Synthesis and Enzyme Hydrolysis Study of Acyloxyalkyl Carbamates as New Prodrugs for Amines

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Abstract:

In this review, we examined studies through 2023 with particular attention to the cases listed below. by investigate the potential of acyloxyalkyl carbamates for the amine-containing drug in order to overcome problems associated with medication transport and pharmacological activity of these drugs by improving drug delivery and penetration for amine drugs.

This review explores how the esterase enzymes can generate effective parent drugs to give pharmacological action.

The findings focus on two main concepts. The first is activating enzymes and targeting their effects. The second concept focuses on creating pro-moieties that can achieve the intended outcome efficiently and how selecting the appropriate pro-moieties is crucial for creating stable compounds that do not produce any toxic byproducts. The review highlights the importance of enhancing drug solubility and permeability, particularly for amino-group prodrugs.

Keywords: acyloxy alkyl carbamates, prodrugs, drug delivery, pharmacological efficacy, enzymatic activation, drug permeability.

دراسة التخليق والتحلل المائي الإنزيمي لأسيلوكسي ألكيل كربامات كعقاقير أولية جديدة للأمينات

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***فرع الكيمياء الصيدلانية/ كلية الصيدلة/ الجامعة المستنصرية*

****كلية الرتبية جنزور , جامعة طرابلس , طرابلس , ليبيا***

خلاصة

في هذه المراجعة، قمنا بفحص الدراسات حتى عام 2023 مع إيلاء اهتمام خاص للحالات المذكورة أدناه. من خلال دراسة إمكانية استخدام أسيلوكسي ألكيل كربامات في الأدوية التي تحتوي على الأمينات من أجل التغلب على المشكلة المرتبطة بنقل الدواء والنشاط الدوائي لهذه الأدوية عن طريق تحسين إيصال الدواء واختراق الدواء الأميني وتستكشف المراجعة كيفية عمل إنزيمات الإيسترايز .حيث يمكن أن تولد ادوية رئيسية فعاله لإعطاء العمل الدوائي.

تركز النتائج النصية على مفهومين رئيسيين. الأول هو تنشيط الإنزيمات واستهداف تأثيراتها، وفي المقابل يركز الثاني على تكوين الاجزاء الاولية التي يمكنها تحقيق النتيجة المقصودة بكفاءة و كيف يعد اختيارالاجزاء الاولية المناسبة أمرًا بالغ الأهمية لإنشاء مركبات مستقرة تقوم بذلك لا تنتج اي منتجات ثانوية سامة. تسلط المراجعة الضوء على أهمية تعزيز قابلية ذوبان الدواء ونفاذيته، خاصة بالنسبة للأدوية الأولية للمجموعة الأمينية.

الكلمات المفتاحية: أسيلوكسي ألكيل كربامات، العقاقير الأولية، توصيل الدواء، الفعالية الدوائية، التنشيط الأنزيمي، نفاذية الدواء.

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Introduction

The concept of prodrugs has gained substantial traction as a potential method to optimize drug delivery and pharmacological efficacy.[1] This approach involves the transformation of active drug moieties into prodrugs that can be converted within the body to release the active parent drug, thereby eliciting the desired therapeutic effects .[1] [2]The prodrug strategy has been considered as an increasingly popular method for overcoming physicochemical, biopharmaceutical, pharmacokinetic, and pharmacodynamics challenges associated with pharmacologically active substances. [3-6] The fundamental rationale behind prodrug development is to enhance the drug-like characteristics of the parent compounds, encompassing factors such as absorption, distribution, metabolism, and excretion properties. [7] Such enhancements are particularly significant given that unfavorable attributes may pose substantial hurdles during the drug development process. Additionally, prodrugs offer avenues for achieving greater site specificity, reduced toxicity, simplified administration, improved formulation, and enhanced drug efficacy. [7]

A variety of methods can be used to classify prodrugs. Some examples of these might be prodrugs which can be classified in one of three ways: first way based on therapeutic categories (e.g., anticancer, antiviral, antibacterial, nonsteroidal anti-inflammatory, cardiovascular), the second based on the types of chemical linkages or moiety/carriers that attach to the active ingredient, such as esteric, glycosidic, bipartite, or tripartite prodrugs, and the third based on the types of enzymes that are directed by antibodies, genes, or viruses. Prodrugs, which are based on functional categories, apply innovative techniques to get around limitations in the active treatment, such as prodrugs to boost site specificity, prodrugs to get over high first-pass metabolism, prodrugs to increase absorption, and prodrugs to minimize adverse effects.[8-10].

