Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 14 (2006) 4227–4240
Bioorganic & Medicinal Chemistry

Recent developments in the identification of novel oxazolidinone antibacterial agents

Adam R. Renslo,* Gary W. Luehr and Mikhail F. Gordeev

Vicuron Pharmaceuticals, 34790 Ardentech Ct., Fremont, CA 94555, USA

Received 17 November 2005; revised 25 January 2006; accepted 26 January 2006
Available online 9 March 2006

Abstract—The oxazolidinones are a promising new class of synthetic antibacterial agents. Here, we review recent efforts directed at the discovery of new antibacterial compounds of this class. New structures and structure–activity relationships (SAR) are discussed in the context of earlier work in the field. Key issues of potency, spectrum, selectivity, in vivo efficacy, and pharmacokinetic profile of the new analogs are addressed.

1. Introduction

The oxazolidinones are a new class of totally synthetic antibacterials that inhibit protein synthesis via binding to a distinct region of 23S RNA near the peptidyl transferase center of the 50S ribosomal subunit in prokaryotes.[1] This novel mode of action results in an important lack of cross-resistance between oxazolidinones and the existing classes of antibacterial agents, including other agents that also inhibit bacterial protein synthesis. This feature is of paramount importance given that the emergence of multidrug-resistant bacterial pathogens is a significant and growing problem in hospitals and in the community.[2]

E. I. du Pont de Nemours & Company scientists were the first to discover, in the late 1970s, the antimicrobial properties of oxazolidinones during their research on plant antimicrobials. These workers identified the acetamidomethyl side chain as an optimal substituent at C-5 of the oxazolidinone ring and demonstrated the importance of C-5 stereochemistry for antibacterial activity. This pioneering work culminated in the identification of the first clinical candidates of the oxazolidinone class, DuP-105 and DuP-721 (Fig. 1).[3] The development of these compounds was discontinued however and the project terminated due to concerns over animal toxicity.[4]

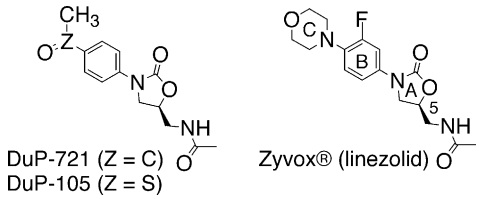

Figure 1. Progenitor oxazolidinones DuP-721, DuP-105, and linezolid.

Scientists at the Upjohn Company in Kalamazoo, Michigan, continued their work on the oxazolidinone class, however, and eventually identified linezolid (Zyvox®, see Fig. 1), which ultimately received regulatory approval and was launched in April of 2000.[5] This milestone event signaled the introduction of the first new class of antibacterials since the quinolones, more than 30 years prior. Linezolid is indicated for the treatment of Gram-positive infections, including community and nosocomial pneumonia, as well as skin and soft tissue infections. The commonly used designations for the key structural elements of oxazolidinones (i.e., the A-, B-, and C-rings; the C-5 position of the A-ring) are denoted in the structural formula of linezolid (Fig. 1) and will be used throughout this review.

Linezolid has proven to be an important therapeutic option for the treatment of serious Gram-positive infections, especially those caused by methicillin-resistant

Keywords: Antibacterials; Oxazolidinones; Structure–activity relationships; Protein synthesis inhibitors.
* Corresponding author. Tel.: +415 514 9698; fax: +415 541 4507; e-mail: adam.renslo@ucsf.edu

0968-0896/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2006.01.068

Staphylococcus aureus (MRSA). Linezolid is currently marketed by Pfizer Inc. and the drug has seen an impressive 50% increase in the annual number of therapy days worldwide since 2003.[6] This growth reflects the clinical efficacy of linezolid in the treatment of nosocomial pneumonia and complicated skin and soft-tissue infections caused by MRSA. The success of linezolid in the marketplace is also driven by its high bioavailability and favorable ADME properties, which permit administration in either intravenous or oral form and without need for dose adjustment when switching between the two.

Favorable clinical experience with linezolid has prompted many pharmaceutical companies to devote resources to the area. In particular, significant efforts have been mounted to expand the antibacterial spectrum of this class to cover fastidious Gram-negative respiratory tract pathogens such as *Haemophilus influenzae* and *Moraxella catarrhalis*. Reports of linezolid-resistant strains resulting from clinical use highlight the importance of research into the mode of action and mechanisms of resistance. Finally, any successful research effort in the field must address the selectivity profile of new oxazolidinone analogs, in particular their inhibition of monoamine oxidase (MAO-A and MAO-B) enzymes, and their potential for hemopoietic toxicity.

This review is intended to provide a summary of work that appeared in the period from 2003 through mid-2005. Specifically, we have chosen to focus on advances in the identification and SAR of structurally novel oxazolidinone agents. For a discussion of earlier work and recent clinical experience with linezolid itself, the reader is directed to a number of excellent reviews.[5,7,8]

2. A-ring replacement

The identification of bioisosteric surrogates for the oxazolidinone ring would seem to be an attractive strategy with the potential to both improve biological activity and establish a strong intellectual property position. This approach has undoubtedly received much attention, and yet relatively few viable A-ring replacements have been reported in the literature. This observation is suggestive of a ribosomal binding site with precise structural requirements in the vicinity of the oxazolidinone ring. The binding site is much more promiscuous with respect to C-ring structure, as will be discussed in a later section. Despite these challenges, at least three viable oxazolidinone ring surrogates have been disclosed. The first was the butenolide A-ring, reported in the mid-1990s by several groups.[9] This advance was followed in the late 1990s by the disclosure of antibacterial isoxazolines, discovered independently by workers at Pharmacia and Bayer,[10] and isoxazolinones, reported by researchers at Bristol–Myers Squibb.[11]

Recently, Barbachyn et al. at Pharmacia provided a full account of their studies of antibacterial isoxazoline analogs such as **1** (Fig. 2).[10d] Structurally, the isoxazoline ring incorporates the A-ring oxygen atom considered

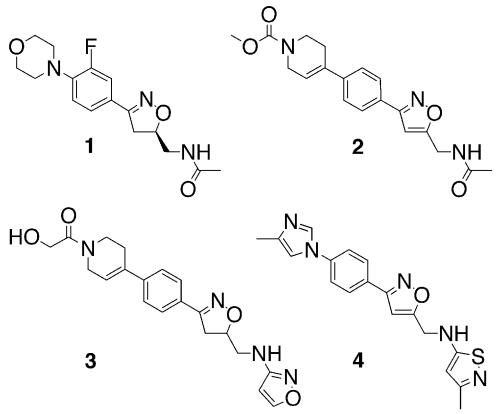

Figure 2. Antibacterial compounds bearing oxazolidinone A-ring surrogates.

crucial for activity, but it is unique in that it lacks the C-2 carbonyl present in all other viable A-ring surrogates. As with oxazolidinones, the stereochemical configuration at C-5 of the isoxazoline ring is critical; only analogs having the *R* configuration at C-5 (as in **1**) were found to have antibacterial activity. The finding that achiral isoxazole analogs such as **2** are devoid of antibacterial activity was seen to support the notion that an sp^3 center at C-5 is required for optimal binding. With regard to in vitro antibacterial activity, the isoxazoline analogs are somewhat less potent than their oxazolidinone congeners, particularly against the fastidious Gram-negative organisms *H. influenzae* and *M. catarrhalis*. On the other hand, much of the established SAR for oxazolidinones appears to hold for this new A-ring series. For example, the incorporation of fluorine atoms in the B-ring of isoxazoline analogs improved their potency, as did substitution of a thioacetamide for the C-5 acetamide.

AstraZeneca has recently disclosed isoxazoline A-ring analogs with a nitrogen-containing heterocyclic ring in place of the traditional *N*-acetylaminomethyl C-5 side chain (e.g., **3**, Fig. 2).[12] The isoxazoline **3** was evaluated as a racemate and had MICs of 4 μg/mL against methicillin- and quinoline-resistant *S. aureus* and 8 μg/mL against *E. faecalis*. Interestingly, researchers at Laboratorios Salvat and Dr. Reddy's Laboratories have separately reported good antibacterial activity for compounds containing achiral isoxazole or triazole A-rings, respectively.[13] Thus, compound **4** was 2- to 4-fold more potent than the linezolid against *S. aureus* and *S. faecalis* strains, and was equipotent to linezolid against *M. catarrhalis*.[13a] These results are perhaps surprising given the findings of the Pharmacia group that isoxazole **2** lacked antibacterial activity.

Antibacterials bearing an isoxazolinone ring were first disclosed in a patent application from Bristol–Myers Squibb. Additional details regarding this new structural type have appeared in recent publications and patents from groups at BMS and Pharmacia.[14,15] Structurally, the isoxazolinone ring possesses both the ring carbonyl and oxygen atom of the oxazolidinone ring, but replaces

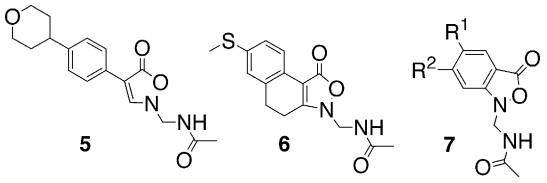

Figure 3. Isoxazolinone A-ring analog **5** and related but inactive fused derivatives **6** and **7**.

the stereogenic C-5 carbon atom with a nitrogen atom. Incorporation of an acetamidomethyl side chain produces an achiral bioisostere of the oxazolidinone pharmacophore (Fig. 3). Isoxazolinone analogs such as **5** display in vitro antibacterial activities comparable to that of linezolid, and a number of related analogs were reported with improved activity against the fastidious Gram-negative bacterium *H. influenzae*. It is perhaps surprising that the achiral isoxazolinones should be so potent, considering the critical nature of C-5 configuration in oxazolidinones and the complete lack of activity reported for achiral isoxazole analogs such as **2**. Presumably the nitrogen atom of the isoxazolinone ring possesses sufficient sp^3-like character as to properly dispose the acetamidomethyl side chain in the ribosomal binding site. Analogs lacking the acetamidomethyl side chain are inactive, implying that the potentially labile *N*-acyl aminal function (as in **5**–**7**) is stable under the assay conditions. A number of isoxazolinone analogs were reported[14] to be orally efficacious in a murine septicemia model, indicating reasonable stability of the isoxazolinone ring and side chain in vivo. Thus, the isoxazolinone ring appears to be a viable A-ring surrogate possessing the practical advantage of not requiring an enantioselective synthesis.

