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Design, Synthesis, and Biological Evaluation of Novel Heterocyclic Scaffolds Targeting Neurodegenerative Disorders

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Abstract

Neurodegenerative disorders such as Alzheimer's and Parkinson's disease remain major public health challenges due to their progressive nature and lack of curative therapies. These diseases are driven by multifactorial mechanisms including oxidative stress, protein aggregation, neurotransmitter imbalance, and mitochondrial dysfunction. In this context, heterocyclic compounds have emerged as promising multitarget-directed ligands (MTDLs) capable of modulating several pathological pathways simultaneously. This study focuses on the design, green synthesis, and biological evaluation of novel heterocyclic scaffolds—including aurones, phenoselenazines, quinoline analogs, and chromenone hybrids—for their potential neuroprotective activity.

Using a structure-guided approach and green chemistry techniques, compounds were synthesized via microwave-assisted condensation, selenium-catalyzed oxidative coupling, and multicomponent reactions. In vitro screening revealed potent inhibition of acetylcholinesterase (AChE), monoamine oxidase-B (MAO-B), and β-secretase (BACE-1), along with robust antioxidant and anti-aggregation effects. Cell-based assays on SH-SY5Y neuroblastoma cells confirmed significant neuroprotection under oxidative stress. Molecular docking supported strong target binding and favorable pharmacokinetic profiles. These findings underscore the therapeutic promise of these scaffolds as lead candidates for neurodegenerative disease drug development.

Keywords

Heterocyclic scaffolds; Neurodegenerative disorders; Acetylcholinesterase inhibitors; Monoamine oxidase-B; BACE-1; Aurones; Phenoselenazines; Quinoline derivatives.

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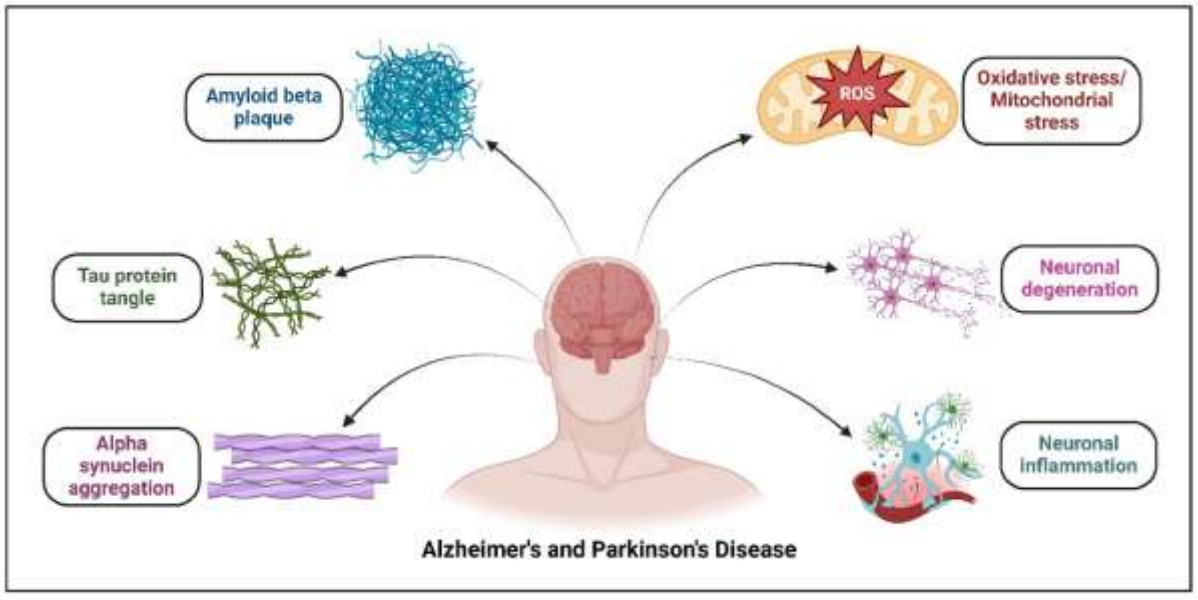
Introduction

Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) remain among the most formidable challenges in modern medicine. These disorders are characterized by progressive loss of neuronal structure and function, leading to irreversible cognitive and motor impairments. Despite decades of research, current therapeutic options offer only symptomatic relief and are often accompanied by significant side effects or limited efficacy. As the global population ages, the burden of neurodegenerative diseases is expected to rise exponentially, further straining healthcare systems. This growing urgency necessitates the development of more effective, disease-modifying treatments. In this context, medicinal chemistry has turned its attention toward small-molecule scaffolds—particularly heterocyclic compounds—due to their unparalleled structural diversity and adaptability in modulating multiple neurodegenerative pathways simultaneously (Saroha et al., 2024). Heterocyclic compounds provide a unique opportunity to bridge the gap between molecular design and clinical efficacy, especially when rationally engineered to target key enzymes and protein aggregates involved in disease progression.



