

Structure-Activity Relationship of Substituted Pyridyl Phenyl Oxazolidinone Derivatives, Including TR-700 (DA-7157)

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Abstract

Background:

We have discovered a series of substituted pyridyl phenyl oxazolidinone analogs with improved antibacterial activities and physical properties. We now report the structure activity relationship of these analogs along with their *in vitro* and *in vivo* potency.

Methods:

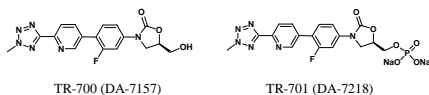
In vitro activities (MICs) of compounds were carried out by the agar dilution method against a panel of organisms consisting of MRSA, VRE and *H. influenzae*. *In vivo* efficacy studies were carried out in mice for selected compounds. Also, several prodrugs were synthesized and assessed for their stability and solubility.

Results:

MICs of pyridine substituted oxazolidinones were in the range of 0.12 to 2.0 µg/mL against MRSA and VRE. These compounds were active against *H. influenzae* with MIC values of 2.0-8.0 µg/mL. Among the compounds evaluated for *in vivo* studies, several compounds showed better protection in mice than linezolid. One of the most potent of these analogs is TR-700 (DA-7157). TR-701 (DA-7218), the phosphate prodrug of TR-700 has excellent aqueous solubility (>50mg/mL in DW) and has significantly more *in vivo* potency than linezolid.

Conclusion:

TR-700 and its phosphate prodrug TR-701 were found to be significantly more potent than linezolid.



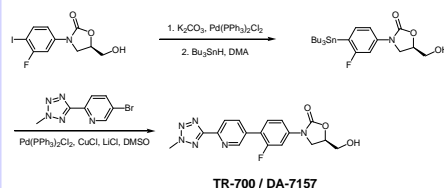
Introduction

The synthesis of derivatives of 4-pyridyl-phenyl oxazolidinones has been previously described (WO 01/94342). These compounds have potent antibacterial activity against a broad spectrum of bacteria, superior to linezolid. However, due to their poor aqueous solubility (<30 mg/mL) these compounds could not be formulated for i.v. injection.

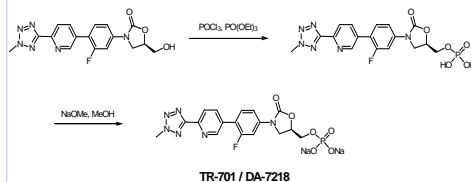
Here we report the results of oxazolidinone derivatives designed to overcome the solubility issue. We have discovered novel oxazolidinone derivatives including phosphate and amino acid prodrugs. We now report the structure activity relationship of these analogs along with their *in vitro* and *in vivo* potency.

Chemistry

Scheme 1. Synthesis of TR-700 (DA-7157)

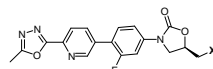


Scheme 2. Synthesis of TR-701 (DA-7218)



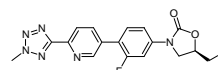
Results

Table 1. *In vitro* and *in vivo* activity of oxadiazole derivatives.



Compounds	X	MIC50 (µg/mL)				ED50 (Linezolid) SA
		SA	MRSA	VREF	HI	
Linezolid		2.0	2.0	1.0	8.0	
DA-7033		1.0	1.0	0.5	>20	6.5 (19.1)
DA-7170		0.25	0.25	0.125	2.0	>30 (14.9)
DA-7174		0.5	0.5	0.5	4.0	4.2 (9.4)

Table 2. *In vitro* and *in vivo* activity of tetrazole derivatives.



Compounds	X	MIC50 (µg/mL)				ED50 (Linezolid) SA
		SA	MRSA	VREF	HI	
Linezolid		2.0	2.0	1.0	8.0	
DA-7025		0.5	0.5	0.25		>30 (11.8)
DA-7042		1.0	1.0	0.5	16	20.5 (11.2)
DA-7044		1.0	1.0	0.5	16	>30 (11.2)
DA-7046		0.5	0.5	0.5		>30 (11.2)
DA-7053		1.0	1.0	0.25		>30 (11.7)
DA-7140		2.0	2.0	1.0		>30 (12.1)
DA-7154		16	16	16		
DA-7155		0.25	0.25	0.125	2.0	5.74 (17.3)
TR-700 (DA-7157)		0.5	0.5	0.125	4.0	8.8 (10.8)
DA-7176		1.0	1.0	1.0	64	
DA-7191		2.0	2.0	2.0		
DA-7199		4.0	4.0	4.0		

SA : *S. aureus* Smith, MRSA : Methicillin-resistant *S. aureus*, VREF : Vancomycin-resistant *E. faecium*, HI : *H. influenzae*.

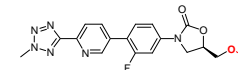
Materials and Methods

Bacterial strains: A set of five strains was used as primary screening panel. *S. aureus* Smith is methicillin susceptible. The methicillin-resistant *S. aureus*, vancomycin-resistant *E. faecium*, and *H. influenzae* are clinical isolates from university hospital in Korea.

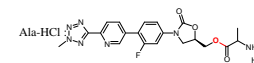
***In vitro* susceptibility tests:** MICs were determined by agar dilution.

Mouse protection assay: *In vivo* efficacy was assessed in a mouse systemic model of infection caused by *S. aureus* Smith. Male ICR mice were infected i.p. with approximately 1×10^7 CFU/mouse of the challenging strain. Protecting compounds were administered orally at one hour after infection. The dose allowing survival of 50% of the animals (ED₅₀) was calculated using the Probit analysis program.

Table 3. TR-700 (DA-7157) prodrug profiles



R	Solubility (mg/mL)	% of remaining in D.W (100µg/mL), 8hr				pH in D.W. (100µg/mL)
		D.W	pH 3	pH 5	pH 7	
Pro-TFA	< 1.63	76.4	81.9	65.2	0.2	6.49
Ala-HCl	> 50	92.34	98.02	88.11	7.48	3.93
Ala-TFA	> 50	90.67	96.98	87.84	6.32	4.64
β-Ala-HCl	20.4	101.8	103.1	94.9	50.5	4.4
β-Ala-TFA	2.6	96.9	99.6	99.5	94.9	6.71
Gly-HCl	12	85.67	95.05	93.29	-	3.77
Gly-TFA	28	79.5	86.6	92.7	8.1	4.23
Val-HCl	4.2	105.27	102.51	97.74	60.86	3.83
Val-TFA	4.7	99.4	100.1	97.3	51.18	5.33
Phos-Na (DA-7218)	> 50	112.9	108.5	108.0	113.2	6.47



Ala : alanine, Pro : proline, β-Ala : beta-alanine, Gly : glycine, Val : valine, Phos : Phosphate
TFA : trifluoro acetic acid

Conclusions

- Compounds with hydroxy and triazole moieties showed potent *in vitro* activity and *in vivo* efficacy.
- Prodrugs of TR-700 (DA-7157) were highly soluble and stable.
- TR-701 (DA-7218), a phosphate prodrug, was selected as a candidate for further development.