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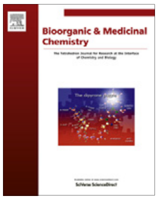

Review

Recent development of potent analogues of oxazolidinone antibacterial agents

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ABSTRACT

The oxazolidinones are a new and potent class of antimicrobial agents with activity mainly against Gram-positive strains. The commercial success of linezolid, the only FDA-approved oxazolidinone, has prompted many pharmaceutical companies to devote resources to this area of investigation. Until now, four types of chemical modifications of linezolid and oxazolidinone-type antibacterial agents, including modification on each of the A-(oxazolidinone), B-(phenyl), and C-(morpholine) rings as well as the C-5 side chain of the A-ring substructure, have been described. Division into sections according to side chain modification or the type of ring will be used throughout this review, although the process of synthesis usually involves the simultaneous modification of several elements of the linezolid substructure; therefore, assignment into the appropriate section depends on the structure–activity relationships (SAR) studies.

This review makes an attempt to summarise the work carried out in the period from 2006 until mid-2012.

Contents

1. Introduction

The problem of severe bacterial infections caused by multidrug-resistant bacteria is still growing. The number of effective antibacterial agents has diminished, because microorganisms are able to create new mechanisms of resistance and rapidly spread the genes encoding them via mobile genetic elements; mostly plasmids and integrons. Although infections caused by Gram-negative rods are especially emerging nowadays, the number of severe infections caused by Gram-positive bacteria, so-called alarm pathogens, for example, methicillin-resistant *Staphylococcus aureus* (MRSA),

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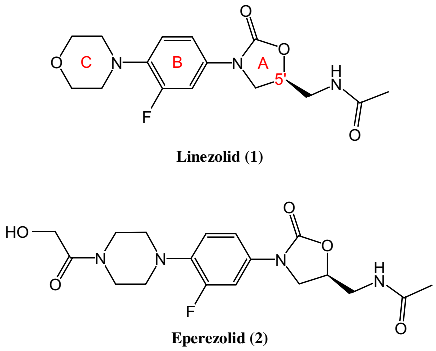


Figure 1. Structures of linezolid and eperezolid.

methicillin-resistant coagulase-negative staphylococci (MRCoNS), glycopeptide-resistant staphylococci (GISA, GRSA, VISA, VRSA) and enterococci (GRE, VRE), as well as *Streptococcus pneumoniae* resistant to beta-lactam antibiotics is also significantly high. The discovery or invention of new potent antibacterial agents is crucial and very urgent. Many scientific groups are performing basic analytical investigations in this field.

The oxazolidinones were discovered at E.I. du Pont Nemours & Company in the 1980s, and later developed at Pharmacia and Upjohn (now part of Pfizer), ultimately leading to linezolid, **1**, and an analogue, eperezolid (**2**) (Fig. 1).[1]

Linezolid is the only FDA-approved oxazolidinone antibacterial agent to have reached the market in over 35 years. It was approved by the FDA on April 18, 2000, and is currently marketed under the trade name Zyvox. Linezolid is highly-effective for the treatment of serious Gram-positive infections, including those caused by *S. pneumoniae*, and the highly challenging MRSA and vancomycin-resistant *Enterococcus faecium* strains (VRE), which are responsible for skin and soft tissue infections, pneumonias and bacteriemias.

Linezolid's mechanism of action is unique. Previous studies have suggested that oxazolidinones inhibit the formation of the initiation complex in bacterial translation systems by preventing the formation of the *N*-formylmethionyl-tRNA-ribosome-mRNA ternary complex.[2] However, the ability of oxazolidinones to inhibit the initiation of complex formation has only been observed at high ratios of oxazolidinones to ribosomes. The mechanism of action of oxazolidinones and the precise location of the drug binding site in the ribosome are not fully understood. Nevertheless, recent studies have revealed that oxazolidinones interact with the 50S A-site pocket at the peptidyltransferase centre (PTC) of the bacterial ribosome, which overlaps the aminoacyl moiety of an A-site bound tRNA, and therefore inhibits the overall protein synthesis process.[3–5] Wilson et al. presented a model for the better understanding of the mechanism of action of the oxazolidinones, which gives a valuable insight into potential pathways towards rational drug development.[4]

Unfortunately, despite this unique mechanism of action, relatively soon after the implementation of linezolid into therapeutic use, some cases of linezolid-resistant *S. aureus*[6,7] and *Enterococcus* spp.[8] were found among hospital isolates, and although the linezolid-resistant strains (LinR) appear relatively infrequently in the clinic, the infections caused by them were found to be life-threatening. Additionally, toxic side-effects of prolonged use of linezolid may result in reversible myelosuppression, including anaemia, leucopaenia, pancytopaenia and thrombocytopaenia. Non-reversible peripheral neuropathy, optic nerve damage and lactic acidosis can also develop. Linezolid has been shown to inhibit monoamine oxidase (MAO) enzymes, potentially leading to drug-drug interactions with adrenergic and serotonergic agents. More recently, knowledge regarding the structure–toxicity relationships of oxazolidinones in the context of mitochondrial protein synthesis (MPS) as well MAO inhibition (MAOi) has been systematised by Renslo.[9] Consequently, researchers have focused on modifying the oxazolidinone structure in order to seek analogues with the following features: (i) extended spectrum of antibacterial activity covering fastidious Gram-negative organisms; (ii) activity against LinR strains; and (iii) improved safety profile leading to circumvention or at least the minimisation of myelosuppression.

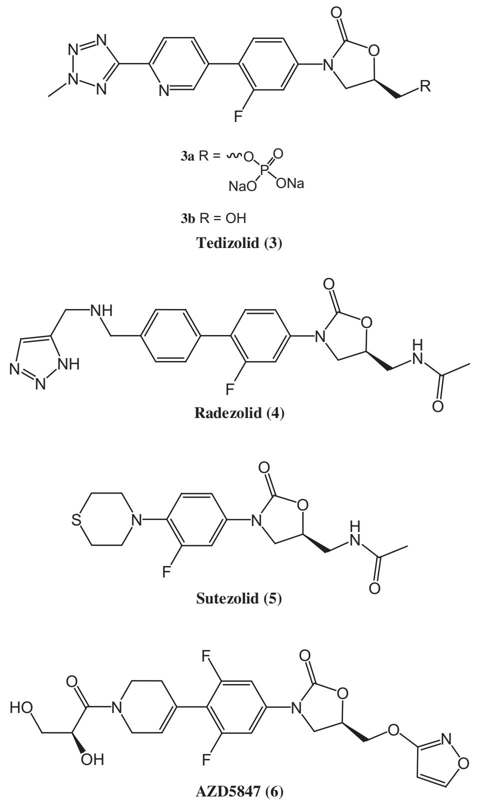


Figure 2. The oxazolidinones currently in clinical development.

The commercial success of linezolid has prompted many pharmaceutical companies to devote resources to this area of investigation. Thus, four oxazolidinones are currently undergoing clinical development (Fig. 2). The Trius Therapeutics prodrug compound tedizolid phosphate (**3a**, formerly known as torezolid phosphate, TR-701, DA-7218, DA-70218, DA-7158), which is the most advanced compound, recently completed the third stage of clinical trials for acute bacterial skin and skin structure infections (ABSSSI)[10]. Rib-X completed two phase 2 clinical trials for radezolid (**4**) (RX-1741, formerly known as Rx-01_667); the first in community-acquired pneumonia (CAP, completed April 2009) and the second trial in uncomplicated skin infections (completed June 2009).[11,12] Pfizer and AstraZeneca are also working on two identified anti-tubercular compounds that have completed phase 1 clinical trials: the thiomorpholinyl oxazolidinone, sutezolid (PNU-100480, PF-02341272) (**5**) and AZD5847 (also known as AZD2563) (**6**), respectively.[13]

In order to achieve complete picture of biological activity of oxazolidinones, it should be mentioned about the variety of applications of oxazolidinone frame considered as important structural motifs in organic chemistry,[14] including: (i) enzyme inhibitors, such as a new generation of selective monoamino oxidase inhibitors of type MAO-A (befloxatone or highly potent and selective 3-(1*H*-pyrrol-3-yl)-2-oxazolidinones,[15]) (ii) anticancer substances,[16,17] (iii) other interesting medicinal properties like aldose reductase inhibitors,[18] as well as (iv) components of biologically active natural products, e.g. the antitubercular compound—cycloserine, the cytokine modulator—cytoxazone and mildly antimicrobial—streptazoline.

With regard to the oxazolidinone chemistry, Ager et al.[19] have discussed the classical as well as nonconventional routes of oxazolidinones synthesis. Early synthesis of chiral oxazolidin-2-ones, using chiral 1,2-amino alcohols and their heterocyclic derivatives as chiral auxiliaries, tended to employ toxic phosgene in reactions with amino alcohols. Later developed more efficient methods of high-yielding synthesis of oxazolidinones from e.g. dialkyl carbonates were also discussed.[20] In addition, Zappia et al.[21] have reported the application of oxazolidin-2-ones as efficient chiral auxiliaries in synthetic organic chemistry, such as in asymmetric alkylation, aldol, cycloaddition, 1,4-conjugate addition reaction, as well as in asymmetric[2+2]-photocycloaddition, or in Lewis acid promoted free-radical copolymerization reactions.

