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Artificial Intelligence-Assisted Green Multi-Component Synthesis and Optimization of Fused Heterocyclic Scaffolds for Neuroprotective Drug Discovery

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Abstract: *The convergence of artificial intelligence, green chemistry, and multi-component reaction (MCR) methodologies is revolutionizing the discovery of neuroprotective agents from fused heterocyclic scaffolds. This paper critically examines the current landscape of AI-assisted synthesis planning, green synthetic strategies, and MCR-based approaches for generating fused heterocyclic compounds with neuroprotective potential. Recent advances in AI-driven retrosynthesis platforms, including template-based and template-free approaches, have demonstrated remarkable capabilities in predicting viable synthetic routes while optimizing for cost, temperature, and environmental sustainability. Concurrently, multi-component reactions such as Ugi, Passerini, Petasis, and Hantzsch reactions have proven highly effective for rapidly generating diverse fused heterocyclic libraries with multitarget-directed ligand (MTDL) properties relevant to neurodegenerative diseases. The integration of green chemistry principles, including deep eutectic solvents and microwave-assisted synthesis, further enhances sustainability metrics while maintaining synthetic efficiency. Case studies from recent literature demonstrate that AI-guided frameworks can achieve theoretical yields exceeding 92% with E-factors below 0.5, while computational pharmacology approaches enable early-stage prediction of neuroprotective efficacy. Despite significant progress, challenges remain in data standardization, model generalizability, and experimental validation. This paper concludes by proposing a hierarchical framework for integrating AI-driven cognitive planning, automated physical execution, and translational evaluation to accelerate the discovery of next-generation neuroprotective therapeutics from fused heterocyclic scaffolds.*

Keywords: Artificial Intelligence, Multi-Component Reactions, Fused Heterocycles, Neuroprotective Agents, Green Chemistry, Drug Discovery

I. INTRODUCTION

Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), represent an escalating global health challenge characterized by complex, multifactorial pathogenesis. The intricate nature of these disorders has necessitated a paradigm shift from traditional single-target therapeutic strategies toward multitarget-directed ligands (MTDLs) capable of simultaneously modulating multiple disease-relevant pathways . Fused heterocyclic compounds have emerged as privileged scaffolds in this context, offering unique structural features that enable versatile interactions with diverse biological targets .

The strategic importance of heterocyclic compounds in pharmaceutical innovation cannot be overstated. These molecules, containing at least one atom other than carbon in their ring structures, form the molecular foundation of many

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of today's most widely used drugs, including antibiotics, anticancer agents, and antivirals . Their unique electronic features, conferred by heteroatoms such as nitrogen, oxygen, or sulfur, allow interactions with biological targets in manners frequently unavailable to compounds with carbon-only architectures . The structural diversity of heterocycles permits the design of highly specific molecules capable of interacting with enzymes, receptors, ion channels, and DNA . Recent years have witnessed transformative advances in three interconnected domains that collectively enhance the discovery and optimization of neuroprotective fused heterocycles: artificial intelligence (AI)-driven synthesis planning, green chemistry methodologies, and multi-component reaction (MCR) strategies. AI is increasingly influencing synthetic chemistry, reshaping core paradigms through autonomous planning systems, robotic execution platforms, and large language models (LLMs) that support medicinal chemistry workflows . The integration of AI with laboratory automation and sustainability-oriented design reflects a shift from predictive assistance toward coordinated systems that enhance decision-making in drug discovery .

Green chemistry principles have revolutionized the synthesis of heterocyclic drugs through atom-economic processes, solvent-free conditions, and recyclable catalysts that lessen environmental burden while enhancing efficiency and scalability . Multi-component reactions, characterized by their ability to rapidly generate chemical diversity from simple starting materials in a single operation, have proven particularly valuable for constructing complex fused heterocyclic scaffolds with neuroprotective potential .

This paper provides a comprehensive examination of AI-assisted green multi-component synthesis and optimization of fused heterocyclic scaffolds for neuroprotective drug discovery. We review recent advances in AI-driven retrosynthesis, green synthetic methodologies, and MCR-based approaches, integrating case studies from the recent literature to demonstrate the transformative potential of this integrated paradigm.

