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Synthesis and Biological Properties of New 1β-Methylcarbapenems Having Tetrazolothioether Moiety

Kye Jung Shin, Ki Dong Koo, Kyung Ho Yoo, Dong Chan Kim, Dong Jin Kim* and Sang Woo Park

Medicinal Chemistry Research Center, Korea Institute of Science and Technology, Seoul 130-650, South Korea

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Abstract—The synthesis and biological activities of a series of new 1β-methylcarbapenems **1a–l** having tetrazolothioether moiety at C-5 position of pyrrolidine were described. Among these compounds, **1c** showed the most potent antibacterial activity and advanced pharmacokinetics compared with imipenem and meropenem. © 2000 Elsevier Science Ltd. All rights reserved.

Since the discovery of carbapenem antibiotics which have a broad antimicrobial spectrum and potent bactericidal activity,[1] tremendous efforts to develop new synthetic carbapenems for clinical use have been made. Currently, a number of carbapenem antibiotics such as imipenem,[2] panipenem[3] and meropenem[4] were launched on the market and several compounds[5] are under clinical evaluation. However, some problems still remain in these compounds. Imipenem and panipenem are unstable to the renal dehydropeptidase-I (DHP-I) and have the convulsive side effect. Meropenem has good stability to DHP-I and an excellent spectrum against Gram-negative bacteria. However, it is relatively less active against Gram-positive bacteria than imipenem.

Our continuous object has been to find the novel carbapenems with better activity and advanced pharmacokinetics than imipenem and meropenem.[6] In our previous works, we found that the liphophilicity was responsible for the activity against Gram-positive strains and the basicity exerted a major influence upon the antibacterial activity against Gram-negative strains. Based on these concepts, we designed new carbapenems bearing a thioether nucleus[7] as a lipophilic site and a tetrazole heterocyclic substituent as a basic part. We expected that the introduction of tetrazolothioether moiety into the C-5 position of pyrrolidine ring would possess well-balanced lipophilicity and basicity, and hence improve the activity against Gram-positive bacteria without the loss of activity against Gram-negative bacteria. Here, we report our efforts in the synthesis and biological properties of new carbapenems having tetrazolothioether moiety.

*Corresponding author. Fax: +82-2-958-5189; e-mail: djk2991@kist.re.kr

Chemistry

The synthesis of the title compounds **1a–l** was started from 1-substituted 5-mercaptotetrazoles **2a–k**. 5-Mercaptotetrazole derivatives were obtained by the reaction of NaN_3 with commercially available isocyanates **4a**, **4c** or methyl dithiocarbamates **5b**, **5d–k** as an isocyanate equivalent[8] (Scheme 1). Methyl dithiocarbamates **5b**, **5d–k** were prepared from the addition reaction of the corresponding amine to CS_2 followed by methylation.

N-Protected 3-thioacetyl-5-iodomethylpyrrolidine **13**, a coupling acceptor for 5-mercaptotetrazoles, was prepared by the reaction sequence described in Scheme 2.

trans-4-Hydroxy-L-proline (**6**) was treated with AcCl in MeOH to give 4-hydroxyproline methyl ester HCl salt **7**, which was protected with allylchloroformate to afford *N*-protected ester **8**. Mesylation of hydroxyl group of **8** with MsCl followed by reduction of resulting ester **9** with $NaBH_4$ in the presence of LiCl provided the alcohol **10**. Without protection of hydroxyl group, mesylate **10** was substituted to thioacetate **11** with AcSK in DMF/toluene. Iodo compound **13** was obtained by the mesylation of **11** followed by substitution with NaI in good yield.

The preparation of pyrrolidine thiols **3a–k** bearing tetrazole moiety is outlined Scheme 3. Treatment of iodide **13** with mercaptotetrazoles **2a–k** and K_2CO_3 in acetone gave methylthiotetrazolopyrrolidine thioacetates **14a–k**. Deacetylation of **14a–k** was performed with 1*N* NaOH in MeOH to afford pyrrolidine thiols **3a–k**.