Renslo et al. provide an excellent summary on the identification of novel oxazolidinone antibacterial agents during the period from 2003 through mid-2005.[22] Around the same time Gravestock independently systematized developments with respect to the discovery of oxazolidinone antibacterials,[23] and a review of investigations in this area before 2003 was summarised by Hutchinson.[24] In addition, Poce et al. have reviewed the state of knowledge on patent applications for oxazolidinone-based antibacterial agents from mid-2004 to the end of 2006.[25]

Consequently, this review outlines developments in the identification of novel oxazolidinone antibacterial agents, which appeared in the period from 2006 to mid-2012, but readers should also refer to other recent reviews on the identification of novel oxazolidinones.[26–28]

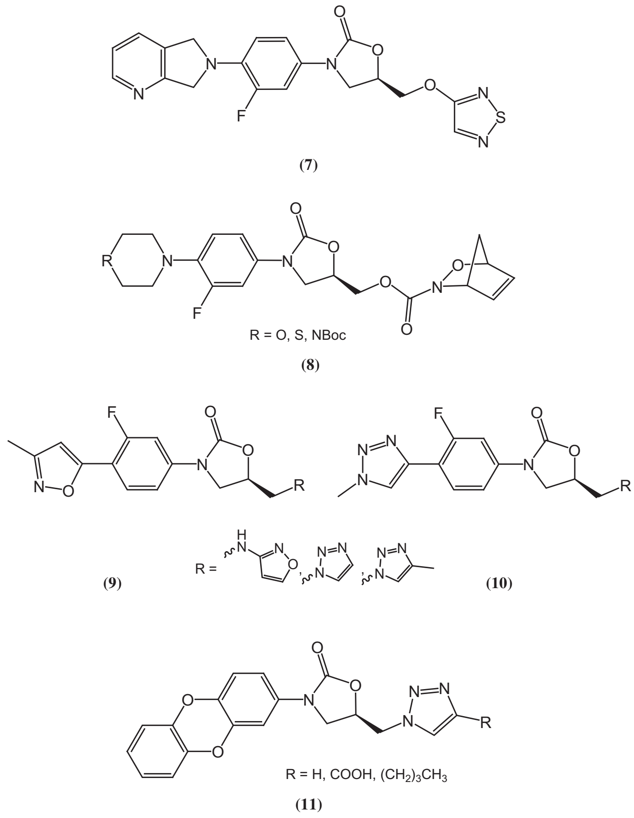


Figure 3. Analogues with heterocycles-containing moiety at the C-5 position of the oxazolidinone ring.

2. C-5 side chain modification

The SAR studies described in the literature indicate an important role of stereochemical configuration (S) for the binding group at the C-5 position of the oxazolidinone ring,[29] and it has been found, surprisingly, that the achiral isoxazolinones display in vitro antibacterial activity comparable to linezolid.[30]

Additionally, the early SAR studies determined at DuPont and at Pharmacia indicated that the C-5 acetamide arm was required for optimal antibacterial activity of the oxazolidinones, because of an interaction with the ribosome binding site. This highlights the fact that N–H participates as a hydrogen bond donor, while the ester-type oxygen in the oxazolidinone ring acts as a hydrogen bond acceptor.[29,31] The paradigm of this approach has been changed by the results of Gravestock et al., in which five-membered heterocycles, such as aminoisoxazole, hydroxyisoxazole, and triazole, still retained comparable activity.[32,33]

The continued exploration by Bayer and Versicor of the SAR of the C-5 side chain of the A-ring substructure has led to the discovery that sulphur isosteres of the acetamidomethyl side chain, such as thioamide, thiourea, thiocarbamate, dithiocarbamate, and halogen-substituted methylamide urea, could also give highly potent analogues of oxazolidinones.[24]

2.1. Strategy involving the addition of heterocycles to the C-5 position of the oxazolidinone ring

Five-membered ring heterocycles are still preferred over larger rings, possibly due to increased steric demand, the need for hydrogen bond donor substituents at the C-5 position, or conformational factors.

Researchers from Johnson & Johnson synthesised a series of pyrrolopyridine-substituted oxazolidinones, which were previously considered the optimal template for antibacterial activity,[34] containing various C-5 acetamide isosteres from simple amide or carbamate derivatives to more exotic isosteres such as N-cyanoethanimidamide, methyl-*N*-cyanocarbimidothioate, *N*-nitroguanidine and a series of alkoxyheterocycles.[35] Unfortunately, no improvement on antibacterial activity was found within the pyrrolopyridinyl analogues with larger amide or other isosteric replacements of the traditional C-5 acetamidomethyl side chain. In contrast to the AstraZeneca series of oxazolidinones O-linked isoxazoles, such as AZD5847 (Fig. 2),[33] both pyrrolo[3,4-*b*]pyridine as well as pyrrolopyridine alkoxyheterocyclic substituents were poorly active. The exception to this was the thiadiazole analogues, such as **7** in Figure 3, which showed modest antibacterial activity and minimum inhibitory concentration (MIC) values of 2- to 16-fold higher than linezolid.

Another approach, involving cyclic oxazolidinone antibacterial agents synthesised via the cycloaddition-like nitroso Diels–Alder (NDA) reaction, has recently been discussed. Yan et al. reported a series of analogues having bicyclic oxazine functionalities at the C-5 position of the oxazolidinone ring, both with modification of the C-ring with piperazine and thiomorpholine, respectively (as in **8**, Fig. 3).[36] Most oxazolidinone analogues with bicyclic oxazine moieties at the C-5 side chain showed antimicrobial profiles similar to linezolid. The compound with [2.2.1]bicyclic oxazines and a thiomorpholine moiety was the most potent.

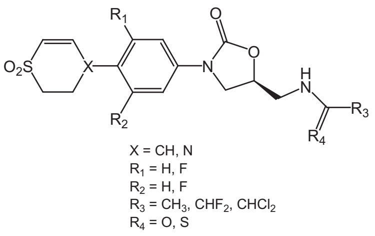
Among the analogues of five-membered heterocycles examined, a N-linked triazole ring conferred excellent antibacterial activity with reduced activity against monoamine oxidase.[37] The most interesting development in heterocyclic C-5 substituents is the finding by Hauck et al. at AstraZeneca, where, based on previous results for isoxazole oxazolidinones,[38] the synthesis and biological evaluation of congeners with a triazole ring at the C-5 position was reported.[39] As for in vitro activity, monoamine oxidase inhibition, pharmacokinetic parameters, and in vivo efficacy were reported for these series of analogues. Compounds **9**, **10** (Fig. 3) were more active than linezolid with MICs of 4-fold lower against *S. aureus* and *S. pneumoniae*, and they caused a decrease in MAO inhibition. In addition, the triazole derivatives showed exceptional efficacy in vivo against *S. pneumoniae*.

On the other hand, Ebner et al. synthesised novel oxazolidinones containing a benzodioxin-fused ring and triazole group at the C-5 position, which are supposed to act as amide surrogates.[40] However, in contrast to the results of Hauck et al.[39] and Phillips et al.,[41–44] compounds with triazole rings, **11**, were devoid of antimicrobial activity.

2.2. Strategy involving the addition of the acyclic substituent to the C-5 position of the oxazolidinone ring

Renslo et al. described a series of unsaturated heterocyclic C-ring analogues, both dihydrothiopyran and dihydrothiazine, including a B-ring and the C-5 side chain modification, exemplified by **12**, Figure 4.[45] Among them, dihydrothiazine analogues were more potent in general than dihydrothiopyran analogues, particularly against *Haemophilus influenzae* strains. Among the C-5 side chains examined, the dichloroacetamide variant provided the best activity toward Gram-negative bacteria (MICs from 2- to 8-fold lower than the MIC of linezolid), while the difluorothioacetamide variant conferred excellent activity against Gram-positive strains (MICs from 2- to 16-fold lower, than the MIC of linezolid).

Researchers from Ranbaxy, encouraged by their previous results on 1,2,4-triazolo[4,3-α]pyrimidines,[46] described the synthesis of more than 20 different C-5 amide, carbamate, urea, thiourea and thioamide analogues.[47] Most of the derivatives displayed higher MIC values against both Gram-positive and Gram-negative strains. The results revealed that a relatively small alkyl group at the C-5 was favoured according to antimicrobial activity. The thioacetamide analogue **13** (Fig. 4) was found to be 2- to 4-fold more potent than linezolid against Gram-positive pathogens. Moreover, the thioacetamide analogue was also found to be metabolically stable. The next report concerning this group[48] evaluated the impact of an additional aromatic ring inserted between the triazolopyrimidine and the oxazolidine heterocycles, as in **14**, to antibacterial activity, as well as the implications of the spatial structure of the molecule in the context of binding to the 50S ribosomal unit. The acetamide derivatives of 2-fluorophenyl, pyridine and thiophene systems displayed an excellent antibacterial activity profile against all of the Gram-positive strains tested. Among them, the 2,4-disubstituted thiophene derivative was 4- to 16-fold more potent than linezolid and was also devoid of any cytochrome P450 liability up to a concentration of 10 μM.



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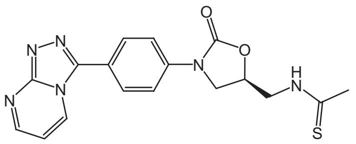

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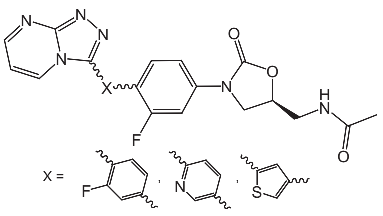

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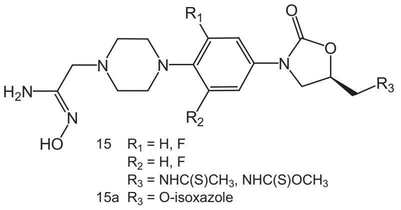
Figure 4. Acyclic C-5 side chain analogues.



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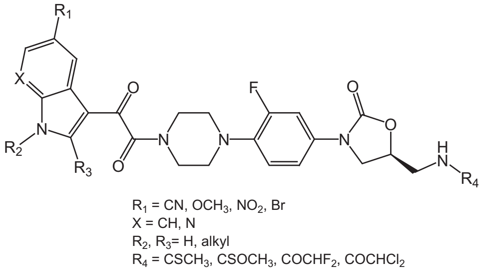

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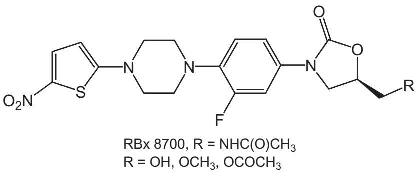

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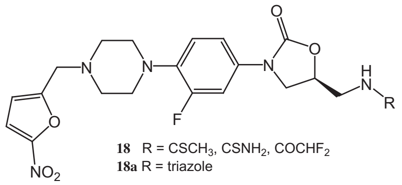

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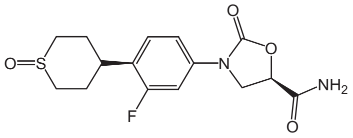

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Figure 5. Analogues with either *N*- or *O*-linked alkyl substituents at the C-5 position of the oxazolidinone ring.