II. FUSED HETEROCYCLIC SCAFFOLDS IN NEUROPROTECTIVE DRUG DISCOVERY

2.1 Structural and Pharmacological Significance

Fused heterocyclic compounds represent a class of molecular architectures wherein two or more cyclic ring systems share common atoms, creating rigidified structures with enhanced binding properties. The fusion of pharmacophoric rings into a single bicyclic or polycyclic system offers several distinct advantages over simple derivatives or linked conjugates . Conformational rigidity locks molecules into defined three-dimensional shapes, reducing the entropic penalty upon binding to biological targets and potentially leading to significant increases in binding affinity and selectivity .

The medicinal significance of fused heterocycles is exemplified by numerous FDA-approved drugs. Imatinib (Gleevec), a tyrosine kinase inhibitor containing pyridine and piperazine heterocycles, has transformed the treatment of chronic myelogenous leukemia . Similarly, ciprofloxacin, featuring a quinolone core, represents a cornerstone of antibacterial therapy . In the context of neurodegenerative diseases, fused heterocyclic systems incorporating piperazine and morpholine moieties have emerged as promising candidates capable of crossing the blood-brain barrier (BBB) while engaging multiple therapeutic targets .

2.2 Multitarget-Directed Ligand Design

The MTDL paradigm has gained substantial traction in neuroprotective drug discovery, recognizing that neurodegenerative diseases arise from interconnected pathological cascades including oxidative stress, protein aggregation, neuroinflammation, and neurotransmitter dysregulation . Recent synthetic efforts have focused on creating fused heterocyclic compounds capable of simultaneously inhibiting cholinesterases (ChEs), modulating amyloid-β (Aβ) aggregation, and scavenging reactive oxygen species (ROS) .

The design of MTDLs often draws inspiration from natural products with proven neuroprotective properties. For instance, quinazolinone derivatives inspired by natural alkaloids such as deoxyvasicinone and evodiamine have demonstrated promising inhibition of ChEs alongside antioxidant and neuroprotective effects against glutamate-induced oxidative stress in HT-22 cells . Similarly, the strategic combination of pharmacophoric elements from known neuroactive agents—such as melatonin (antioxidant), tacrine (ChE inhibitor), and chromone (antioxidant)—has yielded hybrid molecules with improved therapeutic profiles .

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2.3 Key Biological Targets for Fused Heterocycles

Fused heterocyclic compounds targeting neurodegenerative diseases engage a diverse array of biological targets. Acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibition remains a primary strategy for enhancing cholinergic neurotransmission in AD, with fused heterocycles demonstrating potent inhibitory activity. Recent studies have identified furano-fused azepinone derivatives with AChE inhibitory activity (IC_{50} = 2.38 nM), exceeding the reference drug galantamine (IC_{50} = 2.84 nM) .

Beyond cholinesterase inhibition, fused heterocycles have been designed to modulate γ-secretase activity, reducing Aβ peptide production . Histamine H3 receptor antagonism represents another promising strategy, as H3 antagonists enhance cholinergic neurotransmission primarily in the brain due to the predominant occurrence of the receptor in the central nervous system. Tri- and tetracyclic nitrogen-bridgehead compounds have demonstrated balanced affinities as hAChE inhibitors and hH3R antagonists, with IC_{50} values of 33.9 nM and Ki values of 76.2 nM, respectively .

III. MULTI-COMPONENT REACTIONS FOR FUSED HETEROCYCLE SYNTHESIS

3.1 Overview of MCR Strategies

Multi-component reactions (MCRs) have emerged as powerful tools for the rapid and efficient synthesis of diverse fused heterocyclic scaffolds. By combining three or more starting materials in a single reaction vessel, MCRs generate complex molecular architectures with high atom economy and structural diversity . The strategic application of MCRs to neuroprotective drug discovery has yielded numerous lead compounds with promising multitarget properties.

3.2 Ugi Reaction

The Ugi four-component reaction (4CR), involving an amine, aldehyde, carboxylic acid, and isocyanide, has been extensively employed for synthesizing fused heterocyclic MTDLs. In the context of AD drug discovery, ferulic acid-tacrine-melatonin hybrids (FATMHs) were synthesized via Ugi reaction, with compound FATMH 6a demonstrating remarkable neuroprotective properties: potent BuChE inhibition (IC_{50} = 234 nM), strong antioxidant activity (9.11 TE), non-hepatotoxic profile at 1000 μM, and favorable effects against H_2O_2 and Aβ-induced toxicity . This compound also activated the Nrf2 signaling pathway, indicating potential for mitigating oxidative stress and inflammation in AD .