Carrier-linked prodrugs have a group that may be quickly and easily removed by enzymes (such as an ester or labile amide) to produce the parent drug. For *in vivo* effective activation, the connected bond must be labile and the removed group should be pharmacologically inactive and harmless. Further classifications of carrier-linked prodrugs include (a) bipartite, which consists of one carrier (group) attached to the drug, (b) tripartite, which includes a carrier group linked to the drug via a linker, and (c) mutual prodrugs, which consist of two drugs linked together [11-14].

Enzymatic Activation and Targeted Effects

Enzymatic catalysis, particularly by hydrolases, plays a key role in transforming prodrugs into active drugs, ideally occurring at specific target tissues to prevent adverse effects [15]. The classic approach involves conjugating the target drug with hydrophilic or lipophilic functional groups, enhancing solubility and permeability [16-19]. This modification aims to overcome biological barriers, such as the gastrointestinal tract, skin, and blood-brain barrier, to improve oral absorption, skin penetration, metabolic pathways, and overall drug safety and effectiveness. Recent advancements have extended prodrug strategies to specifically target membrane transporters or enzymes, enabling precise drug delivery [20, 21].

Designing Effective Pro-moieties

The selection of a suitable pro-moiety, vital for prodrug design, involves creating chemically stable compounds that do not produce harmful metabolites upon bioconversion [22]. Drug permeability is pivotal for efficacy, closely tied to physicochemical properties and transport

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across biological membranes [23, 24]. Water solubility and lipophilicity significantly influence drug interactions with absorptive surfaces of the gastrointestinal tract, influencing transport pathways and preferences (25, 26). Classifying compounds according to the Biopharmaceutical Classification System (BCS) aids in understanding solubility and permeability characteristics. Class 3 compounds, characterized by high solubility and low permeability, often encounter poor bioavailability due to limited intestinal permeability [27].

Amino Group Prodrugs for Improved Penetration

One of the most prevalent functional groups in many prescription medications is the amine group. Amines in medications have the ability to limit their safety and effective transport to desired locations of action through physicochemical barriers. As a result, numerous amine prodrugs have been developed to get around formulation and delivery issues. Many prodrug approaches created for amines have made use of the carbamate capability. [12]

Amine prodrugs enhance water solubility and lipophilicity to facilitate membrane penetration, aiming for effective drug delivery [28]. Such prodrugs can also enhance the chemical and metabolic stability of their parent drugs, especially those undergoing intermolecular aminolysis. Moreover, amine prodrugs hold promise for targeted drug delivery][12]. The ionization tendency of amino groups under physiological conditions limits their performance, particularly for amino drugs needing blood-brain barrier penetration for pharmacological efficacy.

N-(Acyloxy)alkyl Carbamates as Amine Prodrugs

Derivatives of N-(acyloxy) alkyl carbamates have garnered interest as potential amine prodrugs [29-32]. These compounds feature an esterase-sensitive terminal group, triggering spontaneous decomposition and parent amine release upon hydrolysis. This enzymatic bio conversion offers a unique pathway for activating prodrugs [29, 30]. The (acyloxy) alkoxy promoiety, initially chosen for its esterase metabolism susceptibility. These derivatives undergo spontaneous breakdown to parent amine via a labile carbamic acid, resulting in an unstable (acyloxy) alkyl carbonyl intermediate. Among the side products of the promotion are carbon dioxide, an aldehyde, and a carboxylic acid figure (1)[29]. The relative enzymatic stability of simple N-acyl groups is effectively addressed by this method. The hydrolytic stability of the ester is improved by increasing steric hindrance around the linker, as shown by the enzymatic stabilities of pro-drugs including (acyloxy) alkyl ester linkers [33] while remaining stable under anhydrous acidic conditions.

