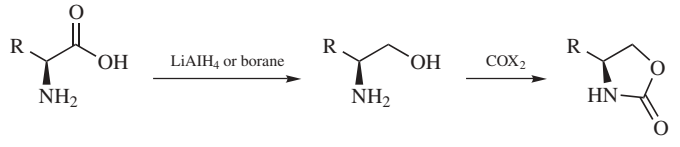
OXAZOLIDINONES, ANTIBACTERIAL

1. Introduction

The onslaught of environmental and clinical pressures and the rapid globalization of many strains through international travel have triggered change and adaptation in bacterial species in a way that is unprecedented in history. One consequence of the constant and accelerated change on bacteria is that they rapidly acquire resistance to drugs, even those whose modes of action seem unconnected. Because of this, the phenomenon of drug resistance, especially multiple drug resistance, has emerged as a primary health concern. It has led to an exhaustion of the clinically useful drug classes available for antibacterial therapies. This resistance phenomenon has also opened up opportunities for the introduction of new drug classes with radically different chemical functionalities not present in any of the classes to which organisms have been exposed to thus far.

Among the bacteria that pose a considerable threat because of drug resistance, *Staphylococcus aureus, Streptococcus pneumoniae*, and *Enterococcus spp* are the most cited among the gram-positive organisms. *Escherichia coli* and *Pseudomonas aeruginosa* are two of the important pathogens among the gram-negative organisms. Several fungi have also shown increasing drug resistance. Some important drug resistant microorganisms and a brief description of their clinical consequences are shown in Figure 1. Vancomycin (Fig. 2) has traditionally been the drug of last resort for the treatment of *S. aureus* infections. It is also active against *Staphylococcus epidermidis* (including heterogeneous methicillin-resistant strains) various streptococci including *Streptococcus pyogenes* and *S. pneumoniae* (penicillin-resistant strains included) and enterococci such as *Enterococcus faecalis*. The oxazolidinones are a very new class of antibacterial drugs. They are being developed to fill the gap caused by the increasing instances of resistance to vancomycin and other last-line of defense drugs. There is also much hope for their development and eventual adoption as therapies with a much wider scope.

The oxazolidinone nucleus (Fig. 3) is a simple heterocyclic system that is not found in drug structures with as much frequency as one might expect. The 4-substituted systems are better known because they are readily obtained from amino acids by reduction and carbonylation (eq. **1**). The 5-substituted oxazolidinones are more difficult to prepare but are of special relevance to the area of antibacterials. Of these, those bearing a substituted methyl group in this 5-position are especially relevant.



(1)

X = Cl or similar leaving group

The first oxazolidinones to show any appreciable activity against bacteria were first described by a South African group in a 1968 patent (1). This group prepared a very extensive series of 3-(5-nitrofurfurylideneamino)-5-($ROCH_2$-substituted)-oxazolidin-2-ones (Fig. 4) having antibacterial, antihelmitic, trypanocidal, and antimalarial activity. They proposed that these should be useful in a range of applications including the treatment of intestinal and urinary track infections. In more recent times, the first attempts to commercialize these compounds came from a group at Du Pont. There were two main candidates from these efforts, DUP-721 and DUP-105 (Fig. 5). These belong to a general class of (*S*)-5-acetamidomethyl-3-aryloxazolidin-2-ones (2,3). Although these candidates did not make it past the very early stages of the clinical trials process, they none the less served as the key structural templates on which the first successful oxazolidinone candidates were based. Some 13 or so years later in April of 2000, linezolid (Fig. 6) was launched as the first of this new class of antibacterial agents. Another related drug eperezolid (Fig. 6) also had very favorable results in clinical evaluations. The indications for which linezolid was therapeutically beneficial included infections caused by vancomycin-resistant *Enterococcus faecium*, and *E. faecium* related bacteremia, complicated and uncomplicated skin and skin structure infections and nosocomial and community-acquired pneumonia (4). The drug shows no activity against gram-negative bacteria. This and instances of resistance coupled with a less than desirable bone marrow toxicity profile has opened up the floodgates for attempts at new and better oxazolidinone drugs.

2. Structure–Activity

Perhaps the most striking feature of the antimicrobial-active oxazolidinones is their structural simplicity compared to vancomycin, the previous last-resort drug. The sheer structural complexity of vancomycin precluded any comprehensive structure–activity relationship studies. In contrast, the relative ease with which oxazolidinone candidates could be made has led to a good understanding of structure–activity relationships and it is possible to see how new oxazolidinone drugs have evolved based on the structures of earlier drugs. For example, the candidates PNU-82965 and PNU-85112 (Fig. 7) preceded linezolid and eperezolid.

Very early in the development of oxazolidinones as antimicrobial drugs, some structure–activity rules began to appear. Activity was determined to be a function of the size and nature of the 5-substituent, the nature of the 3-substituent, and the configuration at the 5-position. This finding is illustrated in Figure 8. If the molecule is oriented with the oxazolidinone group to the left and the carbonyl group pointing up then the active molecule is the isomer in which the substituent at the 5-position is coming forward (proximal) and not the one in which it is receding (distal) (5). In the case of linezolid and PNUX-82965 and PNUX-85112 this corresponds to the (*S*)-isomer. It is important to note that if the acetamido group in linezolid were changed to an acetoxy or thioacetamido group, the Cahn–Ingold–Prelog designation would be (*R*), hence the distal and proximal orientations are used here. Another structure–activity feature of oxazolidinones was that the 3-substituent was invariably a phenyl group.

It was observed that molecules containing 3-aryl substituents with 2,4 and 2,5 disubstituents had weak or no antibacterial activity. 3,4-Disubstituted or 4-monosubstituted compounds had good activity provided the 3-substituent was small (6). In one study (7), where a series of 4-substituents (specifically alkyl, ethenyl, ethynyl, hydroxyalkyl, aldo and keto, oximinoalkyl, carboalkoxy, nitro, amino, halo and Ψ-halo, alkylthio, alkylsulfinyl and alkylsulfonyl) was evaluated, several broad trends were observed. In several series of homologue (specifically alkyl, keto, oximinoalkyl, amino, halo and -Ψ-halo, and alkylthio), it was observed that antibacterial activity increased with increasing lipophilicity. A different trend was observed in series where the 4-substituent was a tri- or tetrasubstituted (substituent >H) quaternary atom attached directly to the aromatic ring (hydroxyalkyl, alkylsulfinyl, alkylsulfonyl). In these cases, the antibacterial activity was a maximum at the member of the series with the "tert-butyl" substitution pattern. It was also observed that conjugated electron-withdrawing substituents in the 4-position of the phenyl group also had increased activity compared to nonconjugated analog of similar lipophilicity.

Among other trends, replacement of the carbonyl oxygen at the 2-position with sulfur was observed to give compounds with good activity (8). The substituent on the methyl group at the 5-position was thought to be optimally small with a nitrogen atom substituting the C-5 methyl. This nitrogen atom was invariably nonbasic and an acetamido function was thought to be optimum (9). That this structural dogma dominated the early candidates could certainly be concluded by an examination of the structures just entering the preclinical stage at the time (Fig. 9).