Another four analogues (**15**–**18**) on the scaffold of eperezolid with either N- or O-linked alkyl substituents at the C-5 position of the A-ring are presented in Figure 5. Researchers from Dr. Reddy's Laboratories have disclosed the synthesis of N-hydroxyacetamidine analogues of eperezolid bearing various N- or O-linked C-5 oxocarbonyl and thiocarbonyl derivatives.[49] Many of these compounds exhibited good to excellent in vitro antibacterial activity, including both Gram-positive and Gram-negative pathogens, and the thiocarbonyl compounds were found to be particularly more potent than the corresponding oxocarbonyl derivatives. From the thiocarbonyl compounds, such as **15** in Figure 5, analogues having difluoro substitutions to the phenyl ring were more active compared to linezolid, as were their monofluoro congeners: against Gram-positive bacteria: MICs = 0.25–0.5 μg/mL versus 1–2 μg/mL, respectively; and against Gram-negative organisms: MICs = 0.5–4 μg/mL versus 8 μg/mL, respectively. With regard to O-linked C-5 isoxazole derivatives, the corresponding isoxazole analogue **15a** was less potent, with MIC values from 2- to 8-fold higher than the linezolid MIC against Gram-positive pathogens.

Additionally, selected oxazolidinones were evaluated for in vivo efficacy in a lethal systemic mouse infection model, employing *S. aureus* as the infectious pathogen. Unfortunately, all of the analogues were less efficacious than linezolid, exhibiting an effective dose, ED_{50} of 12.1–32.2 mg/kg versus 5.3 mg/kg for linezolid, respectively, where ED_{50} is the dose in which 50% of infections had been successfully treated after oral administration.

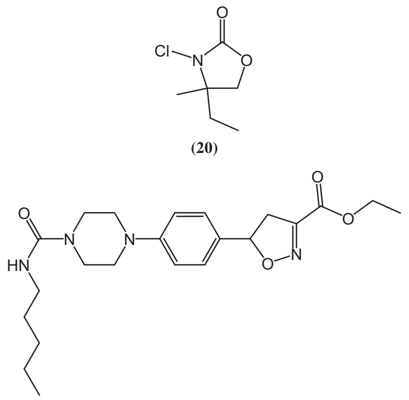
Dr. Reddy's Laboratories disclosed the synthesis and activity of oxazolidinone derivatives with 3-indolylglyoxamide attached to the piperazine scaffold of eperezolid bearing a variety of N- or O-linked alkyl and aryl substituents at the C-5 position.[50] Among the C-5 substituents, amides, carbamates and azoles occurred. Once more, the N-linkage thiocarbonyl compounds were more potent than the corresponding oxocarbonyl analogues. The thioacetamide and thiocarbamate, as well as the dihaloacetamide compounds, such as **16** in Figure 5, showed excellent in vitro activity against both sensitive (MICs = 0.25–2 μg/mL) and linezolid-resistant *S. aureus* and *Enterococcus faecalis* (MICs = 2–4 μg/mL), which is particularly noteworthy. This characteristic is similar to the C-5 modifications reported by the Pfizer[45] and Ranbaxy[51] groups using various N-linked haloalkyl moieties. Most of the analogues exhibited significant activity against fastidious Gram-negative strains, such as *Moraxella catarrhalis* (MICs = 2–4 μg/mL), but a lack of activity against *H. influenzae*. With regard to N-linked aryl derivatives, the triazole was comparable to acetamide analogues, while the O-isooxazole substitution at the C-5 position was less effective. Unfortunately, none of the analogues showed better efficacy than linezolid in vivo against *S. aureus* in a systemic infection model via the oral route (mostly ED_{50} >30 mg/kg). This can most probably be attributed to the poor pharmacokinetics exhibited by these analogues.

Researchers at the Ranbaxy group, encouraged by their previous results on RBx 8700, continued to work with various O-linked carbamates, thiocarbamates, and heterocycles (5- or 6-membered rings), as well as with S-linked alkyl and aryl derivatives at the C-5 position.[52] The best results were achieved for only small O-linked groups at the C-5 position, hydroxyl compound and its acetate derivative. Compounds, such as **17** (Fig. 5), exhibited comparable activity to RBx 8700, and superior activity to linezolid, with MICs of 4-fold lower against tested Gram-positive strains. Unfortunately, the in vivo efficacy of hydroxyl compounds against MRSA was unsatisfactory, with ED_{50} >25 mg/kg versus 5.6 mg/kg of linezolid.

Another report from the Ranbaxy group[51] described a number of C-5 substituted derivatives of Ranbezolid (RBx 7644) bearing haloalkyl, formamide, carbamate, thioamide, thiocyanide, thioester, thioketone, thiourea, methoxymethylacetamide, and cinnamoyl functionalities, as well as various heterocyclic substituents. Only a few N-linked alkyl derivatives, such as **18** in Figure 5, were tolerated in the place of the acetamidomethyl group of Ranbezolid, such as the thioamide, thiourea and haloalkyl-difluoro-, and dichloromethyl derivatives, with MICs in the range of 0.06–2 μg/mL. On the other hand, the in vitro activity of hydroxylmethyl derivatives against Gram-positive strains was in contrast to RBx 8700 analogues, as mentioned above. With regard to N-linked aryl derivatives, only isoxazole compounds had potencies comparable to linezolid. In contrast, analogues of RBx 7644 bearing N-linked 5-triazolyl moiety, such as **18a**, were several-fold more potent than linezolid.[53] The in vitro activities of compound **18a** were as follows: MICs = 0.06–0.25 μg/mL against MSSA, MIC = 0.06–4 μg/mL against MRSA, MICs = 0.03–0.125 μg/mL against *S. pneumoniae* and MICs = 0.25–0.5 μg/mL against *E. faecalis*.

Researchers from Pfizer described novel C-5 carboxamide oxazolinones in a patent application.[54] A continuation of the SAR study led to the identification of a new compound of analogue **19** (PF-00422602).[55] Analogue **19** showed 2-fold more potent antibacterial activity against Gram-positive strains and, more interestingly, reduced human MAO-A inhibition and myelotoxicity in comparison to linezolid. This compound also showed excellent PK properties and was of low risk for drug–drug interactions.

The most advanced member of this class, tedizolid (**3**, Fig. 2), completed the third stage of a clinical trial for ABSSSI in September 2011.[56] This analogue contains a biaryl ring system, which is structurally similar to other pyridylphenyl oxazolidinone congeners, as described in a later Section 5.4.1.[57,58] The SAR of the variations at the C-5 position on the oxazolidinone ring, including ethers, amides, and triazole, as well as hydroxyl groups, revealed an unexpectedly strong activity of the hydroxyl group. This result was in sharp contrast with the SAR of 3-aryl-2-oxooxazolidinones system, an oxotriazolyl oxazolidinone, as well as piperazinylphenyl oxazolidinones, where the corresponding 5-hydroxymethyl analogues showed significantly weaker antibacterial activity than those analogues containing the acetamide group.[59–61] Otherwise, this characteristic is similar to the C-5 modifications reported by Ranbaxy, where only small groups were acceptable.[52] Tedizolid, the parent compound of **3b** showed MIC values of 4-fold superior potency advantages against both susceptible and resistant *S. aureus* strains over linezolid. In the MRSA and MSSA systemic infection models, the ED_{50} values for the prodrug compound tedizolid phosphate were 2.8 mg/kg and 3.3 mg/kg for intravenous administration and 3.7 mg/kg and 5.0 mg/kg for oral administration, compared to 12.9 mg/kg and 29.1 mg/kg (iv) and 15.6 mg/kg and 21.4 mg/kg (oral) for linezolid, respectively. The most interesting factor is activity against strains possessing the *cfr* methyltransferase gene responsible for staphylococcal resistance to linezolid.[62] Activity against *cfr* strains was retained both in relation to hydroxymethyl, present in the tedizolid, or in relation to triazole groups at the C-5, but was reduced in compounds with acetamide substituents. Additionally, the enhanced potency of this molecule against LinR strains has been achieved thorough the optimisation of the C- and D-ring system—pyridine and tetrazole rings, which play critical roles in



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(21)

Figure 6. Antimicrobial compounds structurally-related 3-chlorooxazolidinon-2-one analogue **20** and isoxazoline A-ring compound **21**.

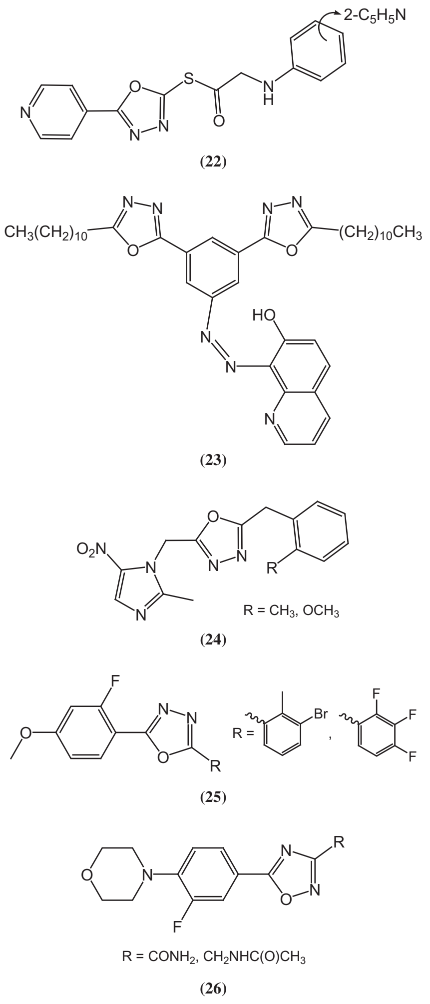


Figure 7. Compounds bearing oxazolidinone A-ring surrogates.

activity, by forming additional binding interactions with the upper region of the peptidyltransferase centre of the 50S ribosomal subunit. Moreover, this compound is very active in vivo for the treatment of Gram-positive pathogens and has a very attractive pharmacokinetic profile consistent with once daily dosing.