In addition to the isoxazolinone heterocycle, the BMS group also investigated tricyclic analogs (**6**) in which the A- and B-rings are joined via a six-membered ring (Fig. 3). In a much earlier work by Brickner, a five-membered fusion between an oxazolidinone A-ring and phenyl B-ring was well tolerated, producing analogs with MICs similar to the unconstrained comparators.[5a] In contrast, tricyclic analogs such as **6** were completely devoid of antibacterial activity, suggesting that an optimal dihedral angle between the A- and B-rings is required for binding and cannot be accommodated by structures such as **6**. Also inactive were analogs based on the benzisoxazolinone ring (e.g., **7**, Fig. 3) and analogs with a pyrrole A-ring, including those substituted with hydrogen bond acceptor group to mimic the ring oxygen and/or carbonyl group of the oxazolidinone ring.

3. Oxazolidinone C-5 side-chain modification

In the years since DuPont chemists first identified the privileged acetamidomethyl C-5 side chain, significant efforts have been aimed at identifying other novel C-5 side chains that confer improved potency, selectivity, or pharmacokinetic properties. Among the early advances was the finding that conversion of the acetamide function to a thioacetamide generally led to improved antibacterial potency.[16,17] A number of research groups have subsequently reported on related C-5 side-chain types bearing thiocarbonyl-containing functionality. Thus, several reports have appeared in the past two years describing oxazolidinones bearing thioamide, thiourea, thiocarbamate, and dithiocarbamate functionality. For a review of work in this area before 2003, the reader is directed to the recent review by Hutchinson.[7]

A recent report on novel tetrahydro-thienopyridyl C-ring oxazolidinones (**8**, Fig. 4) included a rather extensive exploration of the C-5 side chain.[18] Methylation of the amide N–H produced an inactive compound as expected, while the C-5 cyclopropylamidomethyl analog was only 2-fold less potent than the corresponding acetamide. Thioacetamide and thiocarbamate analogs were 2- to 4-fold more potent than the acetamide and a thiourea analog was better still. In contrast, a dithiocarbamate analog was devoid of activity against *S. aureus* and *E. faecalis* strains but retained activity against *S. pneumoniae*. The thiourea moiety was also found to be optimal in a related series of arylpiperazinyl oxazolidinone analogs (e.g., **9**, Fig. 4) described recently.[19] The corresponding thioacetamide, thiocarbamate, and dithiocarbamate analogs were slightly less potent. One analog of each C-5 sub-type was examined in an in vivo efficacy model but with discouraging results ($ED_{50} > 16$ mg/kg for all analogs tested as compared to 4 mg/kg for the linezolid control). A group at Ranbaxy prepared a series of imidazolidinyl and oxazolidinyl C-ring analogs bearing C-5 methylthiocarbamates and reported excellent activity against methicillin-resistant *S. aureus* and *Enterococcus* species.[20]

A report from Dr. Reddy's Laboratories on tricyclic oxazolidinones (**10**, Fig. 4) described the synthesis of more than 20 different C-5 amide, carbamate, thioamide, and thiocarbamate analogs.[21] Stepwise extension of the C-5 amide substituent from acetamide to heptanoylamide showed the expected erosion of antibacterial activity with increasing alkyl chain length. A branched-chain (isopropyl) amide analog was notably less active

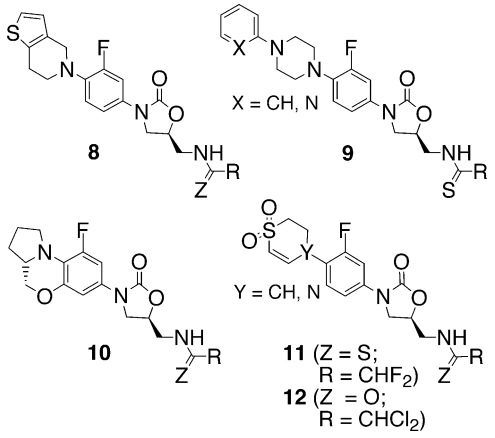

Figure 4. Analogs with a thiocarbonyl-containing moiety at C-5 of the oxazolidinone ring.

than the straight chain comparator. A thiopropionamide analog had activity comparable to that of the thioacetamide and 2-fold better than that of the acetamide, but further extension of the side chain resulted in a loss of activity. In this class of C-ring analogs, thiocarbamate, dithiocarbamate, and thiourea analogs exhibited excellent in vitro activity. The in vivo efficacy of a number of the tricyclic analogs **10** was evaluated in a murine systemic infection model. In general, the tricyclic analogs displayed efficacy inferior to that of linezolid in this model, with the acetamide analog having ED_{50} values 2-fold higher than those of linezolid. Among the most promising compounds in vivo was a methyl thiocarbamate analog that exhibited efficacy comparable to that of linezolid (ED_{50} = 4.9 mg/kg). Interestingly, almost all of the other thiocarbonyl analogs tested displayed poor in vivo efficacy (ED_{50} > 20 mg/kg).

Researchers at Vicuron (in collaboration with Pfizer Kalamazoo scientists) reported on a series of dihydrothiazine and dihydrothiopyran C-ring analogs (Fig. 4).[22–24] Among the various C-5 groups examined were novel difluorothioacetamide (**11**) and dichloroacetamide (**12**) analogs. Analogs of the difluorothioacetamide type were 2- to 4-fold more potent than the comparable acetamides against Gram-positive strains, but were no more potent against fastidious Gram-negative strains. Dichloroacetamide analogs were more potent against both Gram-positive and Gram-negative strains and demonstrated the best overall spectrum of activity. Two difluorothioacetamide analogs had in vivo efficacy comparable to that of linezolid in a murine septicemia model.

Researchers from Pfizer and Vicuron describe in a patent application oxazolidinones with truncated C-5 side chains in which a carboxamide function is attached directly to the C-5 position.[25] The C-5 carboxamide analog **13** (Fig. 5) is reported to have *S. aureus* activity comparable to that of linezolid (MIC = 4 μg/mL).

Workers at Vicuron have shown that certain large extended acyl groups can be well tolerated at the C-5 position (Fig. 6).[26] Thus, cinnamic acid amide **14** shows remarkable potency against *S. pneumoniae* and vancomycin-resistant *E. faecium* strains with MICs of 0.06–0.125 μg/mL and 0.06 μg/mL, respectively, but is inactive against *H. influenzae*.[27] Researchers at Lupin[28] described 4-oxobutanamides represented by compound **15** with in vivo activity against *Mycobacterium tuberculosis* in a murine pulmonary tuberculosis model.

One of the more interesting developments in recent years is the finding by Gravestock et al. at AstraZeneca that

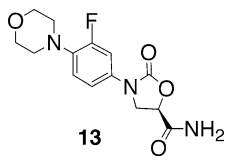

Figure 5. Linezolid variant with a novel carboxamide C-5 substituent.

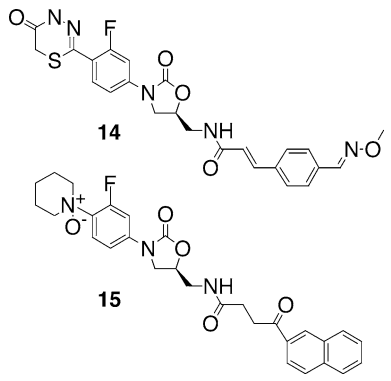

Figure 6. Extended C-5 side-chain analogs.

some five- and six-membered heterocyclic rings are valid surrogates for traditional amide-type C-5 side chains (for leading references, see the review by Hutchinson[7]). These findings have questioned the conventional wisdom that a hydrogen bond donor (i.e., the N–H of the C-5 acetamide) is essential for antibacterial activity. Indeed, it has been suggested that the inactivity of *N*-alkyl C-5 acetamide analogs might result from a steric or conformational effect rather than from the loss of a crucial hydrogen-bonding interaction.[29] It is also possible that the heterocyclic C-5 side chains of the AstraZeneca analogs adopt a different binding mode than do traditional acetamide-type oxazolidinones and are therefore subjected to different requirements for binding.

Recently, Gravestock et al. described some of their early work on oxygen-linked five- and six-membered heterocyclic C-5 side chain types in the context of analogs with either the dihydropyranyl or tetrahydropyridyl C-ring types.[29] Among the six-membered heterocycles examined at C-5, pyridine and pyrazine analogs were the most potent, although they were still inferior to the acetamide comparator. Substitution on the heterocyclic ring was very poorly tolerated, suggesting that smaller, less sterically demanding heterocycles might prove advantageous. Indeed, the move to five-membered heterocycles such as isoxazole produced analogs with potencies approaching that of the acetamide comparator. Analogs incorporating sulfur-containing heterocycles (e.g., the thiadiazole **16**, Fig. 7) were more potent still, a finding reminiscent of the thiocarbonyl effect in traditional acyclic C-5 groups. A number of novel C-5 group analogs were evaluated in vivo using a mouse thigh infection model. Poor results for several dihydropyranyl analogs were attributed to high in vivo clearance for this C-ring type and not any deficiency with respect to the C-5

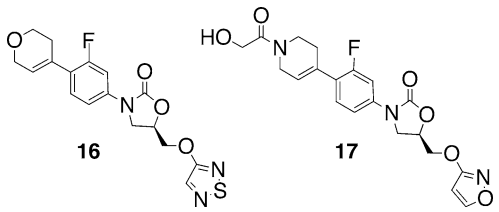

Figure 7. Heterocyclic C-5 side-chain analogs.

group. Indeed, in the tetrahydropyridine C-ring series, the O-linked isoxazole analog **17** demonstrated efficacy that was on par with linezolid.

The nitrogen-linked azolylmethyl oxazolidinones **18**–**20** (Fig. 8) are a related class of heterocyclic C-5 type oxazolidinones reported by the AstraZeneca group.[30–32] These analogs differ from those discussed above in that the heterocyclic ring is connected directly (rather than through a heteroatom) to the C-5 methylene carbon. Five-membered ring heterocycles are again preferred over larger ring systems in the C-5 side chain. Among the five-membered heterocycles examined, N-linked triazole and tetrazole rings conferred antibacterial activity comparable to the traditional acetamidomethyl side chain. Within the triazole series, 1,2,3-triazoles were at least 8-fold more potent than 1,2,4-triazole or N-2-linked 1,2,3-triazole congeners. Less dramatic effects were observed in the tetrazole series, where the N-1- and N-2-linked isomers showed similar potency. A murine thigh infection model was used to assess the in vivo efficacy of various triazole and tetrazole analogs. For analogs with a tetrahydropyridine C-ring (e.g., **18**), the triazole analog was more efficacious than the tetrazole. In the case of analogs with an imidazole C-ring (**19**), the tetrazole analogs (N-1- or N-2-linked) outperformed both the triazole analog and the linezolid control.

