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Novel 1β-methylcarbapenems with isoxazoloethenyl moieties containing carboxylic acid sodium salt

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Abstract—The synthesis of novel 1β-methylcarbapenems **1a**,**b** having sodium 5-(3- and 5-carboxylic acid)isoxazoloethenyl moieties at C-5 position of pyrrolidine ring and their biological evaluation are described. Both compounds showed potent and well-balanced antibacterial activity as well as high stability to DHP-I. The selected sodium 3-carboxylic acid derivative **1a** possessed excellent DHP-I stability and advanced pharmacokinetic parameters in comparison with **2** and meropenem.

1. Introduction

In our previous work,[1,2] we reported the synthesis and biological properties of new 1β-methylcarbapenems bearing ethenyl group between pyrrolidine ring and five-membered heteroaromatics. In this series, 5-isoxazole derivative **2** showed excellent antibacterial activity and high stability to DHP-I compared to meropenem.[3]

Ertapenem[4,5] is a novel carbapenem with a long serum half-life. It shows similar activity against Gram-positive bacteria but less active against *Pseudomonas aeruginosa* isolates to that of imipenem and meropenem. Its sodium carboxylic acid as a side chain, ionized at physiological pH, is presumably responsible for once a day dosing.

On the basis of these results, we carried out the introduction of sodium carboxylic acid substitute into isoxazole nucleus in order to improve the chemical and metabolic stability like ertapenem. As expected, sodium 5-(3-carboxylic acid)isoxazoloethenyl carbapenem **1a** showed markedly enhanced DHP-I stability without the loss of activity against *P. aeruginosa* isolates and advanced pharmacokinetic profiles in rat and dog than those of **2** and meropenem (Fig. 1).

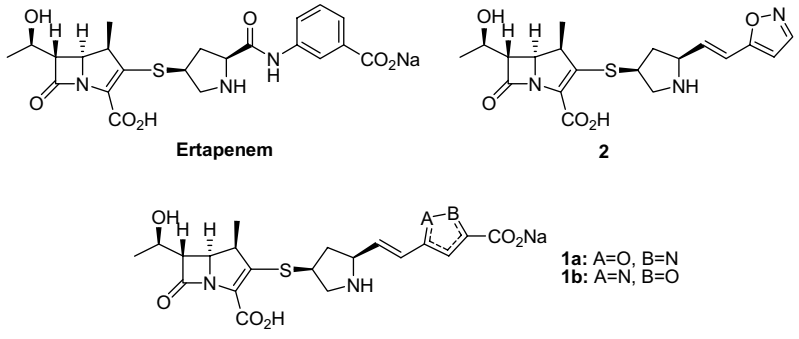

Figure 1.

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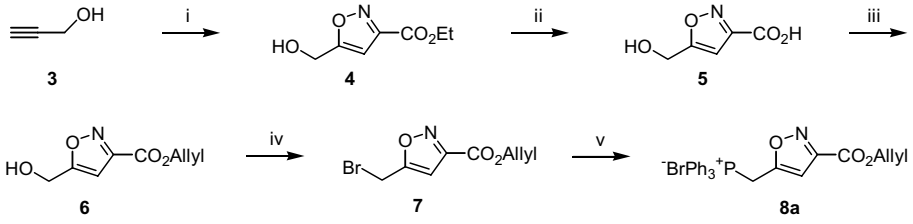
In this paper, we report the synthesis of novel 1β-methylcarbapenems **1a**,**b** bearing sodium 5-(3- and 5-carboxylic acid)isoxazoloethenyl moieties and biological evaluation for the selected carbapenem **1a**.

