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Original Article

Carboxamide-Based Pharmacophores: Structure–Activity Relationships and Multi-Target Therapeutic Potential

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Abstract

Carboxamide-containing compounds represent a versatile and privileged class of pharmacophores widely utilized in drug discovery due to their structural stability and strong hydrogen-bonding ability. The amide functional group (–CONH–) imparts unique physicochemical properties, enabling effective interactions with diverse biological targets, including enzymes and receptors. This review highlights the significance of carboxamide-based scaffolds in medicinal chemistry, focusing on their multi-target therapeutic potential in cancer, microbial infections, and malaria. Recent advancements in synthetic methodologies, including mechanochemical, photoredox, and electrochemical approaches, are discussed in the context of green and sustainable chemistry. The review also summarizes key structure–activity relationship (SAR) trends that guide rational drug design and provides insights into the mechanisms of action underlying their biological activity. Despite their promising applications, challenges such as drug resistance, toxicity, and pharmacokinetic limitations remain. Future perspectives emphasize the integration of computational tools and novel synthetic strategies to accelerate the development of carboxamide-based therapeutic agents with improved efficacy and safety.

Keywords: *Carboxamides; Amide pharmacophore; Drug discovery; Structure–activity relationship; multi-target ligands; Green synthesis; Medicinal chemistry; Heterocyclic compounds; Therapeutic agents*

Introduction

Carboxamide-containing compounds constitute one of the most fundamental classes of organic molecules in medicinal chemistry. The amide functional group (–CONH–) is widely present in natural products, pharmaceuticals, and biomacromolecules such as proteins, where it contributes to structural stability and molecular recognition [1]. Owing to resonance stabilization, conformational rigidity, and dual hydrogen-bond donor–acceptor capability, the carboxamide moiety is considered a privileged pharmacophore [2]. Carboxamide-based scaffolds exhibit broad therapeutic potential, including anticancer, antimicrobial, and antimalarial activities [3-6]. Their structural adaptability enables interactions with diverse biological targets such as enzymes and receptors, facilitating multi-target drug design [7,8]. This property is particularly valuable in complex diseases requiring modulation of multiple pathways [8]. Significant advances in synthetic chemistry have improved access to carboxamide derivatives. Traditional amidation methods have evolved into greener approaches such as mechanochemical, photochemical, and electrochemical strategies, enhancing efficiency and sustainability [9-13]. Recent developments have expanded amide chemistry beyond classical synthesis. Strategies such as C–H functionalization and amide bond activation enable transformation of inert amides into valuable intermediates [15-17]. Incorporation into heterocyclic frameworks has further yielded compounds with promising biological activities [18-22]. Despite these advances, challenges such as drug resistance, toxicity, and pharmacokinetic limitations remain [23-26]. This review summarizes key structural features, synthetic strategies, biological applications, SAR trends, and future perspectives of carboxamide pharmacophores.

Structural and Chemical Features

The defining feature of carboxamide pharmacophores is the amide bond, which exhibits partial double-bond character due to resonance [1, 2]. This results in planarity and restricted rotation, influencing molecular conformation and target binding. The amide group acts as both hydrogen-bond donor and acceptor, enabling strong and directional interactions with biological targets [3, 8]. These interactions are essential for ligand binding and pharmacological activity. Substituent variation around the amide modulates electronic and steric properties, influencing lipophilicity, solubility, and metabolic stability [5,7].

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Incorporation into heterocycles enhances structural diversity and biological activity [6]. Emerging strategies include the use of bioisosteres (e.g., amino-oxetanes) to improve physicochemical properties while maintaining activity [18]. Additionally, modern catalytic and photoredox approaches have expanded the synthetic utility of amides [11-14]. Beyond drug discovery, amide functionalities are important in materials science and environmental chemistry due to their stability and persistence [21-23].

Synthetic Strategies for Carboxamide Derivatives

Amide bond formation remains a cornerstone of organic synthesis. Conventional methods involve coupling of carboxylic acids or activated derivatives with amines, though these often suffer from poor atom economy and harsh conditions [1].

Modern approaches emphasize efficiency and sustainability. Mechanochemical, photoredox, electrochemical, and enzyme-mediated reactions provide mild, selective, and environmentally friendly alternatives [9-13].

Advanced transformations such as amide bond activation, C–H functionalization, and skeletal remodeling have significantly expanded synthetic possibilities [15-17]. These methods enable access to structurally complex molecules.

Multicomponent and metal-catalyzed reactions further allow rapid construction of heterocyclic carboxamide derivatives with biological relevance [23-26].

