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REVIEW ARTICLE

A review of the past decade of Azlactones: Synthesis, Reactions, Biomedical and Pharmaceutical applications

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ABSTRACT

Azlactones (2,4-disubstituted oxazol-5-ones) are pivotal building blocks in pharmaceutical design due to their dual electrophilic-nucleophilic reactivity and structural plasticity. Their strained ring system enables diverse ring-opening pathways, facilitating rapid construction of peptidomimetics and bioactive conjugates. Recent studies demonstrate potent antibacterial and antifungal properties such as pyridinyl-functionalized azlactones exhibit efficacy against MRSA (MIC = 0.78 µg/mL), while azlactone-triazole hybrids inhibit Candida auris (MIC = 1.56 µg/mL) and Aspergillus fumigatus via ergosterol synthesis disruption. Additionally, spiro-azlactones show anticancer potential against MCF-7 and A549 cell lines through DNA interaction, tubulin polymerization inhibition, and cell cycle disruption. The spirocyclic structure enhances selectivity, target affinity, and metabolic stability.

Keywords: anticancer agents; antifungal agents; azlactones synthesis and ring-opening; DNA interaction, green synthesis; oxazolones; spiro-azlactones; tubulin inhibition

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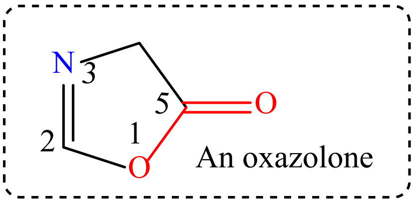
1. Introduction

Azlactones, first reported in the early 1900s, emerged as crucial intermediates in organic synthesis due to their unique cyclic imide structure[1].

In view of these interesting and as part of continuous program directed toward the Synthesis of some new spiro 1,3,4-oxadiazolines derived from azlactone[2,3], it was becoming of interest to do this review of the past decade of azlactones, synthesis, reactions, biomedical and pharmaceutical applications.

Azalactones are compounds derived from 5-(4H)-oxazolone, which have an ethylene radical on carbon 2, **Figure (1)**[4].



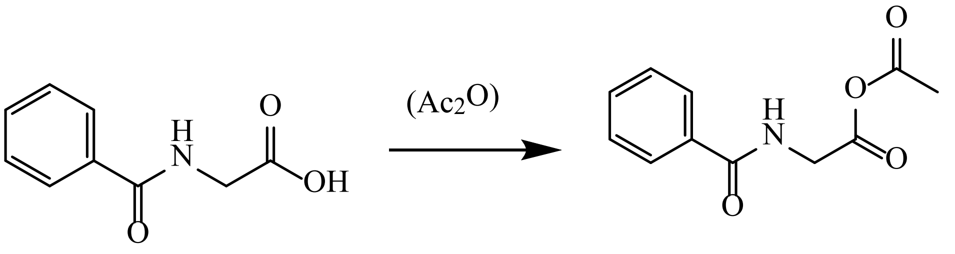
An ester-like linkage (in red) incorporates a nitrogen atom(blue), making it a lactam derivative or more specifically, an oxazolone.

Figure 1. The 5-(4H)-oxazolone chemical structure.

Due to the importance of these compounds and their derivatives, many organic synthetic chemists have long sought to synthesize them. Research in this area began with Gabriel in 1904, who described the cyclodehydration of *N*-acyl amino acids to yield azlactones—providing a versatile route to α-amino acid derivatives[5].

This initial discovery opened pathways to the development of peptides and heterocyclic compounds, establishing azlactones as fundamental building blocks in synthetic organic chemistry[6,7].

To synthesize azlactone of hippuric acid, i.e. the 2-phenyl-5(4*H*)-oxazolone the Gabriel synthesis involved the activation of acyl group of hippuric acid by acetic anhydride, which was recognized that it was acted as both solvent and dehydrant, facilitating rapid activation to form a mixed acetic-carboxylic anhydride intermediate as shown in **Figure (2)**[8].