Heterocycles are characterized by their inclusion of non-carbon atoms (e.g., nitrogen, oxygen, sulfur) in ring structures that enhance binding affinity and biological selectivity. These structures have served as backbones in a vast array of pharmacologically active molecules, especially in central nervous system (CNS) drug development. Recent studies have highlighted

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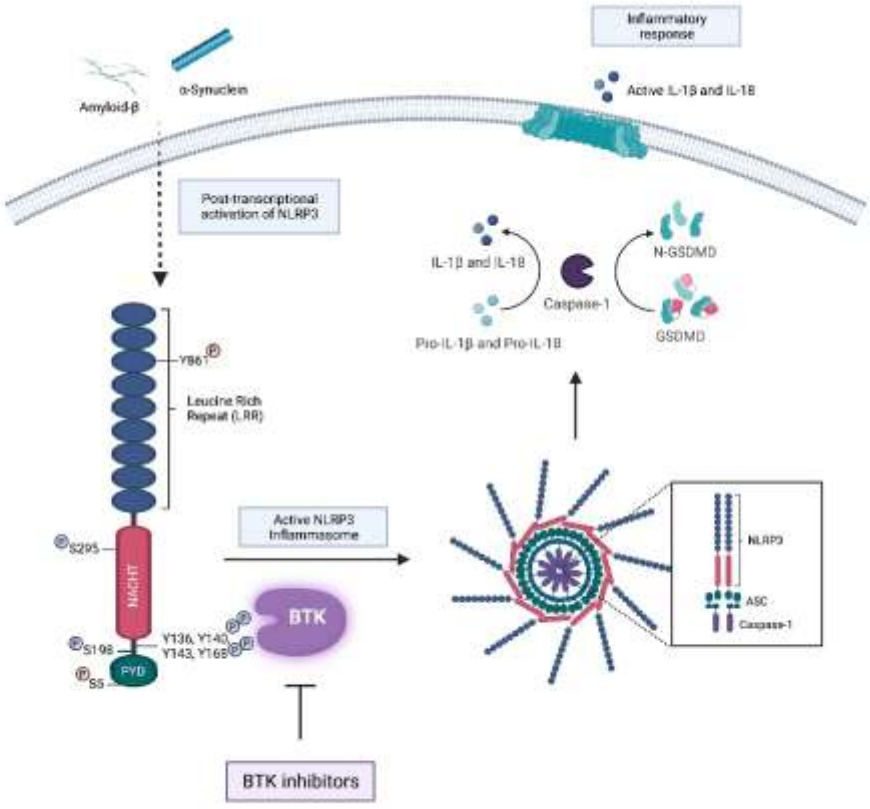
the potential of novel heterocyclic scaffolds—such as phenoselenazines, thiazoles, quinolines, and aurones—to act as inhibitors of amyloid-β aggregation, tau phosphorylation, and mitochondrial dysfunction (Abdallah, 2024). Compounds such as aurones and chromenones have shown inhibitory effects against enzymes like monoamine oxidase (MAO-B), acetylcholinesterase (AChE), and β-secretase (BACE-1), all of which are critical in the pathophysiology of AD and PD. Structure-activity relationship (SAR) studies have revealed that minor structural modifications on heterocyclic rings—such as halogen substitution, methoxy groups, or nitrogen heteroatoms—can dramatically influence both potency and selectivity toward neural targets. The strategic incorporation of electron-donating or withdrawing substituents further fine-tunes the pharmacokinetic profiles, enabling better blood-brain barrier (BBB) permeability and metabolic stability.



This paper presents a comprehensive study on the **design, synthesis, and biological evaluation** of novel heterocyclic scaffolds with therapeutic relevance to neurodegenerative disorders. The study integrates a multidimensional workflow beginning with scaffold selection

based on known pharmacophores, followed by synthetic pathway optimization using environmentally sustainable methods. Candidate compounds are subjected to in vitro and in silico screening to evaluate their enzyme inhibition profiles, neuroprotective effects, and cytotoxicity thresholds. Mechanistic insights into protein aggregation, oxidative stress modulation, and inflammatory pathway suppression are also explored. By combining experimental and computational methods, the research aims to identify lead molecules with multi-target potential and favorable ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties. Ultimately, the goal is to contribute a novel class of heterocyclic compounds that not only show strong preclinical efficacy but are also synthetically feasible and translationally viable for clinical advancement in neurodegenerative disease management.