3. A-ring modification

The attempts to modify the structure of the oxazolidinone A-ring were undertaken to improve the biological activity of oxazolidinones. Due to the significance of the oxazolidinone A-ring, relatively few modifications have been observed. Among them, at least three oxazolidinone ring surrogates have been reported: 3-chlorooxazolidinon-2-ones, isoxazolines and oxadiazoles.

A group from Novabay Pharmaceuticals described the synthesis, antibacterial and antifungal activity of a series of structurally-related 3-chlorooxazolidinon-2-one analogues, such as **20** in Figure 6.[63] Crucial for this structure is the N–Cl bond and the electronic structure of the attached substituents, which has an impact on activity and cytotoxicity. The addition of charged solubilisers at the 4- and 5-position displayed linezolid-like potency.

On the other hand, Rakesh and co-workers et al. reported the synthesis of a series of isoxazoline compounds, such as **21** (Fig. 6), with appreciable anti-tuberculosis activity.[64] The SAR studies included both: (i) replacement of the ester group at the C-3 position of isoxazoline A-ring with a variety of bioisosteric head groups such as acids, amines, amides, reverse amides, alcohols, hydrazides, and 1,3,4-oxadiazole; and (ii) substitution of the distal benzyl piperazine ring in the C-5 position of the isoxazoline ring with piperazyl-urea, piperazyl-carbamate, biaryl system, piperidine and morpholine moieties. The SAR studies have shown that the ester at the 3-position is required for anti-tuberculosis activity, but this was not a satisfactory outcome, because it failed to replace the metabolically labile ester groups. The ester revealed the compound's serum instability, therefore precluding this analogue for testing of their efficacy in animal models of tuberculosis. However, the SAR studies on the left-hand side of the molecule indicated that the piperazyl-urea and piperazyl-carbamate analogues were the most potent among the synthesised compounds. The most interesting finding was that the isoxazoline ester represents a new synthetically anti-tuberculosis chemotype.

Other oxazolidinone A-ring surrogates are isomers of oxadiazole structures, such as **22–26** (Fig. 7). Unfortunately, the majority of analogues containing 1,3,4-oxadiazole exhibit poor activity in comparison to linezolid, as found for **22**, **23**.[65–67] The best results were obtained for secnidazole derivatives (**24**) possessing electron-donating substituents (methyl and methoxy groups), which displayed MIC ranges of <3.13 μg/mL against *Escherichia coli* and *Pseudomonas aeruginosa* and 1.56 μg/mL against *Bacillus subtilis*.[68] Some compounds also possess similar activity against Gram-negative pathogens containing 3-bromo-2-methyl phenyl and 2,3,4-trifluoro phenyl groups, such as **25**.[69] Recently, Piccionello et al. reported 1,2,4-oxadiazole A-ring analogues containing two types of side-chains and various numbers of B-ring fluorine atoms, exemplified by **26**.[70] Unfortunately, each of the compounds was entirely devoid of antibacterial activity.

4. B-ring modification

The crystal structure of linezolid bound to the 50S ribosomal subunit has revealed that the fluorophenyl moiety sits ideally in a heteroaromatic crevice formed by the PTC site. This moiety is engaged in a typical aromatic stacking interaction with C2487 and a T-shaped interaction with the base of A2486 of 50S ribosomal subunit of *Haloarcula marismortui*.[5] This observation suggests that modification of the B-ring may alter the interaction with the binding site, and thus cause the lack of activity. Consequently, there have been no recent studies of B-ring modification.

5. C-ring modification

The morpholino ring does not appear to make significant interactions with the ribosome, suggesting that many different functional groups can be substituted for the morpholine without a significant loss of activity. Accordingly, the piperazinyl phenyl oxazolidinone SAR optimisation program showed that a wide range of

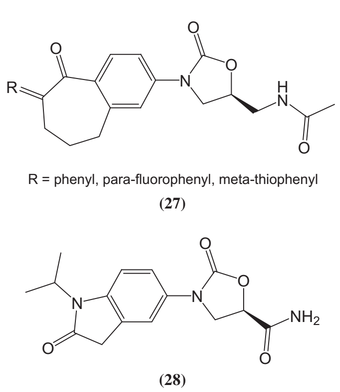
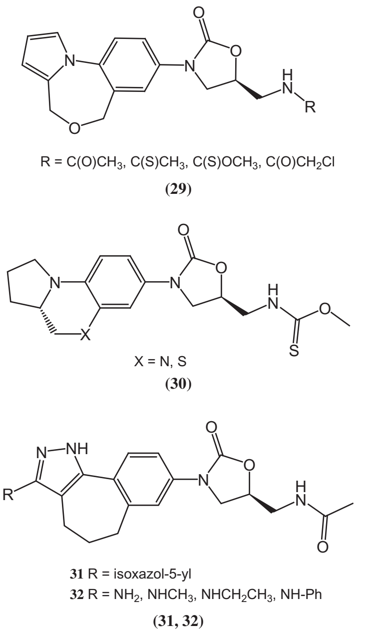


Figure 8. Oxazolidinones containing fused B- & C-rings.


R = $C(O)CH_3$, $C(S)CH_3$, $C(S)OCH_3$, $C(O)CH_2Cl$

(29)

X = N, S

(30)

31 R = isoxazol-5-yl

32 R = NH_2, $NHCH_3$, $NHCH_2CH_3$, NH-Ph

(31, 32)

Figure 9. Fused tricyclic oxazolidinones.

alkyl, carbonyl, and sulphonyl substituents were tolerated on the distal piperazine nitrogen atom,[29] indicating that the 4′-position on the C-ring is undoubtedly the most tolerant to variation. Renslo et al.[22] divided sections concerning the C-ring modification into: (i) fusion of the B- and C-ring; (ii) appendage of additional groups or rings to established C-rings; (iii) separation of the C- and D-rings by a spacer; and (iv) novel C-rings. This division will also be used in this review.

5.1. Fusion of the B- & C-rings

Highly promising results for the MICs of the novel benzocycloheptanone moiety substituted on the phenyl ring of oxazolidinone were obtained by scientists of the Pfizer group.[71] Vara Prasad and co-workers reported the synthesis and antibacterial activities of ketone analogues of various benzocycloalkyl ring sizes, including five-, six-, seven- and eight-membered rings of novel oxazolidinone congeners. In comparison, the benzenoheptanone analogues, such as **27** (Fig. 8), showed the best antibacterial activities against Gram-positive pathogens, with MICs of 2- to 4-fold lower than linezolid. More importantly, oxazolidinones containing a substituted benzocycloheptanone moiety showed surprisingly potent activity against the fastidious Gram-negative pathogens compared to linezolid (*H. influenzae* MIC = 2 μg/mL vs 16 μg/mL and *M. catarrhalis* MIC = 1 μg/mL vs 8 μg/mL, respectively), as well as with MICs from 2- to 16-fold lower than linezolid against Gram-positive pathogens. All of these substituted benzocycloheptanone analogues showed activities similar to or better than linezolid in the translation assay (TnT), thereby confirming a mechanism of action that is similar to that of linezolid.

A group from Pharmacia & Upjohn, later Pfizer, disclosed oxazolidinones with a fused oxindole B/C-ring subtype bearing reverse amide or carbamate side chains at C-5 in a patent application.[72–74] The selected analogues for which data was provided appeared to have a favourable profile with respect to MPSi and MAOi. One of the compounds, **28** (**PF-708093**), entered Phase I clinical trials, but the development was discontinued after one year.[75]

5.1.1. Fused tricyclic oxazolidinones

Researchers from Dr. Reddy's Laboratories, taking into consideration the entropically favoured bioactive conformation approach, reported a series of tricyclic oxazolidinones, wherein rotation around the C–N bond was restricted.[76] Das et al. designed benzazepine derivatives with more flexibility around the C–N bond, but the molecule was inactive, possessing more freedom of rotation. However, it was found that intermediate compound toward benzazepine derivatives showed promising antibacterial activity having obtained rigidity due to the pyrrole ring, exemplified by **29** (Fig. 9). Among various azolo benzoxazepinyl oxazolidinones, the most potent were acetamide, thioamide, and thiocarbamate, as well as chloro-derivatives, with potency comparable to that of linezolid. Unfortunately, none of these compounds achieved a better value of ED_{50} than linezolid. The most promising acetamide compound exhibited ED_{50} values from 5- to 2-fold higher than those of linezolid. Other thioamide, thiocarbamate, and chloro-derivative analogues displayed poor in vivo efficacy, with ED_{50} >30 mg/kg.

The second reports from Dr. Reddy's Laboratories described tricyclic oxazolidinones possessing substituted nitrogen and sulphur atoms instead of oxygen on the tricycle.[77,78] The SAR studies indicated that the tricyclic oxazolidinone analogues possessing a nitrogen atom instead of oxygen exhibited no antibacterial activity, while introducing sulphur resulted in some potent compounds. In particular, thiocarbamate analogue, such as **30** (Fig. 9), was highly potent, with MIC values of 2- to 8-fold lower than linezolid against Gram-positive pathogens.

Building on the previous results, researchers from Pfizer utilised the principles of conformation-restriction towards the synthesis of a series of analogues with a pyrazole ring restricting the rotation along the C–C bond.[79] The SAR studies included a series of fused pyrazole oxazolidinone analogues with substitution on the 5-position of the pyrazole ring by alkyl, aryl and heteroaryl substituents. Among the heteroaryl-substituted pyrazole series one compound stood out, the isoxazol-5-yl analogue (**31** in Fig. 9), which exhibited excellent in vivo activity towards both Gram-positive and Gram-negative pathogens. This compound had a MIC <0.06 μg/mL against *S. pneumoniae* and *Streptococcus pyogenes*, MIC = 0.125 μg/mL against *E. faecalis*, MIC = 0.25 μg/mL against *S. aureus*, and MIC = 1 μg/mL and 2 μg/mL against *M. catarrhalis* and *H. influenzae*, respectively. Moreover, the isoxazol-5-yl analogue showed activity IC_{50} value 0.76 μM versus 0.95 μM of linezolid in enzymatic tests, where IC_{50} is the concentration required to inhibit in vitro 50% of cell growth. Subsequently, the researchers[80] tried to improve the aqueous solubility of the pyrazole congeners. In order to reach this objective, the 3-position of the pyrazole ring was substituted with various hydrophilic amino groups, as in **32**. Several analogues showed excellent aqueous solubility >70 μg/mL. However, despite this achievement, only derivatives with small alkylamino substituents at the 3-position of the pyrazole ring showed slightly more potency against Gram-positive bacteria (MICs in the range of 0.25–4 μg/mL) and Gram-negative organisms (MICs in the range of 2–8 μg/mL) in relation to linezolid.