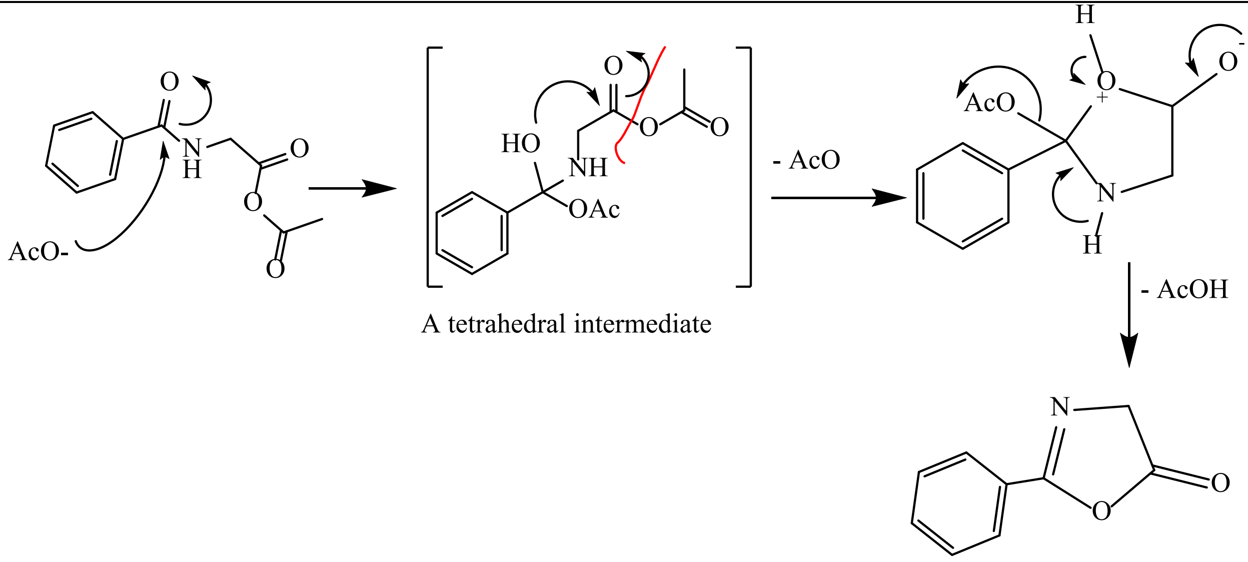


N-Benzoyl glycine
(Hippuric acid)

1-Benzamido-2-methylpropan
-2-yl acetate

Figure 2. The mixed acetic-carboxylic anhydride.

The second step, which was called the base-mediated enolization and cyclization, this nucleophilic enolate was produced from the deprotonated amide group of the amino acid by the sodium acetate (the base (AcO^-) which accelerates the reaction by promoting enolization). This enolate attacks the electrophilic carbonyl carbon of the mixed anhydride, forming a tetrahedral intermediate (converted from sp2 to sp3). This followed by the final step of ring closure and elimination via the tetrahedral intermediate collapsed and ejected the acetate (AcO^-) and closing the 5-membered oxazolone ring, as shown in **Figure (3)**[9,10].



2-Phenyloxazol-
5-(4*H*)-one

Figure 3. Synthesis of Azlactone derivative, 2-Phenyl-5-(4H)-oxazolone.

Structural protocols for azlactones were significantly improved in the fifties of the last decade, and the classical methods chiefly depend on the condensation of amino acids or their derivatives with acid anhydrides or chlorides under dehydrating conditions[11-14].

Ten to twenty years later (notably by 1979), catalytic dehydration methods emerged alongside activating agents such as carbodiimides, enhancing reaction yields and functional group tolerance. Concurrently, investigations into azlactones bearing diverse ring substituents broadened their chemical versatility, enabling syntheses of heterocycles and peptidomimetics[15,16]. Many studies have used chalcones as catalysts or catalytic compounds with nanomaterials to obtain novel catalysts[17,18].