Recently, some marked departures in structure from the earlier candidates have been seen. Most of these departures occur in the nature of the 3-substituent on the oxazolidinone ring. There are far fewer variations in the 5-methyl substituent. This notwithstanding, structures such as **1** (10), **2–4** (11) with modifications outside of the earlier structure–activity relationships (Fig. 10) have been developed and show very good activity against several classes of bacteria. There are other examples in which the nitrogen normally attached to the 5-methyl group has been replaced by a sulfur atom bound to a more complex functionality (12,13).

Although there have been great strides in the evolution of active oxazolidinone structures and (to a much more limited extent) the refining of SAR models, the expansion of oxazolidinones to cover gram negative organisms or a much larger sphere of gram positives has had only very limited success. The use of thioamide substituents in the 5-methyl group in compounds such as PNU 255889 (Fig. 11) has led to more active compounds with an increased therapeutic range including the gram-negative bacteria *Moraxella catarrhalis* and *H. influenzae* (14–16). Strains for which activity was observed also included *S. aureus, S. epidermidis, S. pneumoniae*, and *E. faecalis*.

Another attempt to broaden therapeutic spectrum involved integrating phenylpyridium and cephem moieties into the 3-substituent of the oxazolidinone ring (Fig. 12). Such compounds proved to be active against both gram-negative and gram-positive bacteria (17).

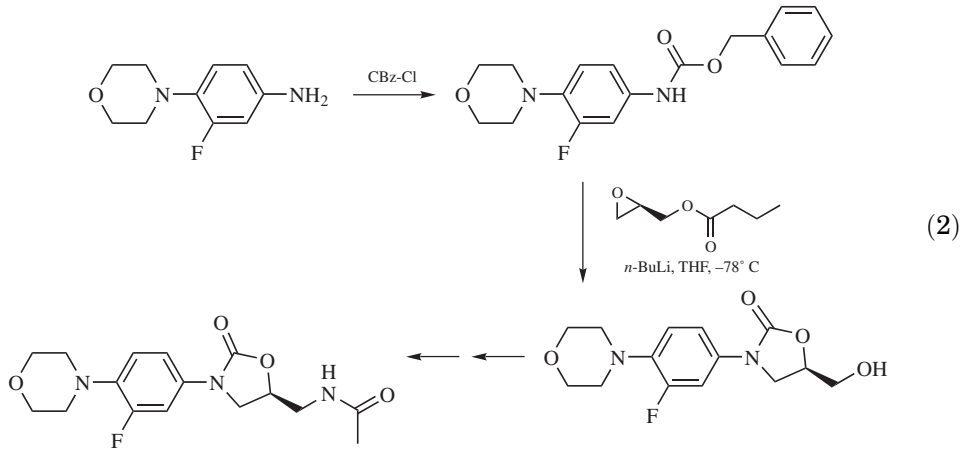
3. Mode of Action

At the time of writing, there is still some debate as to the mode of action of oxazolidinones. Very early in the development of these compounds as antibacterial agents, it was determined that their mode of action was not by inhibition or impairment of cell wall synthesis (18). Studies on the ability of linezolid and eperezolid to inhibit cell-free transcription-translation in *E. coli* indicated that inhibition of protein synthesis by this mechanism was the mode of action (19). Based on studies such as this, it became generally accepted that oxazolidinones inhibit protein synthesis by interacting with the ribosome. Further studies defined more closely the nature of this interaction. In one such study (20), ultraviolet-induced cross-linking using an azido oxazolidinone derivative and chemical footprinting with dimethyl sulfate were used to evaluate the binding interactions of oxazolidinones to 70S ribosomes from *E. coli*. Oxazolidinone binding sites were found on both the 30S and the 50S subunits. The ribosomal RNA (rRNA) was the only binding site. An oxazolidinone footprint was found on the 16S rRNA, at A864 in the central domain. Several residues (viz. U2113, A2114, U2118, A2119, and C2153, all in domain V) in the 23S rRNA residues were also shown to be involved in oxazolidinone binding. This occurred in a region close to the binding site of protein L1 and of the 3′ end of transfer RNA (tRNA) in the E site. This study followed one in which it was concluded that oxazolidinones do not interfere with translation initiation during mRNA binding or during formation of 30S preinitiation complexes but inhibits the puromycin-mediated release of 35S-formylmethionine from 70S initiation complexes in a dose-dependent manner (21). In a more recent study (22), results led to the proposal that oxazolidinones inhibit bacterial protein biosynthesis by interfering with the binding of initiator fMet-tRNAiMet to the ribosomal peptidyltransferase P-site.

There have recently been some major developments in ribosome chemistry with the solution of the crystal structure of the entire ribosome (23) a high resolution structure of the 50S subunit (24) and a structure for the 30S subunit (25). The 30S subunit is the site that controls the fidelity of the translation process by mediating the interaction between the mRNA codons and the tRNA anticodons. The larger subunit (50S) contains the catalytic site for peptide bond formation (peptidyl transferase activity) and is involved in the regulation of other aspects of protein synthesis by binding G-proteins and initiation, elongation, and termination factors. The 50S subunit contains the 23S component, which is composed entirely of RNA. Based on this X-ray crystallography information, the 23S ribosomal RNA component of the 50S subunit has been shown to be the binding site of several antibiotics that inhibit protein synthesis. These include such as chloramphenicol, clindamycin, erythromycin, clarithromycin, tylosin, carbomycin A, spiramycin, azithromycin, and roxithromycin (26,27). To date, a crystal structure of an oxazolidinone bound to a ribosomal subunit has not been described. The availability of these ribosome structures will, no doubt, act as a tremendous boost to the structural biology and rational design component of oxazolidinone discovery chemistry.