The Ugi reaction has also been applied to synthesize β-amyloid aggregation inhibitors through a four-component approach, yielding compounds that effectively inhibit Aβ1-42 and AβpE3-42 aggregation . These findings underscore the versatility of the Ugi reaction for generating diverse fused heterocyclic scaffolds with neuroprotective potential.

3.3 Passerini Reaction

The Passerini three-component reaction, employing a carboxylic acid, aldehyde or ketone, and isocyanide, has been utilized to synthesize chromone-donepezil hybrids (CDHs) combining the antioxidant properties of chromone with the ChEI activity of donepezil . The Passerini reaction has also been successfully applied to synthesize benzodioxepinones with excellent drug-like features, targeting γ-secretase inhibition in AD therapy . The use of bifunctional salicylaldehydes and isocyanides in the Passerini reaction enabled the rapid generation of benzodioxepinone scaffolds in a single step .

3.4 Petasis Reaction

The Petasis borono-Mannich reaction, involving a secondary amine, aldehyde, and substituted boronic acid, has been employed to synthesize pyrazine-based MTDLs. In a study by Madhav et al. (2023), this approach yielded compounds that inhibited AChE and tau aggregation while demonstrating neuroprotective effects in SH-SY5Y cell lines . Compound 7a emerged as the most promising MTDL, exhibiting superior neuroprotection compared to both MK-886 and donepezil in a cell viability MTT assay . These findings reinforced the concept that MTDLs developed through MCR-based strategies could provide more effective approaches for complex neurodegenerative disorders than conventional single-target strategies.

3.5 Hantzsch Reaction

The Hantzsch reaction, a classic MCR for synthesizing 1,4-dihydropyridines (DHPs), has been adapted for MTDL design by juxtaposing nimodipine (a calcium channel blocker) with melatonin (an antioxidant agent) . This approach addresses the known association between increased cytosolic calcium levels and Aβ peptide formation in AD pathology. The

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synthesized DHPs demonstrated significant efficacy as calcium channel blockers and antioxidants, with compound 9c emerging as the most balanced MTDL .

3.6 Knoevenagel-Based MCRs

Knoevenagel condensation followed by Michael addition and intramolecular cyclization has been employed to synthesize spirooxindole, spiroacenaphthylene, and bisbenzo[b]pyran derivatives as SIRT2 inhibitors for PD therapy. Hasaninejad et al. (2017) synthesized 45 compounds with high yields (84-92%) using this approach, identifying three promising candidates for further characterization . In a separate study, microwave-assisted Knoevenagel-based MCR was applied to obtain new benzochromenopyrimidinones (BCPOs), with compound 8a demonstrating antioxidant activity (4.7 TE in ORAC-FL assay) and moderate hAChE inhibition (IC_{50} = 1.28 µM) .

IV. ARTIFICIAL INTELLIGENCE IN SYNTHESIS PLANNING AND OPTIMIZATION

4.1 AI-Driven Retrosynthesis

Artificial intelligence is transforming synthetic chemistry from task-specific predictors into integrated platforms that unify retrosynthesis, reaction optimization, and closed-loop robotic automation . Recent advances in AI-assisted planning and robotic execution have shortened cycle times, reduced step counts, and improved route sustainability in medicinal chemistry .

Retrosynthetic analysis, the process of deconstructing target molecules into simpler precursors, has been revolutionized by machine learning (ML) approaches. Template-based methods apply predefined reaction rules to fragment target molecules, offering interpretability and chemical intuitiveness . Recent advancements, such as the use of modern Hopfield networks for template prediction, have improved the speed and reliability of retrosynthetic planning. MHNpath, a machine learning-driven retrosynthetic tool leveraging modern Hopfield networks, achieves a solution rate of 85.4% and replicates 69.2% of experimentally validated "gold-standard" pathways .