Chalcone compounds have also been used as reagents to determine the concentration of some important pharmaceutical compounds (dopamine, Mesalazine, etc.)[19,20] yielding excellent results at low cost. In these reactions, Chalcones acted as reagents for amino groups[21,22].

To study the chemical structure of these compounds, researchers adopt that the azlactones which possess the five-membered ring, this ring contains an ester-like linkage) but incorporates a nitrogen atom, making it a lactam derivative or more specifically, an oxazolone, **Figure (1)**. This largely planar, especially around the C4-C5 bond and the C5 carbonyl[23] **Figure (4)**.

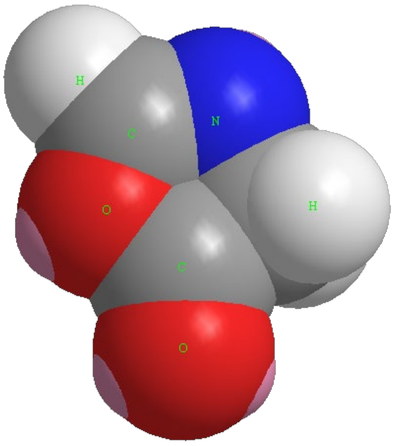


Figure 4. The large planar, especially around the C4-C5 bond and the C5 carbonyl.

The oxazolone ring is largely planar, Drawn by this review using Chem3D, MM2 minimizes energy, space filling display model.

The polarity of flanking exocyclic carbonyl group give two properties to the ring, the first is make the carbonyl carbon (C5) extremely poor electrons and thus highly susceptible to nucleophilic attack by amines, alcohols and water which lead to ring opening, while the second is making the proton(s) on C4 (if it is unsubstituted) relatively acidic[24,25].

Finally, and less common, characterized by an endocyclic double bond between C2 and N3 and an exocyclic carbonyl on C5 result of the commonly conversion from the relocation of a hydrogen atom within the C4, this phenomenon is called tautomerism, which is generally favored the predominance of the 5(4H)-tautomer over the less stable 5(2H)-oxazolone tautomer[26] **Figure (5)**.

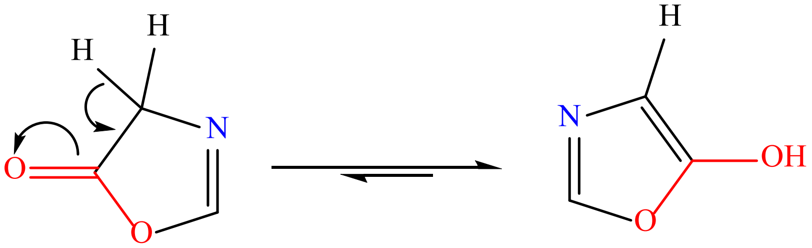


Figure 5. The 5(4H)-tautomer over the less stable 5(2H)-oxazolone.

The ring-opening of the azlactone moiety dominates the chemistry of these derivatives, this was done by nucleophilic attack, while azlactones undergo [2+2] cycloadditions or enolization, nucleophilic attack at C2 dominates their reactivity, driving ring-opening to form linear adducts. This versatility enables peptide synthesis and heterocycle construction. This ring-opening has occurred by amines (especially primary amines) as nucleophile that attack the carbonyl carbon to produce the dipeptide precursor as following **Figure (6)**:

