Administration (FDA) include donepezil, rivastigmine, tacrine, and galantamine. These medications are now used to treat Alzheimer's disease (AD). These inhibitors have several undesirable side effects. Therefore, for the effective therapy, there is a huge demand for novel selective AChE inhibitors with fewer negative side effects. Thus, we described a novel approach of medicinal chemistry for the development of small molecules.[24]

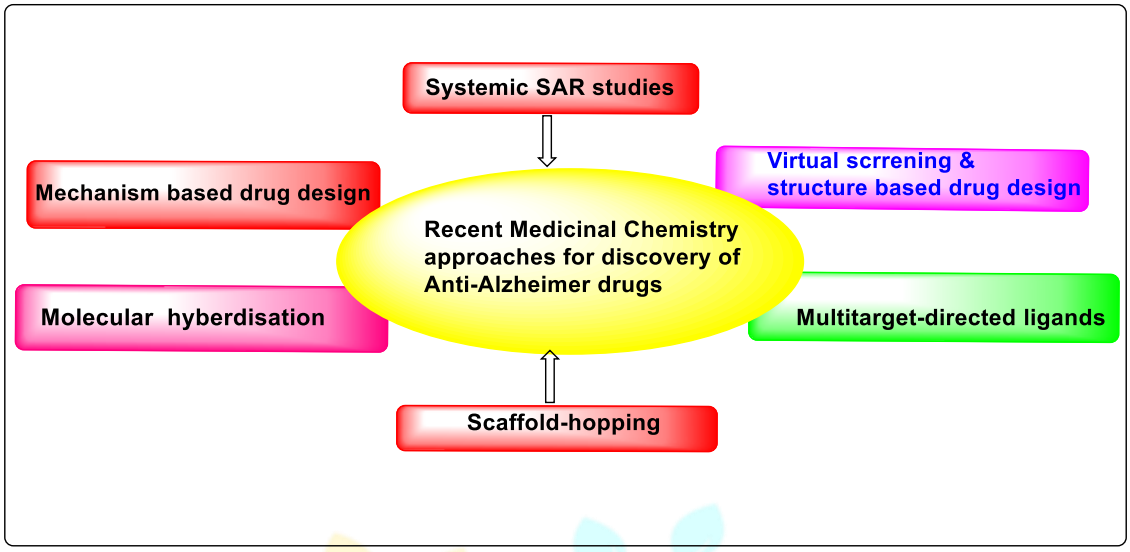


Figure 10: Several medicinal chemistry approaches for discovery of Anti-Alzheimer agents

To find innovative and selective BChE/AchE inhibitors, new medicinal chemistry approaches and methods can be used as follows.

5.1 Virtual Screening and structure-based drug design:

Structure-based virtual screening has recently established as a standard technique in pharmaceutical companies and academic institutions as a complementary technique to high-throughput screening for the early hit-finding phase.[31] Brus et al. discovered novel selective BChE inhibitor using a hierarchical virtual screening protocol and they found more than 40 compounds but only three molecules were identified selective BChE inhibitor with IC_{50} value 21.3nM. [25]Moreover, they have considered it as a potent molecule (Compund 4). These factors were considered when designing, synthesizing, and bio assaying a targeted library of amide derivatives of 4. In the picomolar concentration range, compound 5 among them demonstrated selective, reversible hBChE inhibition.[32] Sahin et al. identified novel AChE inhibitors using virtual screening medicinal chemistry approach. In their research, the National Cancer Institute (NCI) small molecule library, consisting of approximately 265,000 small molecules, was used to identify new hit compounds using a combination of ligand-based and structure-based virtual screening techniques. As a result, scientists found new promising hit chemicals in an extensive database that may be used to block AChE's enzyme activity.[26]