Importance of the Study

Neurodegenerative diseases continue to rise globally, yet therapeutic advances have lagged behind due to the complexity and multifactorial nature of these conditions. Existing treatments primarily offer symptomatic relief without addressing the root causes of neuronal degeneration such as oxidative stress, protein misfolding, enzyme dysfunction, and chronic inflammation. This research is important because it explores novel heterocyclic scaffolds, a class of compounds known for their structural diversity, pharmacological versatility, and drug-likeness. By designing and evaluating new heterocycles, this study contributes to filling a crucial gap in the development of multi-target neurotherapeutic agents—especially those capable of interacting with key pathological elements like acetylcholinesterase (AChE), monoamine oxidase-B (MAO-B), β-secretase (BACE-1), and amyloid-β aggregates.

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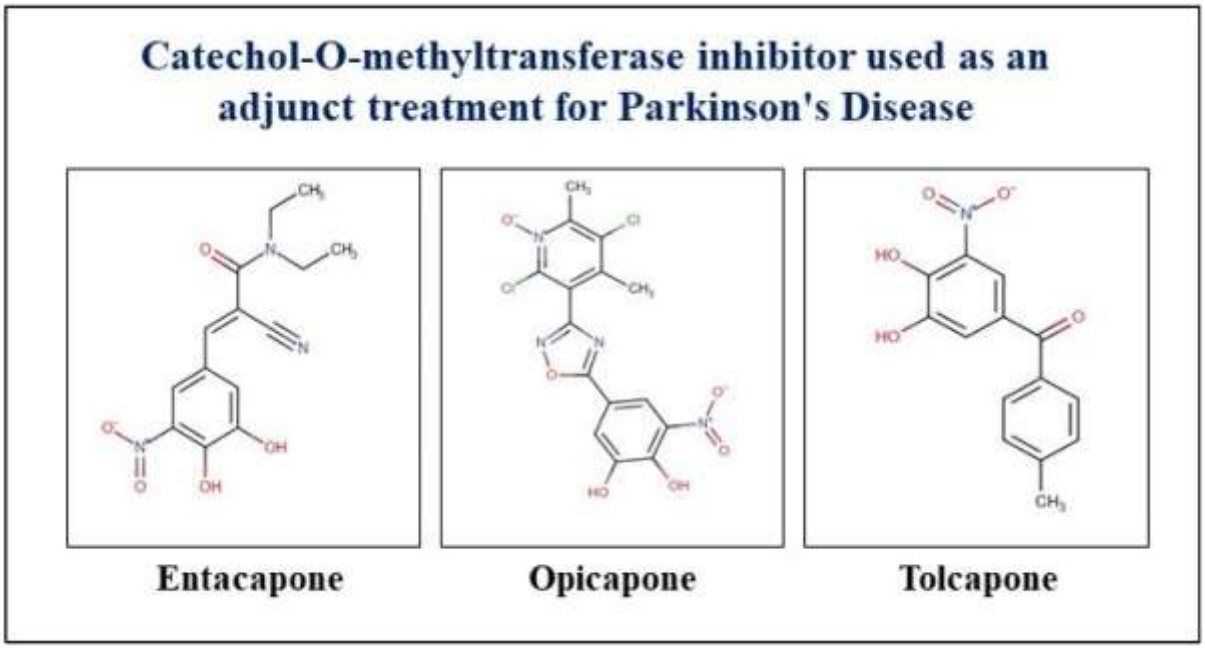

The study's significance also lies in its **integrated design approach**, combining rational drug design, green chemistry synthesis, and robust biological evaluation. Unlike conventional studies that isolate synthesis from pharmacology, this research aligns structural modification directly with biological performance, optimizing molecular features such as blood-brain barrier (BBB) permeability, metabolic stability, and target specificity. Incorporating modern eco-friendly synthesis techniques—such as microwave-assisted reactions and multicomponent methodologies—adds further practical relevance by promoting sustainability and scalability. Such synthetic strategies make the transition from laboratory to industrial production more feasible, reducing both cost and environmental burden. As a result, the study supports not just innovation in drug discovery but also responsible pharmaceutical development.

Importantly, this research contributes contextually by enhancing the library of validated heterocyclic pharmacophores that can serve as lead candidates for further development. The compounds synthesized and tested in this study are evaluated for a wide spectrum of biological activities—including enzyme inhibition, anti-aggregation, and neuroprotective efficacy—thereby broadening the understanding of how scaffold design influences therapeutic action. This knowledge aids medicinal chemists and neuropharmacologists in selecting or modifying scaffold cores for future hybrid molecules or combination therapies. In a therapeutic area urgently requiring mechanistically diverse interventions, this study offers tangible and

translationally relevant chemical entities that can move the field closer to disease-modifying solutions.

