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Synthesis and Biological Evaluation of Benzazepine Oxazolidinone Antibacterials

Paul D. Johnson,[a,*] Paul A. Aristoff,[a] Gary E. Zurenko,[b] Ronda D. Schaadt,[b] Betty H. Yagi,[b] Charles W. Ford,[b] Judith C. Hamel,[b] Douglas Stapert[b] and Judy K. Moerman[b]

[a]*Discovery-Chemistry, Pharmacia Corporation, 7000 Portage Road, Kalamazoo, MI 49001, USA*
[b]*Discovery-Infectious Diseases, Pharmacia Corporation, 7000 Portage Road, Kalamazoo, MI 49001, USA*

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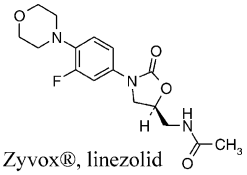
Abstract—Novel benzazepine oxazolidinone antibacterials were synthesized and evaluated against clinically relevant susceptible and resistant organisms. The effect of ring nitrogen position and *N*-substitution on antibacterial activity is examined.

The oxazolidinones are a totally synthetic class of antibiotics with a novel mechanism of action being investigated for the treatment of bacterial infections. As the first member of a new class of antibacterials in three decades, ZYVOX® (linezolid injection, tablets and oral suspension) is approved in the United States for the treatment of nosocomial pneumonia, community-acquired pneumonia, uncomplicated and complicated skin and soft tissue infections caused by Gram-positive bacteria.[1–4] Importantly, linezolid's spectrum of activity includes the methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE), and vancomycin-resistant enterococci (VRE). The oxazolidinones have been shown to selectively bind to the 50S ribosomal subunit and inhibit bacterial protein synthesis prior to chain initiation.[5,6]



1 Zyvox®, linezolid

A number of SAR studies of the oxazolidinones have demonstrated that the phenyl oxazolidinone core structure is important for antibacterial activity.[2,7,8] However, analogues with a variety of substituents including nitrogen and carbon-linked heterocycles with five-, six-, and seven-membered ring systems attached to the 4-position of the phenyl ring demonstrate antibacterial activity.[9,10] Thus, a high tolerance for structural diversity in this region of the pharmacophore is tolerated. In addition, free rotation about the bond between the substituents and the phenyl core provide for multiple possible conformations of the drug molecule in the active site. Limiting the degrees of freedom by conformationally constraining the molecule could provide an entropically advantageous situation in the active site. Some fused-bicyclic oxazolidinones, including indolines and tetrahydroquinolines have been reported.[11,12] In addition, tricyclic oxazolidinones have also been synthesized.[13] We report herein the synthesis and antibacterial activity of novel benzazepine oxazolidinones.[14]

Benzazepines are available via a variety of routes (Scheme 1). Ring expansion of α-tetralone **2** with hydrazoic acid gives the lactam **3**.[15,16] Nitration with fuming nitric acid in sulfuric acid at 0–5 °C gave primarily the 7-nitro benzazepinone **4** with minor amounts of the 9-nitro and 7,9-dinitro benzazepines. The lactam **4** was reduced with borane to give **5** followed by hydrogenation and Cbz-protection with benzyl chloroformate under Schotten–Bauman conditions to give **9**. If the lactam **3** is reduced with lithium aluminum hydride and then nitrated, one obtains the 8-nitrobenzazepine **7**. Hydrogenation and Cbz-protection gave

*Corresponding author. Tel.: +1-269-833-2372; fax: +1-269-833-2232; e-mail: paul.d.johnson@pharmacia.com