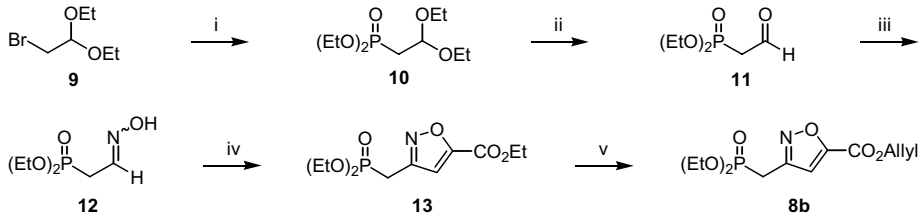
2. Chemistry

5-(Triphenylphosphonium)methylisoxazole bromide **8a**, key intermediate, was served for the synthesis of sodium 5-(3-carboxylic acid)isoxazoloethenyl moiety as a Wittig agent as shown in Scheme 1. 3-Ethoxycarbonyl-5-hydroxymethylisoxazole (**4**) was prepared by 1,3-dipolar cycloaddition of propargyl alcohol (**3**) with ethyl chlorooximidoacetate as a nitrile oxide source.[6] The ethyl ester **4** was transformed to allyl ester **6** by hydrolysis with Claisen's alkali[7] and subsequent allylation with allyl bromide. The bromination of **6** with carbon tetrabromide and triphenylphosphine afforded 5-bromomethylisoxazole **7**, which was treated with triphenylphosphine in CH_3CN to yield **8a**.

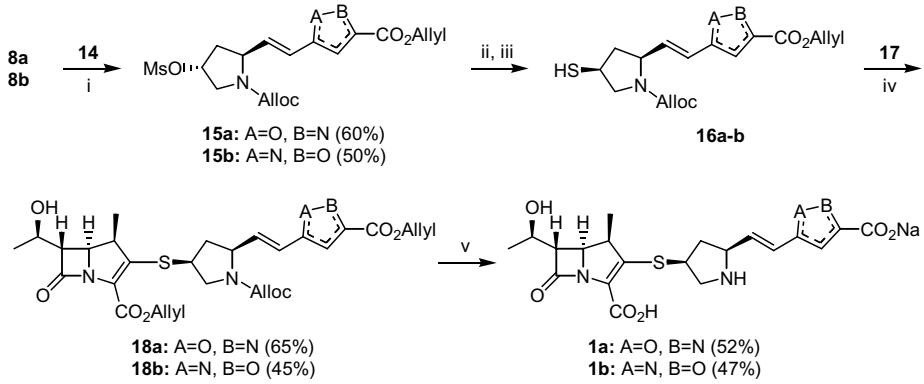
5-Allyloxycarbonyl-3-(diethoxyphosphoryl)methylisoxazole (**8b**), Honor–Emmons olefination agent for the synthesis of sodium 5-(5-carboxylic acid)isoxazoloethenyl moiety, was prepared by the sequence outlined in Scheme 2. Arbuzov reaction of bromoacetaldehyde diethyl acetal (**9**) with triethylphosphite followed by deacetalization under acidic condition[8] gave (diethoxyphosphoryl)acetaldehyde (**11**), which was converted into the oxime **12**. Subsequently 1,3-dipolar cycloaddition reaction was performed from ethyl propiolate with (diethoxyphosphoryl)acetonitrile oxide, which was generated in situ from oxime **12**, NBS and triethylamine,



Scheme 1. Reagents and reaction conditions: (i) ethyl chlorooximidoacetate, Et_3N, Et_2O, rt, 5 h (61%); (ii) Claisen's alkali, MeOH, 0 °C, 0.5 h (92%); (iii) allyl bromide, K_2CO_3, DMF, rt, 7 h (76%); (iv) PPh_3, CBr_4, CH_2Cl_2, −20 °C, 0.5 h (56%); (v) PPh_3, CH_3CN, reflux, 3 h (90%).



Scheme 2. Reagents and reaction conditions: (i) $(EtO)_3P$, 160 °C, 3 h (70%); (ii) 2% HCl, reflux, 10 min (70%); (iii) $NH_2OH{\cdot}HCl$, H_2O, EtOH, rt, 12 h (85%); (iv) ethyl propiolate, NBS, DMF, Et_3N/H_2O, rt, 18 h (59%); (v) DMAP, allyl alcohol, reflux, 30 h (73%).



