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Structure–Activity Relationships of *trans*-3,5-Disubstituted Pyrrolidinylthio-1β-methylcarbapenems. Part 2: J-111,225, J-114,870, J-114,871 and Related Compounds

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Abstract—Through further derivatization of J-111,347 (**1a**), a *trans*-3,5-disubstituted pyrrolidinylthio-1β-methylcarbapenem, undesired epileptogenicity in a rat intracerebroventricular assay (200 μg/rat) could be eliminated to afford J-111,225 (**2a**), J-114,870 (**3a**) and J-114,871 (**3b**) which preserved comparable broad antimicrobial activity. © 2000 Elsevier Science Ltd. All rights reserved.

In the preceding paper,[1] we reported that J-111,347 (**1a**) having *trans*-3,5-disubstituted pyrrolidinylthio-moiety as a C-2 side chain showed extremely broad spectrum antibacterial activities, inhibiting methicillin-resistant *Staphyloccocus aureus* (MRSA) as well as *Pseudomonas aeruginosa*. In addition, **1a** exhibited undesired epileptogenic potential in a rat intracerebroventricular assay. Subsequently, further derivatization of *trans*-3,5-disubstituted pyrrolidinylthio-1β-methylcarbapenems has been conducted using **1a** as a prototype in order to eliminate epileptogenicity at 200 μg/rat-head without losing the potent antibacterial activities of **1a** against MRSA and *P. aeruginosa*. As a result, three analogues, J-111,225 (**2a**), J-114,870 (**3a**) and J-114,871 (**3b**), were found to be promising compounds. In this paper, we describe the synthesis and antibacterial activities of J-111,225 (**2a**), J-114,870 (**3a**), J-114,871 (**3b**) and related compounds (Fig. 1),[2–4] and some biological properties of the selected compounds.

Synthesis

The synthesis of new carbapenems having 5-(substituted aryl)pyrrolidin-3-ylthio-moiety as the C-2 side chain is summarized in Scheme 1. As described in the report by Mori, alcohol **5** was obtained as a mixture of diastereomers by addition of lithiated aromatic compounds to aldehyde **4**,[5] and then converted to a diol intermediate **6** via the separation of diastereomers. Dimesylation of **6** and the subsequent cyclization under basic conditions gave pyrrolidine **7**, which provided a C-2 side chain **8** by substitution with potassium thioacetate and following alkaline hydrolysis. The desired carbapenems were obtained as lyophilized amorphous solids by the usual procedures as follows: (1) coupling reaction of the corresponding thiol **8** with the carbapenem enol phosphate **9**,[6,7] (2) deprotection[8] of the resulting coupling product, and (3) purification using reversed phase column chromatography. These carbapenems obtained above were quite stable in view of the isomerization of the side chain to the corresponding *cis* form. Details of the syntheses of selected compounds (**2a**, **3a** and **3b**) and determination of stereochemistry of **3a** and **3b** will be reported in a future paper.

Biological Activity

Newly synthesized carbapenems were evaluated for their in vitro antibacterial activities against *S. aureus*, including MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE), *E. coli* and *P. aeruginosa*, dehydropeptidase-I (DHP-I) suceptibility, and epileptogenicity at 200 μg/rat-head. Both imipenem and vancomycin are included as reference drugs. In order to identify new analogues exhibiting reduced epileptogenic potential while retaining antibacterial activities comparable to **1a**, we initially modified **1a** by keeping a

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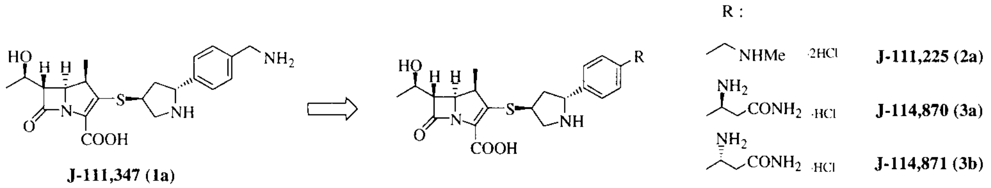
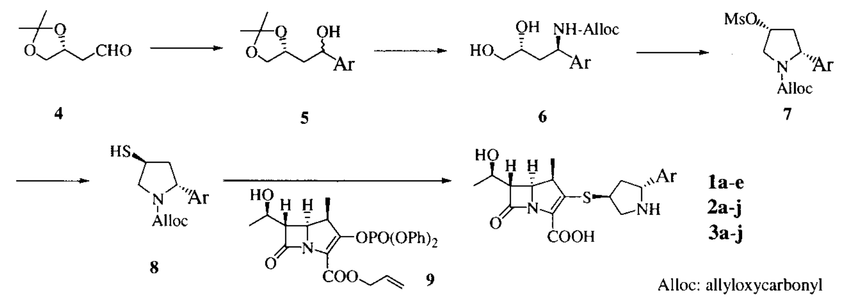


Figure 1. Novel *trans*-3,5-disubstituted pyrrolidinylthio-1β-methylcarbapenems.



