F1-1357d Potent Antibacterial (4-Heteroarylphenyl)oxazolidinones

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Background

New oxazolidinone compounds, (4-heteroarylphenyl) oxazolidinones ITU-5002, ITU-5101, ITU-5141 and ITU-5142 were synthesized targeted for antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA), linezolid-resistant *S. aureus* (LZDR), vancomycin-resistant *S. aureus* (VRSA) and vancomycin-resistant *Enterococcus faecalis* (VRE). The in vitro and in vivo non-clinical evaluation was investigated for these compounds.

Methods

The in vitro activity of ITU-5002 and several other compounds were tested against various strains of Gram-positive strains including MRSA, LZDR, VRE and VRSA.

For in vivo evaluation, ITU-5002 and three others were tested using the murine thigh infection model caused by MRSA. In the test, transient neutropenic mice were challenged in their thighs with *S. aureus* SR3637 (9.3×10^4 or 1.2×10^5 CFU/mouse). Two hours after the infection, the mice were treated by oral administration of the compounds and then at twenty four hours after treatment the bacteria in their thighs were counted for evaluation. PK studies were also performed.

Results

The (4-heteroarylphenyl)oxazolidinones ITU-5002, ITU-5101, ITU-5141 and ITU-5142 were found to have the improved antibacterial activity against Gram-positive bacteria both in in vitro and in vivo studies. In the in vitro tests, they exhibited 8 to 16 times higher potency compared to linezolid, having MIC of ≦0.5 μg/mL towards various strains of Gram-positive bacteria including MRSA, VRE and VRSA. Some of the results are shown in the Table. These compounds also had excellent activity towards clinical isolates, showing 8 to 16 times higher potency than linezolid in terms of MIC90.

In the in vivo MRSA infection model in mice, ITU-5002 and others exhibited 10-fold higher potency compared to linezolid. For example, the doses required for the static effect for ITU-5002 and linezolid were 5.64 and 67.7 mg/kg/dose, respectively.

PK studies of these compounds in mice exhibited good profiles with long half life in plasma, showing the potential for once-daily administration.

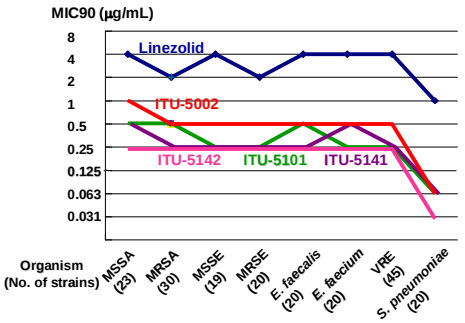
The safety evaluation towards mice is in progress.

in vitro Antibacterial Activities

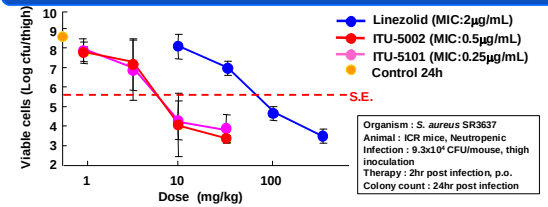
in vitro Antibacterial Activity against Antibiotic-resistant MRSA

Strain (phenotype)	MIC (μg/mL) of Linezolid	ITU5002	ITU5101	ITU5141	ITU5142
ATCC 700698 (VISA)	2.	0.5	0.25	0.25	0.125
ATCC 700699 (VISA)	2.	0.5	0.25	0.25	0.125
ATCC 700787 (VISA)	1.	0.25	0.125	0.125	0.125
ATCC 700788 (VISA)	2.	0.25	0.125	0.25	0.125
ATCC 700789 (VISA)	2.	0.5	0.125	0.25	0.25
VRS1 (VRSA)	2.	0.25	0.125	0.125	0.125
VRS2 (VRSA)	2.	0.25	0.125	0.125	0.125
VRS3 (VRSA)	2.	0.25	0.25	0.25	0.25
VRS4 (VRSA)	2.	0.5	0.25	0.125	≦0.063
VRS5 (VRSA)	2.	0.5	0.25	0.25	0.25
NRS 119 (linezolid R)	64.	8.	4.	4.	4.
NRS 120 (linezolid R)	64.	8.	4.	4.	4.
NRS 121 (linezolid R)	64.	8.	4.	4.	4.
NRS 127 (linezolid R)	8.	1.	1.	1.	1.
NRS 271 (linezolid R)	32.	4.	2.	2.	2.
NRS 269 (tigecycline R)	1.	0.25	0.125	0.125	0.125

in vitro Antibacterial Activity (MIC90) against Clinical Isolates of Gram-Positive Bacteria



Therapeutic efficacy against murine thigh infection caused by MRSA (Oral administration)