5.2. Appendage of additional groups or rings to established C-rings

Several different groups explored approaches whereby the established piperazine ring on the core structure of eperezolid was substituted by additional groups, analogues such as **33–37**, Figure 10. Researchers from Dr. Reddy's Laboratories reported novel oxazolidinone analogues having urea functionality, such as unsubstituted, aromatic and heterocyclic urea, respectively [81]. Among the first group, the most active was the analogue without any substitution (MICs in the range of 2–4 μg/mL), and isocyanomethane and benzyl urea moieties were roughly equivalent to linezolid in vitro in the second group. Among the heterocyclic urea analogues, superior properties were found in substituents containing thiazole and pyridine rings (**33**), with MIC = 1 μg/mL against

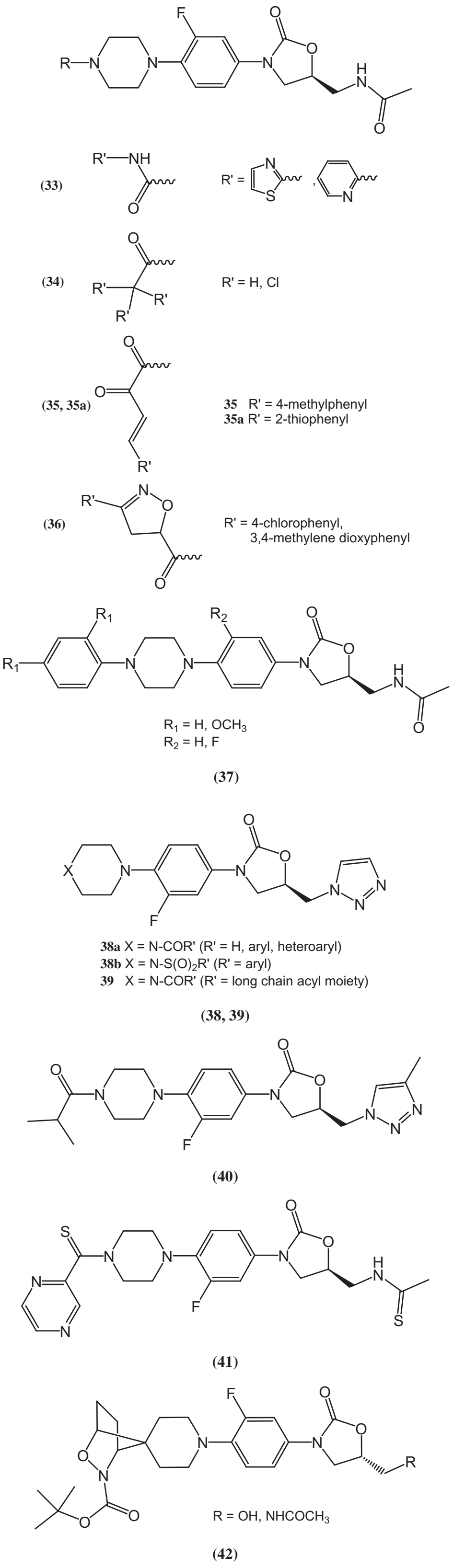


Figure 10. Analogues on the scaffold of eperezolid with additional groups or rings to established C-rings.

vancomycin-susceptible and -resistant *E. faecalis* and *E. faecium* strains. Unfortunately, the in vivo studies displayed less efficiency than linezolid.

A recent study by Wang et al. reported a series of α-substituted acetylpiperazinyl oxazolidinones,[82] which exhibited equipotent or enhanced activity compared to linezolid. The most active were the α-chloroacetyl and dichloroacetyl analogues, such as **34**, with MIC = 1 μg/mL against MRSA, MICs = 1–2 μg/mL for *Staphylococcus epidermidis*, and MICs = 0.5–1 μg/mL against *E. faecalis*, respectively. Another approach was proposed by Varshney et al. on 4-N-substituted aryl but-3-ene-1,2-dione analogues of piperazinyloxazolidinones.[83] Most of the ten compounds tested possessed equivalent or superior potency in comparison to linezolid against Gram-positive pathogens. The most potent analogue of the series was the methylphenyl compound **35** with MIC ranges of 0.19–0.39 μg/mL versus 1.56–3.12 μg/mL for linezolid against staphylococcal strains, 0.04 μg/mL versus 3.12 μg/mL against *E. faecalis*, and 0.09 μg/mL versus 1.56 μg/mL against *S. pyogenes*, respectively. With regard to heterocyclic compounds, a structure containing 2-thiophenyl (**35a**) exhibited the best potency, with MIC values of 2- to 4-fold lower, and was even more potent than linezolid against all of the screened strains. The same group reported a series of differently-substituted rings of isoxazoline attached to the piperazinylphenyl oxazolidinone core structure of eperezolid, such as **36**.[84] The results revealed that the antibacterial activity mostly depended on various substitutions in the aryl ring present at the 3-position of the isoxazoline ring. Most of the analogues were more potent than linezolid against Gram-positive pathogens, and even more interestingly, these compounds showed promising activity against the resistant Gram-negative bacteria *K. pneumoniae*.

Another modification was reported by scientists at the Innovation Centre of Drugs in Shanghai.[61] Taking into consideration the previous results from SAR studies on the 4′-substituted piperazine subclass of oxazolidinones, the effects of a small electron donating group at *ortho*- and *para*-position of the phenyl ring (D-ring) attached to the piperazinylphenyl oxazolidinone core structure of eperezolid, as in **37**, were investigated. The SAR studies included two series of 5-hydroxymethyl and 5-acetylamidomethyl oxazolidinones, with or without fluorine on the phenyl ring (B-ring). Unfortunately, 5-hydroxymethyl oxazolidinones had no significant effect against Gram-positive pathogens, while some of the 5-acetylamidomethyl analogues with a fluorine group showed activity against Gram-positive organisms.

In the past couple of years, a group chaired by Phillips has published several reports on piperazinyloxazolidinones.[41–44] Researchers have recently disclosed a series of 4-methyltriazolyl oxazolidinone analogues with various alkyl- or arylcarbonyl substituents at the piperazine N-4 position.[41] Previous results on triazolyl groups at the C-5 position, including alkyl- and phenylcarbonylpiperazine derivatives,[42] substituted arylcarbonyl- (**38a**) and arylsulphonyl oxazolidinones, such as **38b**,[43] as well as derivatives having the N-linked long chain acyl moiety (**39**),[44] suggested that the incorporation of an alkyl- or alkoxy- and arylcarbonyl substituent at the distal piperazine N-4 position of the 5-triazolylmethyl oxazolidinone can lead to an improvement of antibacterial activity. Additionally, studies by Reck et al.[37] and Hauck et al.[39] demonstrated that triazole oxazolidinones bearing small substituted groups at the 4-position can diminish MAO-A inhibition. Thus, taking into account the above-mentioned results, various N-4 substituents, from small groups to bulkier moieties such as benzoyl and cinnamoyl, have been studied. Among them, only those with small groups at the piperazine N-4 position showed antimicrobial activity comparable to linezolid, with MICs in the range of 0.5–4 μg/mL against Gram-positive organisms. Unfortunately, the most active compound, with an isopropylcarbonyl group at the piperazine nitrogen (**40**), showed an 8-fold higher MIC value against *S. aureus* in the presence of human plasma which, as the authors suggest, is associated with increased

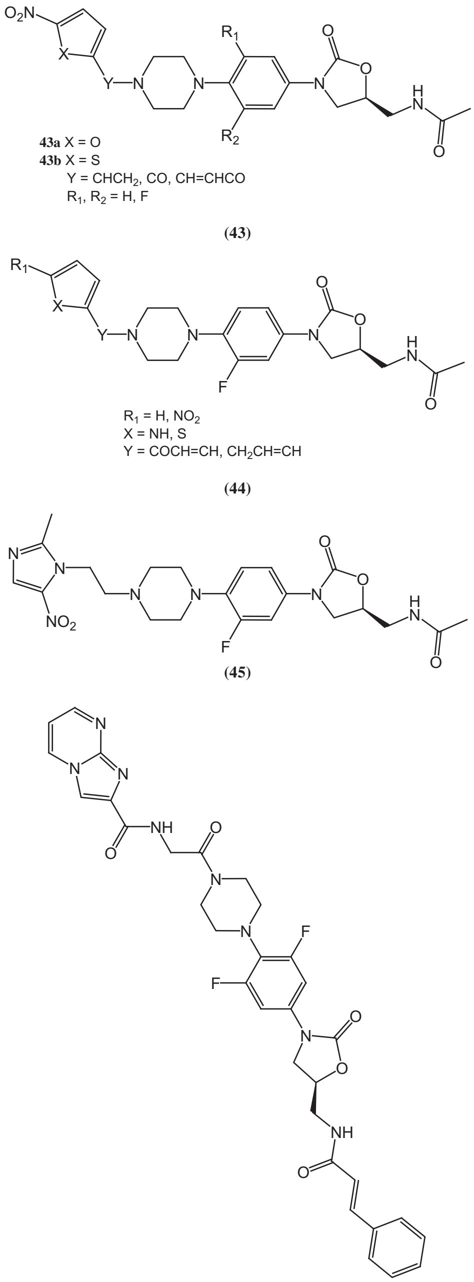


Figure 11. Oxazolidinone analogues with a spacer between the C- and D-rings.