Early work on heterocyclic C-5 groups suggested poor tolerance for substitution on the heterocyclic ring, as mentioned above. Despite this, recent work from the AstraZeneca group on 1,2,3-triazole analogs indicates that certain substituents are not only well tolerated, but can impart improved selectivity as well.[30] In this work, Reck and co-workers describe the synthesis and biological evaluation of 4- and 5-substituted 1,2,3-triazole analogs. Analogs with 5-substituents were devoid of antibacterial activity, but many of the 4-substituted analogs were equipotent to the parent triazole. In particular, 4-methyl or 4-halogen substitution was tolerated with little or no loss of antibacterial activity and the 4-methyl modification led to attenuation of MAO-A inhibition. Homologation to an ethyl group further reduced MAO-A inhibition but at the price of reduced antibacterial activity (*S. aureus* MIC = 4 μg/mL vs 1 μg/mL). Introduction of larger substituents or an acetyl group[33] resulted in nearly complete loss of activity. Short, linear groups such as terminal alkynyl (as in **20**, Fig. 8) or cyanomethyl were optimal, providing analogs with acceptable antibacterial activity but lacking the MAO-A liability of the parent triazole. The MAO-A inhibition of these analogs was studied computationally using a homology model based on the crystal structure of MAO-B (see Section 7).

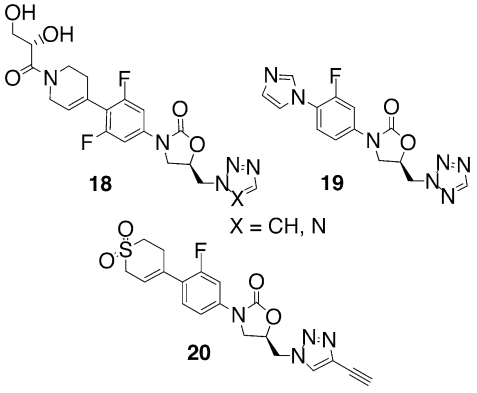

Figure 8. Triazolylmethyl and tetrazolylmethyl C-5 side-chain analogs.

The cumulative SAR generated in these studies suggests that the C-5 group occupies a binding pocket with very specific steric and electronic requirements but one that can nonetheless accommodate a variety of different structural sub-types. Thus, the C-5 side chain presents both a challenge and an opportunity to the medicinal chemist in search of novel oxazolidinones with improved potency, spectrum, and target selectivity.

4. B-ring replacement

A recent report describes the synthesis of oxazolidinone analogs in which the phenyl B-ring is replaced with a pyrrole heterocycle.[34] These analogs were designed to target mycobacteria. Unfortunately a linezolid derivative with a morpholine C-ring was inactive against all mycobacteria tested. The fluorophenyl C-ring analog **21** (Fig. 9) did have antimycobacterial activity but even this compound was many-fold less potent than a traditional phenyl B-ring comparator. The reduced antimicrobial activity of these analogs was ascribed to the unfavorable bent geometry introduced by the pyrrole B-ring.

5. C-ring replacements

The 4′-position (C-ring) of phenyloxazolidinones is without question the most tolerant of variation and has therefore received significant attention from medicinal chemists intent on identifying improved molecules and/or carving out a proprietary position in the field. Most of the recent work in this area falls within one of the following conceptual frameworks: (a) fusion of the B- and C-rings; (b) separation of the B- and C-rings by a spacer; (c) appendage of additional groups or rings to established C-rings; and (d) novel C-rings. Each of these approaches will be covered separately in the following discussion. Hybrid antibacterials, in which an antibacterial pharmacophore of a different class is appended in various ways to an oxazolidinone, will be covered separately.

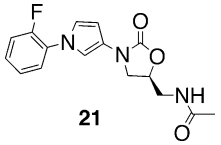

Figure 9. Heteroaromatic B-ring analog **21**.

Two recent reports from Pfizer (Kalamazoo) researchers describe oxazolidinone analogs in which the heterocyclic C-ring is fused to the B-ring at the 3′- and 4′-positions. Johnson et al.[35] prepared and evaluated a series of isomeric benzazepine analogs (e.g., **22** and **23**, Fig. 10) differing in the location of the azepine ring nitrogen. Among the N-1 benzazepines, the *N*-formyl derivative **22** possessed linezolid-like potency and spectrum, while analogs with larger amino substituents had poor activity. The N-5 benzazepine isomer was even less tolerant of substitution; only the unsubstituted analog had measurable activity. In contrast, N-3 benzazepine analogs bearing a variety of acyl and carbonyl groups were active. The best among these was the hydroxyacetamide **23** which displayed linezolid-like activity in vitro and was also efficacious in a murine septicemia model (ED_{50} = 8.5 mg/kg vs 5.6 mg/kg for linezolid).

Barbachyn and co-workers recently described their work on a related series of indolinyl, tetrahydroquinolyl, and dihydrobenzoxazinyl oxazolidinones.[36] As in the benzazepine series, analogs bearing formyl or hydroxyacetyl appendages on the ring nitrogen were more potent than the parent amines. An interesting aspect of this work relates to the effect of substitution at the 2-position of the fused bicyclic ring. Thus, the (*R*)-2-methyl indoline analog **24** (Fig. 10) had 2-fold better activity than the desmethyl parent compound and was 4-fold more potent than the epimeric (*S*)-2-methyl diastereomer. The introduction of a 2-methyl group had similar, beneficial effects in the related tetrahydroquinolyl and dihydrobenzoxazinyl analogs (**25**, Fig. 10), and again the (*R*)-isomers were more potent. The indoline analog **24** furthermore demonstrated oral efficacy comparable to that of linezolid in a murine septicemia model (ED_{50} = 1.8 mg/kg vs 2.5 mg/kg for linezolid).

In the late 1990s, Bayer disclosed a variety of bicyclic and tricyclic oxazolidinones in which a six-membered ring joins the B- and C-rings forming a tricyclic system.[37] Many of these analogs were reported to exhibit enhanced activity against Gram-negative organisms. Recently, researchers at Pfizer[38] disclosed a variety of heteroaryl tricyclic analogs with seven-membered rings connecting the B- and C-rings (e.g., **26** and **27**, Fig. 11). These analogs are likewise reported to have an expanded spectrum of activity. For example, tricyclic

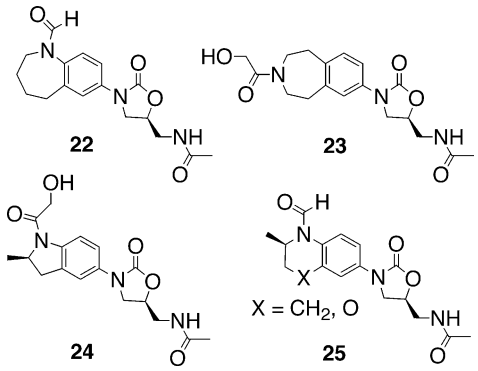

Figure 10. Oxazolidinones containing fused B/C-rings.

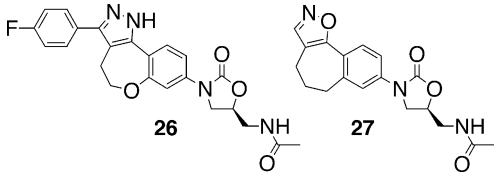

Figure 11. Fused tricyclic oxazolidinone analogs.

isoxazole C-ring analog **27** showed MICs of 0.25 μg/mL or less against Gram-positive strains and MICs of 2 μg/mL against *H. influenzae* and *M. catarrhalis*. The incorporation of a fluorophenyl 'D-ring,' as in benzoxepinyl pyrazole **26**, resulted in only a slight loss of activity against *H. influenzae* (MIC = 4 μg/mL).

At least four different groups have explored approaches whereby established C-ring types are separated from the phenyl B-ring by a flexible spacer. Selvakumar et al. at Dr. Reddy's Laboratories[39] describe analogs such as **28** (Fig. 12) in which an aryloxyethyl linker connects the phenyl B-ring and various known C-rings (e.g., morpholine, piperidine, and thiomorpholine). The effect of this additional flexibility on antibacterial activity is quite significant. The morpholine congener (**28**, X = O) was found to be 4- to 8-fold less potent than linezolid against *S. aureus* and *E. faecalis* strains. Much of the lost activity could be regained however, by converting the C-5 acetamide to a thioacetamide. Interestingly, analogs lacking the 3′-fluorine substituent were entirely devoid of antibacterial activity. A group from Abbott[40] reported better results when employing a less flexible linkage between the B- and C-rings, as in fluoroalkene analog **29**. This compound exhibited antibacterial activity comparable to that of linezolid and also had reduced inhibition of mitochondrial protein synthesis and MAO-B. The inhibition of mitochondrial protein synthesis by oxazolidinones was postulated to be at least partially responsible for the hemopoietic toxicity associated with the use of linezolid for extended periods.

Research groups at Johnson and Johnson[41] and in India[42] reported independently on analogs in which a single atom (oxygen or sulfer) forms the link between the B- and C-rings (e.g., **30** and **31**, Fig. 12). This structural modification introduces a significant kink in the normally linear B- to C-ring connection. On the other hand, analogs like **30** and **31** possess significantly less conformational flexibility than ethylene-oxy-linked analogs **28**. The Johnson and Johnson group examined the effect of various C-ring amide side chains in a series of oxygen-linked piperidine C-ring analogs (**30**). The single-atom spacer was better tolerated than the longer spacer of analogs such as **28**. Thus, compound **30** was only slightly less active than linezolid against *S. aureus* and *E. faecalis* strains (MIC = 4 μg/mL and 8 μg/mL, respectively, vs 2 μg/mL for linezolid). Efforts to improve the activity of **30** by modification of the hydroxyacetamide function were not fruitful. Conversion of the hydroxy group to various ethers or replacement with a basic amino group produced analogs four to eight times less potent than **30**. Thiocarbonyl C-5 analogs were not reported. Analog **30** was administered subcutaneously in a murine systemic

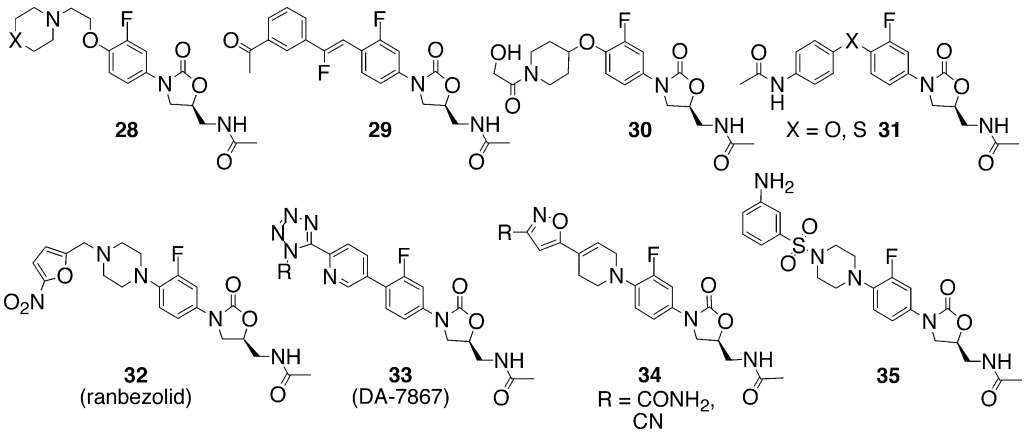

Figure 12. Oxazolidinone analogs with a spacer between the B- and C-ring (**28**–**31**) and analogs bearing heterocyclic D-rings (**32**–**35**).

infection model and was found to be efficacious, albeit with a significantly higher ED_{50} value than that for linezolid (ED_{50} = 13 mg/kg vs 2.7 mg/kg for linezolid).