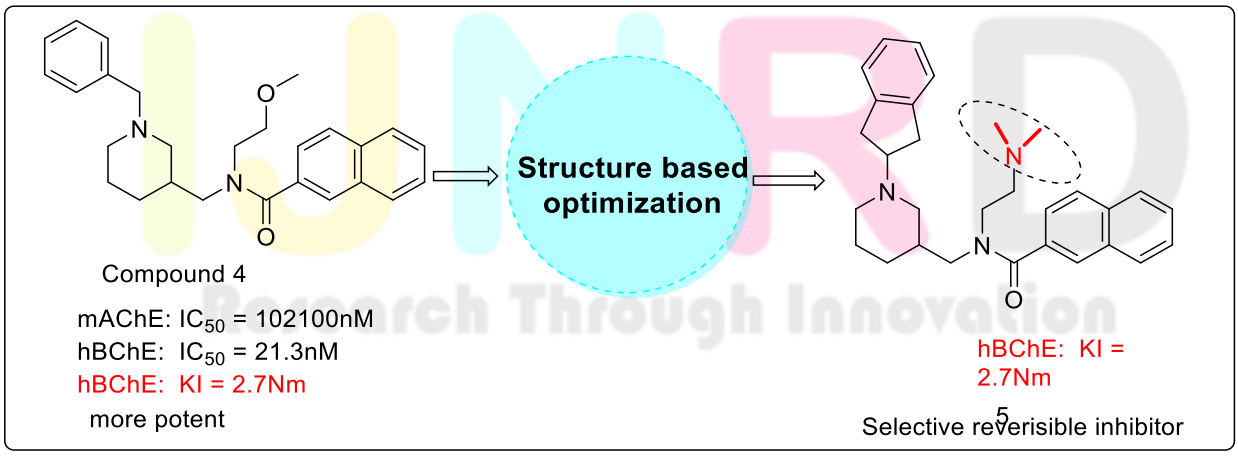


Figure 11: Structure based optimization to produced selective reversible inhibitors.

5.2 Analog based drug discovery of novel small molecules:

One of the most successful methods for producing more effective and selective BChE inhibitors is analog-based drug development, which involves systematic SAR examinations by decorating existing BChE inhibitors with peripheral substituents while keeping the basic

scaffold. For instance: discovery of tetrahydro carbazole benzyl pyridine **26** and tricyclic pyrazolo[1,5-*d*][1,4]benzoxazepin-5(6*H*)-one **27.** Ghobadian et al. identified and synthesized dual binding site series BuChE inhibitors based on 2,3,4,9-tetrahydro-1*H*-carbazole coupled benzyl pyridine moieties. And Compound **6i** (IC_{50} = 0.0880.0009M) was the most powerful BuChE inhibitor with mixed-type inhibition. Docking research demonstrated that 6i is a BuChE inhibitor with two binding sites. Furthermore, the pharmacokinetic features of 6i were consistent with Lipinski's rule. Additionally, they have also explained neuroprotective and β-secretase (BACE1) inhibition activities.[27]

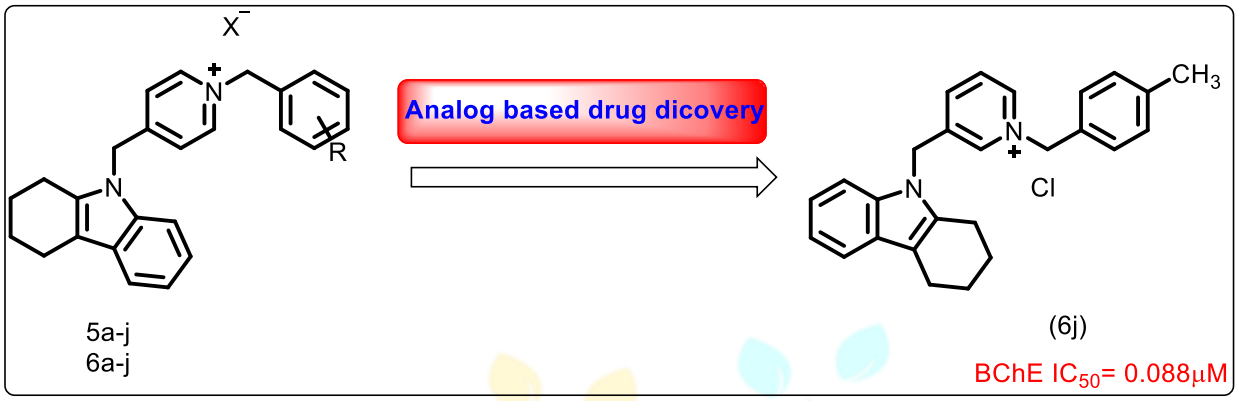


Figure 12: Analog based drug discovery of BChE inhibitors

Chen et al reported another potent selective BuChE inhibitor through analog drug discovery. They discussed the rationale behind their discovery of novel tricyclic scaffold of pyrazolo[1,5-*d*][1,4] benzoxazepin-5(6*H*)-one. And they synthesized several derivatives of this scaffold as potential ChE inhibitors.[28]

