Synthesis, mechanism of action, and structure-activity relationships of 1,3-oxazolidinones as anti-bacterial Agent: A review

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ABSTRACT:

Background: 1,3-oxazolidinones are an important class of antibiotics that are recognized with higher activities against Gram-positive bacteria. linezolid, tedizolid phosphate, and radezolid are important examples of this group.
Aim: The aim of this review is to study the effect of 1,3-oxazolidinone derivatives as Gram-positive antibacterial agents.
Results: There are many methods for preparing the oxazolidinone derivatives. Many patents Three new antibacterial oxazolidinones are linezolid, tedizolid phosphate, and radezolid. They differ in the side chain according to their structure-activity relationship.
Conclusion: Study the structure-activity relationship (SAR) of oxazolidinone derivatives as new antibacterial agents.

Keywords: SAR, oxazolidinones, linezolid, tedizolid.

تحضير، ميكانيكية عمل ودراسة علاقة الشكل بالفعالية 1،3-اوكسازيلوليدون كمضادات للبكتريا—دراسة مراجعه

الخلفية: 1،3-اوكسازوليدوينون هي مجموعه مهمة من المضادات الحيوية، وتتمثل لينزوليد، تديزوليد فوسفات، والان راديزوليد، وتعمل بشكل اساسي ضد البكتريا الموجبة الكرام.
الهدف: الهدف من هذه الدراسة المراجعة هو دراسة تاثير مشتقات 1،3-اوكسازوليدونيون كمضادات للبكتريا الموجبة الكرام.
النتائج: توجد عدة طرق لتحضير مشتقات الاوكسازوليدون. ثلاثة اوكسازوليدنيون من العوامل الجديدة المضادة للبكتريا مثل لينزوليد، تديزوليد الفوسفات والراديزوليد. جميع المركبات بانها تختلف في السلسلة الجانبية الى 1،3-اوكسازوليدونيون حسب وفقا لعلاقة الشكل بالفعالية.
الملخص: دراسة علاقة الشكل بالفعالية لمشتقات الاوكسازوليدينون كادوية مضادة للبكتريا.

الكلمات المفتاحية: علاقة الشكل بالفعالية (أس أي ار)، أوكسازوليدينون، لينازوليد، تيدازوليد.

INTRODUCTION

The 1,3-Oxazolidin-2-one is five-membered heterocyclic compounds, the 2-D and 3-D structures as shown Figure 1.

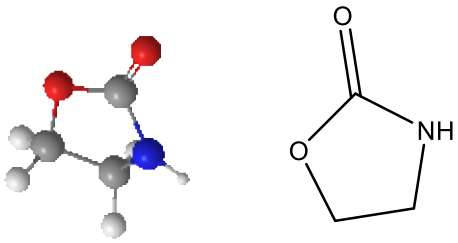


Figure1: Chemical structure 2-D & 3-D of 1,3 oxazolidin-2-one

These members of the group were primarily active against Staphylococci and Streptococci bacteria types (1987) (2).

At present, several new methods of oxazolidinone derivatives were synthesized, the first compound of this class is Linezolid (antibacterial). With significant efficacy against Gram-positive bacteria, these agents are novel antibacterial classes to emerge in the previous 30 years (3,4).

All oxazolidine derivatives have a chiral center at 4-substituted and give optically active compounds (4).

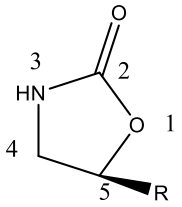


Figure 2: Chemical structure of optically active 5- substituted oxazolidinone (4).

The new antibiotic pipeline, however, stopped up between the early 1970s and 1999. Except for mupirocin, an antibiotic active against bacteria, all newly introduced antibiotics were equivalents of existing medications (5).

In 1985, a campaign against Gram-positive bacteria was initiated. Since 2000, the situation improved with the addition of five more classes linezolid (LZD)Figure 3, is an antibiotic that has been licensed and released (6).

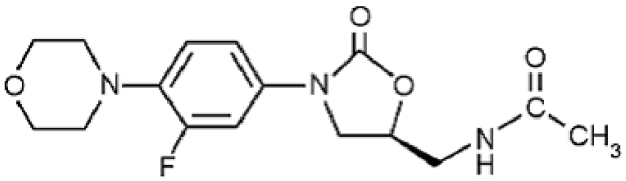


Figure 3: Chemical structure of Linezolid.

Linezolid belongs to the family of 3-aryl-2-oxzalidinones. Most Gram-positive bacteria and vancomycin-resistant enterococcus are susceptible to linezolid (7) New patents are discussed different protocols for synthesis and their SAR.