Table 1. Representative Synthetic Strategies

Method	Key Feature	Advantage
Conventional amidation	Acid derivatives + amine	Simple, established
Mechanochemical	Solvent-free grinding	Green, efficient
Photoredox	Light-driven	Mild conditions
Electrochemical	الكهرباء-driven	No external reagents
Biocatalysis	Enzyme-mediated	High selectivity
Amide activation	Skeletal remodeling	Expands reactivity
Multicomponent	One-pot synthesis	Rapid diversification
Metal-catalyzed	Pd/Mn systems	Complex scaffolds

Multi-Target Therapeutic Potential

Carboxamide pharmacophores are versatile due to their ability to interact with multiple biological targets [2,3].

4.1 Anticancer Activity

These compounds inhibit key enzymes (e.g., kinases, HDACs), induce apoptosis, and disrupt cell cycle progression [8,28]. Heterocyclic derivatives such as indole and triazole carboxamides show strong cytotoxicity [20, 21, 25].

4.2 Antimicrobial Activity

Carboxamides exhibit broad-spectrum antibacterial and antifungal activity, often by inhibiting enzymes or disrupting cell wall synthesis [4, 7].

4.3 Antimalarial Activity

They are promising against drug-resistant *Plasmodium* strains, targeting essential parasitic pathways [5].

4.4 Other Activities

Anti-inflammatory, antiviral, and metabolic regulatory effects further highlight their versatility [3].

Table 2. Therapeutic Applications

Area	Mechanism	Key Feature
Anticancer	Enzyme inhibition, apoptosis	Heterocyclic scaffolds
Antimicrobial	Enzyme/cell wall targeting	Broad-spectrum
Antimalarial	Parasite pathway inhibition	Resistance activity
Anti-inflammatory	Enzyme inhibition	Reduced inflammation
Antiviral	Viral enzyme targeting	Emerging role

General Structure–Activity Relationship (SAR) Trends

Biological activity of carboxamides depends on substituents, heterocycles, and amide functionality [2, 3].

Electron-withdrawing groups generally enhance activity and stability, while electron-donating groups influence lipophilicity [5, 8].

Heterocycles (indole, triazole, tetrazole) improve binding through π–π and hydrogen-bond interactions [6, 9].

The amide linkage itself is critical for hydrogen bonding and binding specificity [1]. Modifications at the amide nitrogen or carbonyl affect pharmacokinetics [3].

Steric and lipophilic balance is essential for optimal activity and bioavailability [7].

Table 3. Key SAR Features

Feature	Effect
Electron-withdrawing groups	↑ Activity, stability
Electron-donating groups	Modulate lipophilicity
Heterocycles	↑ Binding, potency
Amide linkage	Hydrogen bonding
N/C substitution	PK modulation
Steric effects	Selectivity control

Mechanisms of Action

Carboxamide derivatives act through multiple mechanisms involving enzymes, receptors, and biomolecules [1,2].
Enzyme inhibition: Binding to active sites blocks catalytic activity (e.g., kinases, HDACs) [8, 28].
Receptor modulation: Hydrogen bonding and hydrophobic interactions enable selective signaling control [3].
DNA/protein interaction: Some derivatives disrupt replication and transcription, especially in cancer cells [20].
Computational insights: Molecular docking confirms the importance of amide-mediated hydrogen bonding in stabilizing ligand–target complexes [29, 30].

Challenges and Limitations

Despite their potential, several challenges persist:

- **Drug resistance:** Reduced efficacy in cancer and infections [4-6].
- **Pharmacokinetics:** Poor solubility and bioavailability [3,7].
- **Toxicity:** Off-target effects and safety concerns [20,26].
- **Metabolic instability:** Amide hydrolysis [3].
- **Synthetic limitations:** Cost and scalability issues [9,11].
- **Environmental concerns:** Persistence of amide compounds [20].

Table 4. Key Challenges

Challenge	Impact
Drug resistance	Reduced efficacy
Poor PK	Limited clinical success
Toxicity	Safety concerns
Metabolic instability	Short drug lifetime
Synthetic cost	Industrial limitations

Future Perspectives

Future research will focus on integrating advanced technologies and sustainable approaches.
Artificial intelligence is expected to accelerate drug discovery by predicting activity and optimizing molecular properties [3].
Green chemistry methods, including solvent-free and electrochemical synthesis, will improve sustainability and scalability [9-12, 14].
Bioisosteric replacement and hybrid molecule design will address pharmacokinetic limitations and enhance selectivity [18].
Overall, interdisciplinary approaches will drive the development of next-generation carboxamide-based therapeutics.

Conclusion

Carboxamide pharmacophores remain central to modern drug discovery due to their structural versatility and strong target interactions [1, 2]. Their broad therapeutic potential, combined with advances in synthesis and computational design, continues to expand their applications [9-13].
Although challenges such as resistance and pharmacokinetic limitations persist, emerging strategies—including AI-driven design and green chemistry—are expected to overcome these barriers [3, 18].
Carboxamide-based compounds will continue to play a key role in the development of innovative and effective therapeutic agents.

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Conflicts of interest
The authors declare that there are no conflicts of interest regarding the publication of this paper.

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