Scheme 3. Reagents and reaction conditions: (i) (2*S*,4*R*)-4-methanesulfonyloxy-2-formyl-1-allyloxycarbonylpyrrolidine (**14**), NaHMDS, THF, −78 °C to rt, 1.5 h; (ii) AcSK, CH_3CN/DMF, 90 °C, 1 h; (iii) NaSMe, allyl alcohol, 0 °C, 0.5 h; (iv) allyl (1*R*,5*S*,6*S*)-2-(diphenylphosphoryloxy)-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**17**), DIEA, CH_3CN, 0 °C, 1.5 h; (v) $Pd(PPh_3)_4$, Bu_3SnH, CH_2Cl_2, sodium 2-ethylhexanoate, 0 °C, 1 h.

to give 3-(diethoxyphosphoryl)methyl-isoxazole **13**.[9] Transesterification of the ethyl ester **13** with allyl alcohol in the presence of 4-DMAP gave **8b**.[10]

The corresponding 1β-methylcarbapenems **1a**,**b**[13] were prepared by conventional procedures (Scheme 3).[1,2,11,12]

3. Biological properties

The title 1β-methylcarbapenems **1a**,**b** prepared above were evaluated for antibacterial activity and stability to porcine DHP-I relative to **2**, imipenem and meropenem as shown in Table 1. Both compounds **1a**,**b** possessed slightly lower antibacterial activity against Gram-positive bacteria than those of **2** and imipenem, but showed comparable activity against Gram-negative bacteria including *P. aeruginosa* isolates to those of **2** and meropenem. In our series, sodium 3-carboxylic acid derivative **1a** showed well-balanced and potent antibacterial activity than sodium 5-carboxylic acid derivative **1b**. Especially, **1a** exhibited excellent DHP-I stability compared to **2**.

Comparative in vitro antibacterial activity of the selected carbapenem **1a**, **2**, and marketed carbapenems against Gram-positive and Gram-negative clinically isolated aerobic pathogens was shown in Table 2. Among these carbapenems, **1a** displayed the best balance against both Gram-positive and Gram-negative organisms. In particular, **1a** exhibited good efficacy against *S. pneumonia* and *K. pneumonia*, which are important respiratory infectious strains.

Table 3 showed that **1a** possessed three times longer half-life, four times higher value in AUC and four times lower value in clearance than meropenem in rat. And also **1a** exhibited better pharmacokinetic profiles than meropenem in dog. In comparison with **2**, **1a** showed more effective AUC value in larger animal.

Table 1. In vitro antibacterial activity and DHP-I stability of **1a**,**b**

Organism	MIC (μg/mL)[a]				
	1a	**1b**	**2**	IPM[b]	MPM[c]
S. pyogenes 308A	0.049	0.007	0.004	0.004	0.013
S. aureus SG 511	0.195	0.098	0.025	0.013	0.195
S. aureus 285	0.195	0.195	0.049	0.013	0.195
S. aureus 503	0.195	0.098	0.098	0.098	
E. coli 078	0.013	0.025	0.025	0.098	0.025
E. coli 1507E	0.025	0.025	0.025	0.098	0.025
P. aeruginosa 9027	0.195	0.195	0.195	0.391	0.195
P. aeruginosa 1592E	0.195	0.391	0.195	0.781	0.195
P. aeruginosa 1771M	0.049	1.563	0.098	0.195	0.049
S. typhimurium	0.049	0.049	0.049	0.781	0.049
K. aerogenes 1522E	0.049	0.049	0.049	0.195	0.049
E. cloacae 1321E	0.025	0.025	0.025	0.098	0.025
DHP-I stability[d]	4.57	1.19	1.95	0.18	1.00

[a] MIC was determined by agar dilution method using Mueller–Hinton.
[b] IPM = imipenem.
[c] MPM = meropenem.
[d] Relative $t_{1/2}$ of hydrolysis to meropenem by partially purified porcine renal DHP-I.

Table 2. Comparative in vitro antibacterial activities of **1a**, **2**, imipenem, meropenem, and ertapenem against Gram-positive and Gram-negative clinically isolated aerobic pathogens