Synthesis of the oxazolidinone

The general route of the synthesis of the aryl oxazolidinone ring via aryl isocyanides and (*R*)-glycidyl butyrate is shown in Figure 4.

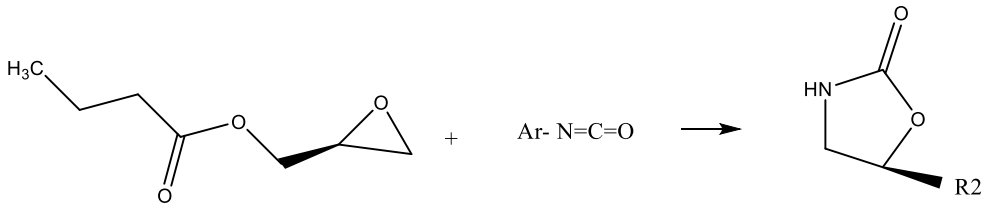


Figure 4: General route of synthesis oxazolidinone ring.

There are different reagents and catalysts were used during the cyclization reaction. This reaction was proceeded 1+3 cycloaddition using the Curtius rearrangement. The catalyst is lithium butyl (BuLi) (8), Cesium carbonate ($CeCO_3$) in acetonitrile (9), Trifluoroacetic acid, or Zinc chloride ($ZnCl_2$) (10), all these methods are used to enhance the percentage yield and no change in the chiral center. Other methods used green chemistry in the synthesis of the oxazolidinone ring. No solvent was used during the reaction of Triethylamine with hydroiodide (HI) as shown in Figure 5.

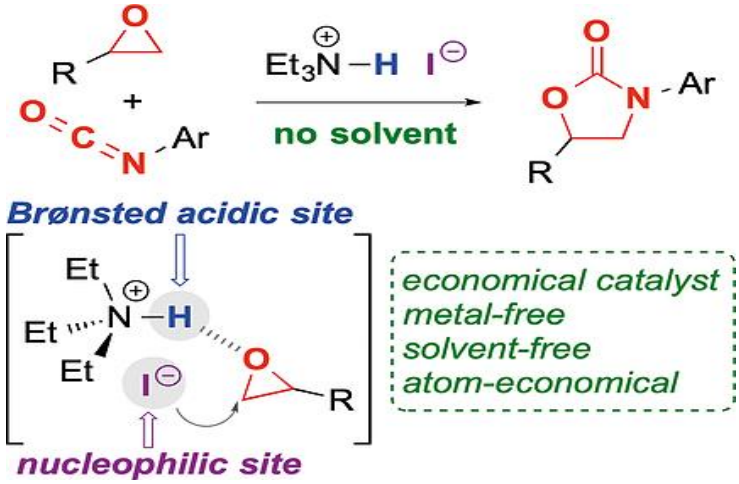


Figure 5: Green chemistry used in the synthesis of 5- substituted oxazolidinone ring .

Another classical method is sodium isocyanide without any solvent to give a 5-substituted oxazolidinone ring as shown in Figure 6 (11).

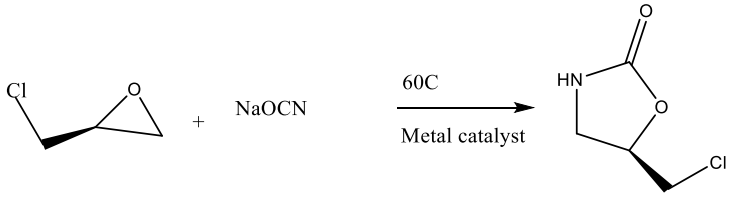


Figure 6: 5- substituted oxazoliodinone-ring using sodium isocynide

This innovative method allows for easy access to related 2-oxazolidinone members as well as the creation of additional Linezolid analogs. In comparison to other current synthetic methods, the adopted method provided high purity and yield.

The important question in the synthesis of linezolid is how to get access to the 2-oxazolidinone ring to the correct S-configuration at its C5 position? Several methods for the synthesis of linezolid were obtained high yield, pure enantiomer (*S*) with low cost.

Mechanism of Action

Oxazolidinone is a new family of antibacterial medicines that inhibits bacterial protein synthesis by preventing aminoacyl-tRNA from adhering to the ribosome's ribosomal site (12). Linezolid was approved by FDA as the first clinically useful oxazolidinone antibacterial drug and the first generation of oxazolidinone.

The rise of linezolid-resistant *Staphylococcus aureus* and *Enterococcus spp*. has grown in recent years as a result of the extensive use of linezolid in clinical practice. As a result, developing novel oxazolidinone antibacterial medicines is critical Figure 7.