Coupling reaction of the enolphosphate **15** with pyrrolidine thiols **3a–k** was carried out to give the protected

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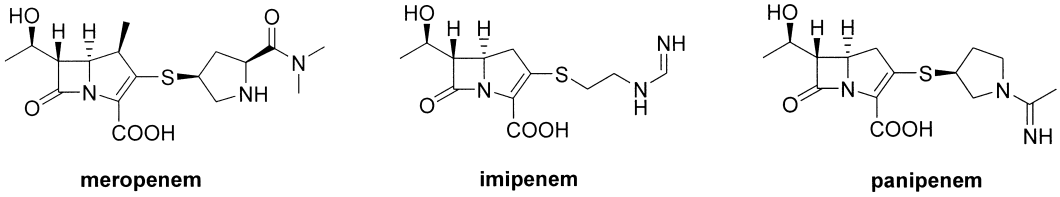
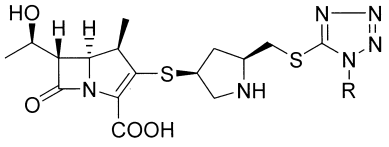
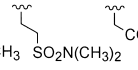
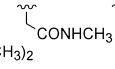
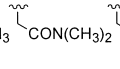
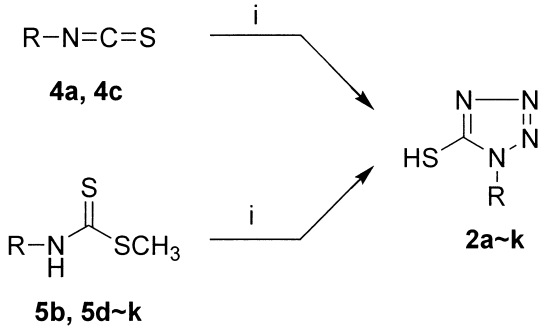




	a	b	c	d	e	f	g	h	i	j	k	l
R												

1β-methylcarbapenems **16a–k**, respectively. Deprotection of **16a–k** with Bu_3SnH in the presence of catalytic amount of $Pd(PPh_3)_4$ (5 mol%) provided the desired carbapenems **1a–k**,[9] which were purified by the column chromatography on Diaion HP-20. Quaternary ammonium salt carbapenem **1l** was obtained by quaternization of **16k** with MeI in acetone followed by deprotection and purification in the same manner described above (see Scheme 4).

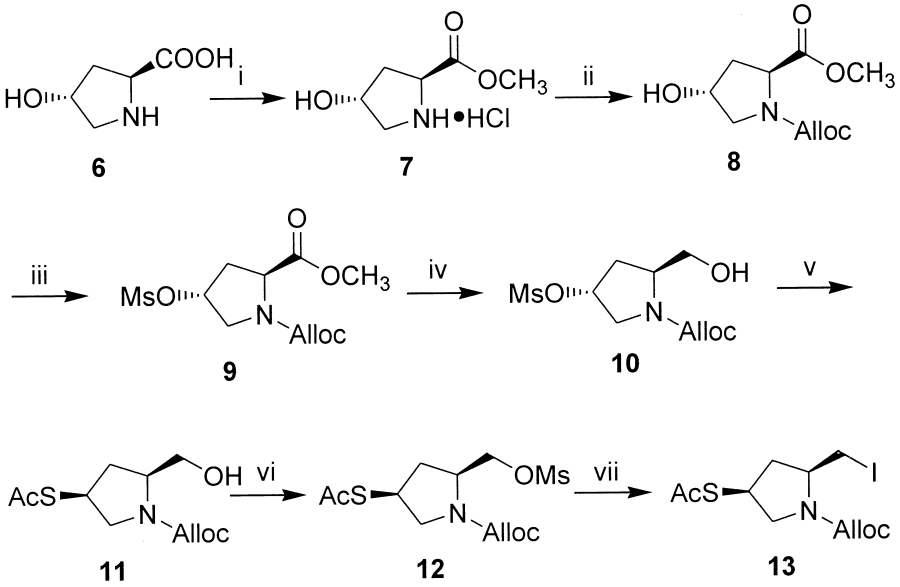


Scheme 1. (i) NaN_3, EtOH, 70 °C, 3 h then c-HCl, 65–98%.