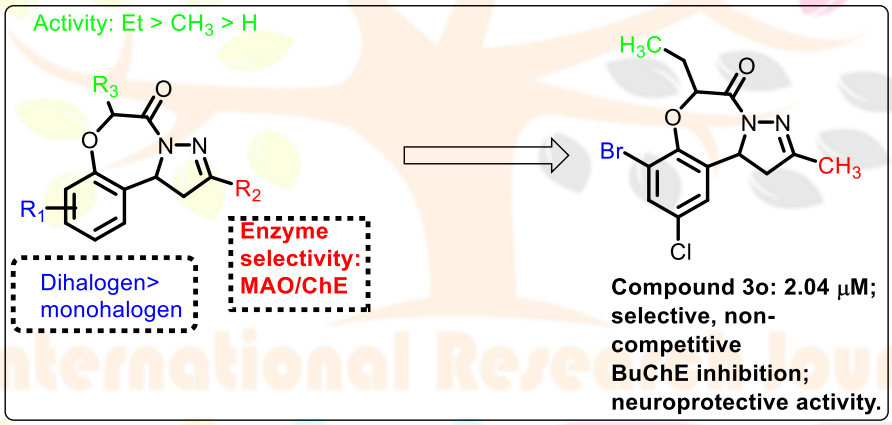


Figure 13: Discovery of tricyclic synthetic compounds

5.3 Molecular hybridization:

Molecular hybridization is a valuable drug development approach that involves mixing pharmacophoric fragments of distinct bioactive substances to create novel hybrids with higher affinity and potency than the parent molecules.[29] Chierrito et al. discovered chameleon like behavior of indolypiperdines scaffold complex with cholinesterase's targets. In their study they have reported the synthesis of a series of indolylpiperidines hybrids that optimize the NP61 structure, maintaining the indole nucleus but substituting the tacrine moiety of NP61 with the benzyl piperidine core seen in donepezil. Fortunately, they found this new class of indolylpiperidine compounds inhibited hBuChE in an extremely powerful and specific manner.[30]

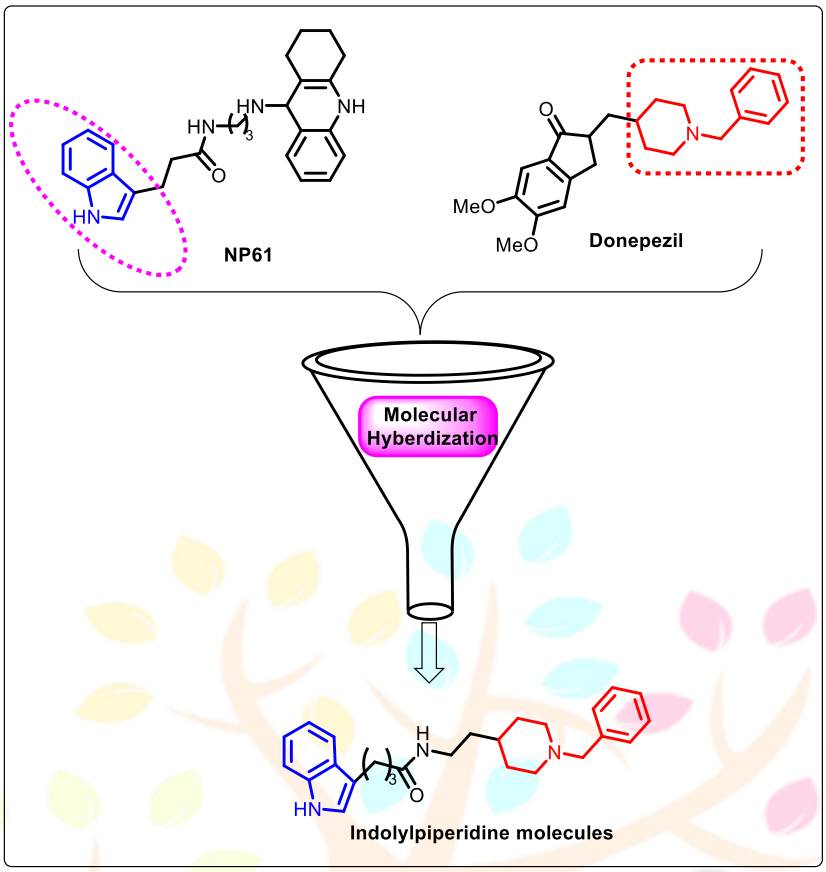


Figure14: Mixing of pharmacophoric fragments to design novel hybrids (Indolylpiperidine) for AD therapy