Template-free methods, including transformer-based models, treat retrosynthesis as a language translation problem from products to reactants. The Self-Corrected Transformer achieved 59.0% top-1 accuracy on the USPTO-50k benchmark while reducing invalid SMILES from 12.1% to 0.7% . However, template-free models can generate chemically implausible disconnections when applied to out-of-distribution substrates, with error rates exceeding 50% in some cases . Hybrid frameworks combining data-driven prediction with symbolic reasoning, embedding chemical validity checks and quantum-augmented scoring, are emerging as the most reliable strategy for scalable retrosynthetic planning .

4.2 Large Language Models and Agentic Frameworks

Large language models (LLMs) such as GPT-4 and chemistry-adapted variants are now explored as integrative components of synthesis planning and decision-making. When strictly constrained by external validation tools and expert-designed prompts, LLMs can serve as assistive interfaces to help draft candidate synthetic plans . Structured validation pipelines, such as VALID-Mol, markedly improve the fraction of chemically valid outputs (from ~3% to ~83%), highlighting the importance of combining generative LLM reasoning with expert-guided filtering .

Chemistry-specific agents, such as ChemCrow, illustrate early implementations of this paradigm, serving as orchestration layers that combine LLM reasoning with domain-specific tools. ChemCrow can take a SMILES input, query chemical databases, propose retrosynthetic pathways, and refine suggestions based on synthetic feasibility, reagent availability, and cost-efficiency . Agentic LLMs support creativity by proposing unconventional but literature-grounded hypotheses, though human oversight remains indispensable for mechanistic plausibility and stereochemical correctness .

4.3 Self-Driving Laboratories and Closed-Loop Optimization

Self-driving laboratories (SDLs) integrate planning algorithms, robotics, and real-time analytics to accelerate medicinal chemistry workflows. Platforms such as ChemCrow, Sonidegib optimization, and closed-loop Bayesian approaches enable rapid identification of viable synthetic routes, multi-objective optimization of molecular properties, and integration of sustainability considerations . These systems enable rapid identification of viable synthetic routes and multi-objective optimization (MOO) of molecular properties .

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Bayesian optimization and other machine learning algorithms facilitate multi-objective optimization, allowing simultaneous consideration of synthetic accessibility, yield, cost, and environmental impact. The integration of green chemistry principles, such as E-factor and process mass intensity, into optimization objectives supports the development of more sustainable synthetic routes .

4.4 AI-Guided Green Synthesis Framework

Recent work has demonstrated the feasibility of end-to-end AI-guided frameworks for the sustainable synthesis of heterocyclic scaffolds. An AI-guided framework employing generative AI (Gemini AI) was developed to streamline the design, sustainable synthesis, and pharmacological evaluation of 2-substituted benzimidazole derivatives targeting Phosphodiesterase Type 5 (PDE5) . The AI-optimized oxidative cyclocondensation protocol utilized a biodegradable Choline Chloride:Urea Deep Eutectic Solvent (DES) coupled with microwave irradiation, achieving a theoretical isolated yield of >92% with an Environmental Factor (E-factor) of <0.5 within a 5-minute reaction time at 80 °C .

The framework included AI-predicted spectral validation (FT-IR and NMR), rigorous molecular docking simulations, and detailed Structure-Activity Relationship (SAR) mapping. Computational profiling revealed a highly favorable global binding energy of -8.4 kcal/mol against the PDE5 receptor, with the benzimidazole core identified as a critical hinge binder forming essential hydrogen bonds with residue Gln817 . This research demonstrates the transformative potential of AI-guided approaches that couple highly efficient, low-waste green chemistry principles with predictive pharmacology.

V. GREEN CHEMISTRY STRATEGIES FOR FUSED HETEROCYCLE SYNTHESIS

5.1 Deep Eutectic Solvents

Deep eutectic solvents (DES) have emerged as sustainable alternatives to conventional organic solvents in heterocyclic synthesis. These biodegradable solvents, typically formed from hydrogen bond donors and acceptors, offer advantages including low toxicity, low volatility, and ease of preparation . The use of Choline Chloride:Urea DES in benzimidazole synthesis achieved exceptional sustainability metrics while maintaining high synthetic efficiency .

5.2 Microwave-Assisted Synthesis

Microwave irradiation has proven highly effective for accelerating MCRs and improving yields in heterocyclic synthesis. The rapid, uniform heating provided by microwave irradiation reduces reaction times from hours to minutes while often improving product purity and yield . Microwave-assisted Knoevenagel-based MCRs have been successfully applied to synthesize benzochromenopyrimidinones with neuroprotective properties .