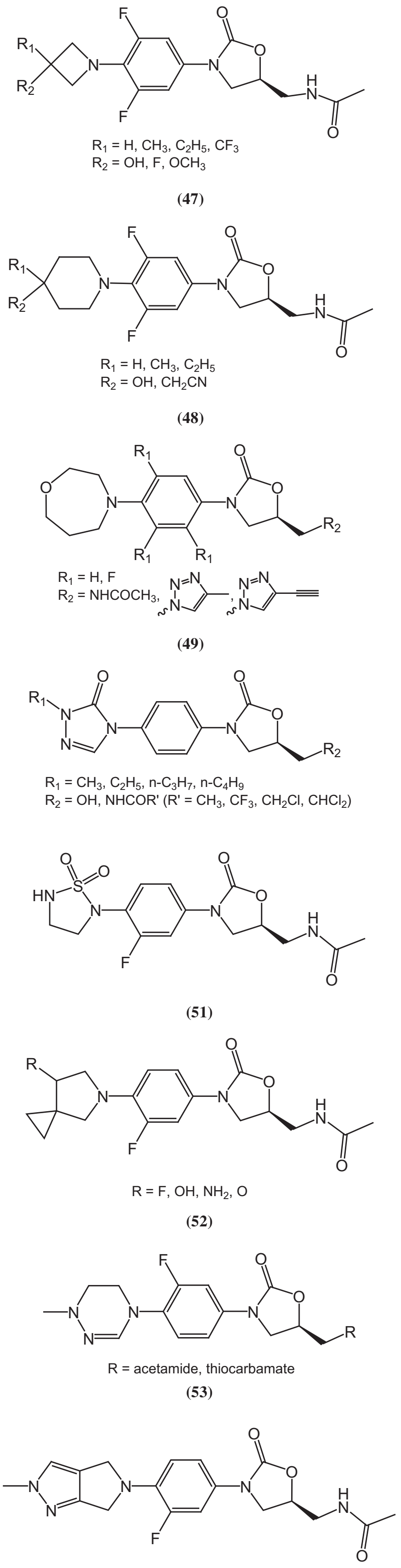


Figure 12. Oxazolidinone analogues with novel C-ring types.

binding to human plasma and/or instability of the analogue. Such instability among analogues of the piperazinyloxazolidinone moiety was described previously.[43,44] Generally, the 4-methyltriazole oxazolidinone derivatives displayed relatively decreased antibacterial activity independent of the absence or presence of human plasma compared with the un-substituted triazole analogues.[42–44] On the other hand, the MAO inhibitory activity of these analogues was also assessed.[85] The analogues containing piperazine and triazolyl functional groups were found to have minimal acute effects on neuronal function, while those containing both the morpholine and triazole had acute neuroactivity and the potential for greater neurotoxicity in comparison to the congeners discussed above. Around the same time, Fan et al. independently reported potent antibacterial activity for compounds containing a triazolyl ring at the C-5 position and a sulphonyl group linked to piperazine ring, as in **38b** (Fig. 12).[86] Despite the favourable results for microbiological activity against Gram-positive organisms, none of these analogues were more effective than linezolid when administered orally; in most cases the ED_{50} was >100 mg/kg.

Scientists from Orchid described the in vitro antibacterial activity of OCID0050, a pyrazinyl thioacetamide oxazolidinone, exemplified by **41** against clinically significant pathogens.[87,88]

OCID0050, such as **41**, demonstrated better inhibitory activity against the tested clinically significant bacterial isolates, by generally showing 2- to 4-fold lower MICs compared with linezolid against *S. aureus*, MRCoNS, VS and VR *E. faecalis* and *E. faecium*, as well as anaerobic pathogens.

Recently, the generation of spiropiperazinyl oxazolidinone through NDA reactions has been reported, but this time, the effect of substitution at the 4′-position of the phenyl ring has occurred.[89] The most active cycloadducts, with hydroxyl and acetyl groups (**42**), displayed in vitro antibacterial activities comparable to linezolid. Interestingly, compounds derived from a reduction of the N–O bond showed decreased activity compared to the parent cycloadducts, as mentioned in the previous report.[36]

5.3. Separation of the C- and D-rings by a spacer

At least two different groups have explored approaches whereby an established piperazine ring (C) is separated from the 5-nitrofuryl (D-ring) by a flexible spacer. Researchers at the Ranbaxy group were encouraged by these earlier experiences, which led them to discover the 5-nitrofuryl analogue of eperezolid, Ranbezolid (RBx 7644), which continued working on the heterocyclic oxazolidinones.[90] Rudra and co-workers synthesised a series of compounds by systematic modification of the linker between the piperazine and five-membered heterocycle of the furyl and thienyl compounds, respectively (as in **43a**, **b**, Fig. 11). All of these compounds possessed excellent in vitro activity against Gram-positive pathogens (with the exception of analogues that were directly bonded). With regard to furyl derivatives, in vivo efficacy was around 1.5-fold higher than linezolid in the cases of 1,1-ethyl and carboxyl group linkers, whereas the rest of the analogues were ineffective, with ED_{50} >25 mg/kg. In the case of thienyl analogues (**43b**), only compounds that were directly bonded and those with the extension of the carboxyl group to the piperazine were active in vivo with ED_{50} = 11.15 mg/kg and 9.77 mg/kg versus 5.6 mg/kg for linezolid, respectively.

Another group from Zydus reported the synthesis and antibacterial activity of oxazolidinones bearing various alkenes or alkenones as spacers between the piperazine scaffold of the eperezolid analogue and different heteroaryl moieties such as thiophene, furan, pyrrole, pyridine, and fused ring, as well as different substituted derivatives of furan.[91] Among them, the most active were analogues with 5-nitrofuran and thiophene rings, such as **44** (see Fig. 11), which showed far superior in vitro activity to linezolid. This result is in accordance with the outcome of RBx 8700.[90] Due to its poor bioavailability, the 5-nitrofuran analogue was converted into an N-oxide derivative resulting in the improvement of pharmacokinetic parameters, reaching 60% versus 100% of linezolid per-oral bioavailability. Different approaches reported by Varshney et al. established a piperazine ring (C) separated from the nitroimidazol moiety (D) by a suitable carbon spacer[92] These novel nitroimidazole analogues exhibited moderate to excellent in vitro antibacterial activity with MICs range of 0.097–3.12 μg/mL. The compound with two carbons as linkers and with nitro groups at 4′-position of imidazole (**45**) was the most potent compound of the series and did not exhibit any toxicity towards mammalian cells.

Researchers from Panacea Biotec described piperazinylphenyloxazolidinone connected with heterocyclic D-ring (imidazo[1,2-*a*]pyrimidine) via 2-oxo-ethylformamide as a spacer such as **46** in a patent application. The selected analogue for which data is provided displayed activity with MIC = 0.125 μg/mL against *S. aureus* (MSSA and MRSA) and *E. faecalis*, MIC = 0.25 μg/mL against VRE strains, and MIC = 1 μg/mL against *S. aureus* (LRSA).[93]

5.4. Novel C-rings

Pfizer scientists have explored a series of oxazolidinone analogues with additional substituents at the distal end of the azetidine or piperidine C-rings, and tried to evaluate their effect on mitochondrial protein synthesis inhibition (MPSi), which is responsible for reversible myelosuppression.[94] The relationship between MPSi and the anti-proliferative effects of oxazolidinones has been provided in a report by McKee et al.[95] In general, the azetidine and piperidine analogues and the corresponding 3-alkyl and 4-alkyl substituted derivatives (**47**, **48**) displayed antibacterial potencies similar, and in some cases superior, to those of linezolid. It appears that analogues with an additional methyl group substituted to the 3-methoxyazetidine ring or to the 4-hydroxypiperidine ring have the most favourable attenuating effect on MPS inhibition, which must be underlined as there is no significant decrease of antibacterial potency.

Wockhardt Ltd recently disclosed substituted piperidinophenyl oxazolidinones[96] that differ from the 4-hydroxypiperidine derivatives described above, by the elongation of the substituent at 4-position from methyl to methoxymethyl, methoxyethyl or trifluoroethoxymethyl in a patent application. The selected analogue for which data is provided displayed MICs in a range of 1–4 μg/mL against the tested Gram-positive strains.

Researchers from Pfizer reported a novel series of oxazolidinones in which the morpholine C-ring of linezolid was replaced with homomorpholine ring.[97] The effect of the C-ring modification, together with the influence of fluoro phenyl B-ring substitution, concurrent with the effect of various C-5 functionalities, exemplified by **49**, in connection with their impact on antibacterial activity of linezolid, MAO inhibition as well as myelotoxicity, was investigated. The homomorpholine C-5 acetamide analogues with mono-, di- and tri-fluoro phenyl B-rings were roughly equipotent in vitro to linezolid, being the most active di-fluoro congener. Furthermore, several difluorophenyl oxazolidinone analogues with various C-5 functionalities such as methyl carbamate, ethyl amide, and triazolo analogues showed in vitro activity comparable to linezolid.

Scientists from the Innovation Centre of Drugs disclosed another modification of the C-ring concerning analogues with an oxotriazolyl, five-membered ring in place of the traditional morpholine ring.[60] The SAR studies included two series of 5-hydroxymethyl and 5-haloalkylamidomethyl oxazolidinones, with the different alkyl group at the 2′-position of the triazolone group, respectively (**50**, Fig. 12). Unfortunately, 5-hydroxymethyl oxazolidinones had no significant effect on Gram-positive pathogens, in contrast to 5-acetylamidomethyl analogue with an ethyl group. Therefore, the subsequent series included different C-5 substituents, such as chloroacetyl, dichloroacetyl and trifluoroacetyl analogues, but in vitro activities of these compounds against Gram-positive pathogens were slightly poorer than that of the 5-acetylamidomethyl analogue.

Kim et al. independently reported analogues containing cyclic sulphonamides[98] and spiro[2,4]heptane compounds[99] instead of morpholine. The best results were obtained for a compound possessing a [1,2,5]thiadiazolidin-1,1-dioxide moiety, exemplified by **51**. This showed MICs from 4- to 8-fold lower than linezolid against staphylococcal and enterococcal strains, 2-fold lower than streptococcal strains, 16-fold lower against MRSA, and from 2- to 8-fold lower against VRE pathogens. Additionally, thiadiazolidine analogues were more potent than compounds bearing a thiadiazinane moiety. Within the thiadiazolidine, the incorporation of an alkyl group at *N*-position resulted in a significant increase of activity compared with an alkyl substitution at C-3 position. Larger extended moieties like benzyl or *tert*-butoxy were less favourable and led to a loss of activity.