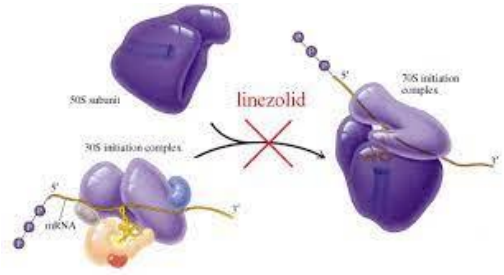
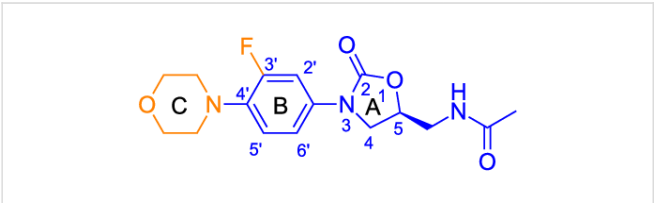


Figure 7: Linezolid inhibiting protein synthesis.

The resistance mechanism that limits the usage of linezolid has significant activity against Tedizolid phosphate. For the time interval 0–24 hours/minimum inhibitory concentration (MIC), the area under the curve is (13).

Structure Activity Relationships of Oxazolidinone derivatives

There are 3 important oxazolidinone derivatives, Linezolide, Tedizolid, and Radezolid. The 1,3-oxazolidin-2-one ring is an unusual cyclic carbamate skeleton in natural product chemistry, but it has become rather important in medicinal chemistry since the introduction of linezolid, an oxazolidin-2-one based antibacterial medication, to the market. Figure 3 shows the structure-activity connection of linezolid (14).



Ring A, the oxazolidinone ring, the (*S*) configuration optimal activity of position 5 acetamido- group. Large substations lose antibacterial activity.

Ring B, is an essential ring because it contains fluorine atom at *meta*-position, and acts as a rigid linker between ring A and ring C. Additional substitution on ring B has deleterious effects on activity.

Ring C, Morphilino ring as electron-donating (N) and improve safety. Any additional substitution on morphlino ring can reduce its total activity. Finally, the morphline ring will enhance the pharmacokinetics and water solubility.

The structure-activity relationship of tedizolid

Tedizolid is another example of 1,3-oxazolidinone derivative, this drug compound having the adopted name tedizolid phosphate, the IUPAC name [(5*R*)-3- [3-fluoro-4- [6-(2-methyltetrazol-5-yl) pyridin-3-yl]phenyl]-2-oxo- 1,3-oxazolidin-5-yl]methyl dihydrogen phosphate, and is represented by the structure of formula Figure 8.

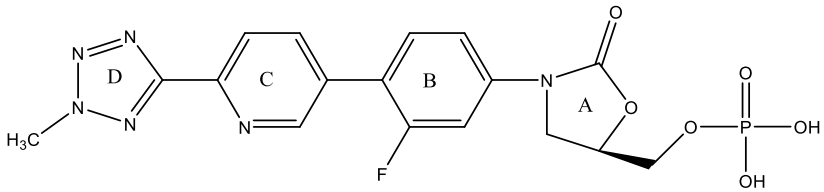


Figure 8: Chemical structure of Tedizolid phosphate

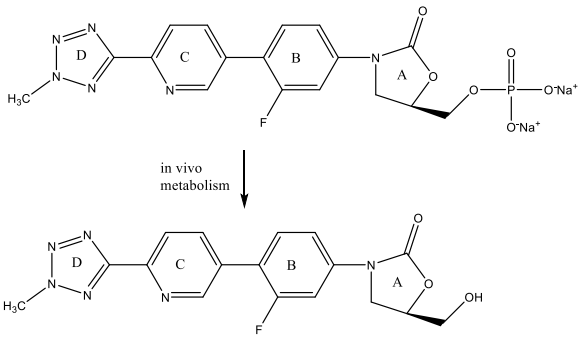
It is used to treat the bacterial skin and skin structure infections (ABSSSI) caused by certain susceptible bacteria, including *Staphylococcus aureus* (including methicillin-resistant strains (MRSA) and methicillin-susceptible strains), various *Streptococcus* species, and *Enterococcus faecalis* (15).

- The SAR of tedizolid can classify according to its structure to four rings Figure 8. This novel agent tedizolid phosphate and known as a prodrug, and can be hydrolyzed *in vivo* to give tedizolid.

  Ring A, the oxazolidinone ring 5-(*R*) configuration is necessary for antibacterial activity. The phosphate group (PO_4^-) is polar and improves water solubility and bioavailability.