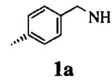
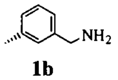
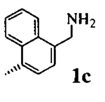
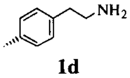
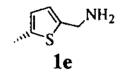
Scheme 1. Synthesis of novel carbapenems.

primary amino function (Table 1). Transferring the aminomethyl moiety to the 3-position of the benzene ring (**1b**) resulted in less potent antibacterial activities than those of **1a**. When the aminomethyl group was replaced with an aminoethyl moiety (**1d**), reduced antibacterial activities against both the MRSA and *P. aeruginosa* strains were also observed. With the exception of reduced antipseudomonal activities of a naphthalene derivative (**1c**), synthesized carbapenems (**1b**–**e**) showed antibacterial activities similar to **1a** against MRSA and *P. aeruginosa* and had sufficient stability to porcine renal DHP-I except thiophene (**1e**). However, all of these compounds showed the same strong epileptogenic effect as **1a**.

Another plan to modify **1a** was based on an observation during the discovery of BO-2727,[9] alkylation of the primary amine nitrogen (Table 2). The *N*-methyl analogue (**2a**)[10] showed almost the same antibacterial activities as **1a**. Among the *N*-alkylated series (**2a**–**i**), **2a** was the most potent against not only the two *S. aureus* strains including MRSA (pMS520/Smith) but the two *P. aeruginosa* strains including a ceftazidime-resistant strain (AKR17). The introduction of a larger substituent than the methyl group, such as ethyl (**2b**), *iso*-propyl (**2c**) and carbamoylmethyl (**2f**), apparently diminished the antibacterial activities against *P. aeruginosa.* Interestingly, **2a** and the *N*-ethyl analogue (**2b**) showed no epileptogenicity at 200 μg/rat-head, while thiophene (**2d**) exhibited significant epileptogenicity at the same dose. After all, only **2a** retained potent antibacterial activities against MRSA and *P. aeruginosa* comparable to those of **1a** with no epileptogenic potency in the *N*-alkylated derivatives (**2a**–**j**).

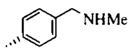
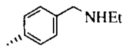
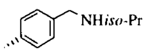
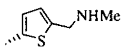
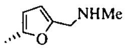
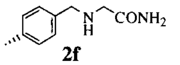
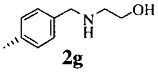
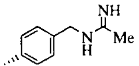
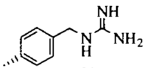
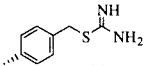
Next, the α-position of the primary amine of **1a** was modified by introducing several substituents (Table 3). Hydrophobic groups such as ethylthiomethyl (**3e**), methyl (**3f**), and allyl (**3j**) moieties yielded decreased antipseudomonal activities. Except for the carbamoylmethyl group in J-114,870 (**3a**)[11] and J-114,871 (**3b**),[12] which provided excellent antibacterial activities

Table 1. In vitro antibacterial activities[a] and biological properties of J-111,347 (**1a**) and related compounds

Organism	Ar	 **1a**	 **1b**	 **1c**	 **1d**	 **1e**	Vancomycin	Imipenem
S. aureus 209P NIHJ JC1		≤0.006	≤0.006	≤0.006	≤0.006	≤0.006	0.39	≤0.006
S. aureus pMS520/Smith[b]		0.78	1.56	1.56	1.56	1.56	0.78	50
S. epidermidis MB5181[b]		1.56	3.13	0.78	3.13	1.56	1.56	50
E. coli NIHJ JC2		0.025	0.1	0.05	0.025	0.025	>100	0.1
P. aeruginosa AK109		0.39	0.78	6.25	0.78	0.78	>100	1.56
P. aeruginosa AKR17[c]		3.13	6.25	>25	6.25	3.13	>100	3.13
DHP-I susceptibility[d]		0.29	0.16	0.16	0.26	0.84	—	1.0
Epileptogenicity (200 μg/rat-head, *n* = 5)		5/5	5/5	5/5	3/5	5/5	—	5/5

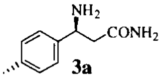
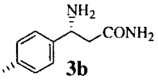
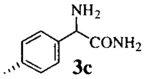
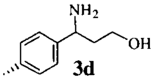
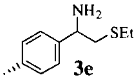
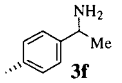
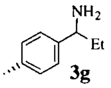
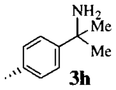
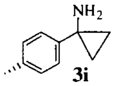
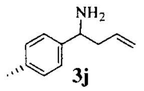
[a] MIC (μg/mL) determined by agar dilution method.
[b] Methicillin-resistant.
[c] Ceftazidime-resistant.
[d] Relative rate of hydrolysis to imipenem, porcine renal DHP-I.