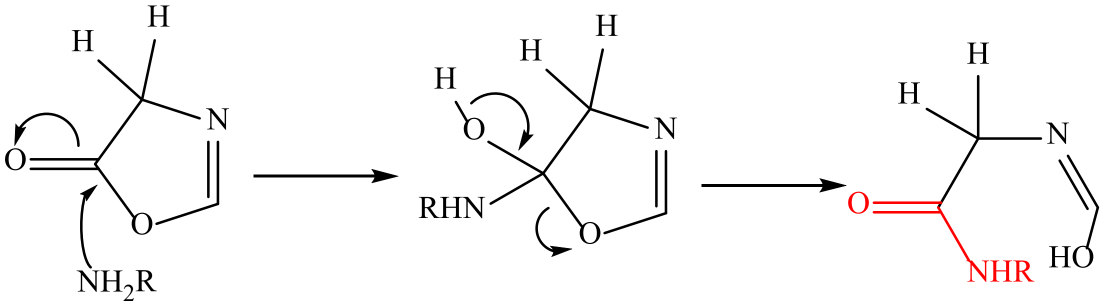


Figure 6. This ring-opening via the nucleophilic attack of primary amine to produce the dipeptide precursor (in red).

Green chemistry principles were incorporated into azlactone synthesis, such as the use of solvent-free conditions, microwave-assisted synthesis, and continuous-flow reactors has improved reaction efficiency and sustainability[1,27].

Poly(2-vinyl-4,4-dimethylazlactone) (PVDMA), derived from VDMA polymerization, exemplifies azlactone ring-opening utility. Its pendant azlactone functionalities react efficiently with nucleophiles (e.g., primary amines) via ring-opening. This reaction installs new side chains, yielding customized polyacrylamide-type polymers, Saied, S. M., Saleh, M. Y., & Hamdoon, A. M. (2022). Multicomponent synthesis of tetrahydrobenzo [a] xanthene and tetrahydrobenzo [a] acridine derivatives using sulfonated multi-walled carbon nanotubes as heterogeneous nanocatalysts. Iranian Journal of Catalysis, 12(2)[28]. **Figure (7)**.

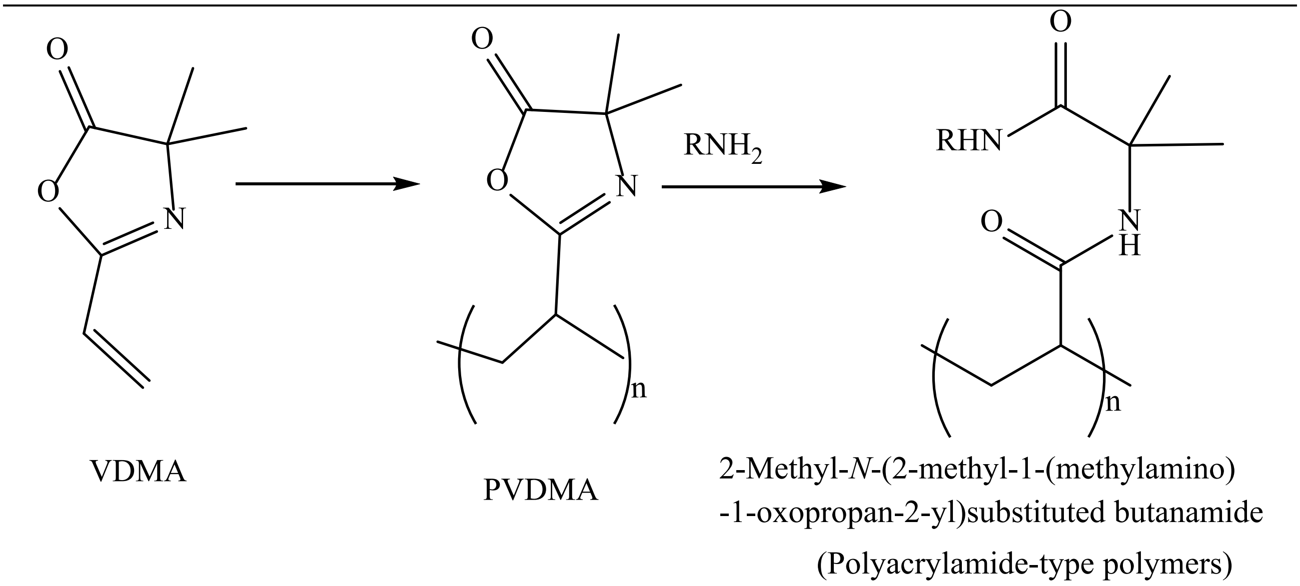


Figure 7. Polymerization of 2-vinyl-4,4-dimethylazlactone (VDMA) and post polymerization of the PVDMA.