In a conceptually similar work, Arora and co-workers described aryloxy and thioaryloxy analogs such as **31** (Fig. 12).[43] All of the analogs described included N-acetyl substitution on the phenyl C-ring and, perhaps surprisingly, only para-substituted isomers (as in **31**) had antibacterial activity comparable to that of linezolid. The corresponding thioaryl analogs (**31**, X = S) were marginally more potent than the aryloxy analogs (X = O), but the incorporation of a thiocarbonyl C-5 group, interestingly, did not further improve the activity of this class.

A number of groups have reported oxazolidinone analogs that incorporate a fourth aryl or heteroaryl 'D-ring,' typically appended to an established C-ring type (e.g., pyridyl or piperazinyl) directly, or via a short linker. Much of this recent work seems to be inspired by the early work of Upjohn researchers on pyridine-, diazene-, and triazene-substituted piperazinyl oxazolidinones.[44] Researchers at Ranbaxy[42] and Orchid[45,46] have described analogs with piperidino or piperazino C-ring analogs bearing a nitro-substituted D-ring heterocycle. The most advanced member of this class, ranbezolid (**32**, RBX 7644, Fig. 12), completed a Phase I clinical trial in April 2003.[47] The compound has an expanded spectrum of activity that includes activity against the fastidious Gram-negative bacterium *M. catarrhalis* and against anaerobes.[48,49] Related analogs with a pyridyl B-ring have been reported to possess activity similar to that of the phenyl B-ring progenitor.[50] Other (non-oxazolidinone) nitrofuran antibacterials are known and are believed to exert their cytotoxic effects through conversion by nitroreductases to reactive nitroso radical intermediates.[51]

Researchers at Dong-A Pharmaceuticals and AstraZeneca separately reported on exceptionally potent oxazolidinones incorporating five-membered heterocyclic D-rings (e.g., tetrazole and isoxazoline) joined to pyridyl or related C-ring types.[32,52,53] The Dong-A researchers examined more than ten different D-ring heterocycles and describe analogs with exceptional in vitro activities, often including activity against the fastidious Gram-negative pathogens *H. influenzae* and *M. catarrhalis*. A notable exception was an acidic tetrazole D-ring analog that was devoid of activity. While the in vitro activities of the various analogs were quite similar, their in vivo efficacies varied widely. Hence, an N-1-linked pyrazole analog was not efficacious (ED_{50} > 80 mg/kg) in a mouse septicemia model, whereas the *N*-methyl tetrazole **33** (Fig. 12) was superior to linezolid in the same model (ED_{50} = 3.4 mg/kg vs 8.0 mg/kg for linezolid). Given the rigid, aromatic nature of this class of compounds, solubility is likely a key issue and may explain the poor efficacy of some analogs. In fact, the AstraZeneca group's work on hydroxymethylisoxazoline D-ring analogs included the synthesis of solubilizing prodrug derivatives.[32,53] Likewise, in two recent posters[54,55] Dong-A researchers reported in vivo efficacy studies of DA-70218, a soluble prodrug of DA-70157 (structures were not provided but it may be surmised that they are related to DA-7867). The prodrug analog DA-70218 exhibited exceptional efficacy in a murine pneumonia model, outperforming linezolid when dosed QD (vs BID for linezolid) at half the total dose. In recent patent applications, Gravestock and co-workers at AstraZeneca claim structures closely related to **33** but with nitrogen-containing heterocyclic C-5 groups.[56] Workers at BMS recently described a variety of highly potent isoxazolinone A-ring analogs bearing a variety of aromatic and heteroaromatic D-ring types.[14b]

A number of groups have reported analogs in which a piperazine or piperidine C-ring is appended to various aryl or heteroaryl rings.[57–62] These D-rings can be considered cyclic surrogates for the privileged hydroxyacetyl side chain present in the progenitor oxazolidinone eperezolid. Most of these analogs did not exhibit useful levels of antibacterial activity, except when combined with a thioacetamide C-5 group. Two acetamides that did show linezolid-like potency were the isoxazolyl piperidines represented by **34**[61] and the aryl sulfonamide **35** (Fig. 12).[57]

The piperazine C-ring analog **36** (PNU-259621, Fig. 13) is a specifically designed photo-affinity probe that was

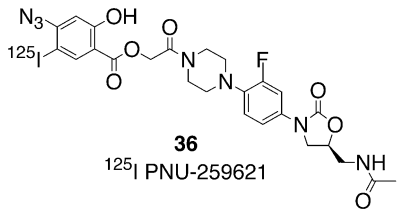

Figure 13. An eperezolid derivative employed as a photo-affinity probe.

used by Colca and co-workers[1e] in cross-linking studies aimed at pinpointing the site of action of antibacterial oxazolidinones. The pendant aryl ring of **36** includes a photo-active azido substituent and an ^{125}I substituent as a radiolabel. In these experiments, **36** was incubated with growing *S. aureus* bacteria and then subjected to photolysis to initiate cross-linking of **36** (presumably bound in the active site) to nearby ribosomal proteins and RNA. Indeed, compound **36** was found to cross-link to a single nucleotide (A-2602) of 23S rRNA and also to two ribosomal proteins. All of the cross-linked moieties are associated with the peptidyltransferase center of the large ribosomal subunit, suggesting that oxazolidinones bind in the immediate vicinity of the peptidyltransferase center in translating ribosomes.

A complementary approach to the appendage of D-rings to C-rings is the fusion of aryl or heteroaryl rings to an aliphatic C-ring to generate bicyclic C-ring types. Examples of this approach include the pyrroloaryl oxazolidinones (**37**, Fig. 14) described by Paget et al.[63] and the tetrahydro-thienopyridyl analogs **8**, discussed previously. A number of pyrroloaryl analogs **37** were examined and those with heteroatoms in the fused ring (e.g., **37**, X = N) were superior to the phenyl (X = CH) analogs in vitro (up to 8-fold more potent) and in vivo (for **37**, ED_{50} = 11 and 80 mg/kg when X = N or CH, respectively). Poor efficacy in the latter case was attributed to increased protein binding for this analog. The most potent analogs of this type were ca. 4-fold more potent than linezolid. In contrast, tetrahydro-thienopyridyl analogs **8** were several-fold less potent than linezolid.

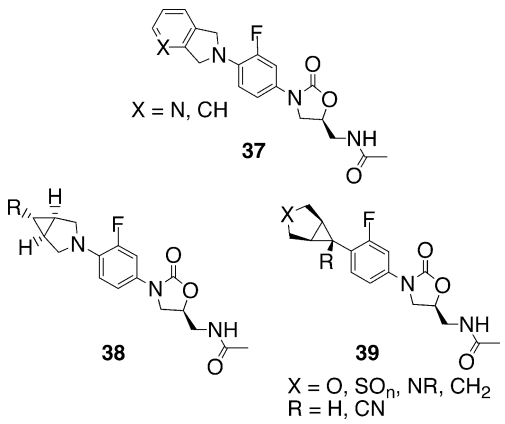

Figure 14. Oxazolidinones with fused bicyclic C-rings.

A new series of oxazolidinone analogs incorporating bicyclic aliphatic C-rings have been reported independently by a Kyorin/Merck group and by researchers at Vicuron. The first bicyclic analogs reported were of the type represented by structure **38** (Fig. 14).[64–66] The azabicyclo[3.1.0]hexylphenyl C-ring tolerates substitution with either basic or acidic functionality and many of the analogs have in vitro activity comparable or superior to that of linezolid. Interestingly, the parent amino C-ring analog (**38**, R = NH_2) had much better activity against *S. aureus* and *H. influenzae* strains (MICs = 2 and 4 μg/mL, respectively) than did the corresponding hydroxyacetamide derivative (MICs = 16 and 64 μg/mL). This contrasts with the case of traditional amino C-ring types where the hydroxyacetyl modification generally improves potency.

A second, related class of bicyclo[3.1.0]hexylphenyl oxazolidinones was disclosed recently and is represented by the structures **39** (Fig. 14). In these analogs, the bicyclic C-ring is connected to the phenyl B-ring via the cyclopropane ring. Researchers from Vicuron and Pfizer disclosed the synthesis and antibacterial activity of three subtypes of this class, the aza-, oxa-, and thiabicyclic C-ring analogs **39** (X = NR, O, and SO_n, respectively).[67] These oxazolidinones were reported to have Gram-positive activity comparable to that of linezolid but with improved activity against fastidious Gram-negative pathogens such *H. influenzae*. The Kyorin/Merck group disclosed a very closely related series of bicyclic analogs **39** in which R = CN and X = NR or CH_2.[68] Antibacterial activity data were reported for a subset of these analogs, indicating 2- to 4-fold improvements in activity as compared to linezolid.

Wockhardt scientists have reported on cyanomethylpiperidinophenyl oxazolidinones[69,70] with bactericidal activity against linezolid susceptible as well as resistant strains. Activity against the resistant strains was proposed to result from a distinct binding mode to the oxazolidinone site and/or binding at an additional ribonucleoprotein site. Compound **40** (Fig. 15) had MICs of 2, 2, and 1 μg/mL against methicillin-resistant *S. aureus*, *E. faecalis*, and *S. pneumoniae*, respectively, and is reported to be efficacious upon oral administration in a murine *S. aureus* infection model. Researchers from Korea Institute of Science and Technology reported a very closely related series of cyanomethylene piperidine C-ring analogs.[71] The cyano analog was more potent than the corresponding oxime- and ketone-substituted analogs and exhibited in vivo efficacy comparable to that of linezolid. Researchers at Merck and Kyorin[72,73] explored cyclopropyl C-ring analogs substituted with nitrile groups. Analogs such as **41** are report-

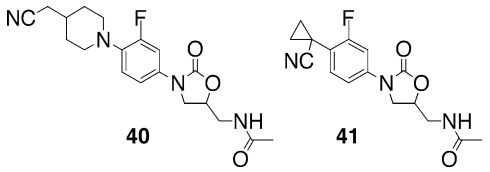

Figure 15. Nitrile-containing analogs.

ed to possess excellent activity against multidrug-resistant Staphylococci and Enterococci strains.