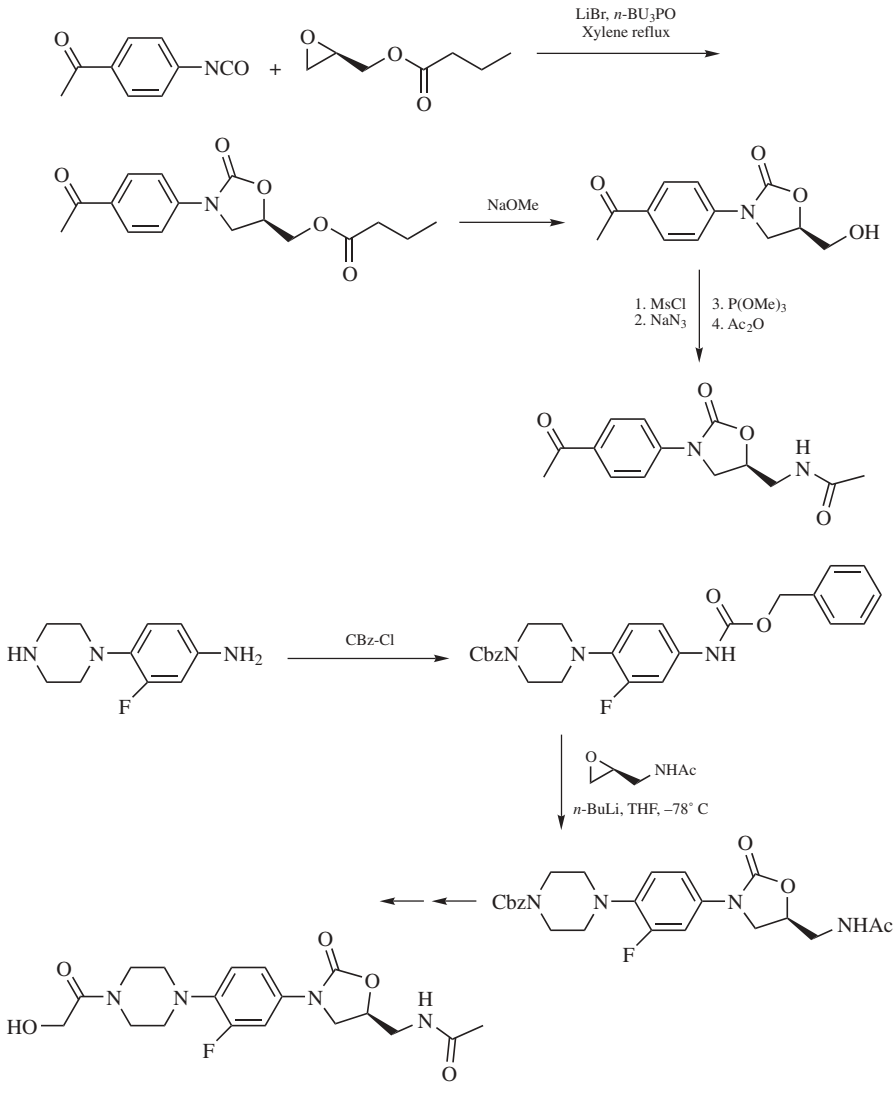
4. Synthesis

Synthetic access to oxazolidinones has been a matter of very high priority. There is a plethora of methods and approaches spanning a wide spectrum of strategies ranging from asymmetric catalysis (transition metal and enzymatic), biotransformations, and chiral pool approaches. The introduction of the important chiral center in the 5-position of the ring is an important general feature of the strategies that have been developed. Methods in which a chiral 3-carbon fragment or synthon is condensed with an activated nitrogen compound (usually an anion) dominate the literature on oxazolidinone synthesis. Probably the most used of these is the one shown in eq. **2** and employed in the preparation of linezolid (28,29). In this method, an amine containing the would-be 3-aryl or alkyl substituent is transformed to a carbamate by reaction with benzyloxycarbonyl chloride. The carbamate is then lithiated and reacted with a glycidyl ester to form a 3-aryl or alkyl-5-hydroxymethyl-2-oxazolidinone. The primary hydroxyl is then transformed to an acetamido group by mesylation, conversion of the mesyloxy group to an azido group, and reduction of the azido group to an amino function followed by acetylation to form the 5-acetamidomethyl group.



(2)

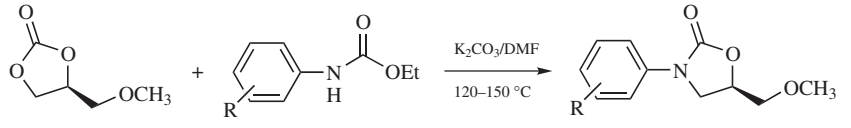
A different approach (eq. **3**) was used in the preparation of DUP-721 (30,31). In this case, an isocyanate was reacted with glycidyl butyrate in the presence of tri-*n*-butylphosphine oxide to yield the N-arylated oxazolidinone nucleus directly. The hydroxymethyl group is then deacylated and transformed to the acetamidomethyl group by the same process involving mesylation, displacement by azide, reduction, and acylation described earlier. A related approach to the two previous methods but in which a chiral oxiranymethylacetamide was used to alkylate a lithiated carbamate has been described (eq. **4**) (32). In this method, the chiral oxiranylmethylacetamide was prepared by kinetic resolution of racemic epichlorohydrin using a chiral transition metal complex as catalyst.



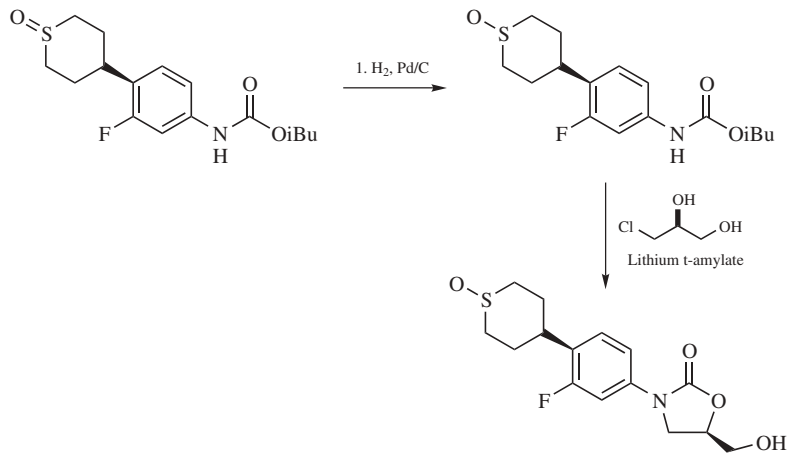
(3)

(4)

The reaction of cyclic carbonates with carbamate esters at elevated temperatures in the presence of a base has been used to prepare oxazolidinones. Hence, the reaction of 4-methoxymethyl-1,3-dioxolan-2-one (a functionalized 3-carbon chiral synthon based on glycerol) with a carbamate ester in the presence of potassium carbonate in dimethylformamide (DMF) yielded an 3-*N*-aryl-5-methoxymethyloxazolidin-2-one directly (33) (eq. **5**). The relatively simple 3-carbon synthon 1-chloro-2,3-dihydroxypropane has been reacted with a lithiated carbamate to yield 3-*N*-aryl-5-hydroxymethyloxazolidin-2-ones directly (34) (eq. **6**).

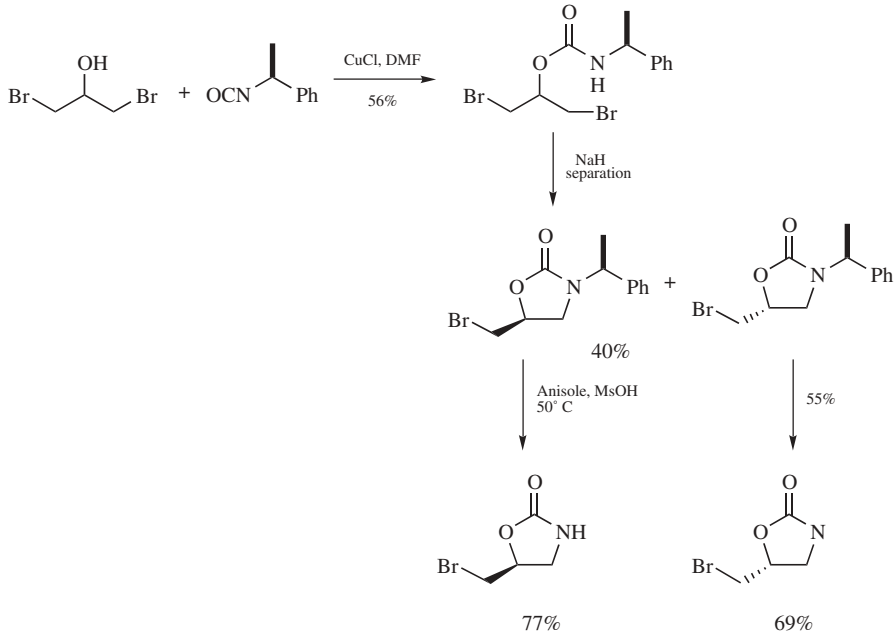


(5)