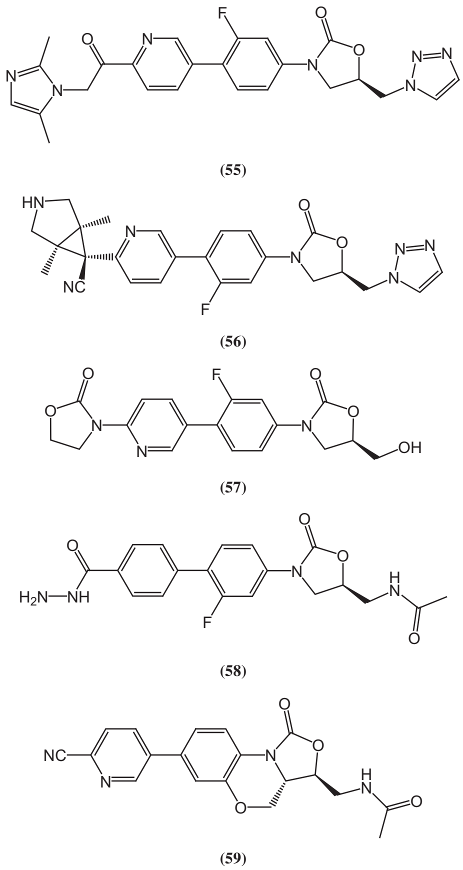


Figure 13. Oxazolidinone analogues with biaryl ring system.

With regard to spiro[2,4]heptane oxazolidinone, the researchers built on the previously obtained results on quinolone antibiotics,[100] revealing that such a substituent largely enhances the activity. Unfortunately, the results were not satisfactory, as only compounds with a fluoro substituted spiro[2,4]heptane moiety, such as **52** (Fig. 12), displayed similar or superior antibacterial activities to linezolid against Gram-positive, methicillin- and vancomycin-resistant strains. Other compounds containing hydroxy and amino substituents exhibited a significant decrease of potency with the exception of structures with carbonyl groups, which were roughly as potent as linezolid. Furthermore, the addition of bulky compounds (from methyl to propyl substituents) resulted in a significant loss of potency.

Researchers from LegoChem Biosciences have recently described oxazolidinone derivatives with cyclic amidoximine or cyclic amidrazone C-ring subtypes bearing various side chains at C-5 in a patent application.[101] The oxazolidinone derivatives showed potent antibacterial activity against some Gram-positive pathogens, such as MRSA, VRE and LinR *E. faecalis*, and were also effective against Gram-negative bacteria, such as *H. influenzae*, and *M. catarrhalis.* With respect to the inhibition of MAO-A, most of the compounds (such as **53**) were safe in terms of cytotoxicity and exhibited less inhibitory effects, K_i, in the range of 4–89 μM versus 7.9 μM and <2.0 μM than linezolid and tedizolid, respectively.

Researchers from Johnson & Johnson disclosed the in vitro antibacterial activity of the pyrrolopyrazolyl-substituted oxazolidinone RWJ-416457, exemplified by **54**.[102] Compound **54** generally retained 2- to 4-fold lower MIC values than those of linezolid against *S. aureus*, MRCoNS, VS and VR, *E. faecalis*, *E. faecium*, and Gram-negative pathogens *H. influenzae* and *M. catarrhalis*, as well as against atypical respiratory tract pathogens.

5.4.1. Biaryl ring system

At least three different groups of researchers have explored approaches whereby biaryl ring system, pyridyl (C) and phenyl (B) rings occur. Among them, the most advanced is tedizolid (**3**), which was described in section concerning alkyl side chain modifications (vide supra, Subsection 2.2).

Researchers from AstraZeneca have reported a series of more than 30 compounds with acyclic substituents in 6-position of a pyridine-3-phenyl oxazolidinone.[57] It was shown that compounds bearing a relatively small alcohol or ketone substituent on the pyridine retained the Gram-positive activity, including linezolid-resistant *S. pneumoniae*. The best properties with regard to microbiological potency, reduced MAO-A inhibition, an absence of CYP inhibition, and acceptable solubility, were exhibited by the imidazole ketone derivatives. However, high clearance remained a problem; therefore steric hindrance of imidazole was increased by introducing a 2,5-disubstituted moiety (**55**, Fig. 13), thus achieving a reduction in clearance. Furthermore, Komine et al. from Kyorin proposed a different approach to the biaryl oxazolidinones bearing bicyclo[3.1.0]hex-6-yl substituents on the pyridyl ring.[58] Most of the synthesised analogues showed improved antibacterial activity against tested Gram-positive strains and the fastidious Gram-negative bacteria *H. influenzae,* compared to linezolid. Among them, compound **56** (AM-7359) with a cyano group at the C-6 position of D-ring, displayed excellent antibacterial potency, with MICs = 0.06 μg/mL against MSSA, MRSA, PSSP and PRSP, MIC = 0.125 μg/mL against VRE, and 2 μg/mL against *H. influenzae*. Moreover, the in vivo efficacy has been demonstrated in the linezolid-resistant MRSA mouse infection model via intravenous and oral administration.

Researchers from MicuRx Pharmaceuticals have presented phenyloxazolidinone derivatives in a patent application, which are connected to the heterocyclic D-ring (e.g., 2-imidazolidinone, 2-pyrrolidinone, and 2-oxazolidinone) via a pyridine or pyrimidine C-ring. The selected analogues for which data are provided displayed activity against *S. aureus* (including MRSA), *Enterococcus* spp., *S. pneumoniae* and *H. influenzae.* The most active compound (**57**) showed MIC values from 8- to 16-fold and from 2- to 4-fold lower than the corresponding values of linezolid and tedizolid, respectively.[103]

In a biaryl ring system, radezolid (**4**, Fig. 2) represented another C-ring subtype, the biphenylooxazolidinones. Application of the phenyl ring was in contrast with the SAR trends of the oxazolidinones bearing bicyclo[3.1.0]hex-6-yl analogues, where the corresponding phenyl ring was not preferable over the pyridyl ring.[58] Radezolid emerged from the Rχ-01 discovery program at Rib-X, which revealed excellent antibacterial activity against linezolid-susceptible staphylococci, enterococci, and pneumococci (MICs from 2- to 8-fold lower), against LinR isolates, especially enterococci and pneumococci. Unlike linezolid, radezolid also showed proper antibacterial activity against causative agents of community-acquired pneumonia, such as *H. influenzae* and *M. catarrhalis*. Interestingly, the affinity of radezolid for the ribosome binding site was higher, thereby overcoming the most common ribosomal mutation (G2576U) associated with linezolid resistance in the clinic.[104,105]

Researchers from LegoChem Bioscience presented biphenylooxazolidinone derivatives bearing various acyclic substituents or heterocyclic rings (e.g., oxadiazole, imidazole, pyrimidine, triazole) in a patent application. The selected compounds displayed antibacterial activity against MDR Gram-positive isolates, including *S. aureus*, *S. epidermidis*, *E. faecalis* and *E. faecium*, as well as *E. coli*, *H. influenzae* and *M. catarrhalis*. The most promising analogue containing an aminocarbamoyl moiety (compound **58**) indicated a 2- to 64-fold improvement in activity as compared to linezolid.[106]

The most interesting work concerning the design, synthesis, and SAR studies of tricyclic fused benzoxazinyl-oxazolidinone, in which the A- and B-rings are joined via a C–O bridge, bearing non-aromatic heterocycle or aromatic rings, have been recently reported.[107] Among them, a pyridyl C-ring was preferable to other 5- or 6-membered aryl C-ring subtypes, while a cyano substitution at the pyridyl ring generated an analogue (**59**) with excellent antibacterial activity, with MIC = 0.125 μg/mL against *S. aureus*, and MIC = 0.25–0.5 μg/mL against MRSA, MRSE and PRSP, as well as MIC = 0.5 μg/mL against *E. faecalis*, respectively. Additionally, compound **59** exhibited supreme in vitro activity against LinR strains of 8- to 16-fold higher potency than linezolid. The SAR studies indicated that an (S, aS) absolute configuration for the [6,6,5]tricyclic ring system of pyridyl benzoxazinyl-oxazolidinones was required for antimicrobial potency. Interestingly, in MRSA systemic infection model, pyridyl analogues exhibited an efficacy of about 4-fold (ED_{50} <2.5 mg/kg) and 3-fold (ED_{50} <5.0 mg/kg) higher than linezolid against *S. aureus* and MRSA, respectively. Furthermore, this compound showed an excellent pharmacokinetic profile.

Researchers from Ranbaxy reported a novel series of compounds (chemical structure was not presented) containing a biaryl ring in place of morpholine of linezolid, RBx 1000075 and RBx 1000276, respectively.[108] Both biaryl oxazolidinone compounds showed excellent activity against sensitive and resistant Gram-positive pathogens, with MIC in the range from 0.12 to 2 μg/mL. In animal models, these compounds showed suitability in staphylococcal and pneumococcal infections. RBx 100075 possessed better overall time-concentration values (AUC_{0-24}) than RBx 1000276.

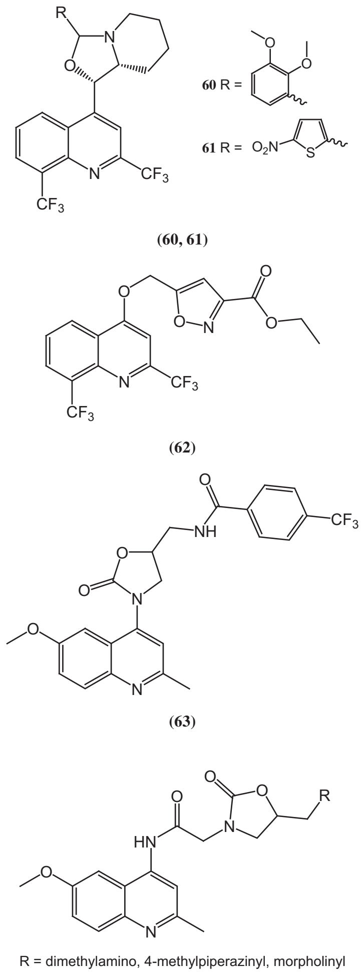
6. Hybrid oxazolidinones

One of the most recent approaches to combating resistant pathogens is the development of hybrid antibiotic molecules in which two drugs with different modes of action and thus different molecular targets are jointed together through covalent attachment.