5.4 Multitarget-directed ligands:

In recent years, for the design of multifunctional BChE inhibitors, pharmacophores that chelate metal ions and/or inhibit monoamine oxidase (MAO), inhibit fatty acid amide hydrolase (FAAH), or act on several receptor systems have been grafted onto BChE inhibitors.[31]These multifunctional ligands are made up of two medicinal entities that are either linked by a spacer or fused into a single chemical entity. Several new multifunctional compounds with anti-AD effects have recently been produced by combining other well-known molecular scaffolds. These multifunctional ligands are made up of two medicinal entities that are either linked by a spacer or fused into a single chemical entity. Several new multifunctional compounds with anti-AD effects have recently been produced by combining other well-known molecular scaffolds. Moreover, using a networked targets method, the carbamate-containing compound **8** was found as a strong dual fatty acid amide hydrolase (FAAH)/BChE inhibitor with well-balanced nanomolar-level activity as shown in figure below.[32]

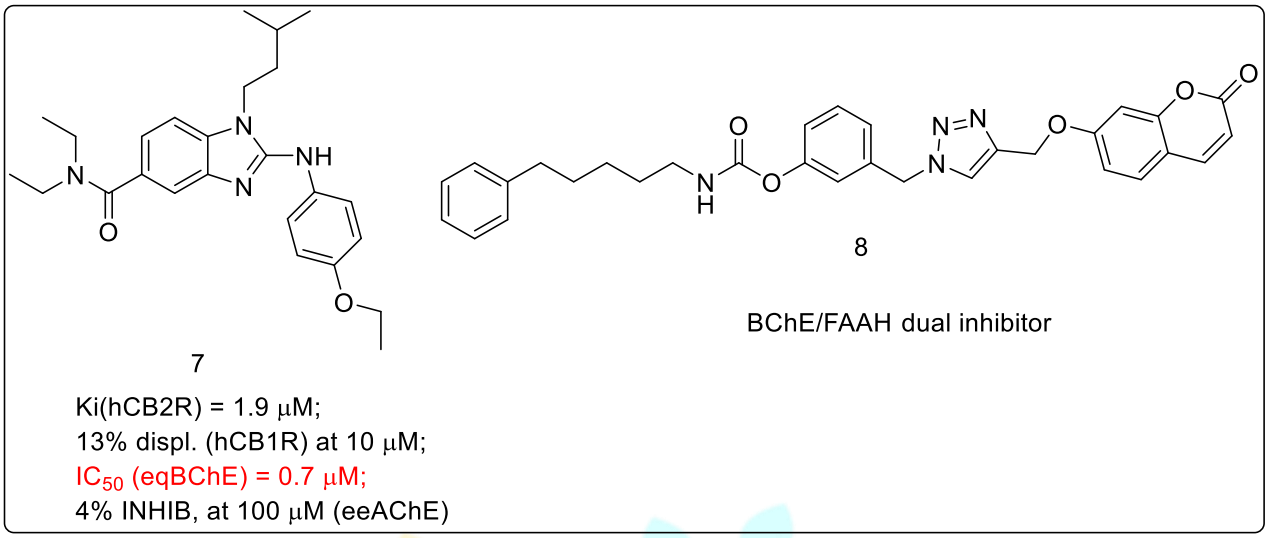


Figure 15: Designed multifunctional BChE inhibitors

6. Novel triazolo pyridopyrimidine scaffold for multitarget small molecules for Alzheimer's disease treatment

Researchers created several novel multitarget small molecules based on azaheterocycle scaffolds. No doubt, nitrogen-containing heterocycles have been frequently employed in medicinal chemistry in recent years to discover new bioactive compounds for Alzheimer's disease.[33] In fact, nitrogen-containing heterocycles have been frequently employed in medicinal chemistry in recent years to discover new bioactive compounds for Alzheimer's disease.[34],[35]

Zribi et al. discussed the synthesis of novel compounds by coupling a triazole ring with a pyridopyrimidine core, as well as their cholinesterase inhibition and antioxidant power, employing an antioxidant strategy connected with cholinesterase (ChE) inhibition based on a new scaffold. they discovered the most balanced triazolo pyridopyrimidine among the synthesized compounds, demonstrating micromolar inhibition of AChE with an IC_{50} of 1.32 M and high antioxidant activity, providing a new and extremely promising hit-triazolo pyridopyrimidine for AD therapy.[36]