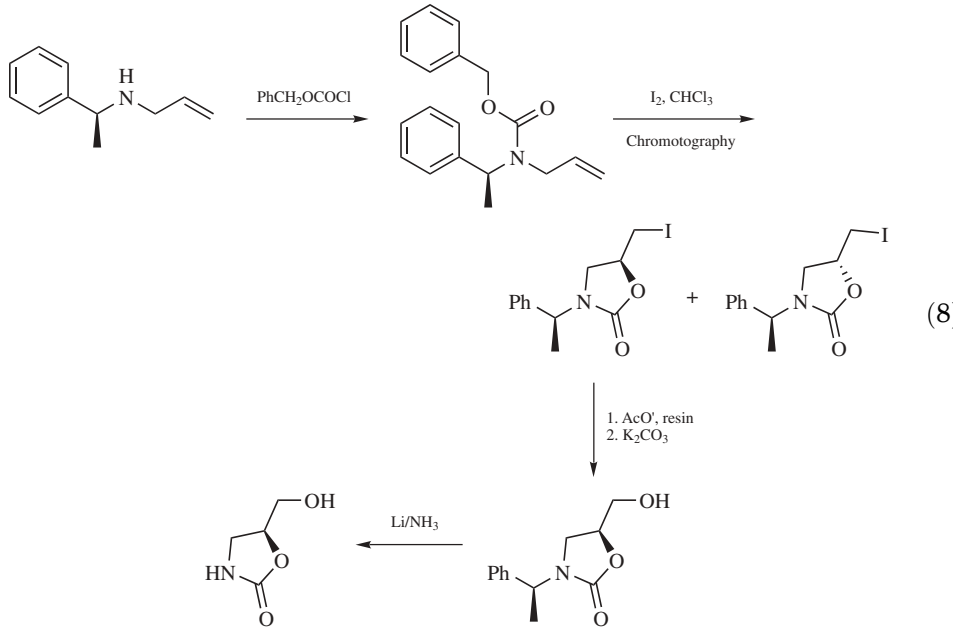


(6)

The use of chiral auxiliaries to form optically pure oxazolidinones formed from achiral 3-synthons represents yet another approach to the synthesis of oxazolidinones. Hence, 1,3-dibromo-2-propane and optically pure 1-phenylethylisocyanate were used to prepare optically pure 5-hydroxymethyloxazolidin-2-ones. The diasteromers were separated by chromatography (35) (eq. **7**). In another report using optically pure phenylethyl derivative as a chiral auxiliary (36), the 3-carbon 5-substituted-2-oxazolidinone core was obtained from an allyl group. In this method (eq. **8**), the chiral auxiliary and the allyl group are installed on the nitrogen atom of *o*-benzylcarbamic acid. The double bond on the allyl group is activated for addition of the benzyloxy oxygen with iodine. The diastereomeric 5-iodomethyl oxazolidinones are separated chromatographically.

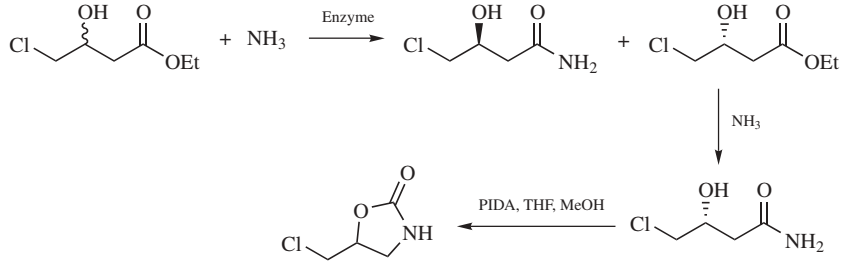


(7)



(8)

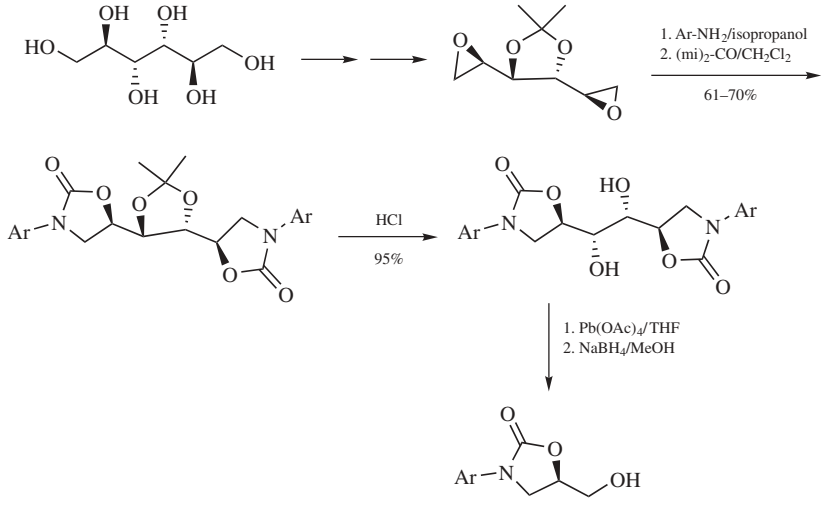
Enzymatic resolution has been used to prepare optically pure oxazolidinones from racemic 4-chloro-3-hydroxybutyric acid ethyl ester by enzymatic amidation using a lipase to selectively form the (*R*)-3-hydroxyamide (37). In this method (eq. **9**), the 5-chloromethyl-2-oxazolidinone was obtained by carrying out a Curtius rearrangement on the amide trapping the intermediate isocyanate with the 3-hydroxyl group to form the oxazolidinone nucleus.