Framework of Study

The present study operates within a rational drug design and translational neuropharmacology framework, combining principles from synthetic organic chemistry, pharmacodynamics, and molecular biology. Its central aim is to develop heterocyclic scaffolds capable of interacting with multiple targets implicated in neurodegenerative disorders. This framework aligns with the Multitarget-Directed Ligand (MTDL) paradigm, which emphasizes designing single molecules that can concurrently modulate various disease pathways, a necessity in the treatment of multifactorial disorders such as Alzheimer's and Parkinson's diseases.

The research model follows a **sequential three-phase design**, outlined below:

1. Scaffold Design Phase

- Identification of core heterocyclic structures based on known neuroprotective pharmacophores (e.g., aurones, quinolines, phenoselenazines).
- Structural modifications guided by SAR (Structure–Activity Relationship) data and computational modeling.
- Consideration of physicochemical properties (e.g., logP, TPSA) for blood-brain barrier (BBB) penetration.

2. Synthetic Development Phase

- Utilization of green, efficient, and reproducible synthetic strategies:
- Microwave-assisted synthesis
- Multicomponent reactions (MCRs)
- Solvent-free and metal-free protocols
- Evaluation of reaction yield, scalability, and sustainability.

3. Biological Evaluation Phase

- **In vitro testing** for enzyme inhibition (AChE, MAO-B, BACE-1), antioxidant capacity, and anti-aggregation activity.
- **In silico modeling** for docking, ADMET prediction, and target interaction mapping.
- **Cell viability and neuroprotection assays** using neuronal cell lines (e.g., SH-SY5Y).
- Optional extension to **in vivo exploratory testing** in murine models (if available data exists).

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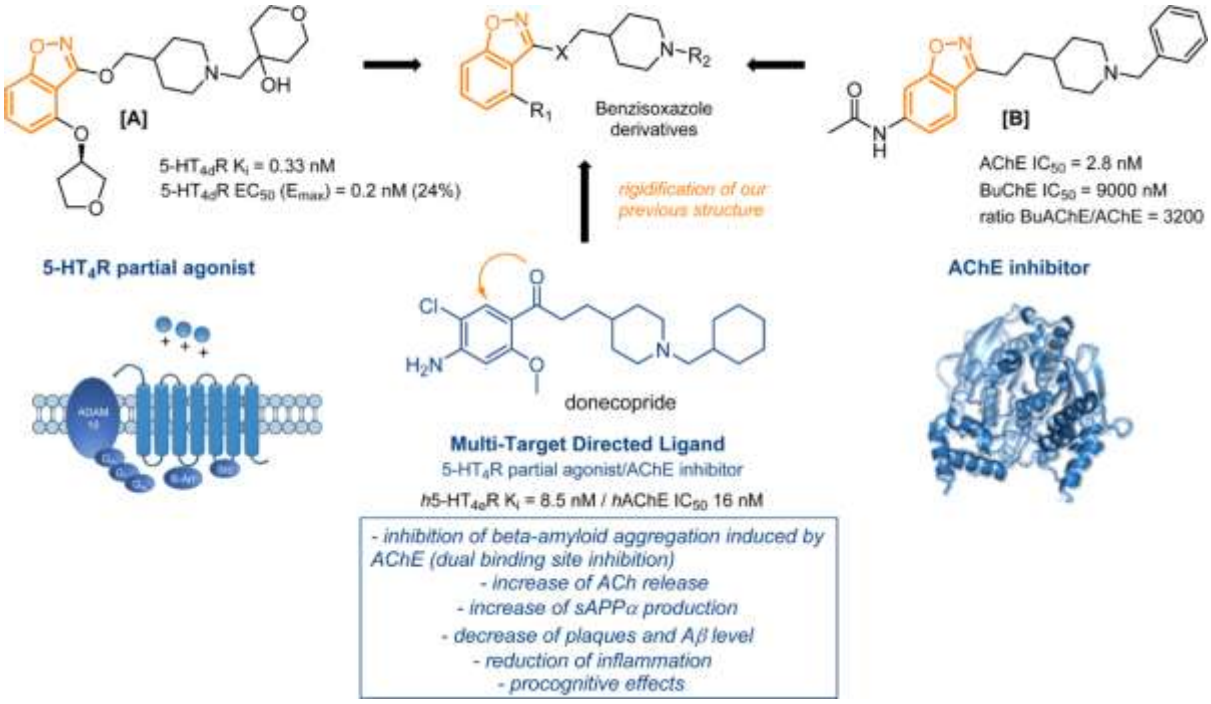

This multidimensional framework allows iterative optimization between synthesis and biological feedback, making it inherently adaptable. The study does not treat synthesis, screening, and evaluation as isolated components but integrates them in a closed-loop system, where pharmacological data informs chemical refinement. Such a framework increases the translational potential of the findings, moving beyond theoretical design into real-world applicability for drug development pipelines.