An early report from Pharmacia scientists on azolylphenyl oxazolidinones illustrated the excellent potency and spectrum inherent to this class of oxazolidinones.[74] Interest in heteroaromatic C-rings remains keen, with Thomasco et al. at Pfizer reporting on a series of 1,3,4-thiadiazole C-ring oxazolidinones.[75] More than 20 analogs were described (differing primarily in thiadiazole ring substitution) and uniformly displayed excellent activity against a panel of Gram-positive and fastidious Gram-negative bacteria. The majority of these analogs were orally efficacious, with the exception of four C-5 thioacetamide analogs. The aminomethyl analog **42** (Fig. 16) was examined in greater detail when it was found to lack efficacy despite having excellent activity (MICs < 0.5 μg/mL). In a pharmacokinetic study in rats, the compound was found to suffer from high clearance (34.3 mL/min/kg) and a bioavailability of only 14%. The workers speculate that the poor performance of these analogs in vivo results from metabolism of the thioamide functionality.

A group from Vicuron described the synthesis and antibacterial activity of a series of structurally related [1,3,4]-thiadiazin-5-one analogs with exceptional potency against both Gram-positive and Gram-negative organisms.[76] Compound **43** (Fig. 16) had MICs of 0.5–1 μg/mL versus *H. influenzae* and *M. catarrhalis*, and displayed in vivo efficacy superior to that of linezolid (ED_{50} = 2.5 mg/kg vs 3.8 mg/kg for linezolid) in a mouse septicemia model. Larger C-5 groups as well as ureas and carbamates were well tolerated, although incorporation of excessively lipophilic groups reduced Gram-negative potency. A series of isoxazoline C-ring oxazolidinones **44** (Fig. 16) were reported by a group from Johnson and Johnson.[77] Incorporation of a nitrile substituent (**44**, R = CN) conferred improved potency, an effect consistent with that reported for azolyl C-ring oxazolidinones. Pyridyl- and carboxamido-substituted analogs displayed potency comparable to that of linezolid, while larger or more basic groups generally reduced activity. The most potent analogs were evaluated in a murine systemic infection model and were found inferior to linezolid (ED_{50} values of 22–40 mg/kg vs 6.8 mg/kg for linezolid). A group from Bristol–Myers Squibb

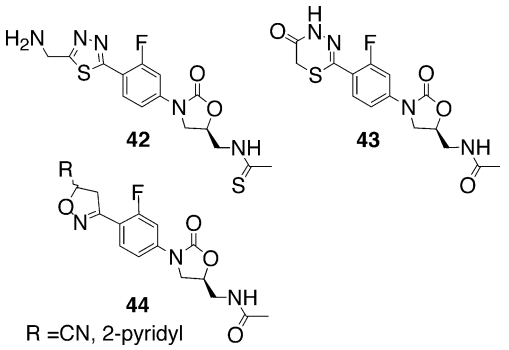

Figure 16. New heterocyclic C-ring types.

recently reported on dihydro-1,2-oxazine and 2-pyrazoline C-ring analogs.[78] The Gram-positive potency of these compounds was uninspiring, with the exception of a 2-pyrazoline analog that showed linezolid-like potency and spectrum. Unfortunately, this analog lacked in vivo efficacy (ED_{50} > 50 mg/kg).

6. Hybrid oxazolidinones

Antibacterial agents that incorporate multiple and mechanistically distinct antibacterial pharmacophores offer the potential advantages of expanded antimicrobial spectrum and reduced resistance frequency. Groups from Pfizer and Vicuron,[79,80] Morphochem,[81–84] and Vita Lab[85] independently described antibacterial oxazolidinone–quinolone hybrids that possess the desired dual mechanisms of action. Notably, the nature of the linker that connects the two pharmacophores was found to impact overall potency and the degree to which each antibacterial mode-of-action operates.

The choice of the quinolone pharmacophore can be rationalized from both a microbiological and synthetic perspective. Oxazolidinones generally display poor activity against fastidious Gram-negative bacteria, whereas these pathogens are often highly susceptible to quinolones. Oxazolidinones on the other hand show excellent activity against quinolone-resistant *S. aureus* and *E. faecium* strains. The two classes possess common structural features as well, notably the piperazine ring common to both eperezolid and ciprofloxacin. Vicuron and Pfizer chemists[79] and a separate group at Morphochem[81,82] described hybrid analogs **45** (Fig. 17) in which the common piperazine ring joins the two pharmacophores. Analogs of this type display antibacterial activity that is more oxazolidinone-like, but with improved activity against Gram-negative and linezolid-resistant *S. aureus* strains. The latter activities are suggestive of DNA gyrase inhibition and this was confirmed in an enzymatic assay. Deletion of the piperazine linker produced an analog with mostly quinolone-like activity, while hybrids joined at the nitrogen atom of the quinolone ring (N-1) were inactive.

Morphochem researchers have extensively explored the nature of the heterocyclic linker between oxazolidinone and quinolone. In this work, the piperazine linker was replaced with various substituted piperidine, pyrrolidine, or azetidine linkers and the resulting analogs were examined for antibacterial and enzymatic activity. A hydroxymethyl pyrrolidine linker produced analogs with the best combination of oxazolidinone and quinolone activities.[81] Hence, the hybrid antibacterial **46** (Fig. 17) was highly active in both DNA gyrase and transcription/translation assays ($IC_{50} \leqslant 2$ μM) and had excellent whole cell activity against *H. influenzae* and quinolone- or linezolid-resistant strains of *S. aureus* (MIC $\leqslant$ 0.125 μg/mL).

A group from Theravance disclosed hybrid oxazolidinone analogs incorporating other antibacterial ribosome-binding pharmacophores.[86] Specific examples include oxazo-

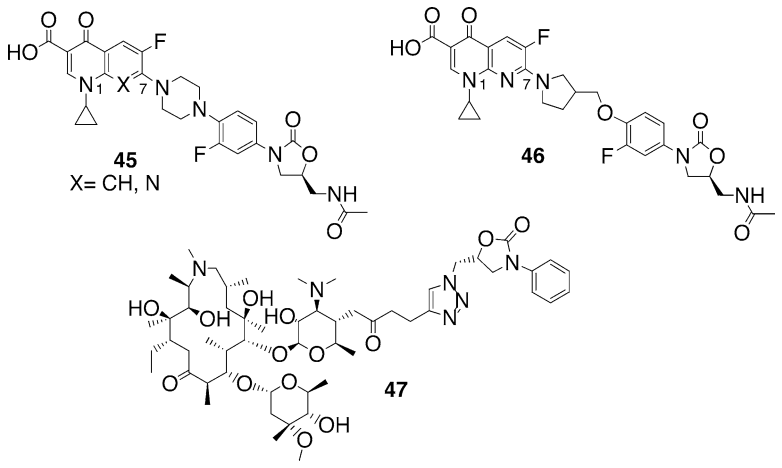

Figure 17. Hybrid oxazolidinones.

lidinones linked via an appropriate spacer to a macrolide (erythromycin), a lincosamide (U-57930E), and a streptogramin (dalfopristin and quinupristin). Rib-X researchers reported an oxazolidinone analog joined to Azithromycin[87] via a heterocyclic triazole linker group (e.g., **47**, Fig. 17). Unfortunately no antibacterial data were disclosed for any of these analogs.

7. Computational studies

Antibacterial oxazolidinone drug discovery has to date been a largely empirical exercise with limited impact from the fields of structural biology or computer-aided drug design. This situation is likely to change given the successful solution of the crystal structure[88] of the ribosome, including co-crystal structures with a bound protein synthesis inhibitor. Two reports have appeared recently describing the application of computational methods to the prediction of biological activities of oxazolidinone antibacterials, both focused on the C-5 substituent of the oxazolidinone ring. In the first of these, a group from Dr. Reddy's Laboratories described three-dimensional quantitative SAR (3D-QSAR) studies of tricyclic oxazolidinone analogs (**10**) with various C-5 substituents.[89] Two different computational methods were compared: comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). Computational models were developed using a training set of 33 tricyclic analogs with either traditional amido or non-traditional (thioamido, urea, carbamoyl, etc.) C-5 side chains. The validity of the models was tested with a separate set of nine compounds that were not included in the original training set. Comparison of predicted and actual MICs for the test set revealed the CoMFA model to be more predictive for the compounds examined. The authors claim that these models have aided the design of novel analogs with improved activity.

A very recent report from researchers at AstraZeneca[30] describes a computational model of oxazolidinone binding to the active site of monoamine oxidase A (MAO-A). The inhibition of MAO is an undesirable, secondary biological activity inherent to many antibacterial oxazolidinones. Understanding this activity at the molecular level could contribute to the design of more selective oxazolidinone antibacterials. The binding model described by the AstraZeneca team was derived from a published 1.7 Å structure of MAO-B bound to isatin. Key active site residues from MAO-B were replaced with the corresponding amino acids present in MAO-A and a docking model was constructed that allowed conformational flexibility in the active site and entrance cavity. Oxazolidinone analogs bearing various substituted triazole groups at C-5 were docked to the model and a correlation between inhibitor structure and MAO-A activity was derived. According to the model, the triazole ring of the oxazolidinone is bound tightly in an aromatic cage formed by two tyrosine residues and the flavin ring of the cofactor. The model indicated that triazole substituents larger than hydrogen or fluorine require that the oxazolidinone ring adopt a different binding conformation. This hypothesis was in agreement with the empirical finding of reduced MAO-A activity for analogs with larger substituents on the triazole ring. Triazole analogs bearing ethyl, alkynyl, or cyanomethyl substituents were optimal in that they retained antibacterial activity but were essentially devoid of MAO-A inhibitory activity (MAO-A $K_i > 200$ μM).

8. Pharmacokinetic studies of oxazolidinone analogs

A key strength of linezolid from a clinical and marketing perspective is the drug's excellent pharmacokinetic profile,[90] which permits BID dosing via either intravenous or oral routes and without need for dose adjustment. With high overall exposure levels and essentially perfect bioavailability, linezolid sets a high bar for researchers seeking to discover a second-generation oxazolidinone. Indeed, the identification of compounds with in vivo efficacy superior to that of linezolid represents a much greater challenge than the identification of analogs with better in vitro MICs. In this section, we review recently disclosed in vivo data, with a focus on structural features that positively or negatively impact the pharmacokinetic properties of oxazolidinone analogs.