(9)

The chiral pool represents an important access to optically pure oxazolidinones. In one such method (38), mannitol was used to prepare 1,2-5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol as a starting point in oxazolidinone synthesis (eq. **10**). This intermediate was reacted with aniline and then with carbonyldiimidazole to form a bis(oxazolidinone). Removal of the acetal group, tetraacetate oxidation of the diol to form two molecules of the 5-formyl-3-phenyl-2-oxazolidinone followed by reduction of the aldehyde group yielded the (*S*)-5-hydroxymethyl-3-phenyl-2-oxazolidinone. Other syntheses of enantiomerically pure

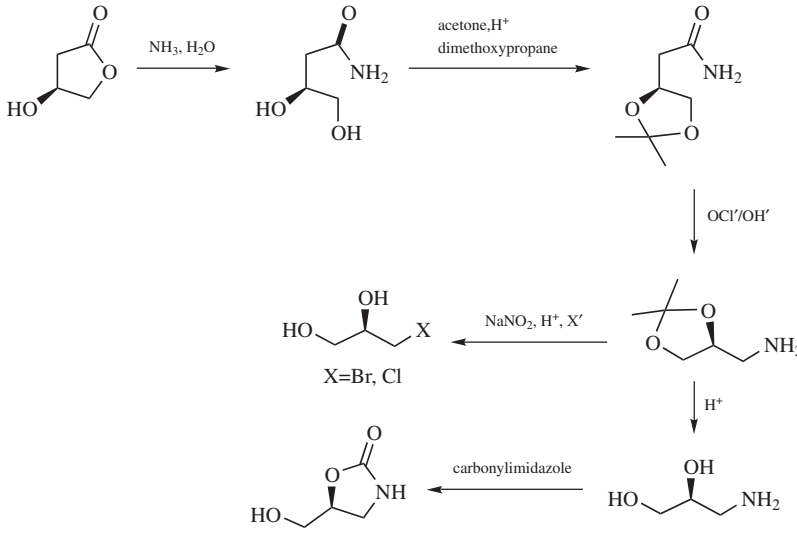
(*R*)- and (*S*)-5-hydroxymethyl-2-oxazolidinones from D-mannitol, L-ascorbic acid, and (*R*)- or (*S*)-malic acid have also been described (39).



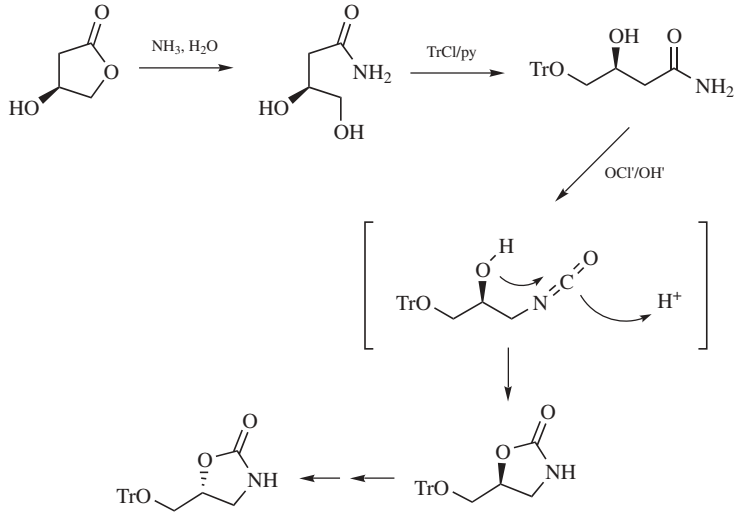
(10)

The introduction of commercially important methods for preparing optically pure 3,4-dihydroxybutyric acids and various 3- and 4-carbon derivatives (40–45) has opened up the way to the preparation of optically pure oxazolidinones. The ready availability of enantiopure 3,4-dihydroxybutyramides by treatment of 3-hydroxy-γ-butyrolactone by ammonia has facilitated several routes. In one method (46), the isopropylidene acetal of 3,4-dihydroxybutyramide was subjected to Curtius rearrangement to afford the protected 3-amino-1,2-dihydroxypropane (eq. **11**). This latter intermediate can be deprotected and converted to 5-hydroxymethyl-2-oxazolidinone by treatment with carbonylimidazole. The 3-amino-1,2-dihydroxypropane can also be converted to 1-halo-2,3-dihydroxypropanes, which can be used in alternative syntheses of oxazolidinones.

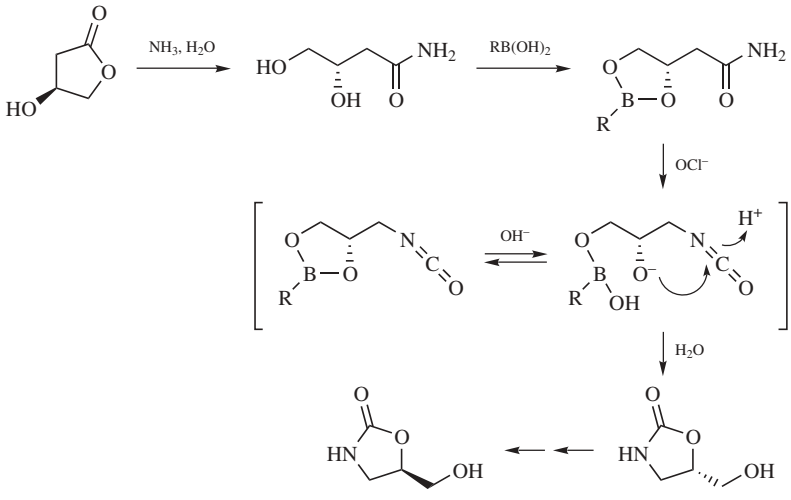
Enantiopure 3,4-dihydroxybutyramides can be converted to their 4-trityloxy derivatives that yield 5-trityloxymethyl-2-oxazolidinones when subjected to Hofmann rearrangement (eq. **12**) (47). These are new intermediates that can be used for the quick and efficient synthesis of oxazolidinone familes. Dynamic protection of enantiopure 3,4-dihydroxybutyramides with alkyl or arylboronic acids followed by Hofmann rearrangement yields the free 5-hydroxymethyloxazolidinones directly (eq. **13**) (48). This is an important new development since enantiopure 3,4-dihydroxybutyramides are available in only two steps from starch, lactose, maltose, and hemicelluloses. The boronic acid derivatives can be generated *in situ* and transformed directly.


NH3, H2O
acetone,H+
dimethoxypropane
OCl′/OH′
NaNO2, H+, X′
X=Br, Cl
H+
carbonylimidazole

(11)


NH3, H2O
TrCl/py
OCl'/OH'
H+

(12)

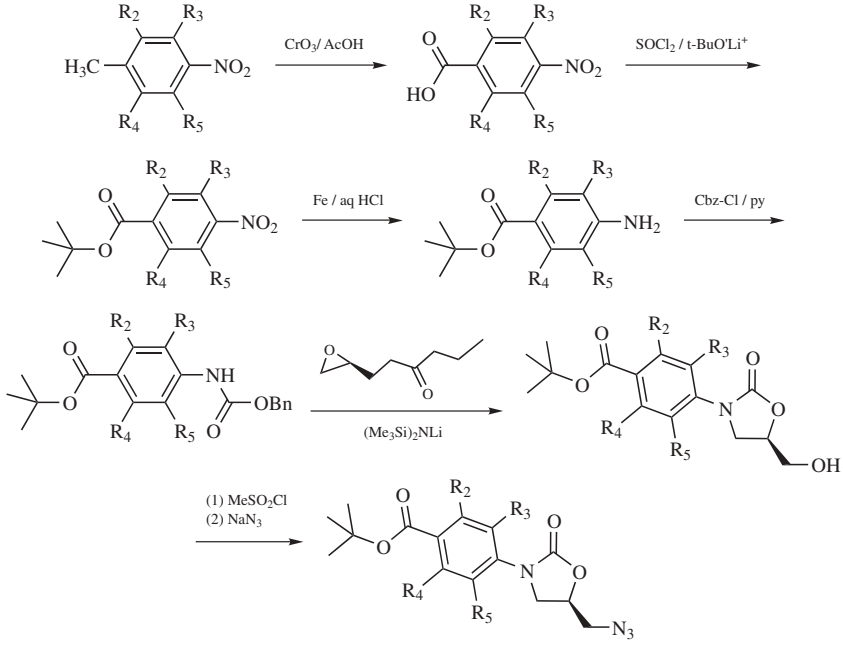


(13)