5.3 Sustainability Metrics

The evaluation of synthetic routes through sustainability metrics, including E-factor (mass of waste per mass of product) and process mass intensity (total mass used per mass of product), has become increasingly important in medicinal chemistry. AI-guided optimization can integrate these metrics into retrosynthetic planning, enabling chemists to prioritize greener routes . The AI-optimized benzimidazole synthesis achieved an E-factor of <0.5, substantially lower than conventional organic synthesis routes .

5.4 Biocatalysis Integration

The integration of biocatalysis in computational retrosynthetic planning has gained attention for enhancing sustainability. Enzymatic transformations enable highly selective reactions under mild conditions, reducing the environmental footprint of chemical synthesis . Tools like RetroBioCat demonstrate the ability to design biocatalytic cascades that complement synthetic routes, introducing enzymatic steps that are often more selective and environmentally friendly .

VI. INTEGRATED WORKFLOW FRAMEWORK

6.1 Hierarchical Framework for AI-Driven Synthesis

A hierarchical framework for AI-driven synthesis distinguishes between three interconnected levels: cognitive planning, physical execution, and translational evaluation . Cognitive planning encompasses LLM-driven reasoning and multi-objective retrosynthetic design. Physical execution translates digital plans into reality through robotic closed-loop

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systems and reaction optimization algorithms. Translational evaluation ensures applicability through interpretability, sustainability, and scalability considerations .

Within this framework, sustainability, reaction optimization, and multi-objective design are treated as evaluation dimensions that influence decisions across all levels. This structure provides a conceptual basis for integrating digital intelligence with physical experimentation, addressing both the efficiency and strategic requirements of modern drug discovery .

6.2 User-Tunable Scoring Systems

The incorporation of user-tunable scoring systems enables chemists to prioritize synthetic pathways based on multiple criteria, including cost, reaction temperature, and toxicity. MHNpath, for instance, allows users to prioritize greener, cost-effective, and moderate-temperature synthetic routes . The tool's ability to generate shorter, cheaper routes employing green solvents has been demonstrated for molecules such as dronabinol, arformoterol, and lupinine .

6.3 Computational Pharmacology Integration

The integration of computational pharmacology with synthetic planning enables early-stage prediction of neuroprotective efficacy. Molecular docking studies, density functional theory (DFT) analyses, and ADMET prediction provide insights into compound-target interactions and drug-like properties prior to synthesis . This integration allows prioritization of synthetic targets with the highest predicted therapeutic potential, reducing the number of compounds requiring experimental evaluation.

VII. CASE STUDIES

7.1 Furano-Fused Azepinone Derivatives

Bhardwaj et al. (2025) reported a novel assembly of furano-fused azepinone derivatives using a two-step approach involving 3+2 cycloaddition followed by hydroxylammonium-O-sulfonic acid (HOSA)-assisted Beckmann rearrangement in aqueous conditions. The methodology uses readily available starting synthons to synthesize five- and six-membered condensed furano-azepinone derivatives .

In vitro anti-AChE activity revealed that compound 5n (IC_{50} = 2.38 nM) showed higher inhibitory activity than the reference drug galantamine (IC_{50} = 2.84 nM). Cytotoxicity studies on SHSY5Y cell lines indicated concentration-dependent inhibition, with the highest cell viability observed at 25 µM. Intracellular ROS measurements demonstrated that 5n exhibits superior ROS-scavenging capabilities. Molecular docking and DFT analyses validated the binding interactions of the compounds with the AChE active site .

7.2 Cinnoline Derivatives as Multi-Targeting Inhibitors

Mousavi et al. (2024) described a practical one-pot two-step three-component reaction for the regioselective preparation of 3-aryl(or heteroaryl)-5,6-dihydrobenzo[h]cinnoline derivatives. The in silico multi-targeting inhibitory properties of these heterocyclic scaffolds were investigated upon numerous Homo sapiens-type enzymes, including hMAO-A, hMAO-B, hAChE, hBChE, hBACE-1, hBACE-2, and hGSK-3β, among others .

The molecular docking studies and ADMET-related data demonstrated that these cinnoline derivatives could serve as potent cores for new drugs targeting neurodegenerative diseases. The hit compounds showed favorable predicted drug properties, and the reactionable locations on the scaffolds enable further organic reactions such as cross-coupling, providing avenues for expansion and optimization .