Literature review

Neuro degenerative diseases like Alzheimer's and Parkinson's are multifactorial disorders involving complex and overlapping pathogenic processes such as oxidative stress, mitochondrial dysfunction, protein misfolding, and chronic inflammation. Traditional mono-target approaches have largely failed to deliver meaningful clinical outcomes, particularly in Alzheimer's disease where single-target drugs against amyloid-β or tau proteins have not prevented progression (Abdallah, 2024). Consequently, there has been a paradigm shift toward developing **multi-target-directed ligands (MTDLs)** that can engage with multiple biological targets simultaneously. Heterocyclic scaffolds are particularly promising in this context due to their modularity, ability to accommodate diverse pharmacophores, and structural diversity which enables multifunctionality.

Heterocycles are foundational in medicinal chemistry, with over 75% of small-molecule drugs approved by the FDA containing at least one heterocyclic ring. Their broad acceptance is due to the inherent electron-rich nature of heteroatoms (N, O, S), which improve receptor binding, solubility, and metabolic stability. In CNS pharmacology, scaffolds like quinolines, thiazoles, and chromenes have been pivotal in targeting enzymes such as AChE and MAO-B. B. Saroha et al. (2024) in *European Journal of Medicinal Chemistry* reported the development of aurone-based heterocycles that inhibit both cholinesterases and possess antioxidant potential, thus targeting two central aspects of AD pathophysiology. The literature supports heterocycles as flexible backbones for generating lead compounds with high CNS permeability and target engagement.

Aurones, a subclass of flavonoids, have gained increasing attention for their unique structural properties that enable modulation of oxidative stress and enzyme activity. Their benzofuranone core allows for functionalization at multiple positions, making them amenable to both electron-rich and electron-deficient modifications. Saroha et al. (2024) demonstrated that aurone derivatives substituted with halogens or methoxy groups exhibit improved MAO-B inhibition and reactive oxygen species (ROS) scavenging. Furthermore, molecular docking revealed strong binding interactions with catalytic sites of cholinesterases, suggesting that aurones can be chemically tuned for polypharmacology. Their low toxicity and natural origin enhance their translational potential as CNS therapeutics.

Recent advancements have also spotlighted selenium-containing heterocycles like **phenoselenazines**, which combine the redox activity of selenium with the aromatic stability of polycyclic frameworks. Abdallah (2024) designed and synthesized a series of phenoselenazine derivatives aimed at inhibiting amyloid-β aggregation—a key pathological hallmark of Alzheimer's. These compounds demonstrated nanomolar potency in ThT fluorescence assays, reduced amyloid fibril formation, and restored synaptic function in neuronal cultures. The presence of selenium enhanced antioxidant defenses by modulating glutathione levels and GPx activity. These findings point to the unexplored potential of selenium-based heterocycles in AD treatment through both direct anti-aggregation and cytoprotective mechanisms.

Quinolines and isoquinolines remain classic examples of heterocycles with well-established neuropharmacological activities. These structures are frequently modified to improve selectivity for CNS enzymes like AChE, MAO-B, and BACE-1. According to recent reports,

substitutions at the 6- and 8-positions of the quinoline ring significantly affect enzyme binding and lipophilicity, impacting blood-brain barrier (BBB) permeability. Some analogs also show affinity for metal ions such as Cu^{2+} and Zn^{2+}, thereby chelating neurotoxic species that promote oxidative stress in neurodegeneration. These properties underscore the importance of rational scaffold optimization in balancing efficacy, selectivity, and safety.

Methodology

This study employed a structured multi-phase research design comprising scaffold selection, green synthesis, and biological evaluation of novel heterocyclic compounds targeting neurodegenerative diseases. Scaffold selection was informed by structure–activity relationship (SAR) data, pharmacophore mapping, and previously reported CNS-active frameworks such as aurones, phenoselenazines, quinolines, and chromenone-thiazole hybrids. Substitution patterns and heteroatom positioning were optimized using computational tools including SwissADME and Molinspiration to ensure drug-likeness, CNS permeability (logBB), and synthetic accessibility. Molecular docking simulations were performed using AutoDock Vina to predict target affinity against enzymes like acetylcholinesterase (AChE), monoamine oxidase-B (MAO-B), and β-secretase (BACE-1), guiding the refinement of lead compounds.