The integration of solvent-free conditions with the inherently atom-economic ring-opening of azlactones by readily available primary amines establishes a significantly greener synthetic pathway. This method contrasts sharply with traditional approaches reliant on hazardous solvents, stoichiometric activating agents, or less selective nucleophiles. By eliminating toxic solvents, minimizing waste through safer reagents (amines), achieving high atom economy, and enabling efficient product diversification, this strategy exemplifies core green chemistry principles. The inherent reactivity of azlactones toward primary amines is pivotal to this versatile and efficient transformation[29,30]. Microwave-assisted synthesis has revolutionized azlactone (oxazolone) chemistry, offering dramatic accelerations, higher yields, and cleaner reactions compared to classical thermal methods.

Continuous-flow reactors enabled the synthesis of 18 dipeptides, including *N*-benzyloxycarbonyl-glycyl-ʟ-phenylalanine methyl ester (Z-Gly-Phe-OMe), achieving >95% purity, **Figure (8)**. This benchmark dipeptide is critically important in methodological development for peptide synthesis, particularly in evaluating azlactone-based coupling efficiency and epimerization control under optimized flow conditions[31,32].

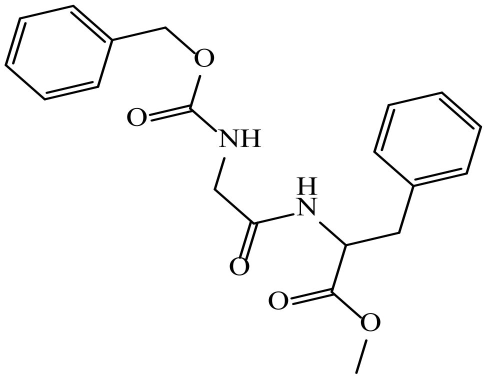


Figure 8. Gly-Phe-OMe chemical structure.

In their 2023 study, Noël and coworkers employed *N*-benzyloxycarbonyl-glycyl-ʟ-phenylalanine methyl ester (Z-Gly-Phe-OMe) as a model dipeptide to validate a continuous-flow azlactone ring-opening platform. This benchmark compound was strategically selected because glycine's achirality eliminates self-epimerization risks, while phenylalanine's chiral α-carbon is highly prone to racemization, making it ideal for assessing epimerization suppression during coupling. The flow method demonstrated superior performance over batch processes: epimerization was limited to >0.5% (vs. 8–12% in batch), reaction time reduced to 1.5 minutes (vs. 3–5 hours), and yield increased to 97% (vs. 75%). This approach, now regarded as a gold standard in azlactone studies, highlights the transformative efficiency of flow chemistry for stereoselective peptide synthesis[31,33].

2. Biomedical and Pharmaceutical Applications of Azlactones

Azlactones (2,4-disubstituted oxazol-5-ones) remain pivotal building blocks in modern pharmaceutical design due to their dual electrophilic-nucleophilic reactivity and structural plasticity. Their strained ring system—featuring an activated carbonyl and conjugated exocyclic alkene—enables diverse ring-opening and functionalization pathways, facilitating rapid construction of peptidomimetics, heterocyclic scaffolds, and targeted bioactive conjugates. This versatility supports critical applications in prodrug development, targeted protein degraders (PROTACs), and biomaterial engineering[34,35].

Azlactones emerged as pivotal acylating intermediates in early peptide synthesis, enabling regioselective coupling with nucleophilic amines under mild conditions. This approach facilitated dipeptide and tripeptide assembly without traditional harsh activating agents, providing a foundational strategy for mid-20th century pharmaceutical peptide development. Their inherent reactivity circumvented racemization risks while offering atom-economical bond formation[36,37].