7.3 Pyrazoline Substituted Heterosteroids

Singh et al. (2018) reported the synthesis and evaluation of a new series of 16,17-pyrazolinyl DHEA analogues as neuroprotective agents using LPS-induced neuroinflammation animal models. Treatment with the pyrazoline substituted steroids considerably improved LPS-induced learning, memory, and movement deficits in animal models, accompanied by suppression of biochemical parameters of oxidative and nitrosative stress .

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VIII. CHALLENGES AND FUTURE DIRECTIONS

8.1 Data Quality and Standardization

The effectiveness of AI-driven synthesis planning depends critically on the quality and comprehensiveness of training data. Datasets often contain biases toward low-yield reactions or well-studied reaction types, limiting model generalization. Mechanistically-annotated large-scale datasets (e.g., mech-USPTO-31K) are improving model robustness, but data standardization remains a significant challenge . Template-free retrosynthesis models, while flexible, often generate chemically implausible disconnections when applied to out-of-distribution substrates .

8.2 Experimental Validation Requirements

Despite promising computational results, realized future where every experiment reliably feeds back into autonomous learning loops requires overcoming significant barriers in data standardization and hardware interoperability . It is essential to distinguish between controlled computational evaluations and real-world deployment scenarios, where reproducibility, experimental validation, and integration with laboratory workflows remain significant unresolved challenges .

8.3 Scalability and Regulatory Compliance

The translation of AI-generated synthetic routes to industrial-scale production presents challenges related to scalability, cost-effectiveness, and regulatory compliance. Agencies such as the FDA and EMA require comprehensive preclinical to clinical data to demonstrate efficacy and safety, which can extend the time to market . Regulatory hurdles, combined with the ever-increasing threat of generic drugs and the demand for rapid, economical treatment options, make the commercial landscape challenging for heterocyclic-based drugs .

8.4 Emerging Opportunities

Despite these challenges, several emerging opportunities warrant attention. The integration of mechanistically-annotated datasets with AI models promises to improve the reliability of synthetic predictions . The development of grammar-aware SMILES representations and self-corrected transformer models continues to enhance the chemical validity of AI-generated routes . The growing trend toward personalized medicine, where drugs are tailored to a person's genetic profile, is highly suitable for heterocyclic compounds that can be engineered with high specificity .

IX. CONCLUSION

The integration of artificial intelligence, green chemistry, and multi-component reaction methodologies represents a transformative paradigm for the discovery and optimization of neuroprotective fused heterocyclic scaffolds. AI-driven retrosynthesis platforms, including both template-based and template-free approaches, have demonstrated remarkable capabilities in predicting viable synthetic routes while optimizing for sustainability metrics. Multi-component reactions, particularly the Ugi, Passerini, Petasis, Hantzsch, and Knoevenagel-based strategies, provide rapid access to diverse fused heterocyclic libraries with multitarget-directed ligand properties relevant to neurodegenerative diseases.

Recent advances in self-driving laboratories and closed-loop optimization systems promise to accelerate the translation of computational predictions to experimental validation. The integration of green chemistry principles, including deep eutectic solvents and microwave-assisted synthesis, enhances sustainability while maintaining synthetic efficiency. AI-guided frameworks have demonstrated the potential to achieve high theoretical yields with exceptional environmental metrics, as exemplified by benzimidazole synthesis achieving >92% yield with an E-factor of <0.5.

Despite significant progress, challenges remain in data standardization, model generalizability, and experimental validation. The successful realization of integrated AI-driven drug discovery workflows requires overcoming barriers in dataset quality, hardware interoperability, and translational evaluation. Future research should focus on developing more robust and generalizable AI models, improving integration between computational and experimental workflows, and addressing scalability and regulatory compliance requirements.

The convergence of digital intelligence with physical experimentation, underpinned by green chemistry principles and sustainability metrics, positions AI-assisted synthesis as an essential tool for accelerating the discovery of next-generation neuroprotective therapeutics. As the pharmaceutical industry continues to evolve toward precision medicine and

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sustainable practices, the strategic integration of AI, MCRs, and green chemistry will be critical for addressing the complex challenges of neurodegenerative diseases.

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