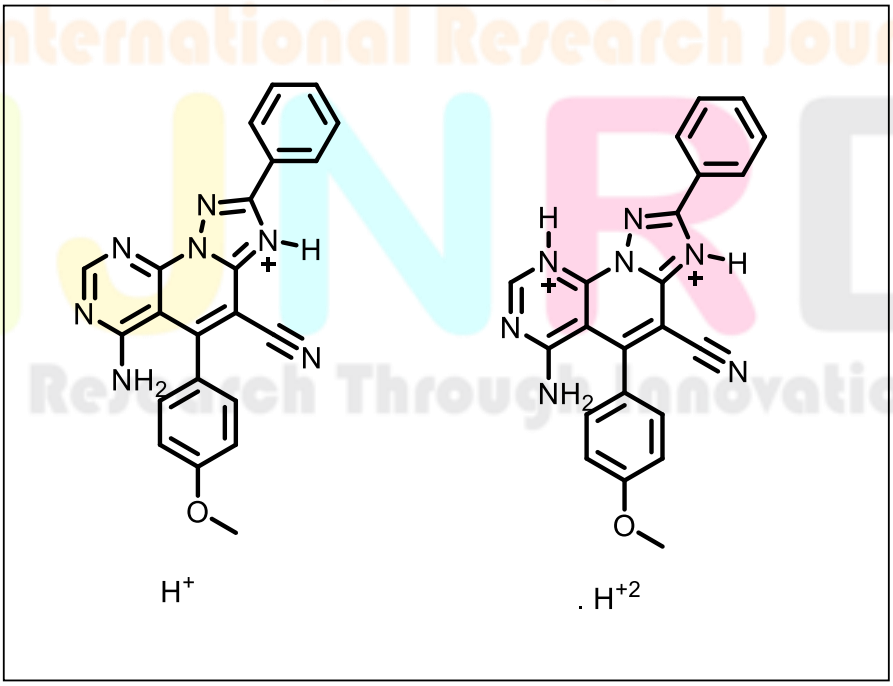


Figure16: Protonated states of triazolo pyridopyrimidine for AD therapy.

7. Recent updates of synthetic molecules developed from natural products as potential Anti-Alzheimer agents

Naturally occurring substances have been demonstrated to exhibit neuroprotective properties via nearly all molecular mechanisms. When focusing on natural product mixtures and extracts, the observed neuroprotective effects have typically been recognized as being obtained through anti-oxidative or anti-neuroinflammatory activities, preventing A and tau protein aggregation, and enhancing cholinergic signaling. Natural compounds that target multiple pathogenic targets may be able to reduce or even prevent the development and progression of Alzheimer's disease.[37]

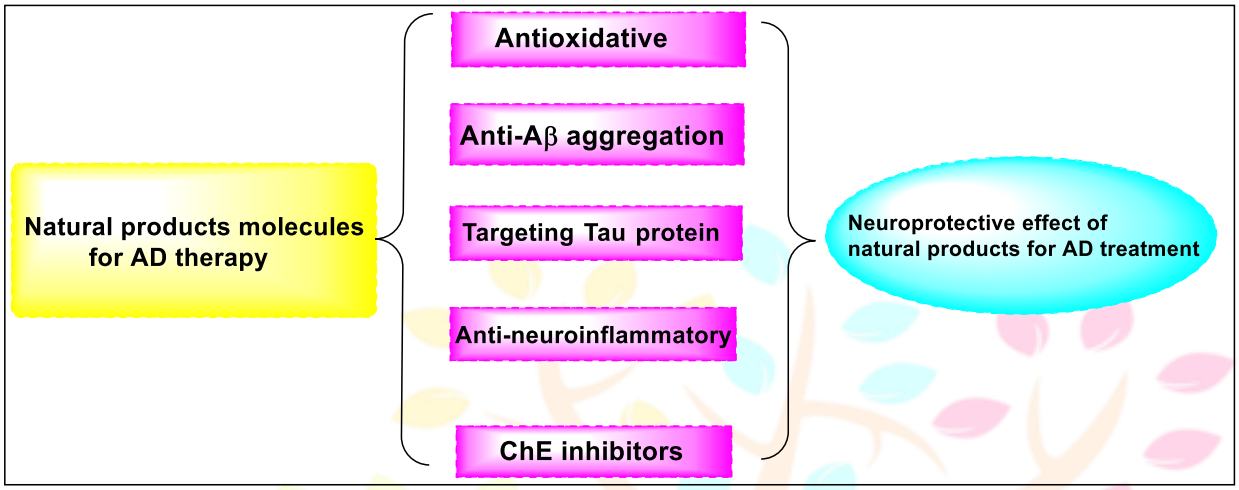


Figure 16: Neuroprotective effects assist with cognitive memory and functions.

