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CARBAMATES AND BIS CARBAMATES IN MEDICINAL CHEMISTRY

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Abstract: Organic carbamates play a crucial role in modern medicinal chemistry due to their stability, bioavailability, and functional versatility. This review explores their chemical properties, synthetic methodologies, and pharmacological applications. The analysis highlights their significance in protease inhibitors, neuroactive drugs, prodrugs, and anthelmintic agents. Advances in sustainable synthesis, particularly CO_2-based carbonylation, enhance their applicability while addressing environmental concerns. Despite their advantages, hydrolytic instability remains a challenge, necessitating further research for improved structural modifications. Future advancements in carbamate-based therapeutics will drive innovation in drug design and development.

Keywords: Organic carbamates, drug design, medicinal chemistry, enzyme inhibitors, prodrugs, synthetic methodologies, pharmacokinetics.

Introduction - Bis-carbamates are a subclass of carbamates containing two carbamate (-NHCOO-) functional groups in their molecular structure. Due to their stability, controlled hydrolysis properties, and ability to interact with biological targets, bis-carbamates have gained significant interest in medicinal chemistry, material science, and agrochemistry. These compounds offer enhanced bioactivity and physicochemical properties compared to mono-carbamates, making them valuable for a wide range of applications. Bis-carbamates are characterized by their dual carbamate groups, which can be symmetrically or asymmetrically substituted. The presence of these groups allows bis-carbamates to exhibit increased hydrogen bonding potential, affecting their solubility, thermal stability, and enzymatic interactions. Depending on the nature of the nitrogen and oxygen substituents, bis-carbamates can be tailored for specific biological or industrial applications.Organic carbamates and bis carbamates are important functional groups in medicinal chemistry, widely used in drug discovery due to their stability, bioavailability and ability to modulate

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molecular interactions. Carbamates serve as peptide bond substitutes and are incorporated into various therapeutic agents including protease inhibitors and prodrugs. [1] The aim of this article is to study the chemical properties, synthetic methodologies and pharmacological applications of organic carbamates, highlighting their role in modern drug discovery. Organic carbamates are important functional groups in medicinal chemistry, widely used in drug development due to their stability, bioavailability, and ability to modulate molecular interactions. Carbamates serve as peptide bond surrogates and are included in various therapeutic agents, including protease inhibitors and prodrugs. For example, bis-carbamate derivatives such as N,N-hexamethylene-bis[(cycloalkanol)-carbamate] exhibit biological activity and are used in the national economy [2]. In addition, carbamates are used as insecticides, derivatives of methylcarbamic acid, due to their ability to inhibit acetylcholinesterase. The synthesis of functionally substituted carbamates without the use of phosgene is an urgent task aimed at improving the safety and environmental friendliness of processes [3]. In the studies of the authors and their colleagues, special attention is paid to the synthesis and characterization of various bis-carbamates. In particular, they synthesized N,N'-hexamethylene bis[(ortho-aminoacetylphenoxy)-carbamate] and studied its physicochemical properties and potential applications [4]. In addition, the physicochemical properties of N,N'-hexamethylene bis[(m-cresolyl)-carbamate] were studied, which expands the understanding of the structure and reactivity of bis-carbamates. These studies contribute to a deeper understanding of the synthesis and properties of bis-carbamates, which is important for their potential applications in various fields of chemistry and pharmaceuticals [5]. Thus, carbamates continue to play a significant role in modern medicinal chemistry, contributing to the development of new therapeutic approaches and the improvement of existing treatments.

Methods - This study is based on a comprehensive review of the synthesis, stability and medicinal applications of organic carbamates. The analysis covers: Chemical properties and stability of carbamates, established and novel synthetic methodologies, application in drug discovery including prodrugs and enzyme inhibitors, case studies of FDA approved carbamate-based drugs.