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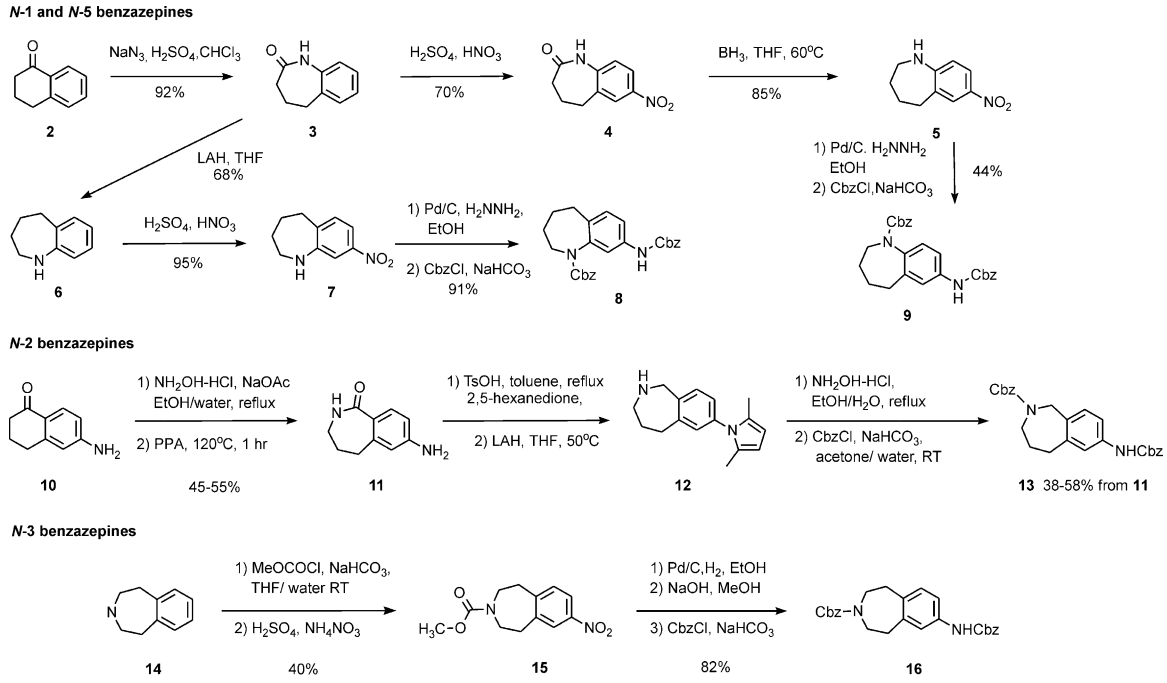
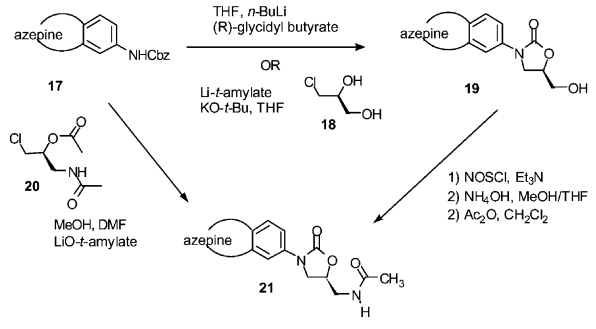


Scheme 1. Synthesis of Cbz-protected benzazepines.

8. The *N*-2-benzazepines are obtained by Beckmann ring expansion of 6-amino-α-tetralone **10** with hydroxylamine and sodium acetate[17] followed by rearrangement of the resulting oxime with polyphosphoric acid (PPA) to give **11**. Treatment of **11** with 2,5-hexanedione and catalytic *p*-toluenesulfonic acid in refluxing toluene[18,19] followed by reduction of the lactam with LAH proceeded smoothly to give **12**. Removal of the unusual amine protecting group with hydroxylamine[20,21] and Cbz-protection gave **13**. *N*-3-benzazepine **14** is available by the method of Pecherer and Brossi.[20] Protection of **14** with methylchloroformate followed by nitration gives primarily **15**. Hydrogenation, removal of the methyl carbamate group with potassium hydroxide in refluxing methanol, and Cbz-protection gives **16**.