The present treatment options, which are based on AChE inhibition or NMDA receptor antagonism, provide some symptomatic relief but have no effect on overall disease morbidity and death. The A method has been used in most modern drug discovery techniques, which have continued to fail in late-stage clinical trials.

Several years of research on such therapeutic targeting by all the major pharmaceutical firms (e.g., Merck, Pfizer, J&J, Eli Lilly, and Roche) have resulted in disastrous results, with 100% failure rates in phase III clinical trials. The only therapies available for Alzheimer's disease are those developed/approved during the 20 years of intensive study between 1981 (tacrine) and 2001 (galantamine). The modest effectiveness of these medications in certain individuals is linked with a slew of negative effects, all of which are documented on the AD website.[38]

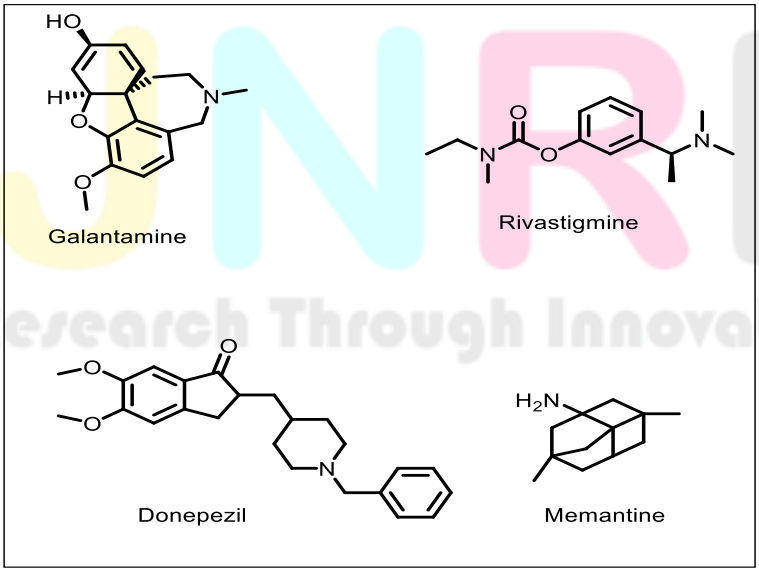


Figure 17: Current treatment options for Alzheimer's disease (AD). Natural products are at the forefront of Alzheimer's medication research.

The number of natural compounds from many structural classes that provide neuroprotection in neurodegenerative diseases is astounding. Several review articles, including those on phenolic acids and their derivatives, have been published. Flavonoids, alkaloids, monoterpenoids, and diterpenoids are among the molecules with therapeutic potential for Alzheimer's disease. -sheet-binding dyes such as Chrysamine G oligopeptides and polyphenols such as curcumin, myricetin, morin, quercetin, kaempferol (+)-catechin, ()-epicatechin, nordihydroguaiaretic acid, and tannic acid.[39],[40] for example, have been shown to target A aggregations and prevent A neurotoxicity. While most of the identified natural compounds exhibit antioxidant effects in several in vitro and in vivo experimental models, they have also been proven to mitigate as shown in figure 17.[41],[42]Moreover, several natural substances, including phenolics such as resveratrol, curcumin, hyperforin, and capsaicin, have also been demonstrated to reduce tau protein hyperphosphorylation and to have pharmacological activity in in vivo AD models.[43]

Natural products stated preventative benefits are the consequence of anti-oxidative or anti-neuroinflammatory actions, which work by preventing the accumulation of A and tau peptides and enhancing cholinergic signalling. Natural compounds that target many pathogenic pathways may be capable of reducing/delaying or even preventing the development and progression of Alzheimer's disease.[44]