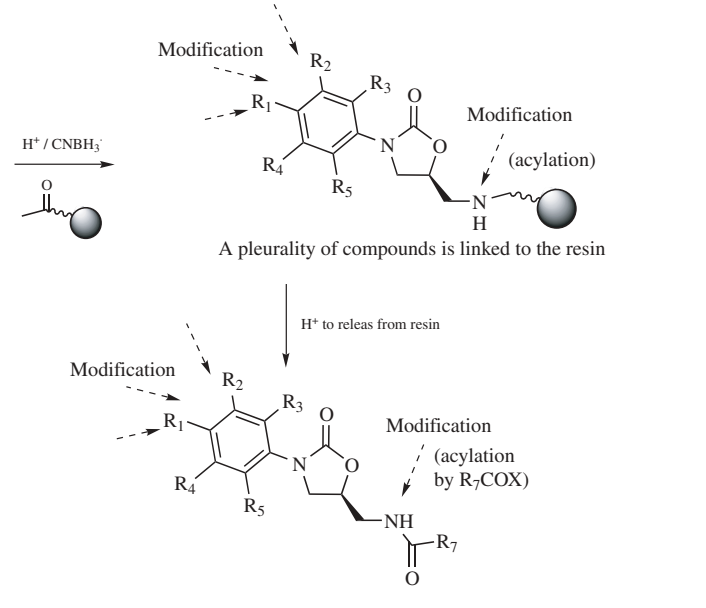
The preparation of libraries of oxazolidinones represents another area of keen interest in the development of synthetic methods for these compounds. One method (49) permits variations at the 3-,4-, and 5-positions of the oxazolidinone ring. A synthetic scheme describing three independent variations at these three positions to give 27 (3^3) compounds has been described. The syntheses start from (triphenylmethoxymethyl)-3-oxa-1-azabicyclo[3.1.0]hexan-2-one as a starting material for library generation. This latter compound was prepared using an intramolecular acylnitrene-mediated aziridination reaction.

There are two very noteworthy patents describing the preparation of oxazolidinone libraries and their uses (50,51). The first of these describes the preparation of basic oxazolidinone libraries and the second one describes more simple transformations and modifications combined with applications. The preparation of libraries revolves around three major themes. The first one is the preparation of libraries of 3-aryl-5-azidomethyl-oxazolidin-2-ones with various functionalities in the aryl group (eq. **14**). In these libraries, the ability to modify the para- position of the phenyl group is a key feature of the design. In the subsequent step (eq. **15**) azido group is reduced to an amino group and a pleurality of 5-aminomethyl-3-aryl-oxazolidin-2-ones is attached via the amino group to a resin. Once attached to the resin, modifications to the aryl group and the amino group at the 5-position are made and the products are then released from the resin. This approach allows the preparation of enantiopure libraries because the oxazolidinone skeleton is prepared from optically pure glycidylbutyrate. The same patent also describes a radically different approach where allylamine is attached to a resin and the vinyl group epoxidized (eq. **16**). The epoxide is then reacted with a pleurality of *N*-alkyl or aryl-*O*-benzyl-amidates in the presence of a strong base to generate a pleurality of bound 3-alkyl (or aryl)-5-aminomethyloxazolidin-2-ones. The bound compounds are further functionalized on the amino nitrogen and then released from the resin liberating a diversity of compounds. Compounds produced by this method are racemic. The second patent describes further transformations and applications of these compounds. The topic of combinatorial synthesis approaches

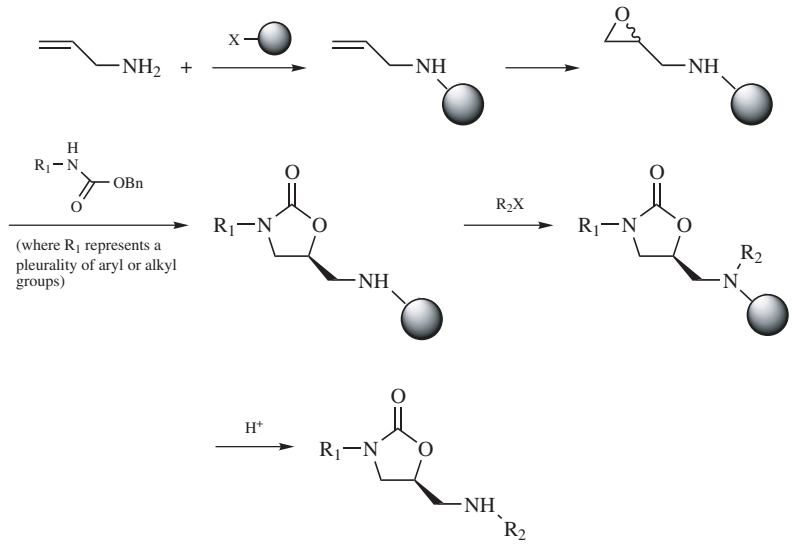
to oxazolidinones has been reviewed (52).



(14)



(15)



(16)

5. Conclusion

The activity in the field of oxazolidinones continues as we struggle to keep pace with the constant evolution of the bacterial genome through an alarmingly large number of pathways. These range from mutation to gene exchange to the acquisition or activation of efflux and related mechanisms. Reports in resistance to oxazolidinones and efforts to mute or eliminate the structural basis for bone marrow toxicity observed in earlier candidates will also fuel the evolution of oxazolidinone drugs. New frontiers for these drugs also include gram-negative bacteria and antifungals. Even the development of truly broad spectrum compounds will represent a significant advance. The chemistry platforms that are available to support these activities continue to evolve. The greatest challenge is the development of a true understanding of the mode(s) of action of these drugs and a better understanding of the relationship between structure and activity.

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ANTIMICROBIAL TARGET ORGANISMS

BACTERIA (Grampositive)

Generally the target class for oxazolidinones. These include the most dangerous pathogens especially those that have become resistant to known drugs. Only one drug, linezolid (Zyvox™) beyond vancomycin is available for treatment of infections by drug resistant *S. aureus, E. faecium* and *S. pneumonia* strains. The area of multidrug resistance involving these pathogens represents one of the largest unmet needs in medicine today.

The linezolid therapeutic spectrum

Staphylococcus aureus

Nosocomial pneumonia
Skin infections
Community-acquired pneumonia

Streptococcus pneumoniae

Community-acquired pneumonia
Nosocomial pneumonia

Enterococus spp.