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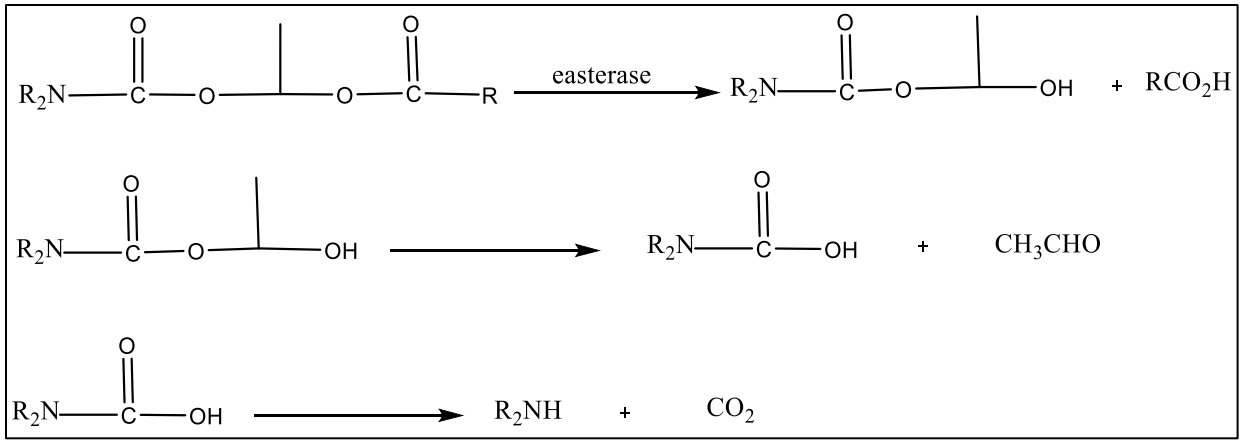

Figure (1): Hydrolysis of an amine prodrugs to give parent drug and carbon dioxide

Carbamates: Stability and Permeability

Carbamates are widely employed in medicinal chemistry due to their chemical stability and cell membrane permeability. Their ability to modify interactions with target enzymes or receptors makes them a unique class of molecules. Non-bonded electrons on nitrogen contribute to conformational limitations, while the carboxyl group and carbamate activity's backbone NH engage in hydrogen bonding. These features allow for tailored biological effects and improved stability and pharmacokinetics [34, 35].

Cases Studieds (Acyloxy)alkyl Carbamates as Prodrugs for Amines

Case Study 1*: Norfloxacin Prodrug Synthesis and Evaluation*

Alexander, J. *et al*. (1991) developed a prodrug for norfloxacin (NFLX) (Figure 2) [36] using acetoxyalkyl carbamates. Their study successfully addressed NFLX's bitter taste by synthesizing NFLXCO-OCHR-OAc type prodrugs]. However, hydrolysis of the ester bond in these prodrugs led to rapid NFLX regeneration .High oral doses of the prodrug caused minor reductions in alcohol metabolism due to acetaldehyde production .Rhesus monkey studies indicated lower bioavailability of NFLX from the prodrug, possibly due to reduced aqueous solubility [36].

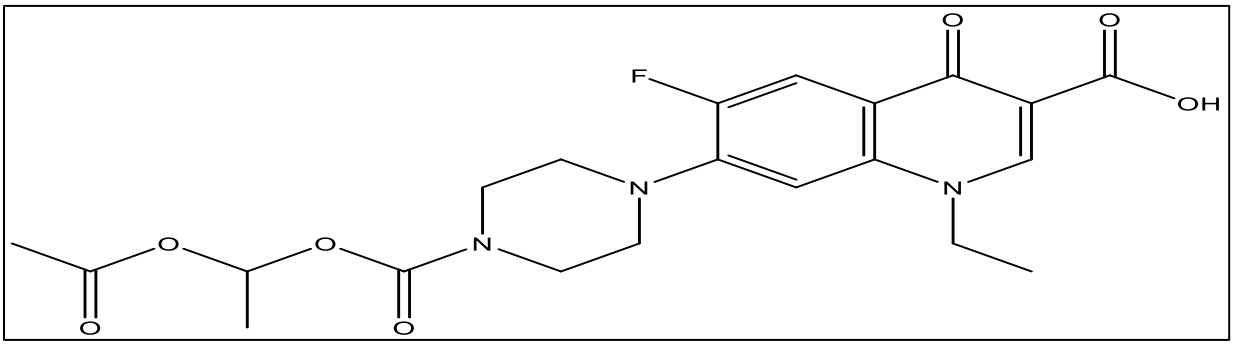

Figure (2): Norfloxacin prodrug

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Case Study 3: Innovative Synthesis of Halofenozide-(Acyloxy) alkyl Derivatives

Mark J. Mulvihill *et al*. (2001) presented an innovative synthesis of halofenozide [(acyloxy)alkoxy]carbonyl derivatives (figure 4) [37]. The approach involved parallel reactions with chloromethyl and 1-chloroethyl chloroformate, leading to halofenozide-N-[(acyloxy)alkoxy]carbonyl derivatives .This novel method enabled the conversion of amines to (acyloxy) alkylamino derivatives [37].