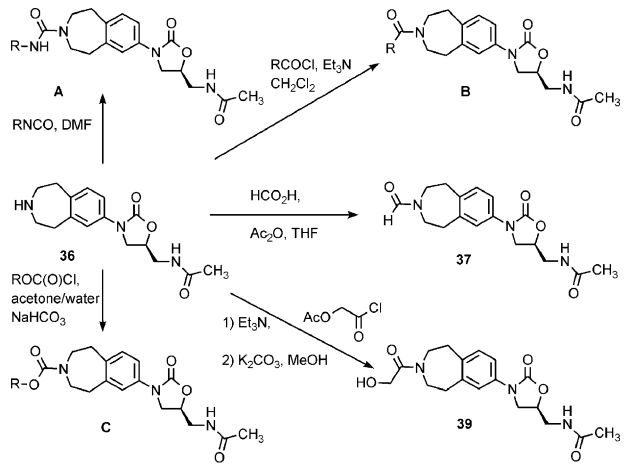
The Cbz-protected benzazepines were converted to the benzazepine oxazolidinones via previously described methods (Scheme 2). Thus, treatment of a Cbz-protected aminobenzazepine (**17**) with *n*-butyl lithium or lithium bis-(trimethylsilyl)amide followed by (*R*)-(−)-glycidylbutyrate gave the hydroxymethyl oxazolidinones **19** in good yields. Nosylation of **19** with 3-nitrobenzenesulfonyl chloride and triethylamine, displacement of the nosyl group with ammonia, and acetylation gave the acetamide oxazolidinones **21**.[7,8] A variant of this procedure first forms the lithium amide of the Cbz (or isobutyl carbamate) from **17** and lithium *t*-amylate which is then treated with the epoxide derived in situ from (*S*)-(−)-3-chloro-1,2-propanediol (**18**) and potassium *t*-butoxide.[21] Generally better yields are obtained by this route and it is more amenable to scale-up. During the course of this work a one-step convergent oxazolidinone synthesis was developed by Pearlman.[22] Thus, treatment of **17** with 2 equivalents of **20** and 3 equivalents of lithium *t*-amylate in DMF with 2 equivalents of methanol at room temperature gave excellent yields of the desired **21**. Finally, the Cbz-protecting group was removed by catalytic hydrogenation.



Scheme 2. Synthesis of benzazepine oxazolidinones.

Based on extensive previous SAR experience with oxazolidinones[1–8,11,14] we proceeded to synthesize some selected analogues as illustrated for *N*-3-benzazepine oxazolidinone in Scheme 3. *N*-Formamides were prepared by treating the free amine with the reagent prepared from formic acid and acetic anhydride (e.g., **36**–**37**).[23] Hydroxyacetamides of the benzazepine oxazolidinones were synthesized by acetylation with triethylamine and acetoxyacetylchloride followed by deacetylation with potassium carbonate in methanol. In addition, selected amides, carbamates and ureas of the benzazepines were prepared by standard methods.

The oxazolidinone analogues were tested in vitro versus a panel of Gram-positive and Gram-negative bacterial isolates (Table 1).[1] Minimum inhibitory concentration



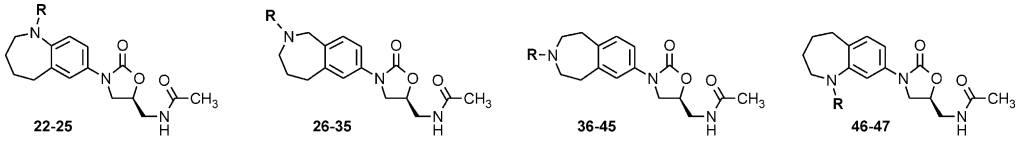
Scheme 3. Synthesis of analogues of benzazepine oxazolidinones.

(MIC) values were determined using standard agar dilution methods.[1] The unfunctionalized benzazepine oxazolidonones (**22**, **26**, **36**, **46**) were only weakly active, if at all when tested in the panel of bacterial isolates. The *N*-1- and *N*-5-benzazepine oxazolidinones (**22**–**25** and **46**–**47**, respectively) were at best only weakly active as antibacterials as measured by the MIC's. The only exception was compound **23**.

The *N*-2-benzazepine oxazolidinones (**26**–**35**) tolerated small functional groups and displayed some activity, but larger substituents caused a diminution in antibacterial activity. Compound **27** exhibited MIC's that were generally better than linezolid and **29** was equipotent to linezolid, except against *Haemophilus influenzae*.