Table 2. In vitro antibacterial activities[a] and biological properties of J-111,225 (**2a**) and related compounds

Organism	Ar	 **2a**	 **2b**	 **2c**	 **2d**	 **2e**
S. aureus 209P NIHJ JC1		≤0.006	≤0.006	≤0.006	≤0.006	≤0.006
S. aureus pMS520/Smith[b]		0.78	1.56	1.56	1.56	3.13
S. epidermidis B5181[b]		1.56	1.56	1.56	3.13	1.56
E. coli NIHJ JC2		0.025	0.025	0.05	0.025	0.025
P. aeruginosa AK109		0.39	1.56	0.78	1.56	1.56
P. aeruginosa AKR17[c]		1.56	6.25	6.25	3.13	12.5
DHP-I susceptibility[d]		0.25	0.44	0.46	0.35	0.10
Epileptogenicity (200 μg/rat-head, $n = 5$)		0/5	0/5	—	3/5	—
Organism	Ar	 **2f**	 **2g**	 **2h**	 **2i**	 **2j**
S. aureus 209P NIHJ JC1		≤0.006	≤0.006	≤0.006	≤0.006	≤0.006
S. aureus pMS520/Smith[b]		3.13	1.56	1.56	1.56	1.56
S. epidermidis B5181[b]		1.56	1.56	0.78	0.78	1.56
E. coli NIHJ JC2		0.025	0.05	0.05	0.012	0.05
P. aeruginosa AK109		1.56	0.78	1.56	0.78	1.56
P. aeruginosa AKR17[c]		6.25	6.25	6.25	3.13	12.5
DHP-I susceptibility[d]		0.31	0.31	0.25	—	0.30
Epileptogenicity (200 μg/rat-head, $n = 5$)		—	—	—	—	3/5

[a] MIC (μg/mL) determined by agar dilution method.
[b] Methicillin-resistant.
[c] Ceftazidime-resistant.
[d] Relative rate of hydrolysis to imipenem, porcine renal DHP-I.

Table 3. In vitro antibacterial activities[a] and biological properties of J-114,870 (**3a**), J-114,871 (**3b**) and related compounds

Organism	Ar	 **3a**	 **3b**	 **3c**	 **3d**	 **3e**
S. aureus 209P NIHJ JC1		≤0.006	≤0.006	≤0.006	≤0.006	≤0.006
S. aureus pMS520/Smith[b]		1.56	1.56	3.13	3.13	1.56
S. epidermidis B5181[b]		1.56	1.56	3.13	6.25	0.78
E. coli NIHJ JC2		0.025	0.025	0.025	0.05	0.025
P. aeruginosa AK109		0.78	1.56	1.56	1.56	3.13
P. aeruginosa AKR17[c]		1.56	1.56	6.25	12.5	12.5
DHP-I susceptibility[d]		0.27	0.27	0.32	—	0.27
Epileptogenicity (200 μg/rat-head, $n = 5$)		0/5	0/5	0/5	0/5	—
Organism	Ar	 **3f**	 **3g**	 **3h**	 **3i**	 **3j**
S. aureus 209P NIHJ JC1		≤0.006	≤0.006	≤0.006	≤0.006	≤0.006
S. aureus pMS520/Smith[b]		1.56	1.56	1.56	1.56	1.56
S. epidermidis B5181[b]		0.78	1.56	1.56	1.56	3.13
E. coli NIHJ JC2		0.025	0.10	0.05	0.025	0.025
P. aeruginosa AK109		0.78	3.13	1.56	3.13	1.56
P. aeruginosa AKR17[c]		3.13	25	6.25	6.25	12.5
DHP-I susceptibility[d]		0.55	0.20	0.37	0.32	0.29
Epileptogenicity (200 μg/rat-head, $n = 5$)		0/5	0/5	0/5	0/5	0/5

[a] MIC (μg/mL) determined by agar dilution method.
[b] Methicillin-resistant.
[c] Ceftazidime-resistant.
[d] Relative rate of hydrolysis to imipenem, porcine renal DHP-I.

comparable to those of **1a**, hydrophilic substituents such as carbamoyl (**3c**) and hydroxyethyl (**3d**) groups also reduced the antibacterial activity against *P. aeruginosa* AKR17. As for the epileptogenicity study, we were surprised to find that none of these derivatives (**3a–j**) exhibited any appreciable effect at 200 μg dose by rat intracerebroventricular assay. Thus, three compounds, **2a**, **3a** and **3b**, were selected for further evaluation because of their excellent antibacterial activities and non-seizure potential.