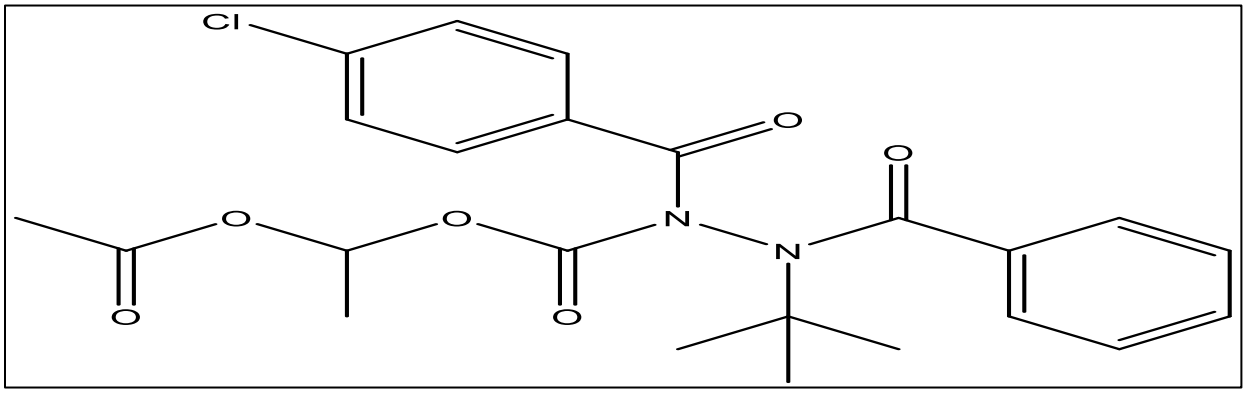

Figure (3): Halofenozide prodrug

Case Study 2: XP13512 - A Novel Gabapentin Prodrug for Enhanced Intestinal Absorption

Cundy, K.C. *et al*. (2004) was synthesize XP13512, a gabapentin prodrug figure (3)[38] designed to improve intestinal absorption. XP13512 has stability at physiological pH and it is rapidly converted to gabapentin in various tissues. This prodrug has minimal effects on major cytochrome P450 isoforms and actively transported across cell monolayers. pH-dependent passive permeability was identified as a mechanism facilitating drug release [38].

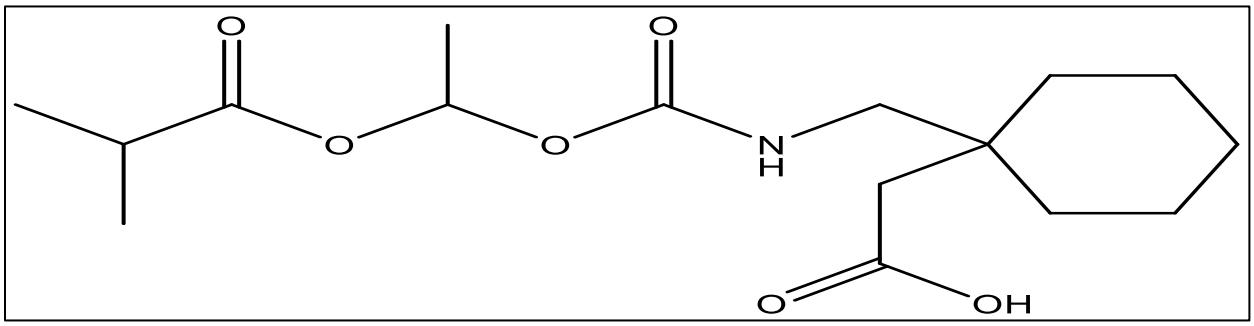

Figure (4): Gabapentin prodrug

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Conclusion

In summary, this review highlighted the crucial effect of acyloxy alkyl carbamate as a potentially effective method to accelerate drug delivery and enhance the pharmacological effect. This approach provides a well-built basis for future consideration and development . Furthermore, it addresses complex issues related to drug transport and pharmacological activity for amine-containing drugs.

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