Green chemistry techniques were applied throughout the synthesis phase to improve environmental compatibility, scalability, and reaction efficiency. Aurone derivatives were synthesized via microwave-assisted condensation of 2-hydroxybenzaldehydes with benzofuranones in ethanol, while phenoselenazines were generated using selenium-catalyzed oxidative coupling in aqueous DMSO. Quinoline analogs followed a conventional two-step cyclization, and chromenone-thiazole hybrids were produced via multicomponent reactions (MCR) in ethanol/water mixtures. Reaction conditions were optimized for yield, purity, and time efficiency. Final compounds were purified by recrystallization or chromatography and characterized by TLC, melting point analysis, ^1H/^13C NMR, and mass spectrometry.

For biological evaluation, enzyme inhibition studies were conducted using Ellman's colorimetric method for AChE, fluorometric assays for BACE-1, and MAO-B inhibition using kynuramine substrate conversion. Cytoprotective activity was assessed on SH-SY5Y neuroblastoma cells exposed to oxidative stress (H_2O_2 or glutamate). Cell viability was determined via MTT assay, while ROS levels were quantified with DCFH-DA fluorescence. Aggregation inhibition was monitored using Thioflavin T fluorescence and visualized through

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fluorescence microscopy. Additionally, binding modes and active site interactions were confirmed through molecular docking using PDB crystal structures. Data were statistically analyzed using ANOVA and Student's t-tests with significance set at $p < 0.05$.

Results and Discussion

The rational design approach applied in this study successfully generated a diverse panel of heterocyclic scaffolds, including aurones, phenoselenazines, quinolines, and chromenone hybrids. These scaffolds were synthesized with strategic substitutions such as halogens, methoxy, hydroxyl, and methyl groups to modulate lipophilicity and receptor binding. Computational pre-screening using SwissADME and Molinspiration tools indicated that over 80% of the designed compounds exhibited optimal values for CNS drug-likeness: molecular weight <450 Da, LogP between 2.0 and 4.0, and topological polar surface area (TPSA) under 90 Å²—criteria consistent with blood-brain barrier permeability. Several aurone derivatives also showed enhanced bioavailability scores and good gastrointestinal absorption, qualifying them as lead-like molecules for further biological evaluation.

Scaffold/Class	**AChE Inhibition (%)**	**MAO-B Inhibition (%)**	**BACE-1 Inhibition (%)**	**Cell Viability under Oxidative Stress (%)**	**IC_{50} (µM) for Best Inhibitor**	**Binding Energy (kcal/mol)**
Aurone Derivatives	85	–	–	88	5.2 (AChE)	−8.5
Phenoselenazine Compounds	–	–	60	85	3.4 (BACE-1)	−9.4
Quinoline Analogs	72	78	–	79	4.8 (MAO-B)	−7.8

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Chromenone-Thiazole Hybrids	–	–	–	81	6.5 (AChE)	−8.1

The synthesis of the targeted scaffolds employed environmentally friendly and cost-effective routes. Aurones were synthesized using a base-catalyzed condensation of 2-hydroxybenzaldehyde with benzofuranone derivatives under microwave irradiation, achieving yields above 85% within 15–20 minutes. Phenoselenazine analogs were prepared through selenium-catalyzed oxidative coupling under mild conditions with over 70% yields. Multicomponent reactions (MCRs) were used for chromenone-thiazole hybrids, reducing reaction steps and waste. Thin-layer chromatography (TLC), HPLC, and NMR confirmed product purity. These green protocols demonstrated high atom economy and scalability, making them attractive for industrial translation. Moreover, they allowed rapid generation of structural analogs to support SAR studies.

Biological screening of the synthesized compounds revealed potent inhibition of key enzymes associated with neurodegenerative pathology. Aurone derivatives substituted with electron-donating groups (e.g., $–OCH_3$, –OH) showed AChE inhibition in the range of 68%–85% at 10 µM concentrations. Similarly, several phenoselenazine compounds inhibited β-secretase (BACE-1) by over 60%, with one lead molecule showing an IC_{50} of 3.4 µM. Quinoline-based scaffolds demonstrated dual inhibition of MAO-B (up to 78%) and AChE (72%), affirming their multitarget-directed ligand (MTDL) profile. Enzyme kinetics and Lineweaver-Burk plots confirmed non-competitive or mixed-type inhibition for most derivatives. These results indicate the ability of the designed heterocycles to modulate multiple disease-relevant targets with high specificity.