Urinary tract infections
Bacteremia
Wound infection
Endocardits

Special issues with Linezolid

Linezolid resistant strains have appeared

Bone marrow toxicity has been observed with Linezolid

Linezolid has a limited therapeutic scope (no Gram -ve activity)

BACTEFUA (Gram Negative)

Generallv difficult to treat because of extra nrotective laver and several resistance mechanisms including efflux, lactamase and other peptidase activities. Especially important area because of susceptibility of immuno-compromised individuals (eg AIDS) and the increased % of the elderly. Multiple drug resistances: 3rd generation cephalosporins, aminoglycosides, carbenicillin, polymixin, quinolones and monobactams all of which have toxicity or resistance profiles.

Pseudomonas aeruginosa

Pneumonia, UTI
Abscesses, Ear and eye infections
Septicemia, Endocarditis
Meningitis, Bronchopneumoia

Escherichia coli

UTI
Ulceration of mucosa

FUNGI

Generally difficult to treat because of cell wall and similarity to mammalian cells. Several resistance mechanisms. Especially important area because of susceptibility of immuno-compromised individuals (eg AIDS) and the increased % of the elderly. Other risk factors include open heart surgery, the use of catheters and stents, prosthetic valves, intravenous and drug use. Neonates and some chemotherapy patients are at special risk. There is a high level of toxicity associated with the use of current antifungal drugs The mechanisms of action are generally limited to inhibition of ergosterol synthesis with cell wall disruption and inhibition of glycan synthesis as two relatively minor mechanisms. This is one of the greatest areas of need.

Candida albicans

Vaginitis
Infection of bone, lung, liver, spleen, lung, pancreas and respiratory and digestive tracks and nervous system.

Aspergillus spp.

Infection of sinuses, lungs, kidney muscosa and skin.

Fig. 1. Important drug resistant microorganisms and their clinical consequences.

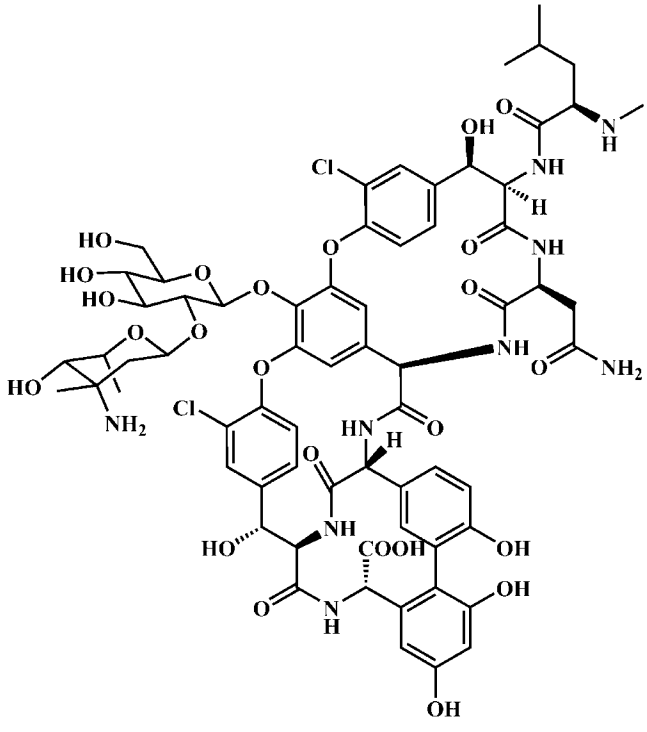
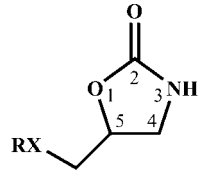


Fig. 2. Vancomycin.



X = a heteroatom (often O or N), R = alkyl or aryl

Fig. 3. Oxazolidinone nucleus.

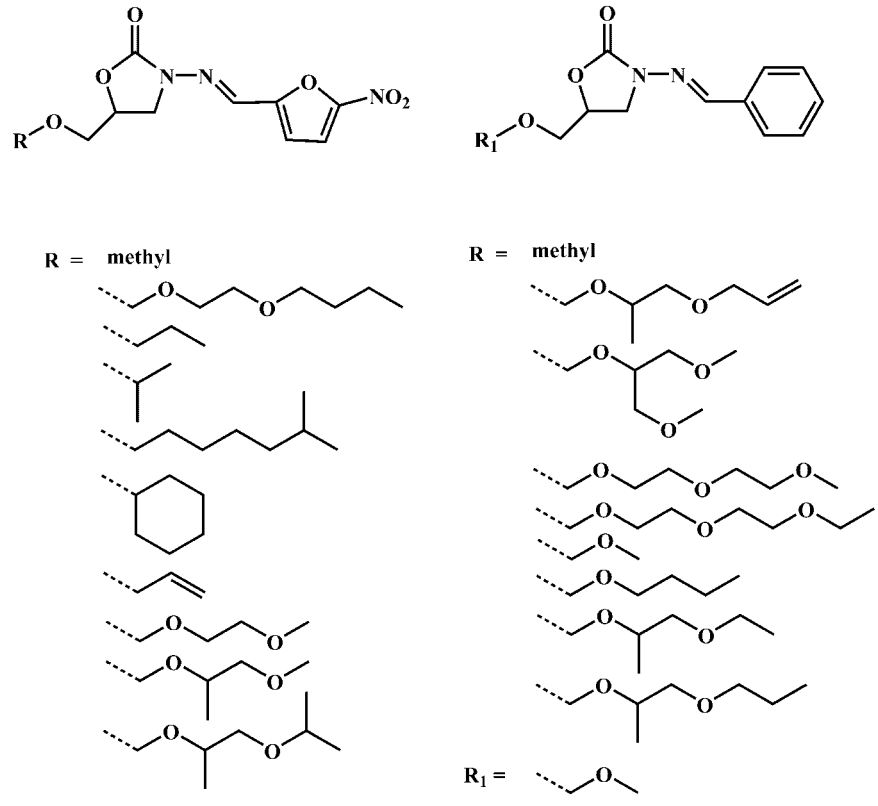


Fig. 4. 3-(5-Nitrofurfurylideneamino)-5-($ROCH_2$-substituted)-oxazolidin-2-ones.

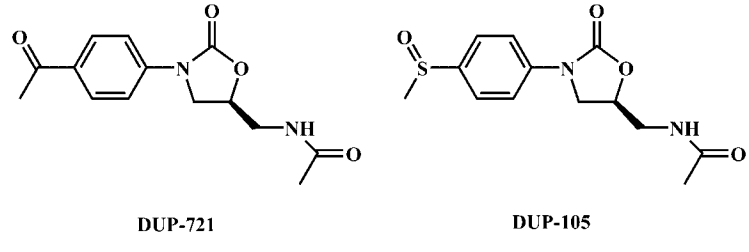
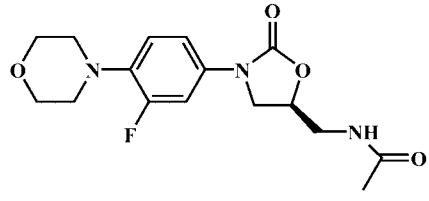
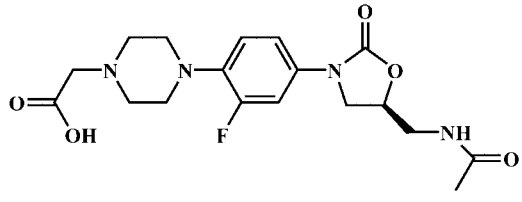


Fig. 5. DUP-721 and DUP-105.

