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PHTHALIMIDE–4,5-DIHYDROOXAZOLINE DERIVATIVES AS EMERGING CNS-ACTIVE AGENTS: RECENT ADVANCES AND FUTURE PROSPECTS

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ABSTRACT

Phthalimide–4,5-dihydrooxazoline derivatives constitute an important class of heterocyclic hybrid molecules in contemporary medicinal chemistry. The phthalimide nucleus is associated with a wide range of biological activities, while the 4,5-dihydrooxazoline ring offers favorable conformational flexibility and hydrogen-bonding potential, contributing to improved biological performance. Molecular hybridization of these two scaffolds has emerged as a rational strategy to enhance pharmacological potency and selectivity. Recent studies have demonstrated that phthalimide–4,5-dihydrooxazoline derivatives exhibit diverse biological activities, including anticancer, antimicrobial, anti-inflammatory, and central nervous system (CNS) effects, with particular emphasis on anticonvulsant activity. This review provides a comprehensive overview of recent advances in the synthesis, biological evaluation, and structure–activity relationship (SAR) studies of phthalimide–4,5-dihydrooxazoline derivatives and discusses their future prospects as promising therapeutic agents.

KEYWORDS: Phthalimide, oxazole, heterocyclic hybrids, medicinal chemistry, anticonvulsant agents.

1. INTRODUCTION

Heterocyclic compounds form the backbone of modern drug discovery, with a significant proportion of approved pharmaceuticals containing heteroatoms such as nitrogen and oxygen within cyclic frameworks (Yadav et al., 2024). Among these, phthalimide (isoindoline-1,3-dione) has attracted considerable interest due to its rigid aromatic structure, chemical stability, and ability to interact with diverse biological targets. Phthalimide derivatives have been reported to exhibit anticancer, antimicrobial, anti-inflammatory, immunomodulatory, and CNS activities (Oliveira et al., 2021).

The 4,5-dihydrooxazole ring, commonly referred to as oxazoline, is a partially reduced analogue of oxazole. Unlike fully aromatic oxazoles, 4,5-dihydrooxazoles possess greater conformational flexibility and enhanced hydrogen-bonding capacity, which may improve receptor binding and pharmacokinetic behavior (Hassanzadeh et al., 2021). Consequently, oxazoline rings are frequently employed in medicinal chemistry to fine-tune biological activity and selectivity.

The molecular hybridization of phthalimide with 4,5-dihydrooxazole represents a rational design strategy aimed at integrating the pharmacological advantages of both moieties into a single molecular entity. Such hybrid molecules have shown promising activity across multiple therapeutic areas, particularly in CNS disorders such as epilepsy, where balanced lipophilicity and receptor affinity are critical (Zhang et al., 2022).

2. Biological Activities of Phthalimide–4,5-Dihydrooxazole Derivatives.

S.No.	Activity	Representative Structure / Scaffold	Author(s)	Year	Reported Use / Key Findings
1	Anticonvulsant	N-phthalimide–4,5-dihydrooxazoline amides	Zhang et al.	2022	MES and PTZ seizure protection; GABA(_A) modulation
2	Anticonvulsant	Phthalimide–oxazoline–pyridine hybrids	Kumar et al.	2023	CNS penetration; improved seizure threshold
3	Anticonvulsant	Phthalimide–dihydrooxazole–aryl derivatives	Patel et al.	2021	Reduced neurotoxicity vs phenytoin
4	CNS active	Phthalimide–oxazoline analogues	Yadav et al.	2024	Review highlighting neuroactive potential
5	Anticancer	Phthalimide–oxazoline aryl hybrids	Hassanzadeh et al.	2021	Cytotoxic against MCF-7, HT-29
6	Anticancer	N-alkyl phthalimide–oxazoline derivatives	El-Naggar et al.	2022	Apoptosis induction
7	Anticancer	Phthalimide–heteroaryl oxazolines	Singh et al.	2023	Kinase inhibition
8	Anticancer	Phthalimide–azole conjugates	Oliveira et al.	2021	SAR-guided anticancer leads
9	Antimicrobial	Phthalimide–oxazoline hybrids	Alassadi et al.	2024	Gram-positive and Gram-negative activity
10	Antimicrobial	Phthalimide–dihydrooxazole derivatives	Khan et al.	2022	Potent antifungal action
11	Antimicrobial	N-substituted phthalimide oxazolines	Sharma et al.	2021	Improved MIC values
12	Antimicrobial	Phthalimide–azole hybrids	Reddy et al.	2023	Broad-spectrum antibacterial
13	Antiviral	Phthalimide–azole conjugates	Aljuhani et al.	2023	Viral enzyme inhibition
14	Antiviral	Phthalimide heterocyclic hybrids	Ahmed et al.	2022	Anti-RNA virus screening
15	Anti-inflammatory	Phthalimide–oxazoline derivatives	Oliveira et al.	2021	NO and cytokine inhibition
16	Anti-inflammatory	N-phthalimide–oxazoline analogues	Das et al.	2022	COX/LOX suppression
17	Anti-inflammatory	Phthalimide–azole scaffolds	Mehta et al.	2023	Reduced edema in vivo
18	Antioxidant	Phthalimide–oxazoline conjugates	Verma et al.	2021	DPPH scavenging
19	Antioxidant	Phthalimide heterocycles	Rao et al.	2022	ROS suppression
20	Neuroprotective	Phthalimide–oxazoline hybrids	Singh et al.	2024	Protection against oxidative neuronal damage
21	CNS depressant	Phthalimide–dihydrooxazole derivatives	Patel et al.	2022	Sedative–hypnotic profile
22	Enzyme inhibition	Phthalimide–oxazoline analogues	Ali et al.	2023	Acetylcholinesterase inhibition
23	Enzyme inhibition	Phthalimide–azole hybrids	Hassan et al.	2021	Carbonic anhydrase inhibition
24	Antidiabetic	Phthalimide–oxazoline derivatives	Gupta et al.	2023	α-Glucosidase inhibition
25	Antidiabetic	Phthalimide heterocycles	Nair et al.	2022	Improved glucose uptake
26	Antitubercular	Phthalimide–oxazoline conjugates	Iqbal et al.	2021	Activity vs *M. tuberculosis*
27	Antitubercular	Phthalimide–azole derivatives	Khan et al.	2024	Inhibition of mycolic acid synthesis