A recent report[91] from Pfizer (Kalamazoo) researchers describes a model for predicting oral bioavailability in the rat based on a maximum absorbable dose (MAD) algorithm.[92] The MAD was determined for a series of 27 oxazolidinone analogs for which bioavailability in the rat was known. The MAD calculation includes an estimate of intestinal volume and residence time as well as the measured values of aqueous solubility and permeation across the intestinal membrane (approximated by permeability across Caco-2 mono-layers). With only a few exceptions, this model performed admirably in predicting oral bioavailability of the oxazolidinone analogs. Hence, analogs with a MAD $\geqslant 5$ mg displayed bioavailabilities of ca. 55–100%, while those with MAD $\leqslant 0.5$ mg were very poorly bioavailable ($F < 5\%$). Most of the analogs with MAD values between 0.5 and 5.0 mg exhibited bioavailabilities between 33% and 88%. Individual parameters such as in vivo clearance or absorptive permeability across Caco-2 cells were only weakly correlated with bioavailability. The MAD algorithm, which takes into account both solubility and permeability, was much more powerful in making predictions of oral bioavailability for the oxazolidinone analogs studied.

The incorporation of a C-5 thiocarbonyl side chain is perhaps the most reliable means of improving the potency of oxazolidinone antibacterials. Unfortunately, this improved potency often comes at the expense of in vivo efficacy, as several recent reports have indicated. Hence, thioacetamides **10** (Z = S) and **42** were not efficacious in a murine infection model, while the corresponding acetamide derivative were.[21,75] Similar results were reported for indoline analogs.[36] Pharmacokinetic studies of *N*-formyl indolinyl oxazolidinones (i.e., **24**, *N*-formyl derivative) indicated that the thioacetamide analog was much more rapidly cleared and achieved lower serum concentration than did the acetamide comparator. In the case of **42**, metabolism of the thioamide function was suggested as a possible explanation for the compound's poor pharmacokinetic profile.[75,93] In the study of oxazolidinone absorption discussed above,[91] several thiourea analogs had much higher secretory (B to A) than absorptive (A to B) permeability across Caco-2 cell mono-layers, suggesting that these analogs may be substrates for p-glycoprotein transporters.

Scientists at Wockhardt[69,70] and Korean Institute of Technology[71] independently reported the favorable pharmacokinetic properties of closely related cyanomethyl- and cyanomethylene-substituted piperidine C-ring analogs such as **40** (Fig. 15). Both classes exhibited extended in vivo half-lives ($T_{1/2}$), suggesting the potential for a once-a-day (QD) dosing regimen. In the Wockhardt study, beagle dogs were administered a single oral dose (5 mg/kg) or iv bolus injection (15 mg/kg) of either compound **40** or linezolid. The compound **40** produced a similar C_{max} value, but had a 4-fold longer half-life ($T_{1/2}$) and three-times greater overall exposure (AUC) than did linezolid. Concentrations of compound **40** remained above its in vitro MIC twelve hours after the initial dose.

A recent report from Korean researchers[94] describes pharmacokinetic studies of the tetrazolyl-pyridine analog DA-7867 (**33**, Fig. 12) in the rat. In a dose proportionality study, AUC values were found to correlate with dose, while clearance was low (0.9 mL/min/kg) and independent of the dose. The half-life ($T_{1/2}$) and mean retention time of **33** were quite long, at ca. 6 and 15 h, respectively. A maximum serum concentration of 11.4 μg/mL was attainted following an oral dose of 20 mg/kg and bioavailability was 71%. The researchers estimated that ca. 21% of orally administered DA-7867 is lost to first-pass metabolism.

9. Conclusions

As the preceding discussion can testify, the field of oxazolidinone antibacterial research remains a very active and competitive one. Several research groups at pharmaceutical companies and academic institutions in Europe, the United States, and Asia are active in the field, with new publications and patents appearing on a regular basis. Important advances have certainly been made, and yet considering the manifold efforts in the area, it is surprising and perhaps telling that not a single investigational oxazolidinone has progressed past Phase I since linezolid reached the market in 2000. Clearly, the identification of a second generation of oxazolidinones represents a significant challenge to the pharmaceutical scientist. Recent work in the field nevertheless demonstrates that significant improvements in potency, selectivity, and pharmacokinetic profile are achievable. These findings bode well for the future and for the identification of a second generation of oxazolidinone antibacterial agents.

References and notes

1. (a) Shinabarger, D. *Exp. Opin. Invest. Drugs* **1999**, *8*, 1195; (b) Kloss, P.; Xiong, L.; Shinabarger, D. L.; Mankin, A. S. *J. Mol. Biol.* **1999**, *294*, 93; (c) Shinabarger, D. L.; Marotti, K. R.; Murray, R. W.; Lin, A. H.; Melchior, E. P.; Swaney, S. M.; Dunyak, D. S.; Demyan, W. F.; Buysse, J. M. *Antimicrob. Agents Chemother.* **1997**, *41*, 2132; (d) Lin, A. H.; Murray, R. W.; Vidmar, T. J.; Marotti, K. R. *Antimicrob. Agents Chemother.* **1997**, *41*, 2127; (e) Colca, J. R.; McDonald, W. G.; Waldon, D. J.; Thomasco, L. M.; Gadwood, R. C.; Lund, E. T.; Cavey, G. S.; Mathews, W. R.; Adams, L. D.; Cecil, E. T.; Pearson, J. D.; Bock, J. H.; Mott, J. E.; Shinabarger, D. L.; Xiong, L.; Mankin, A. S. *J. Biol. Chem.* **2003**, *278*, 21972.
2. (a) Jones, R. N.; Sader, H. S. *Challenges Infect. Dis.* **1993**, *1*, 1; (b) Appelbaum, P. C. *Drugs* **1996**, *51*(Suppl. 1), 1; (c) Hiramatsu, K.; Hanaki, H.; Ino, T.; Yabuta, K.; Oguri, T.; Tenover, F. C. *J. Antimicrobial Chemother.* **1997**, *40*, 135; (d) Sievert, D. M.; Boulton, M. L.; Stoltman, G.; Johnson, D.; Stobierski, M. G.; Dowens, F. P.; Somsel, P. A.; Rudrik, J. T.; Brown, W.; Hafeez, W.; Lundstrom, T.; Flanagan, E.; Johnson, R.; Mitchell, J.; Chang, S. *Morbidity and Mortality Weekly Report* **2002**, *51*, 565.
3. Slee, A. M.; Wuonola, M. A.; McRipley, R. J.; Zajac, I.; Zawada, M. J.; Bartholomew, P. T.; Gregory, W. A.; Forbes, M. *Antimicrob. Agents Chemother.* **1987**, *31*, 1791.