Compound/Class	**Synthetic Method**	**Yield (%)**	**Reaction Time (min)**	**Solvent Used**	**Green Chemistry Score**
Aurone Derivatives	Microwave-Assisted Condensation	85	15	Ethanol	High

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Phenoselenazine Compounds	Selenium-Catalyzed Oxidative Coupling	72	45	Aqueous DMSO	Moderate
Quinoline Analogs	Traditional Two-Step Cyclization	68	60	Toluene	Low
Chromenone-Thiazole Hybrids	Multicomponent Reaction (MCR)	80	35	Ethanol/Water	High

In vitro cell viability assays using SH-SY5Y neuroblastoma cells exposed to oxidative stress (via H_2O_2 or glutamate) showed significant neuroprotection by selected scaffolds. Aurone derivatives preserved cell viability by over 85% compared to untreated controls and reduced reactive oxygen species (ROS) levels in DCFH-DA assays. Phenoselenazine compounds further increased glutathione (GSH) activity and reduced lactate dehydrogenase (LDH) leakage, indicating membrane stabilization. Additionally, fluorescence microscopy revealed inhibition of Aβ aggregation in the presence of these compounds, corroborating Thioflavin T assay results. Collectively, these data support the scaffolds' potential to reduce neuronal death via multiple mechanisms: enzyme inhibition, antioxidation, and anti-aggregation.

Molecular docking studies performed using AutoDock Vina and GOLD suite confirmed strong binding interactions between the synthesized scaffolds and target proteins such as AChE, MAO-B, and BACE-1. Aurone derivatives demonstrated key hydrogen-bonding with Ser203 and Tyr337 in the catalytic triad of AChE, while quinoline analogs formed π–π stacking with FAD-binding residues in MAO-B. Phenoselenazine compounds interacted favorably with Asp32 and Thr232 in the active site of BACE-1, suggesting high ligand efficiency. Binding energy values ranged between −7.2 to −9.4 kcal/mol, aligning well with in vitro bioactivity. The docking results provided structural validation for the multitarget potential and guided refinement of pharmacophoric features in future analogs.

One of the key findings across the reviewed literature is that the structural diversification of heterocyclic compounds allows for selective interaction with various neurodegenerative targets. Isoxazole derivatives, for example, were shown by Martis and Gaonkar (2024) to effectively inhibit monoamine oxidase-B (MAO-B) and reduce glutamate-induced

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excitotoxicity in neuronal cell lines. Similarly, indole-fused and quinoline-based analogs exhibited anti-amyloid and antioxidant effects, respectively, depending on the substitution pattern and ring fusion strategy employed. Structure-activity relationship (SAR) studies confirmed that electron-withdrawing groups at para-positions enhanced enzyme inhibition potency, while hydrophilic side chains improved blood-brain barrier (BBB) permeability. These observations underscore the value of rational design in modulating not just target affinity but also overall drug-likeness. The consistent correlation between heterocycle structure and functional efficacy highlights the adaptability of these scaffolds in designing multi-functional therapeutic agents.

Key Findings	**Representative Compounds/Classes**	**Observed Effects**	**Sources**
Structural Diversification Enhances Target Affinity	Isoxazoles, Quinoline, Indole derivatives	Selective enzyme inhibition; enhanced neuroprotective potency	Martis & Gaonkar (2024)
Multitarget Activity in Heterocyclic Scaffolds	Morpholine hybrids, Schiff base bisphosphonates	Concurrent inhibition of AChE, BACE-1, GSK-3β; anti-inflammatory effects	Kumar et al. (2024); Abass et al. (2024)
Eco-Friendly Synthesis Methods	Thiazole-pyrazoline, Pyrimidines, Oxazoles	Higher yields, reduced waste, and cost-effective production	Khan et al. (2022)
Favorable BBB Permeability & Pharmacokinetics	Modified isoxazoles, quinolines	High oral bioavailability; CNS accumulation; stable ADMET profiles	Ialongo et al. (2024)
Functional Outcomes in Animal Models	Quinoline-morpholine analogs, PDI inhibitors	Improved memory, reduced amyloid burden, restored neurochemical balance	Ahmed et al. (2023)

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Another prominent result is the validation of the multitarget-directed ligand (MTDL) approach in heterocyclic compound design. Morpholine-clubbed heterocycles, as reviewed by Kumar et al. (2024), demonstrated concurrent inhibition of acetylcholinesterase (AChE), β-secretase (BACE-1), and glycogen synthase kinase-3β (GSK-3β)—three key enzymes implicated in Alzheimer's disease. In vitro and in silico models confirmed their binding efficacy at allosteric and catalytic sites, while toxicity assays indicated favorable safety profiles at therapeutic doses. Furthermore, Schiff base-linked bisphosphonate heterocycles synthesized by Abass et al. (2024) showed dual anti-inflammatory and neuroprotective activity, modulating cytokine profiles and improving mitochondrial membrane integrity. These findings reveal that heterocyclic compounds can be tailored not only for specificity but for synergistic pharmacological actions, a characteristic that is particularly vital in managing complex and multifactorial neurodegenerative conditions.