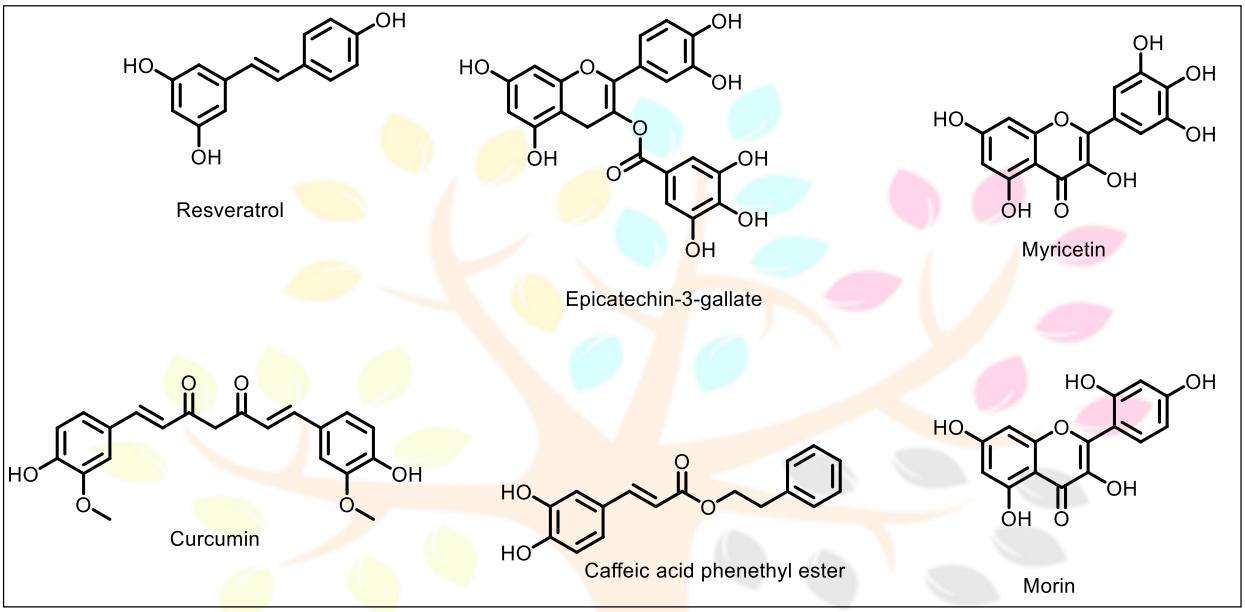


Figure 18: Natural products from many structural classes as potential anti Alzheimer agents.

8. Conclusion:

In this review, we have discussed the recent advancements in the chemistry of synthetic molecules for effective AD therapy. We presented the statistical data of the synthetic compounds that have been in clinical trials for the last 5 years. Meanwhile, we considered the importance of heterocyclic chemistry to design and develop novel compounds for an effective treatment of AD. A holistic overview of the recent advancements in harnessing the potential of heterocyclic compounds as a foundation for the next generation of anti-Alzheimer's drugs, thereby contributing to the advancement of therapeutic interventions for this complex disorder. These recent developments represent a significant stride in the field, highlighting the strategic utilization of diverse heterocyclic frameworks to engineer compounds possessing therapeutic potential against Alzheimer's disease. We described medicinal-chemistry strategies used to find BChE inhibitors, such as virtual screening and structure-based optimization, mechanism-based drug design, refining of existing BChE inhibitors through the design of heterobivalent ligands and homobivalent dimers, molecular hybridization, and Structure-activity relationship (SAR) research using a substituent-decorating technique, as well as multitarget ligand. We reviewed the natural product chemistry; several synthetic molecules were discovered from natural products. Natural compounds that target multiple pathogenic targets may be able to reduce or even prevent the development and progression of Alzheimer's disease. We found that natural substances and their bioactive phytochemicals have been demonstrated to offer great neuroprotective potential in the treatment and management of Alzheimer's disease (AD), with little negative side effects. An innovative synthetic method in Alzheimer's disease chemistry research may open the door for focused therapies and early detection, ultimately impacting the field with the promise of improved patient treatment and a deeper understanding of this dreadful disorder, revealing novel therapeutic agents and diagnostic tools.

9. Author Contribution:

J. Singh: Whole work plan, Idea, Coordination, and implementation, discussed initial five parts of this article.

S.Sabale: Discussed other four parts of this article.

10. Acknowledgment:

Authors thankful to Mr. Rushikesh and Mr. Pankaj for assisting during review writing and acknowledges the Sachdeva college of pharmacy, Mohali for their kind support.

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