4. Batts, D. H.; Kollef, M. H.; Lipsky, B. A; Nicolau, D. P.; Weigelt, J. A. In *Creation of a Novel Class: The Oxazolidinone Antibiotics*; Innova: Tampa, 2004; p 31.
5. (a) Brickner, S. J. *Curr. Pharm. Des.* **1996**, *2*, 175; (b) Barbachyn, M. R.; Ford, C. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2010; (c) Nilus, A. M. *Curr. Opin. Invest. Drugs.* **2003**, *4*, 149.
6. Pfizer SEC Form 8-K, January 19, 2005.
7. Hutchinson, D. K. *Curr. Top. Med. Chem.* **2003**, *3*, 1021.
8. Reeves, D., Wilson, P., Eds.. *J. Antimicrob. Chemother.* **2003**, *51*(Suppl. S2), ii1–ii53.
9. (a) Denis, A.; Villette, T. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1925; (b) Borthwick, A. D.; Biggadike, K.; Rocherolle, V.; Cox, D. M.; Chung, G. A. C. *Med. Chem. Res.* **1996**, *6*, 22; (c) Hester, J. B., Jr.; Brickner, S. J.; Barbachyn, M. R.; Hutchinson, D. K.; Toop, D. S. U.S. Patent 5,708, 169, 1998; (d) Gravestock, M. B. PCT WO199714690, 1997.
10. (a) Barbachyn, M. R.; Thomas, R. C.; Cleek, G. J. U.S. Patent 6,093,736, 2000; (b) Barbachyn, M. R.; Morris, J.; Wishka, D. G.; Thomas, R. C.; Graber, D. R. PCT WO199943671, 1999; (c) Wild, H.; Raddatz, S.; Haerter, M.; Rosentreter, U.; Bartle, S.; Endermann, R.; Kroll, H.-P. German Patent 19909785, 2000; (d) Barbachyn, M. R.; Cleek, G. J.; Dolak, L. A.; Garmon, S. A.; Morris, J.; Seest, E. P.; Thomas, R. C.; Toops, D. S.; Watt, W.; Wishka, D. G.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H.; Adams, W. J.; Friis, J. M.; Slatter, J. G.; Sams, J. P.; Oien, N. L.; Zaya, M. J.; Wienkers, L. C.; Wynalda, M. A. *J. Med. Chem.* **2003**, *46*, 284.
11. (a) Snyder, L. B.; Zheng, Z. PCT WO2000010566, 2000; (b) Springer, D. M.; Goodrich, J. T.; Meng, Z.; Snyder L. B. U.S. Patent 6,465,456, 2002; (c) Snyder, L. B.; Meng, Z.; Mate, R.; D'Andrea, S. V.; Marinier, A.; Quesnelle, C. A.; Gill, P.; DenBleyker, K. L.; Fung-Tomc, J. C.; Frosco, M.; Martel, A.; Barretta, J. F.; Bronson, J. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4735.
12. Gravestock, M. B.; Betts, M. J. PCT WO200140222, 2001.
13. (a) Farrerons Gallemi, C.; Lagunas Arnal, C.; Fernandez Serrat, A.; Catena Ruiz, J. L.; Miquel Bono, I. J.; Balsa Lopez, D.; Salcedo Roca, C.; Toledo Mesa, N.; Fernandez Garcia, A. U.S. Patent Application 2005/0014806, 2005; (b) Das, J.; Natesan, S.; Trehan, S.; Iqbal, J.; Magadi, S. K.; Mamidi, N. V. S. R.; Ramanujam, R. U.S. Patent 6,914,058, 2005; (c) Das, J.; Takhi, M.; Natesan, S.; Trehan, S.; Iqbal, J.; Magadi, S. K.; Kandepu, S. PCT WO2005082892, 2005; (d) Natesan, S.; Das, J.; Takhi, M.; Trehan, S.; Iqbal, J.; Magadi, S. K.; Kandepu, S. PCT WO2005035528, 2005.
14. (a) Marinier, A.; Quesnelle, C. A.; Gill, P.; Roy, S.; Dodier, M.; Martel,A.; Snyder, L. B.; D'Andrea, S. V.; Bronson, J. J.; Frosco,M.; Warr, G. A.; Denbleyker, K. L.; Stickle, T. M.; Yang, H.; Chaniewski, S. E.; Ferraro, C. A.; Taylor, D.; Russell, J. W.; Santone, K. S.; Clarke, J.; Drain, R. L.; Knipe, J. O.; Mosure, K.; Barrett, J. F.; Beaulieu, D. 225th ACS National Meeting, New Orleans, LA, March 23–27th, 2003, MEDI-046; (b) Quesnelle, C. A.; Gill, P.; Roy, S.; Dodier, M.; Marinier, A.; Martel, A.; Snyder, L. B.; D'Andrea, S. V.; Bronson, J. J.; Frosco, M.; Beaulieu, D.; Warr, G. A.; Denbleyker, K. L.; Stickle, T. M.; Yang, H.; Chaniewski, S. E.; Ferraro, C. A.; Taylor, D.; Russell, J. W.; Santone, K. S.; Clarke, J.; Drain, R. L.; Knipe, J. O.; Mosure, K.; Barrett, J. F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2728.
15. Genin, M. J., Barbachyn, M. R., Hester, J. B.; Johnson, P. D.; Ciske, F. L. U.S. Patent 6,825,225, 2004.
16. Riedl, B.; Haebich, D.; Stolle, A.; Ruppelt, M.; Bartel, S.; Guarnieri, W.; Endermann, R.; Kroll, H.-P. German Patent 19604223, 1997.
17. Hester, J. B.; Nidy, E. G.; Perricone, S. C.; Poel, T.-J. PCT WO199854161, 1998.
18. Lohray, B. B.; Lohray, V. B.; Srivastava, B. K.; Kapadnis, P. B.; Pandya, P. *Bioorg. Med. Chem.* **2004**, *12*, 4557.
19. Jang, S.-Y.; Ha, Y. H.; Ko, S. W.; Lee, W.; Lee, J.; Kim, S.; Kim, Y. W.; Lee, W. K.; Ha, H.-J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3881.
20. Natsan, S; Das, J; Iqbal, J.; Magadi, S. K.; Mamidi, S. R. N. V.; Ramanujam, R.; Sundarababu, B.; Lohray, B. B. U.S. Patent Application 2003/0065175, 2003.
21. Selvakumar, N.; Srinivas, D.; Khera, M. K.; Kumar, M. S.; Mamidi, R. N. V. S.; Sarnaik, H.; Charavaryamath, C.; Rao, B. S.; Raheem, M. A.; Das, J.; Iqbal, J.; Rajagopalan, R. *J. Med. Chem.* **2002**, *45*, 3953.
22. Luehr, G. W.; Renslo, A. R.; Hackbarth, C. J.; Gómez, M.; Trias, J.; Patel, D. V.; Gordeev, M. F. Interscience Conference on Antimicrobial Agents and Chemotherapy, 2004, Washington, DC, poster F-1421.
23. Renslo, A. R.; Hackbarth, C. J.; Gómez, M.; Trias, J.; Patel, D. V.; Westlund, N.; Gordeev, M. F. Interscience Conference on Antimicrobial Agents and Chemotherapy, 2004, Washington, DC, poster F-1422.
24. Gordeev, M. F.; Renslo, A.; Luehr, G. W.; Lam, S.; Westlund, N. E.; Patel, D. V. U.S. Patent 6,884,813, 2005.
25. Thomas, R. C.; Poel, T.-J.; Barbachyn, M. R.; Gordeev, M. F.; Luehr, G. W.; Renslo, A.; Singh, U. U.S. Patent 6,919,329, 2005.
26. Nie, Z.-J.; Lam, S.; Hackbarth, C. J.; Lopez, S.; Wu, C.; Yuan, Z.; Gordeev, M. F.; Patel, D. V. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2000, Toronto, poster 1830.
27. Luehr, G. W.; Wang, S.; Hackbarth, C. J.; Gomez, M.; Trias, J.; Patel, D. V.; Gordeev, M. F. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 2004, poster 1420.
28. Arora, K. S.; Patil, J. V.; Nair, S. P.; Dixit, P. P.; Ajay, S.; Sinha, K. R. PCT WO2004026848, 2004.
29. Gravestock, M. B.; Acton, D. G.; Betts, M. J.; Dennis, M.; Hatter, G.; McGregor, A.; Swain, M. L.; Wilson, R. G.; Woods, L.; Wookey, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4179.
30. Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. *J. Med. Chem.* **2005**, *48*, 499.
31. Gravestock, M. B.; Acton, D.; Betts, M.; McGregor, A.; Shendon, C.; Swain, M.; Wilson, R.; Wookey, A. 43rd Interscience Conference on Antimicrobial Agents and Chemptherapy, Chicago, 2003, poster F-2099.
32. Gravestock, M. B.; Hales, N. J.; Carcanague, D. R. PCT WO2004078753, 2004.
33. Phillips, O. A.; Udo, E. E.; Ali, A. A. M.; Al-Hassawi, N. *Bioorg. Med. Chem.* **2003**, *11*, 35.
34. Sbardella, G.; Mai, A.; Artico, M.; Loddo, R.; Setzu, M. G.; La Colla, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1537.
35. Johnson, P. D.; Aristoff, P. A.; Zurenko, G. E.; Schaadt, R. D.; Yagi, B. H.; Ford, C. W.; Hamel, J. C.; Stapert, D.; Moerman, J. K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4197.
36. Ciske, F. L.; Barbachyn, M. R.; Genin, M. J.; Grega, K. C.; Lee, C. S.; Dolak, L. A.; Seest, E. P.; Watt, W.; Adams, W. J.; Friis, J. M.; Ford, C. W.; Zurenko, G. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4235.
37. (a) Bartel, S.; Guarnieri, W.; Haebich, D.; Raddatz, S.; Riedl, B.; Rosentreter, U.; Ruppelt, M.; Stolle, A.; Wild, H.; Endermann, R.; Kroll, H.-P. PCT WO199937641, 1999.; (b) Bartel, S.; Guarnieri, W.; Riedl, B.; Haebich, D.; Stolle, A.; Ruppelt, M.; Raddatz, S.; Rosentreter, U.; Wild, H.; Endermann, R.; Kroll, H.-P. PCT WO199903846, 1999.

38. (a) Chupak, L. S.; Kaneko, T.; Josyula, V. P. V. N.; Kim, J.-Y.; Choy, A. L.; Hagen, S. E.; Boyer, F. E. PCT WO2004069832, 2004; (b) Chupak, L. S.; Kaneko, T.; Josyula, V. P. V. N.; Petterson, M. Y.; Lall, M. S.; Hagen, S. E.; Boyer, F. E. WO2004069244, 2004; (c) Chupak, L. S.; Kaneko, T.; Josyula, V. P. V. N.; Jiao, W.; Lumb, J. T. PCT WO2004069245, 2004.
39. Selvakumar, N.; Raheem, M. A.; Khera, M. K.; Rajale, T. V.; Kumar, M. S.; Kandepu, S.; Das, J.; Rajagopalan, R.; Iqbal, J.; Trehan, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4169.
40. Sciotti, R. J.; Pliushchev, M.; Wiedeman, P. E.; Balli, D.; Flamm, R.; Nilius, A. M.; Marsh, K.; Stolarik, D.; Jolly, R.; Ulrich, R.; Djuric, S. W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2121.
41. Weidner-Wells, M. A.; Boggs, C. M.; Foleno, B. D.; Melton, J.; Bush, K.; Goldschmidt, R. M.; Hlasta, D. J. *Bioorg. Med. Chem.* **2002**, *10*, 2345.
42. Mehta, A.; Sudershan, H.; Ray, A.; Rudra, S.; Rattan, A. U.S. Patent 6,734,307, 2004.
43. Arora, V.; Salunkhe, M. M.; Sinha, N.; Sinha, R. K.; Jain, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4647.
44. Tucker, J. A.; Allwine, D. A.; Grega, K. C.; Barbachyn, M. R.; Klock, J. L.; Adamski, J. L.; Brickner, S. J.; Hutchinsom, D. K.; Ford, C. W.; Zurenko, G. E.; Conradi, R. A.; Burton, P. S.; Jensen, R. M. *J. Med. Chem.* **1998**, *41*, 3727.
45. Agarwal, S. K.; Guha, K. M.; Pandey, S. S.; Samuel, M. M. PCT WO2004018439, 2004.
46. Akella, S. S. V. S.; Agarwal, S. K.; Shinde, A. D., Samuel, M. M. PCT WO2004113329, 2004.
47. Bush, K.; Macielag, M.; Weidner-Wells, M. *Curr. Opin. Microbiol.* **2004**, *7*, 466.
48. Rattan, A. *Drugs Future* **2003**, *28*, 1070.
49. Ednie, L. M.; Rattan, A.; Jacobs, M. R.; Appelbaum, P. C. *Antimicrob. Agents Chemother.* **2003**, *47*, 1143.
50. Akella, S. S. V. S.; Mathiyazhagan, K.; Samuel, M. M.; Solanki, S. S.; Magesh, U.; Agarwal, S. K. PCT WO2005003087, 2005.
51. McCalla, D. R. *J. Antimicrob. Chemother.* **1977**, *3*, 517.
52. (a) Jo, Y. W.; Im, W. B.; Rhee, J. K.; Shim, M. J.; Kim, W. B.; Choi, E. C. *Bioorg. Med. Chem. Lett.* **2004**, *12*, 5909; (b) Lee, J.-G.; Leem, W.-B.; Cho, J.-H.; Choi, S.-H.; Lee, J.-J.; Park, S.-K.; Lee, T.-H.; Kim, D.-G.; Sung, H.-J. U.S. Patent 6,689,779, 2004.
53. (a) Gravestock, M. B.; Hales, N. J.; Swain, M. L.; Hauck, S. I.; Mills, S. D. PCT WO2003022824, 2003; (b) Carcanague, D. R.; Gravestock, M. B.; Hales, N. J.; Hauck, S. I.; Weber, T. P. PCT O2004048392, 2004.
54. Choi, S. H.; Lee, T. H.; Im, W. B.; Rhee, J. K.; Kim, W. B. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2004, Washington, DC, poster F-1417.
55. Choi, S. H.; Lee, T. H.; Son, T. K.; Im, W. B.; Rhee, J. K.; Kim, W. B. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2004, Washington, DC, poster F-1418.
56. (a) Gravestock, M. B.; Hales, N. J.; Turner, P. PCT WO2004056816, 2004; (b) Gravestock, M. B.; Hales, N. J.; Reck, F.; Zhou, F. PCT WO2004048350, 2004.
57. Cui, Y.; Yang, Y.; Chen, K.; Ji, R.; Zhang, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2311.
58. Yu, D.; Huiyuan, G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 857.
59. Lohray, B. B.; Lohray, V. B.; Srivastava, B. K.; Gupta, S.; Solanki, M.; Kapadnis, P.; Takale, V.; Pandya, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3139.
60. Srivastave, B. K.; Kapadnis, P. B.; Pandya, P.; Lohray, V. B. *Eur. J. Med. Chem.* **2004**, *39*, 989.
61. Lee, J. S.; Cho, Y. S.; Chang, M. H.; Koh, H. Y.; Chung, B. Y.; Pae, A. N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4117.
62. (a) Samuel, M. M.; Agarwal, S. K. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, 2003, Chicago, poster F-2103; (b) Sathish Kumar, D.; Swaminathan, S. R., Selwyn, W.; Velmurugan, R.; Solanki, S. S.; Badiger, S.; Kapoor, A. K.; Guha, M. K.; Agarwal, S. K.; Samuel, M. M. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2004, Washington, DC, poster F-1411; (c) Solanki, S. S.; Kumar, D. S.; Velmurugan, R.; Samuel, M. M.; Mathiyazhagan, K.; Singh, G.; Pandey, S.; Srinivas, A. S. S. V.; Agarwal, S. K.; Guha, M. K. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2004, Washington, DC, poster F-1412.
63. Paget, S. D.; Foleno, B. D.; Boggs, C. M.; Goldschmidt, R. M.; Hlastra, D. J.; Weidner-Wells, M. A.; Werblood, H. M.; Wira, E.; Bush, K.; Macielag, M. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4173.
64. Fukuda, Y.; Hammond, M. L. U.S. Pantent 6,897,230, 2005.
65. (a) Renslo, A. R.; Jaishankar, P.; Venkatachalam, R.; Hackbarth, C. J.; Gómez, M.; Trias, J.; Patel, D. V.; Gordeev, M. F. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, 2003, Chicago, poster F-2100; (b) Renslo, A. R.; Jaishankar, P.; Venkatachalam, R.; Hackbarth, C. J.; Lopez, S.; Patel, D. V.; Gordeev, M. F. *J. Med. Chem.* **2005**, *48*, 5009.
66. Gordeev, M. F.; Renslo, A.; Patel, D. V. U.S. Patent 6,875,784, 2005.
67. Renslo, A. R.; Gordeev, M. F.; Patel, D. V.; Gao, H.; Josyula, V. P. V. N. PCT WO2004089943, 2004.
68. Hammond, M. L.; Fukuda, Y. PCT WO2005005399, 2005.
69. Patel, M. V.; Deshpande, P. K.; Sindkhedkar, M. D.; Gupte, S. V.; Chugh, Y.; Shetty, N.; Shukla, M,. C.; Yeole, R. D.; De Souza, N. J. U.S. Patent Application 2004/0063954, 2004.
70. Chugh, Y; Shetty, N.; Deshpande, P. K.; Sindkhedkar, M. D.; Jafri, M. D.; Yeole, R. D.; Shukla, M. C.; Gupte, S. V.; Patel, M. V.; De Souza N. J. U.S. Patent Application 2004/0235900, 2004.
71. (a) Koh, H. Y.; Cho, Y. S.; Pae, A. N.; Cha, J. H.; Kim, H. Y.; Lee, J. S.; Kim, H. S.; Kim, S. U.S. Patent Application U.S. 2004/0087633, 2004; (b) Kim, H. Y.; Lee, J. S.; Cha, J. H.; Pae, A. N.; Cho, Y. S.; Chang, M. H.; Koh, H. Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2227.
72. Fukuda, Y. PCT WO2003048136, 2003.
73. Fukuda, Y. PCT WO2005005420, 2005.
74. Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953.
75. Thomasco, L. M.; Gadwood, R. C.; Weaver, E. A.; Ochoada, J. M.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Stapert, D.; Moerman, J. K.; Schaadt, R. D.; Yagi, B. H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4193.
76. (a) Luehr, G. W.; Gordeev, M. F.; Patel, D. V. U.S. Patent 6,828,317, 2004; (b) Luehr, G. W.; Wang, S.; Hackbarth, C. J.; Gómez, M.; Trias, J.; Patel, D. V.; Gordeev, M. F. Interscience Conference on Antimicrobial Agents and Chemotherapy, 2004, Washington, DC, poster F-1420.
77. Weidner-Wells, M. A.; Werblood, H. M.; Goldschmidt, R.; Bush, K.; Foleno, B. D.; Hilliard, J. J.; Melton, J.; Wira, E.; Macielag, M. J. *Bioorg. Med. Chem. Lett* **2004**, *14*, 3069.