The *N*-3 benzazepine oxazolidinones (**36**–**45**) displayed linezolid-like antibacterial activity with a broad range of nitrogen substituents. The formamide **37**, hydroxy-

Table 1. MIC (μg/mL) for benzazepine oxazolidinones



Compd	R	*S. a.*[a]	*S. a.*[b]	*S. e.*[c]	*S. p.*[d]	*E. f.*[e]	*H. inf.*[f]	*M. cat.*[g]	ED_{50}[h]
1	Linezolid	4	2	1	1	4	16	8	5.6 (2.9–8.5)[i]
22	H	64	32	16	16	64	>64	>64	
23	CHO	2	2	<0.05	<0.05	2	16	4	
24	$COCH_2OH$	64	32	8	8	64	>64	>64	
25	Cbz	>64	>64	>64	>64	>64	>64	>64	
26	H	>64	>64	32	8	>64	>64	>64	
27	**CHO**	**1**	**1**	**2**	**1**	**2**	**32**	**4**	**8.1** (6.0–12.5)
28	$COCH_3$	8		4	2	8	>64		
29	$COCH_2OH$	4	4	1	1	4	64	16	
30	$C(O)OCH_3$	8		2	2	4	>64		
31	Cbz	16		16	8	32	>64		
32	$COCH_2Ph$	32		8	4	16	>64		
33	CONHPh	16		4	1	4	64		
34	$CONHCH_2CH_2Ph$	64		32	8	32	>64		
35	$CONHCH(CH3)_2$	64		32	8	32	>64		
36	H	32	64	8	8	32	>64	>64	
37	CHO	4	2	<0.05	<0.05	4	>64	8	
38	$COCH_3$	4		1	1	2	64		
39	**$COCH_2OH$**	**2**	**2**	**1**	**<0.05**	**4**	**32**	**8**	**8.5** (5.0–11.0)
40	Cbz	4	2	1	<0.05	4	>64	16	
41	$C(O)OCH_3$	4		1	1	2	>64		
42	C(O)OPh	4		2	2	4	>64		
43	$COCH_2Ph$	4		1	1	2	>64		
44	COPh	8		1	1	2	>64		
45	SO_2Me	16		16	8	32	>64		
46	H	32	16	8	8	32	>64	>64	
47	CHO	>64	>64	>64	>64	>64	>64	>64	

Minimum inhibitory concentration (MIC): lowest concentration of drug (μg/mL) that inhibits visible growth of the organism.
[a]Methicillin-suceptible *S. aureus* UC9218.
[b]Methicillin-resistant *S. aureus* UC6685.
[c]Methicillin-resistant *S. epidermidis* UC12084.
[d]*Streptococcus pneumoniae* UC9912.
[e]*Enterococcus faecalis* UC9217.
[f]*Haemophilus influenzae* UC30063.
[g]*Moraxella catarrhalis* UC30610.
[h]ED_{50} is the amount of drug required after oral administration (mg/kg/day) to cure 50% of infected mice subjected to a lethal systemic infection of *S. aureus*.
[i]Numbers in parentheses are 95% confidence ranges.

acetamide **39**, and benzylcarbamate **40** all exhibited comparable or slightly better Gram-positive antibacterial activity compared to linezolid. The methylcarbamate **41**, phenylcarbamate **42**, and benzylamide **43** analogues had respectable in vitro activity against the Gram-positive strains, but were also less active against *H. influenzae*. Compounds **27** and **39** were selected for testing in vivo in a lethal systemic *S. aureus* infection in mice.[1] Oral antibacterial activity (ED_{50}) in this model was comparable to linezolid.

In conclusion, a number of novel benzazepine oxazolidinones have been prepared. Compounds **23**, **27**, and **39** displayed in vitro Gram-positive antibacterial activity better than linezolid against clinically relevant organisms. Initial in vivo efficacy results are also encouraging. Diverse functional groups are tolerated on *N*-3-benzazepine oxazolidinones with comparable Gram-positive activity to linezolid, but generally they were less active versus the Gram-negative species.

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