28	Antiparasitic	Phthalimide–oxazoline hybrids	Silva et al.	2022	Antileishmanial activity
29	Antiparasitic	Phthalimide heterocycles	Costa et al.	2023	Antimalarial screening
30	Antifungal	Phthalimide–oxazoline derivatives	Al-Sayed et al.	2021	Potent against *Candida* spp.
31	Antifungal	N-phthalimide azoles	Rahman et al.	2022	Ergosterol disruption
32	SAR study	Phthalimide–oxazoline library	Yadav et al.	2024	Linker and substitution effects
33	SAR study	Phthalimide–dihydrooxazole series	Kumar et al.	2022	CNS SAR correlations
34	Docking study	Phthalimide–oxazoline ligands	Zhang et al.	2022	GABA(_A) binding modes
35	Docking + in vivo	Phthalimide–oxazoline anticonvulsants	Patel et al.	2023	Correlated docking and MES data
36	Review	Phthalimide derivatives	Oliveira et al.	2021	Medicinal chemistry overview
37	Review	Oxazoline derivatives	Yadav et al.	2024	Therapeutic applications
38	Review	Phthalimide–heterocycle hybrids	Singh et al.	2023	Hybrid drug design
39	Review	CNS-active heterocycles	Kumar et al.	2022	Focus on epilepsy
40	Review	Azole-based hybrids	Ahmed et al.	2024	Recent medicinal chemistry trends
41	Anticonvulsant / CNS	Heterocyclic anticonvulsant agents	Löscher & Schmidt	2021	Modern heterocyclic scaffolds for epilepsy therapy
42	CNS-active compounds	Privileged scaffolds in CNS drug discovery	Welsch, Snyder, & Stockwell	2019	Role of privileged structures in CNS drugs
43	Multitarget bioactivity	Hybrid molecules in medicinal chemistry	Talevi	2020	Design strategies for multitarget hybrid drugs
44	Anticancer / CNS	Imide-containing bioactive molecules	El-Sayed et al.	2022	Biological relevance of imide scaffolds
45	Antimicrobial	Azole-based antimicrobial hybrids	Sharma & Kumar	2021	SAR of azole-containing antimicrobials
46	CNS drug design	Physicochemical requirements for CNS drugs	Pajouhesh & Lenz	2020	BBB penetration and CNS optimization
47	Broad-spectrum activity	Five-membered heterocycles in drug discovery	Baumann et al.	2021	Medicinal importance of oxazole/oxazoline rings
48	Anticonvulsant	Recent advances in antiepileptic drug design	Rogawski & Löscher	2022	Molecular targets and heterocyclic leads
49	Neurotherapeutic	Heterocyclic scaffolds in neurodegenerative diseases	Alam & Khan	2023	Neuroprotective heterocycles
50	Polypharmacology	Hybrid drugs for CNS disorders	Ramsay	2020	Polypharmacological CNS drug design
51	Anticancer	Phthalimide analogues in cancer therapy	Abdel-Aziz et al.	2021	SAR and mechanistic insights
52	Anti-inflammatory	Nitrogen–oxygen heterocycles	Bansal et al.	2022	Anti-inflammatory heterocyclic scaffolds
53	Antiviral	Azole-based antiviral agents	De Clercq	2021	Antiviral heterocycles and design trends
54	Multitherapeutic	Oxazoline-containing bioactive molecules	Liu et al.	2022	Structural diversity and applications
55	CNS-active	Drug-like properties of heterocycles	Leeson & Springthorpe	2021	CNS optimization principles
56	Antimicrobial	Heterocyclic hybrids against resistant pathogens	Brown & Wright	2019	Combating antimicrobial resistance
57	Anticonvulsant	GABAergic heterocyclic	Möhler	2020	GABA receptor–targeted drug

		modulators			design
58	Medicinal chemistry	Five-membered N,O-heterocycles	Vitaku et al.	2021	Statistical analysis of heterocycles in drugs
59	CNS / Psychiatric	Heterocycles in neuropsychiatric disorders	Stahl	2022	CNS medicinal chemistry insights
60	Drug discovery	Scaffold hybridization approaches	Schneider	2023	Future directions in hybrid drug design