  Ring B, the N-atom at position 3of the oxazolidinone ring attach substituted aromatic ring with (F), it enhances the antibacterial activity.

Ring C is a pyridine ring active and increases the potency over the linezolid. Both rings B&C are the bridge between ring A the ring D. This class are known as the biaryl ring system. Ring D is a five-membered tetrazole ring that can improve antibacterial activity by interacting with the Peptidyl transferase core in a different way. Tedizolid phosphate is an antibiotic with a broad spectrum of action against Gram-positive and Gram-negative bacteria (16). Tedizolid works in the same way as other oxazolidinones by inhibiting bacterial protein synthesis by binding to the 23S ribosomal RNA (rRNA) of the 50S subunit of the ribosome. Tedizolid is four to eight times more active than linezolid. Scheme 1 depicts the enzymatic hydrolysis in vivo metabolism (17).



Scheme 1: The metabolism of Tedizolid phosphate disodium *in vivo*.

The structure-activity relationship of Radezolid

- Radezolid (RDZ) is an investigational oxazolidinone with excellent *in vitro* and *in vivo* activity against a variety of Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA)(18,19).
- Is a novel antibiotic being developed by Melinta Therapeutics, Inc. for the treatment of bacterial acne. Chemically, this organic compound belongs to the class known as biphenyls (biaryloxazolidinone) as shown in Figure 9. The linker between the phenyl and the triazole ring is the amine moiety (20,21).

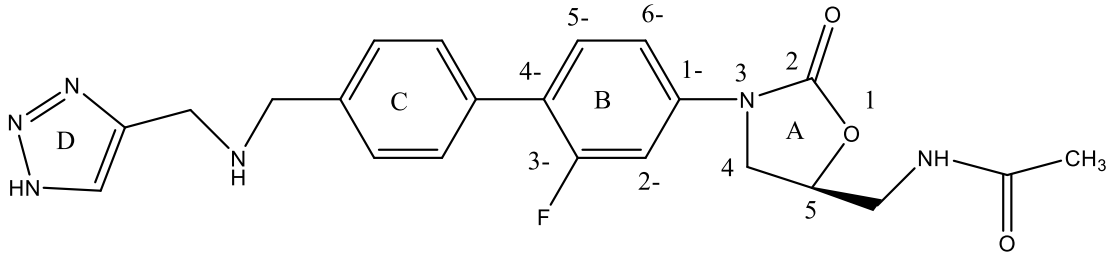


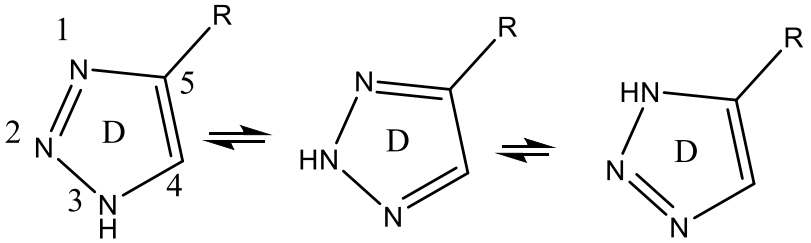
Figure 9: Chemical structure od Radezolid

Radezolid (RDZ) is active against Gram-positive bacteria that are susceptible to linezolid and resistant to it, as well as Gram-negative bacteria including *Haemophilus influenzae* and *Moraxella catarrahalis* (22). In comparison to linezolid, it is 11 times more active.

Ring A, the interaction with the peptidyltransferase center (PTC) of 50S ribosome subunit.

Rings B&C are a biphenyl group attached to the nitrogen position 3 of the oxazolidinone ring and increase the pi(π)-stacking. The phenyl ring (ring C) can modulate the pharmacokinetic parameters.

Ring D, to improve the lipophilicity of the radezolid. The secondary amine is the spacer between ring C & ring D(23,24). The ring D of the radezolid is triazole with 3*H*-tautomer and all tautomers are shown in Figure 10.



3*H*-tautmer 2*H*-tautomer 1*H*-tautomer

Figure 10: Three tautomer of the triazole ring.

Finally, and most crucially, the development of novel antibacterial drugs with unique modes of action holds a lot of potential. Existing antimicrobial medications would not be able to cross-resist such substances. The research that led to the development of linezolid, the first clinically useful oxazolidinone antibacterial drug, is described in this study.

CONCLUSION:

Oxazolidinones are new synthetic small organic compounds (Linezolid, Tedizolid phosphate, and Radezolid) that differ in their activity against Gram-positive bacteria according to their SAR. Tedizolid phosphate is more active than linezolid.

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