One of the objectives of the development of novel oxazolidinones is to broaden the spectrum of antibacterial activity via fastidious Gram-negative organisms. Thus, it seems that the combination of different drugs with different pharmacophors in one structure will be an interesting option to overcome the intrinsic resistance of most Gram-negative bacteria to oxazolidinones.

The most advanced oxazolidinone and quinolone hybrid, ACT-179811 by Actelion, is currently recruiting participants into a Phase 2 clinical trial for the treatment of *Clostridium difficile* infections.[109] Another recent hybrid, MCB 3837 by Morphochem (now Biovertis; prodrug of MCB-3681), that had previously reached Phase 1 (since 09/2006) has since been halted.[110]

Among the important heterocyclic compounds, quinoline-based heterocycles are well known to exhibit excellent antimicrobial activities, particularly anti-tuberculosis properties. This knowledge has been used by Gonçalves et al., who reported the synthesis and anti-tubercular activity of mefloquine–oxazolidinone derivatives.[111,112] The results confirmed that the construction of an oxazolidinone ring in mefloquine's structure can enhance the activity against *M. tuberculosis*. Advanced studies revealed that a dimethoxy derivative (**60**) exhibits superior potency, illustrated by 2.8-fold increase of anti-tubercular activity. Between the heterocyclic moieties, 5-nitrothien-2-yl substitution (**61**) showed the best potency against *Mycobacterium tuberculosis*, especially MDR-TB strains. Another approach was presented by Mao et al., who synthesised mefloquine–isoxazole carboxylic acid ethyl ester, which exhibits a 14.4-fold superior activity in comparison to mefloquine and also shows no cytotoxity,[113] qualifying it as a prodrug. Further investigations showed that various modifications performed on the ester and the quinoline ring reduced the anti-tubercular potency. Interestingly, the acid form of ethyl ester (**62**) demonstrated improved activity at pH 6.0, suggested that it may be effective in vivo in the acidic environment of lungs that appears during tuberculosis infection.[114]



(60, 61)

(62)

(63)

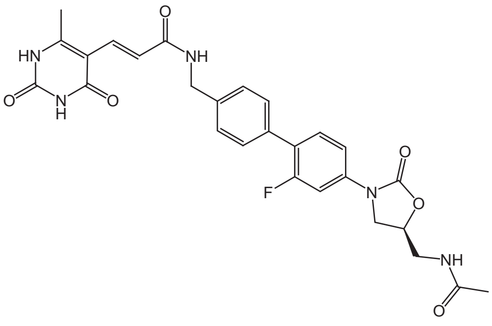
R = dimethylamino, 4-methylpiperazinyl, morpholinyl

(64)

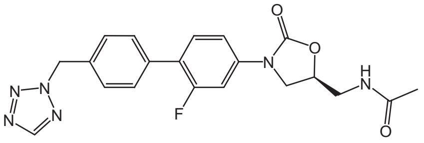
Figure 14. Hybrid molecules of quinoline derivatives carrying oxazolidinone ring as an active pharmacophore.

Recently, another approach was proposed. Thomas et al. designed and synthesised hybrid molecules of quinoline derivatives carrying an oxazolidinone ring as an active pharmacophore.[115] Experiments were carried out in parallel, with the first series of compounds displaying substantial antibacterial and antimycobacterial activities against the tested Gram-positive and Gram-negative pathogens, especially those analogues carrying fluoro, methoxy and trifluoromethyl substituted phenyl rings in their structures, such as **63** (Fig. 14). In the second series, the quinolone-oxazolidinone hybrid molecules bearing acetamide as a spacer between two pharmacophoric groups obtained promising antimycobacterial activities for simple alkyl amines, methyl, ethyl and acetyl substituted piperazines as well as morpholine groups, as in **64**.

Researchers from Rib-X, the authors behind the success of Radezolid, derived a novel hybrid biarylooxazolidinones.[116] The bridge element was a phenyl linking incorporated on one side with the thymine ring of sparsomycin and on the other side with the phenyloxazolidinone fragment of linezolid. This compound (**65**, Fig. 15) demonstrated both superior translation and bacterial inhibition when compared to linezolid and sparsomycin, with MICs from 8-



(65)



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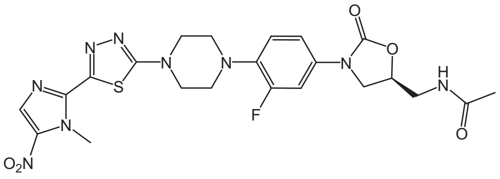

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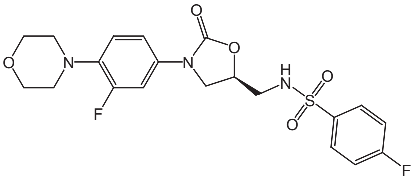

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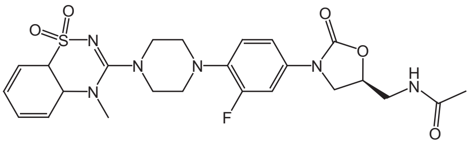
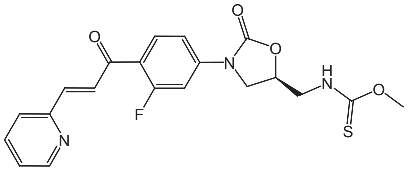


(69)



(70)

Figure 15. Hybrid oxazolidinones.

to 32-fold more active against Gram-positive organisms. However, performed computational studies indicated that the above described bridge element was not optimal relative to orientation for a π–π interaction between the terminal thymine element and the 50S ribosomal subunit.[117] Taking this into consideration, further optimisation on both (i) shortening the chemical functionality bridging the terminal aromatic group to the biarylooxazolidinone and (ii) modifying the nature of the terminal aromatic group, was performed using a proprietary suite of computational tools. These compounds (e.g., **66**) showed superior activity across the MIC panel, which included clinically relevant and challenging Gram-positive strains. Additionally, all analogues displayed efficacy when applied orally and possessed appropriate pharmacokinetic properties.

Khalaj et al. reported a novel series of nitroaryl-thiadiazole-oxazolidinone hybrids[118] that possessed excellent antibacterial activity against the tested Gram-positive organisms, from 2 to 32 times better than linezolid towards MRSA strains. Most analogues displayed very weak or no activity against Gram-negative bacteria, with the exception of compound **67** against *K. pneumoniae*. Nitroimidazolyl-oxazolidinone hybrids, such as **67**, displayed the potency at non-cytotoxic concentration (IC_{50} >200 μg/mL).

Based on the fact that benzothiadiazine-1,1-dioxides (BTDs) belong to the class of cyclic sulphonamides exhibiting activity against *M. tuberculosis*, Kamal et al. synthesised benzothiadiazine or arylsulphonamido conjugates with oxazolidinones.[119] Among the compounds with C-5 side chain modifications, the superior activity was associated with arylosulphonyl fluorides instead of acyl groups (**68**), with MIC = 1 μg/mL versus 2 μg/mL for linezolid. In case of the C-ring modified oxazolidinone-BTD structures, promising in vitro antimicrobial activity at non-cytotoxic concentrations created the 4-methyl-1,2,4-benzothiadiazine-1,1-dioxide analogue, **69**.

Selvakumar et al. described a systematic SAR study on hitherto unknown chalcone-oxazolidinone hybrid molecules.[120] Although both of the regioisomeric hybrid molecules were inactive, the introduction of pyridine instead of an aromatic ring led to new derivatives possessing moderate in vitro activity. Further modifications involving the conversion of the acetamide group to the corresponding thiocarbamate led to the generation of compound **70**. The molecule (**70**) exhibited in vitro activity in the range of 0.25–1 μg/mL against MRSA and MSSA, as well as 1–2 μg/mL against *Enterococcus* spp.

7. Conclusions

Linezolid has been in the armamentarium of antibacterial agents for nearly a decade, and to date is the only oxazolidinone agent which has been registered. Due to the fact that linezolid possesses many attributes making it an attractive starting point for the design of novel antibacterial agents, many structural modifications of linezolid have emerged in recent years. Although researchers have divulged a number of novel analogues, which were generally more active than linezolid, as yet none of them have been approved by the FDA. Primarily because of pharmacokinetic or toxicological deficiencies, many analogues have not managed to pass Phase 1 clinical trials, for example PF-708093. Only two compounds containing biaryl ring systems, tedizolid and radezolid, have progressed into later clinical-stage trials. Both of them have a higher affinity to the ribosome binding site, thus overcoming ribosomal mutation and possessing activity against LinR strains. Additionally, radezolid shows proper antibacterial activity against causative agents of CAP, such as *H. influenzae* and *M. catarrhalis*. Unfortunately, the MPSi and MAOi values of tedizolid and radezolid have not been disclosed publicly. However, in the patent application,[101] the K_i value for tedizolid was <2.0 μM against MAO-A, while for toloxatone—an inhibitor of MAO used to treat depression and Parkinson's disease—the K_i was 1.5 μM, which may indicate that the selection of tedizolid was based on the maximal therapeutic ratio rather than on the reduction of the side effects.

Analogues bearing C-5 reverse amide as well as oxazolidinones having substituted piperidine or azetidine C-rings have aroused great expectations, due to reduced human MAO-A inhibition and the most favourable attenuating effect on MPSi, without a significant decrease of antibacterial potency when compared to linezolid, as well as the excellent pharmacokinetic profiles. With respect to hybrid oxazolinones, the hope of overcoming the intrinsic resistance of Gram-negative bacteria to oxazolidinones proved to be in vain. It is thought that reduced penetration of the outer membrane due to increased molecular weight is a major limiting factor of Gram-negative inefficacy.

As previously described, new compounds should be directed towards broadening the spectrum of antibacterial activity as well as towards improving safety profile. As such, it seems that scientists have still not synthesised highly potent and perfectly selective analogues but are hopefully getting closer to success with each undertaken attempt.

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