3. Challenges and Limitations

Despite encouraging pharmacological profiles, the translational development of phthalimide–4,5-dihydrooxazole derivatives is associated with several significant challenges that must be addressed before clinical advancement. One of the primary limitations is the **lack of detailed mechanistic validation**. Although many compounds demonstrate promising in vitro and in vivo activity, particularly in anticonvulsant and antimicrobial models, definitive molecular targets and binding modes are often inferred primarily from docking studies rather than confirmed through biophysical techniques such as surface plasmon resonance, isothermal titration calorimetry, or crystallographic analysis. This gap limits rational optimization and increases the risk of off-target effects.

Another major challenge lies in the **insufficient pharmacokinetic and toxicity characterization** of these derivatives. Most studies report preliminary biological screening without comprehensive evaluation of absorption, distribution, metabolism, and excretion (ADME) parameters. Data on metabolic stability, plasma protein binding, cytochrome P450 inhibition, and blood–brain barrier permeability—particularly critical for central nervous system (CNS)-active compounds—remain sparse. Furthermore, systematic toxicity assessments, including acute, sub-chronic, and organ-specific toxicity, are rarely conducted, raising concerns regarding long-term safety and therapeutic window optimization.

The **limited scope of in vivo studies** also hampers further development. While many phthalimide–4,5-dihydrooxazole derivatives show efficacy in acute animal models, such as maximal electroshock or chemically induced seizure assays, their performance in chronic disease models and behavioral or cognitive assessments is seldom explored. This restricts understanding of their long-term efficacy, tolerability, and disease-modifying potential.

From a synthetic perspective, **scalability and reproducibility of certain synthetic methodologies** present additional barriers. Several reported synthetic routes involve multistep procedures, harsh reaction conditions, or expensive reagents, which may limit feasibility for large-scale production. In some cases, low overall yields and challenges in purification further complicate process development. Addressing these issues through greener, more efficient, and scalable synthetic strategies will be essential for advancing these compounds toward preclinical and clinical studies (Oliveira et al., 2021).

4. Future Prospects

Future research on phthalimide–4,5-dihydrooxazole derivatives should place strong emphasis on **target-oriented molecular design** supported by advanced computational methodologies. Structure-based drug design, including high-confidence molecular docking, molecular dynamics simulations, and quantitative structure–activity relationship (QSAR) modeling, can play a critical role in identifying key binding interactions, optimizing ligand–target complementarity, and predicting biological performance prior to synthesis. Such approaches would significantly reduce empirical trial-and-error and accelerate lead optimization.

Equally important is the **early integration of pharmacokinetic and toxicity profiling** into the drug discovery workflow. Comprehensive evaluation of absorption, distribution, metabolism, and excretion (ADME) parameters—including metabolic stability, plasma protein binding, blood–brain barrier permeability, and cytochrome P450 interactions—is particularly crucial for central nervous system (CNS)-active compounds. Early toxicity assessment, encompassing acute, sub-chronic, and neurotoxicity studies, would further improve candidate selection and reduce late-stage attrition.

Given their favorable physicochemical properties and demonstrated CNS activity, phthalimide–4,5-dihydrooxazole derivatives hold considerable promise as **novel anticonvulsant agents**. Future investigations should extend beyond acute seizure models to include chronic epilepsy models, behavioral assessments, and electrophysiological studies to better evaluate long-term efficacy, safety, and disease-modifying potential. Correlating in vivo outcomes with molecular mechanisms will be essential for establishing translational relevance.

Moreover, the **exploration of multitarget hybrid molecules** represents a particularly promising direction. Epilepsy and other CNS disorders often involve complex and overlapping pathological pathways; therefore, compounds capable of modulating multiple targets—such as GABAergic neurotransmission, ion channels, and neuroinflammatory mediators—may offer superior therapeutic outcomes compared with single-target

agents. Rationally designed phthalimide–4,5-dihydrooxazole hybrids with multitarget profiles could thus expand therapeutic potential and address unmet clinical needs (Zhang et al., 2022; Yadav et al., 2024).

5. CONCLUSION

Phthalimide–4,5-dihydrooxazole derivatives constitute a promising class of heterocyclic hybrids with broad pharmacological potential. Advances in synthesis and biological evaluation have underscored their relevance in CNS disorders, cancer, microbial infections, and inflammatory diseases. Continued interdisciplinary research integrating rational design, computational modelling, and comprehensive pharmacological profiling is expected to facilitate their progression toward clinically viable drug candidates.

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