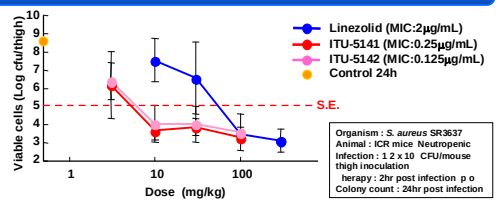


Dose (mg/kg)	S.E.*	1 log reduction**
ITU-5002	5.64	8.14
ITU-5101	5.56	9.83
Linezolid	67.7	119

Static Effect	Dose (mg/kg)	AUC (μg·hr/mL) total	AUC (μg·hr/mL) free	AUC/MIC total	AUC/MIC free
ITU 5002 fu*39.6% MIC 0.5 μg/mL	5.64	59.43	23.53	118.86	47.06
ITU 5101 fu 49.1% MIC 0.25 μg/mL	5.56	30.93	15.19	123.72	60.76
Linezolid fu 91.9% MIC 2 μg/mL	67.7	161.85	148.74	80.93	74.37

1 Log Reduction	Dose (mg/kg)	AUC (μg·hr/mL) total	AUC (μg·hr/mL) free	AUC/MIC total	AUC/MIC free
ITU 5002 fu 39.6% MIC 0.5 μg/mL	8.14	78.71	31.17	157.42	62.34
ITU 5101 fu 49.1% MIC 0.25 μg/mL	9.83	40.91	20.09	163.64	80.36
Linezolid fu 91.9% MIC 2 μg/mL	119	398.3	366.04	199.15	183.02

ITU 5002 and ITU 5101 showed good AUC despite higher protein binding ratio resulting in the good efficacy reflecting the MIC result, in comparison with linezolid.



Dose (mg/kg)	S.E.*	1 log reduction**
ITU-5141	5.26	10.5
ITU-5142	6.70	19.5
Linezolid	57.5	98.7

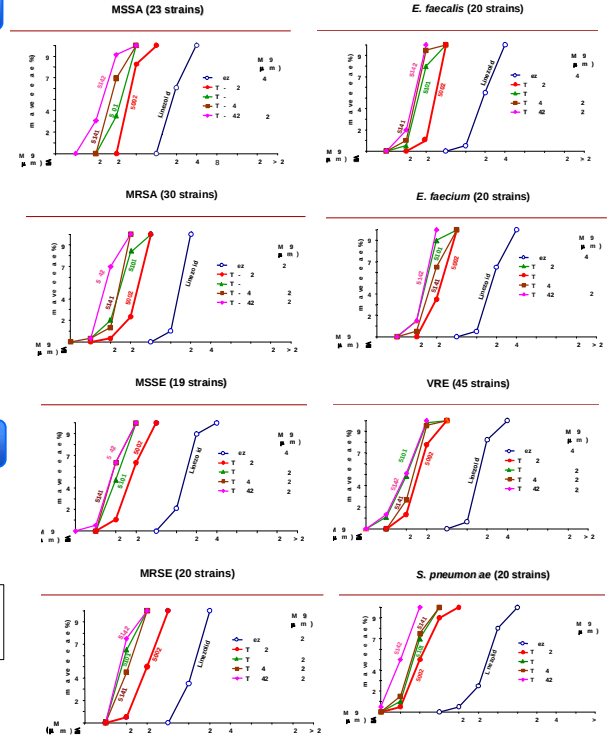
S.E. : Static Effect
1 $\log_{10}$ reduction from S.E.

Static Effect	Dose (mg/kg)	AUC (μg·hr/mL) total	AUC (μg·hr/mL) free	AUC/MIC total	AUC/MIC free
ITU-5141 fu*46.9% MIC:0.25 μg/mL	5.26	53.36	25.01	213.44	100.0
ITU-5142 fu:34.0% MIC:0.125 μg/mL	6.7	19.57	6.66	156.56	53.2
Linezolid fu:91.9% MIC:2 μg/mL	57.5	138.54	127.3	69.27	63.65

1 Log Reduction	Dose (mg/kg)	AUC (μg·hr/mL) total	AUC (μg·hr/mL) free	AUC/MIC total	AUC/MIC free
ITU-5141 fu:46.9% MIC:0.25 μg/mL	10.5	87.5	41.0	350	164
ITU-5142 fu:34.0% MIC:0.125 μg/mL	19.5	36.11	12.29	288.88	98.32
Linezolid fu:91.9% MIC:2 μg/mL	98.7	299.64	275.37	149.8	137.7

The PK/PD parameters of ITU-5002 were similar to those of Linezolid.

(* fu: fraction unbound to murine serum protein)



Conclusion

These new (4-heteroarylphenyl)oxazolidinones have a good potential for the next generation antimicrobial agents, having potential superiority over linezolid and other existing antimicrobial agents in their activity and the pharmacokinetic profile.

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