In summary, the epileptogenicity (200 μg/rat-head) of a *trans*-3,5-disubstituted pyrrolidinylthio-1β-methylcarbapenem, J-111,347 (**1a**), was successfully eliminated by methylation of amino nitrogen, producing J-111,225 (**2a**), or introduction of carbamoylmethyl onto α-position of amino function, producing J-114,870 (**3a**) and J-114,871 (**3b**), without sacrificing the extremely broad antibacterial spectrum of **1a**, which is effective against both MRSA and *P. aeruginosa*. The detailed in vitro and in vivo antibacterial activities of these carbapenems will be reported in near future.

Acknowledgement

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References and Notes

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10. **2a**. IR (KBr) ν_{max} 3373, 1751, 1587, 1392, 1086 cm^{-1}; ^{1}H NMR (500 MHz, D$_2$O, as a hydrochloride) δ 1.02 (3H, d, *J* = 7.3 Hz), 1.08 (3H, d, *J* = 6.4 Hz), 2.33 (1H, dd, *J* = 14.0, 6.7 Hz), 2.52 (3H, s), 2.57 (1H, m), 3.17 (1H, dq, *J* = 9.1, 7.3 Hz), 3.27 (2H, m), 3.70 (1H, dd, *J* = 12.8, 5.8 Hz), 4.04 (5H, m), 4.88 (1H, dd, *J* = 11.0, 6.7 Hz), 7.35 (4H, m); FAB–HRMS calcd for $C_{22}H_{30}N_3O_4S$ (M + H)$^+$: 432.1957. Found 432.1950. Anal. calcd for $C_{22}H_{29}N_3O_4S{\cdot}2HCl{\cdot}H_2O$: C, 50.57; H, 6.37; N, 8.04; S, 6.14. Found: C, 50.87; H, 6.45; N, 7.83; S, 6.02.
11. **3a**. IR (KBr) ν_{max} 1751, 1672, 1585, 1388, 1259, 1147, 773, 665 cm^{-1}; ^{1}H NMR (500 MHz, D$_2$O) δ 1.04 (3H, d, *J* = 7.0 Hz), 1.08 (3H, d, *J* = 6.4 Hz), 2.36 (1H, dd, *J* = 14.0, 7.0 Hz), 2.61 (1H, m), 2.81 (1H, dd, *J* = 15.6, 7.3 Hz), 2.88 (1H, dd, *J* = 15.6, 7.3 Hz), 3.18 (1H, dq, *J* = 8.8, 7.0 Hz), 3.28 (1H, dd, *J* = 5.8, 2.8 Hz), 3.31 (1H, br d, *J* = 12.8 Hz), 3.72 (1H, dd, *J* = 12.8, 5.8 Hz), 4.05 (3H, m), 4.59 (1H, t, *J* = 7.3 Hz), 4.92 (1H, dd, *J* = 11.0, 7.0 Hz), 7.36 (4H, m); FAB–HRMS calcd for $C_{23}H_{31}N_4O_5S$ (M + H)$^+$: 475.2015. Found 475.201. Anal. calcd for $C_{22}H_{30}N_4O_5S{\cdot}HCl{\cdot}2H_2O$: C, 50.50; H, 6.45; N, 10.24; S, 5.86. Found: C, 50.61; H, 6.55; N, 10.32; S, 5.60.
12. **3b**. IR (KBr) ν_{max} 3417, 1751, 1673, 1583, 1390, 1261, 1147, 572 cm^{-1}; ^{1}H NMR (500 MHz, D$_2$O) δ 1.04 (3H, d, *J* = 7.3 Hz), 1.08 (3H, d, *J* = 6.4 Hz), 2.36 (1H, dd, *J* = 14.0, 6.7 Hz), 2.60 (1H, m), 2.81 (1H, dd, *J* = 15.8, 7.3 Hz), 2.88 (1H, dd, *J* = 15.8, 7.3 Hz), 3.18 (1H, dq, *J* = 9.4, 7.3 Hz), 3.28 (1H, dd, *J* = 6.1, 2.8 Hz), 3.31 (1H, br d, *J* = 12.8 Hz), 3.72 (1H, dd, *J* = 12.8, 5.8 Hz), 4.05 (3H, m), 4.59 (1H, t, *J* = 7.3 Hz), 4.92 (1H, dd, *J* = 11.0, 6.7 Hz), 7.36 (4H, m); FAB-HRMS calcd for $C_{23}H_{31}N_4O_5S$ (M + H)$^+$: 475.2015. Found 475.201. Anal. calcd for $C_{22}H_{30}N_4O_5S{\cdot}HCl{\cdot}2H_2O$: C, 50.50; H, 6.45; N, 10.24; S, 5.86. Found: C, 50.80; H, 6.66; N, 10.18; S, 5.65.