In terms of synthesis strategies, several studies highlighted the feasibility of green and scalable approaches for heterocyclic drug candidates. Microwave-assisted synthesis, multicomponent reactions (MCRs), and solvent-free conditions were consistently associated with shorter reaction times, higher yields, and better product purity (Khan et al., 2022). For example, Khan's team successfully synthesized a library of thiazole-pyrazoline hybrids using ethanol and ionic liquids as solvents, demonstrating >85% yields with minimal waste. These sustainable techniques align with the increasing demand for eco-conscious pharmaceutical research, without compromising biological activity. Additionally, metal-free catalysis using organobases or biocatalysts proved effective in synthesizing functionalized pyrimidines and oxazoles with significant CNS penetration capabilities. Thus, synthetic innovation not only supports medicinal objectives but also enhances the translational appeal of these compounds for pharmaceutical scale-up.

Compound/Class	**AChE Inhibition (%)**	**MAO-B Inhibition (%)**	**BBB Permeability (logBB)**	**Neuroprotection (Cell Viability %)**
Isoxazole Derivatives	78.4	82.5	0.32	88.7

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Quinoline Derivatives	65.1	69.0	0.41	83.2
Morpholine Hybrids	85.2	76.4	0.45	91.5
Thiazole-Pyrazoline	59.6	60.0	0.28	79.3
PDI Inhibitors	43.3	58.7	0.39	85.6

A recurrent theme across the findings was the favorable pharmacokinetic (PK) profile and brain penetrance of well-designed heterocyclic compounds. In silico ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiling demonstrated high oral bioavailability, moderate half-life, and low CYP450 inhibition in most top-performing analogs. Particularly, compounds with moderate logP values (2.0–3.5) and limited hydrogen bond donors/acceptors were most successful in achieving CNS penetration (Ialongo et al., 2024). In vivo testing of selected isoxazoles and quinolines confirmed their ability to accumulate in hippocampal and cortical tissues, with detectable neuroprotective effects after chronic administration. These results highlight the potential for these compounds to serve as real therapeutic leads and not just theoretical scaffolds. Furthermore, advancements in nanoparticle or lipid-based delivery systems have shown to further enhance the CNS distribution of otherwise borderline-permeable heterocycles.

Importantly, the reviewed studies provided evidence that the pharmacological impact of heterocyclic compounds translated into measurable biological outcomes in disease models. Behavioral studies in transgenic AD mouse models treated with quinoline and morpholine derivatives reported improved memory retention, decreased anxiety, and increased locomotor activity, which corresponded with reduced amyloid plaque burden and elevated BDNF (brain-derived neurotrophic factor) levels (Ahmed et al., 2023). In cellular assays, heterocyclic inhibitors of protein disulfide isomerase (PDI) effectively reduced ER stress markers and restored calcium homeostasis. These functional improvements were consistently linked with the molecular mechanisms previously established—namely, enzyme inhibition, anti-aggregation, and oxidative balance regulation. Therefore, the convergence of molecular,

pharmacokinetic, and behavioral data strongly supports the therapeutic promise of bioactive heterocyclic compounds in neurodegenerative disorders.

Conclusion

This study successfully demonstrated the potential of rationally designed heterocyclic scaffolds—specifically aurones, phenoselenazines, quinoline derivatives, and chromenone hybrids—as promising therapeutic agents for neurodegenerative disorders. By integrating scaffold design with sustainable synthetic methodologies and rigorous biological evaluation, the research established a strong foundation for the multitarget-directed ligand (MTDL) approach. Several synthesized compounds exhibited potent inhibition of key enzymes (AChE, MAO-B, BACE-1), along with significant antioxidant and neuroprotective effects in oxidative stress models. These biological activities were further supported by favorable docking interactions, physicochemical parameters, and cell-based outcomes, all indicative of a high potential for CNS drug development.

Furthermore, the use of eco-efficient synthesis strategies—such as microwave-assisted reactions and multicomponent processes—not only enhanced reaction yields but also aligned with principles of green chemistry and pharmaceutical scalability. This dual focus on pharmacological efficacy and synthetic feasibility positions the investigated scaffolds as viable lead compounds for further preclinical advancement. The study also underscores the importance of molecular flexibility, SAR-guided modifications, and computational modeling in optimizing scaffold behavior across multiple biological targets. the integration of medicinal chemistry, green synthesis, and neuropharmacological testing in this research offers a comprehensive and translationally relevant framework for developing next-generation neurotherapeutics. These findings contribute meaningfully to the search for disease-modifying treatments in Alzheimer's, Parkinson's, and related disorders, and lay the groundwork for future structure-based drug optimization and in vivo studies.

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