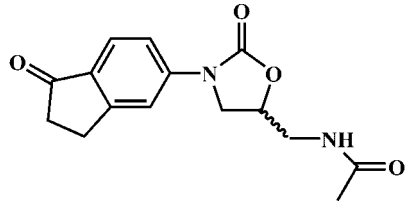


Linezolid (Zyvox)

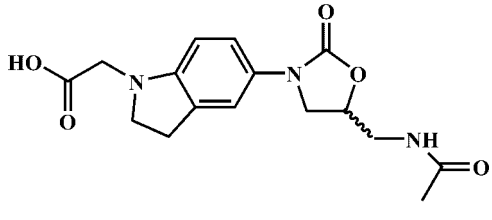


Eperezolid

Fig. 6. Linezolid and eperezolid.



PNU-82965



PNU-85112

Fig. 7. PNU-82965 and PNU-85112.

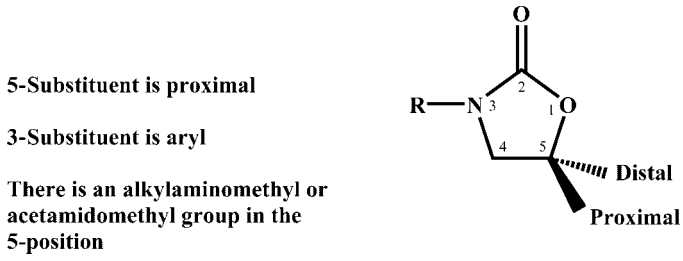


Fig. 8. Typical features for oxazolidinone antibacterial activity.

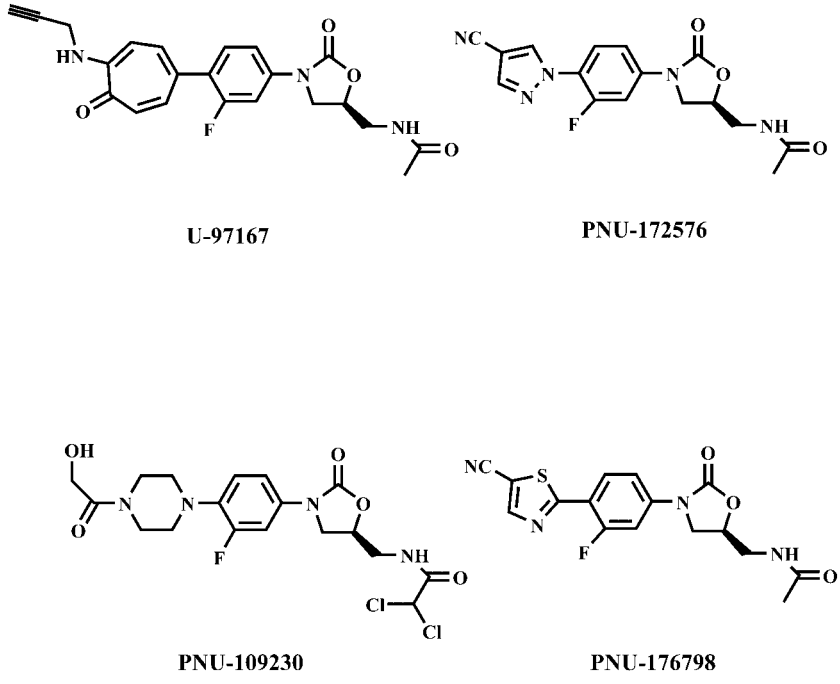
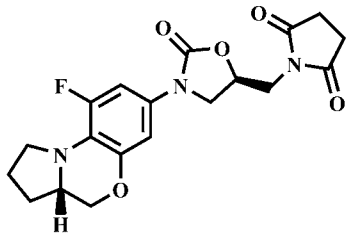
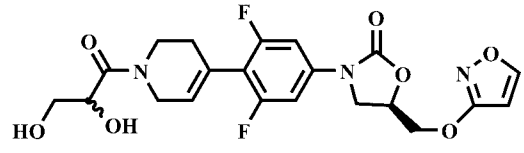


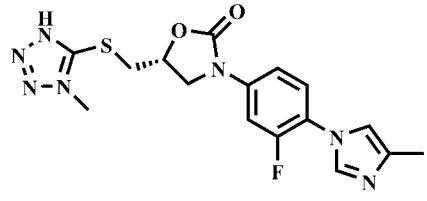
Fig. 9. U-97167, PNU-172576, PNU-109230, and PNU-176798.



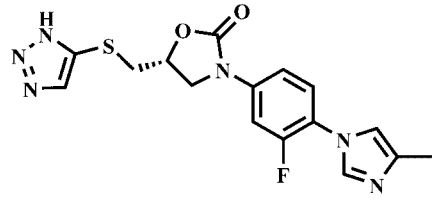
(1)



(2)

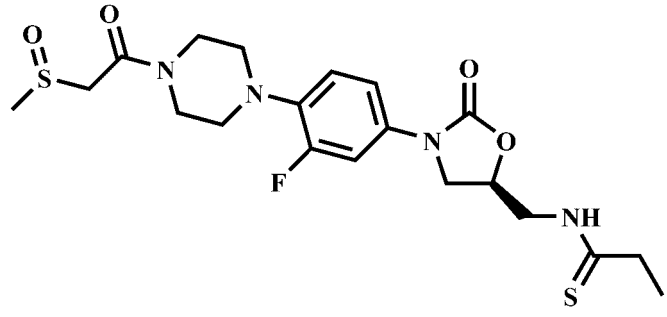


(3)



(4)

Fig. 10. Oxazolidinones.



PNU-255889

Fig. 11. PNU-255889.

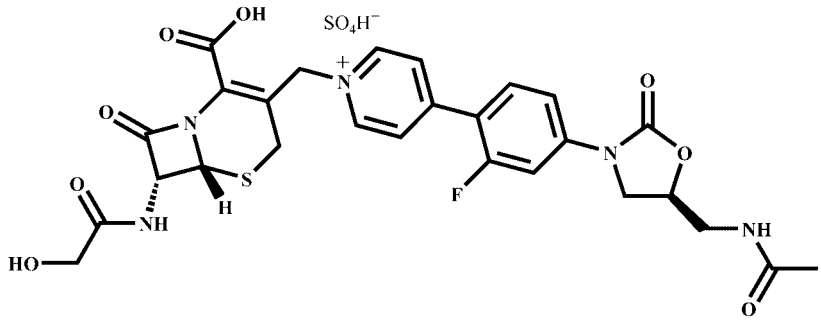


Fig. 12. Phenylpyridium and cephem moieties into the 3-substituent of the oxazolidinone ring.