78. D'Andrea, S.; Zheng, Z. B.; DenBleyker, K.; Fung-Tomc, J. C.; Yang, H.; Clark, J.; Taylor, D.; Bronson, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2834.
79. Gordeev, M. F.; Hackbarth, C.; Barbachyn, M. R.; Banitt, L. S.; Gage, J. R.; Luehr, G. W.; Gomez, M.; Trias, J.; Morin, S. E.; Zurenko, G. E.; Parker, C. N.; Evans, J. M.; White, R. J.; Patel, D. V. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4213.
80. Gordeev, M. F.; Patel, D. V.; Barbachyn, M. R.; Gage, J. R. Antimicrobial quinolone derivatives and use of the same to treat bacterial infections. U.S. Patent 6,689,769, 2004.
81. Hubschwerlen, C.; Specklin, J.-L.; Baeschlin, D. K.; Borer, Y.; Haefeli, S.; Sigwalt, C.; Schroeder, S.; Locher, H. H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4229.
82. Hubschwerlen, C.; Specklin, J.-L.; Sigwalt, C.; Schroeder, S.; Locher, H. H. *Bioorg. Med. Chem.* **2003**, *11*, 2313.
83. Locher, H. U.S. Patent Application 2004/0132764, July 8, **2004**.
84. Hubschwerlen, C,; Specklin, J.-L.; Baeschlin, D. K.; Locher, H.; Sigwalt, C. PCT WO2004096221, 2004.
85. Bae, S. K.; Chung, W.-S.; Kim, E. J.; Rhee, J. K.; Kwon, J. W.; Kim, W. B.; Lee, M. G. *Antimicrob. Agents Chemother.* **2004**, 659.
86. Griffin, J. H.; Pace, J. L. U.S. Patent Application 2003/0176670, 2003.
87. Farmer, J. J.; Sutcliffe, J. A.; Bhattacharjee, A. PCT WO2004078770, 2004.
88. (a) Schlunzen, F.; Zarivach, R.; Harms, J.; Bashan, A.; Tocilj, A.; Albrecht, R.; Yonath, A.; Franceschi, F. *Nature* **2001**, *413*, 814; (b) Hansen, J. L.; Ippolito, J. A.; Ban, N.; Nissen, P.; Moore, P. B.; Steitz, T. A. *Mol. Cell* **2002**, *10*, 117; (c) Hansen, J. L.; Moore, P. B.; Steitz, T. A. *J. Mol. Biol.* **2003**, *330*, 1061.
89. Golpalakrishnan, B.; Khandelwal, A.; Rajjak, S. A.; Selvakumar, N.; Das, J.; Trehan, S.; Iqbal, J.; Kumar, M. S. *Bioorg. Med. Chem.* **2003**, *11*, 2569.
90. Recent reviews: (a) Stalker, D. J.; Jungbluth, G. L. *Clin. Pharmacokinet.* **2003**, *42*, 1129; (b) MacGowan, A. P. *J. Antimicrob. Chemother.* **2003**, *51*(Suppl. S2), ii17–ii25.
91. Hilgers, A. R.; Smith, D. P.; Biermacher, J. J.; Day, J. S.; Jensen, J. L.; Sims, S. M.; Adams, W. J.; Friis, J. M.; Palandra, J.; Hosley, J. D.; Shobe, E. M.; Burton, P. S. *Pharm. Res.* **2003**, *20*, 1149.
92. Johnson, K. C.; Swindell, A. C. *Pharm. Res.* **1996**, *13*, 1795.
93. (a) Researchers at Pharmacia and Vicuron recently disclosed oxazolidinones incorporating a novel difluorothioacetamide group which is reported to have improved metabolic and in vivo stability, see: Hester, J. B.; Adams, W. J.; Stevens, J. C.; Gordeev, M. F.; Singh, U.; Scott, C. U.S. patent Application 2004/0072842, 2004; (b) Hester, J. B.; Adams, W. J.; Stevens, J. C.; Gordeev, M. F.; Singh, U.; Scott, C. U.S. Patent Application 2004/0077626, 2004.
94. Bae, S. K.; Chung, W.-S.; Kim, E. J.; Rhee, J. K.; Kwon, J. W.; Kim, W. B.; Lee, M. G. *Antimicrob. Agents Chemother.* **2004**, *48*, 659.

Adam R. Renslo was born in 1971 in Tripoli, Libya, and raised in Wisconsin. He received a B.A. degree in Chemistry from Saint Olaf College in 1993 and went on to receive a Ph.D. from the Massachusetts Institute of Technology (1998) for work on new cycloaddition methods with Rick L. Danheiser. After post-doctoral work with Julius Rebek, Jr. at the Scripps Research Institute, he accepted a position at Vicuron Pharmaceuticals (then Versicor, Inc.) where he was involved in antibacterial and antifungal drug discovery projects, most recently as Associate Director of Medicinal Chemistry. His research interests include the use of small organic molecules to interrogate and disrupt the biological processes of infectious disease. He is currently Associate Director of the Small Molecule Discovery Center at the University of California, San Francisco, and an Adjunct Assistant Professor of Pharmaceutical Chemistry.

Gary W. Luehr was born in Sacramento, California, in 1963. He obtained a B.Sc. degree in Chemistry in 1985 from the University of California, Davis. After graduating, he worked as a research chemist at Novartis Crop Protection in Palo Alto, California, for nearly 10 years and then joined Vicuron Pharmaceuticals (then Versicor, Inc.) in 1997. At Vicuron, he was involved in antibacterial and antifungal discovery projects, most recently as Senior Research Fellow. He has been especially active in the area of novel oxazolidinone antibacterials and is an inventor or co-inventor on more than 10 patents in the field.

Mike F. Gordeev was born in Yoshkar-Ola, Russia, in 1959. He obtained a Ph.D. in Organic Chemistry from the Moscow State University (Russia) in 1984. He held research positions of increasing seniority at the Zelinsky Institute of Organic Chemistry, Russian Academy of Science, while working in the areas of ligand recognition and chelation-controlled synthesis. In 1990, he joined the laboratories of Prof. Alan Katritzky at the University of Florida to pursue his interest in biologically active heterocycles. Following his tenure with Prof. Katritzky, he joined the Affymax Research Institute to participate in early efforts directed at small molecule combinatorial drug discovery. In 1996, he was among the first scientists recruited to form Versicor, Inc. (now Vicuron Pharmaceuticals) and most recently served as Vice President of Chemistry Drug Discovery. He has authored over 70 publications and contributed to over 20 patents.