Organism (no. of strains)	Antibiotics	MIC (μg/mL)		
		Range	MIC_{50}	MIC_{90}
Streptococcus pneumoniae (22)	**1a**	0.008–0.25	0.008	0.12
	2	0.008–0.25	0.03	0.12
	IPM	0.008–0.5	0.12	0.25
	MPM	0.008–0.5	0.5	0.5
	EPM[a]	0.008–1	0.5	1
Moraxella catarrhalis (24)	**1a**	0.015–0.06	0.03	0.06
	2	0.008–0.06	0.015	0.03
	IPM	0.008–0.25	0.06	0.06
	MPM	0.008–0.03	0.008	0.008
	EPM	0.008–0.12	0.015	0.03
Klebsiella pneumoniae (30)	**1a**	0.015–0.25	0.03	0.12
	2	0.03–0.25	0.06	0.12
	IPM	0.06–1	0.12	0.5
	MPM	0.015–0.06	0.03	0.06
	EPM	0.008–1	0.03	0.5
Pseudomonas aeruginosa (60)	**1a**	0.06–128	4	64
	2	0.025–128	8	64
	IPM	0.5–128	2	16
	MPM	0.06–128	2	16
	EPM	1–128	32	128

[a] EPM = ertapenem.

Table 3. Pharmacokinetic parameters[a] of **1a**

		1a	**2**	MPM
$t_{1/2}$ (min)	Rat	12	16	4
	Dog	41	23	33
AUC (μg min/mL)	Rat	1519	1133	383
	Dog	861	186	695
CL (mL/min/kg)	Rat	13	18	52
	Dog	6	27	7

[a] At a single intravenous administration of 20 mg/kg in rat and 5 mg/kg in dog, respectively.

As can be seen from the above data, the introduction of sodium carboxylic acid group into isoxazole nucleus led to significant enhanced DHP-I stability and pharmacokinetic profiles. Taking the overall biological and physical properties into account, **1a** was selected as a good candidate.

Acknowledgements

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References and notes

1. Kim, D. J.; Seo, K. J.; Lee, K. S.; Shin, K. J.; Yoo, K. H.; Kim, D. C.; Park, S. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2799.
2. Kang, Y. K.; Lee, K. S.; Yoo, K. H.; Shin, K. J.; Kim, D. C.; Lee, C.-S.; Kong, J. Y.; Kim, D. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 463.

3. Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiot.* **1990**, *43*, 519.
4. Betts, M. J.; Davies, G. M.; Swain, M. L. U.S. Patent 5478820, 1995.
5. Hilliard, N. J.; Johnson, C. N.; Armstrong, S. H.; Quarles, S.; Waites, K. B. *Int. J. Antimicrob. Agents* **2002**, *20*, 136.
6. (a) Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366; (b) Kang, Y. K.; Shin, K. J.; Yoo, K. H.; Seo, K. J.; Hong, C. Y.; Lee, C.-S.; Park, S. Y.; Kim, D. J.; Park, S. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 95.
7. Tarbell, D. S.; Wilson, J. W.; Fanta, P. E. In Organic Syntheses; Wiley: New York, 1955, Collect. Vol. III, p 267.
8. Wataru, W.; Toshio, W.; Yoshio, H. In Organic Syntheses; Wiley: New York, 1988, Collect. Vol. VI, p 448.
9. Tsuge, O.; Kanemasa, S.; Suga, H. *Chem. Lett.* **1986**, *183*, 323.
10. Hatakenyama, S.; Satho, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2713.
11. Shin, K. J.; Koo, K. D.; Yoo, K. H.; Kim, D. C.; Kim, D. J.; Park, S. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1421.
12. Wallace, O. B.; Springer, D. M. *Tetrahedron Lett.* **1998**, *39*, 2693.
13. **1a**: ^{1}H NMR (300 MHz, D_2O) δ 6.46–6.62 (m, 3H), 4.06–4.13 (m, 2H), 3.99 (m, 1H), 3.82 (m, 1H), 3.39 (m, 1H), 3.18–3.32 (m, 1H), 3.07 (m, 1H), 2.59 (m, 1H), 1.59 (m, 1H), 1.15 (d, 3H, J = 6.3 Hz), 1.09 (d, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, D_2O) δ 176.4, 168.2, 167.8, 166.2, 161.4, 140.0, 132.5, 128.7, 118.8, 102.3, 65.1, 60.5, 58.5, 55.9, 53.0, 42.7, 40.5, 36.4, 20.0, 15.0; FABHRMS *m/z* Calcd for $C_{20}H_{22}N_3O_7SNa_2$ $(M + Na)^+$ 494.0975. Found: 494.0974.