Modern pharmaceutical applications of azlactones have shifted toward drug design and prodrug strategies,the azlactone ring can be used as a masked electrophile, which reacts selectively with biological nucleophiles such as lysine or serine residues in proteins, this property has been harnessed in site-specific bioconjugation and drug delivery, where azlactones are incorporated into linker technologies for antibody–drug conjugates. These systems enable precise control over payload release and target in oncology[38,39].

3. Antibacterial and antifungal properties:

In antimicrobial drug design, azlactone-based derivatives have demonstrated potent antibacterial and antifungal properties, particularly when functionalized with aryl or heteroaryl moieties at the α-position. For example, azlactone analogs bearing halogenated phenyl rings exhibited enhanced activity against Staphylococcus aureus and Candida albicans, attributed to improved membrane penetration and oxidative stress induction[40-42].

Recent studies highlight the continued promise of azlactone-based scaffolds in combating resistant pathogens as antibacterial activity and novel α-aryl azlactones bearing pyridinyl substituents, **Figure (9)** demonstrated potent efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA), with compound achieving MIC values of 0.78 µg/mL., this activity stems from disruption of membrane integrity and interference with peptidoglycan biosynthesis[43].

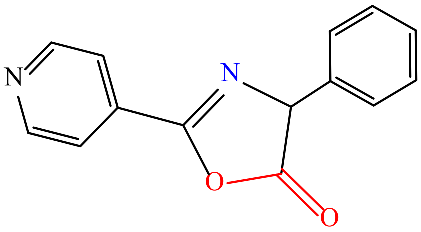


Figure 9. A novel a -aryl azlactones bearing pyridinyl substituent, demonstrated potent efficacy against methicillin-resistant Staphylococcus aureus (MRSA).

Finally, the antifungal activities of azlactone-triazole hybrids exhibited broad-spectrum inhibition against *Candida auris* (MIC = 1.56 µg/mL) and *Aspergillus fumigatus* by targeting ergosterol synthesis and inducing apoptosis-like cell death[44].

4. The anticancer properties:

The anticancer potential of azlactone derivatives has also been explored. Certain spiro-azlactones and oxazolone analogs have shown cytotoxicity against human cancer cell lines, including MCF-7 and A549, through apoptosis induction and inhibition of tubulin polymerization. Mechanistic studies revealed that the conjugated imide system interacts with DNA and disrupts cell division cycles, suggesting promise as chemotherapeutic leads. The spirocyclic structure introduces 3D complexity and rigidity, potentially enhancing the selectivity, and better discrimination between cancer and normal cells, in addition to the target binding affinity and specificity which improved fit into specific protein pockets. Finally, the metabolic stability is resistance to degradation in the body[45]. In addition to all previous properties , azlactone derivatives has a neuropharmaceutical properties[46], enzymes inhibitors properties[47], biotechnological applications[44] and bio-orthogonal chemistry[48].

5. Conclusion

Azlactones inherent reactivity enables their efficient synthesis from hippuric acid, i.e. the 2-phenyl-5(4*H*)-oxazolone via the Gabriel synthesis, with recent green methods (e.g., solvent-free microwave techniques) enhancing sustainability. These compounds exhibit remarkable breadth as antifungal activity, which is exemplified by azlactone-triazole hybrids targeting *Candida auris* and *Aspergillus fumigatus* through ergosterol biosynthesis disruption and apoptosis induction, anticancer potential which is highlighted by spiro-azlactones, which demonstrate cytotoxicity against MCF-7 and A549 cell lines via DNA binding, tubulin inhibition, and cell-cycle arrest. The spirocyclic framework enhances selectivity, metabolic stability, and target specificity. Also, antibacterial applications feature pyridinyl-functionalized derivatives effective against multidrug-resistant pathogens like MRSA.

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Conflict of interest

The authors declare no conflict of interest.

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