Results - Chemical Properties and Stability - Carbamates exhibit a hybrid amide-ester structure that provides both proteolytic stability and the ability to cross cell membranes. The presence of a pseudo-double bond restricts free rotation, resulting in various syn- and anti-isomeric conformations, influencing molecular interactions with enzymes and receptors. Carbamate Synthesis - Carbamates can be synthesized using a variety of methods, including:

- Hofmann and Curtius rearrangements: effective but require hazardous reagents;

- Amine carbonylation: environmentally friendly using CO_2 as a reagent;

- Reaction of alcohols with isocyanates: widely used in the polyurethane and pharmaceutical industries;

- Use of mixed carbonates: provides high selectivity and yield, improving the synthesis of bioactive carbamates.

Medicinal uses - Carbamates are common in a variety of therapeutic classes:

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- Protease inhibitors: HIV protease inhibitors such as ritonavir and darunavir incorporate carbamate moieties to enhance stability and affinity for enzymes;

- Neuroactive drugs: Rivastigmine, a cholinesterase inhibitor, is used to treat Alzheimer's disease;

- Prodrugs: Carbamate-based prodrugs such as irinotecan improve drug delivery and metabolic stability;

- Anthelmintics: Albendazole and mebendazole rely on carbamate functionality for a broad spectrum of activity.

Discussion - The structural adaptability and stability of carbamates make them indispensable in drug development. Their ability to act as enzyme inhibitors, improve pharmacokinetics, and serve as bioisosteres in peptide-based drugs underscores their significance. The development of green synthesis methods such as CO2-based carbonylation further enhances the sustainability of carbamate drug production. Despite their advantages, some carbamates exhibit hydrolytic instability, requiring structural modifications to prolong efficacy. Growing interest in carbamate-based inhibitors for the treatment of neurological disorders and viral infections opens new avenues for pharmaceutical innovation.

Conclusion - Furthermore, the continuous development of novel synthetic routes, particularly those emphasizing green chemistry principles, is crucial for expanding the accessibility and applicability of organic carbamates. The incorporation of environmentally friendly methods, such as CO_2-based carbonylation and enzyme-catalyzed synthesis, can significantly reduce the reliance on hazardous reagents while improving efficiency and yield. These innovations will not only benefit large-scale pharmaceutical production but also contribute to the sustainability of the chemical industry. In addition to their well-established roles as enzyme inhibitors, neuroactive agents, and prodrugs, organic carbamates have shown promise in emerging therapeutic areas. Recent studies suggest their potential application in targeted drug delivery systems, where their controlled hydrolysis can facilitate site-specific drug release. Furthermore, research into carbamate-based compounds as potential antiviral agents has gained traction, particularly in response to global health challenges. Their ability to form reversible covalent bonds with biological targets offers new opportunities for designing more selective and potent therapeutics.

The versatility of carbamates extends beyond medicinal chemistry into materials science, where they are used in the development of advanced polymers, coatings, and adhesives. Their stability and ability to form strong intermolecular interactions make them ideal candidates for high-performance materials in biomedical engineering, such as biocompatible implants and drug-eluting stents. Moreover, bis-carbamate derivatives have been investigated for their potential use in biodegradable polymers, which can significantly impact the future of sustainable materials. Despite these advancements, challenges remain in optimizing the pharmacokinetic properties of carbamate-based drugs. Some carbamates exhibit hydrolytic instability in physiological conditions, necessitating structural modifications to enhance their metabolic stability while retaining their therapeutic efficacy. Computational modeling and machine learning approaches can aid in the rational design of

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new carbamate compounds, enabling the prediction of their stability, bioavailability, and target specificity before synthesis.

As the demand for innovative therapeutic agents continues to grow, interdisciplinary collaboration between medicinal chemists, pharmacologists, and materials scientists will be essential for unlocking the full potential of organic carbamates. By integrating synthetic advancements with cutting-edge drug discovery techniques, researchers can further refine these compounds, ensuring their continued relevance in the ever-evolving landscape of modern medicine. In conclusion, organic carbamates will remain a key component of future pharmaceutical and materials innovations. Through sustainable synthesis, targeted drug design, and interdisciplinary research, these compounds will continue to shape the development of next-generation therapeutics, contributing to improved patient outcomes and advancements in chemical technology.

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