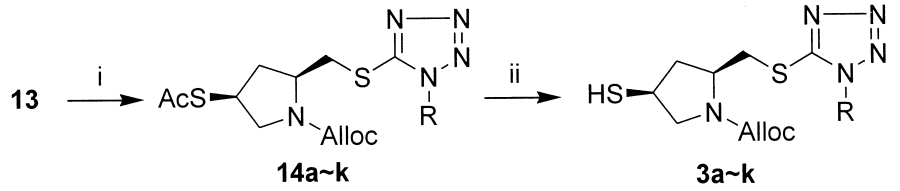
Biological Properties

The in vitro antibacterial activities and stability to porcine renal DHP-I of new carbapenems in comparison with imipenem and meropenem are shown in Table 1.

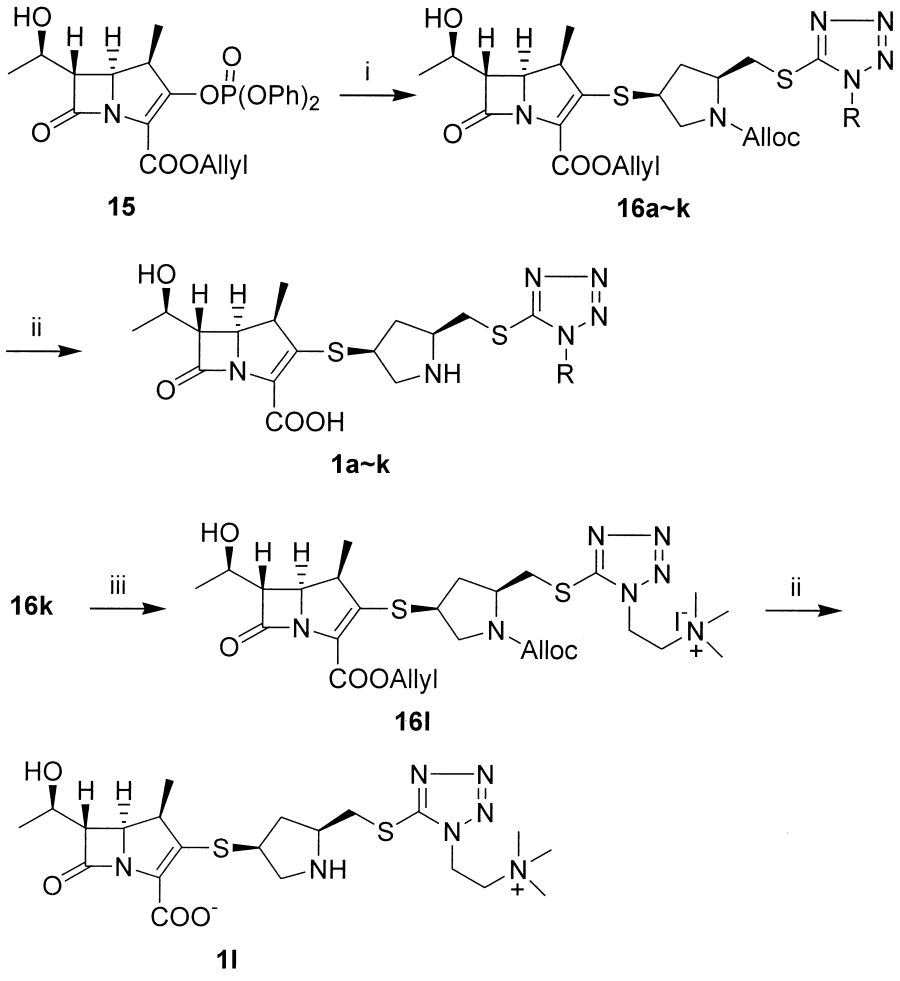
Most compounds except for **1a** and **1b** exhibited well-balanced antibacterial activities and good stability to DHP-I. Aryl substituent compounds, **1a** and **1b**, showed excellent antibacterial activities against Gram-positive organisms. However, they had poor activities against



Scheme 2. (i) AcCl, MeOH, 60 °C, 18 h, 97%; (ii) AllocCl, TEA, CH_2Cl_2, rt, 12 h, 92%; (iii) MsCl, TEA, CH_2Cl_2, 0 °C, 1 h, 95%; (iv) LiCl, $NaBH_4$, EtOH, THF, 0 °C, 88%; (v) AcSK, DMF/toluene, 60 °C, 3 h, 82%; (vi) MsCl, TEA, CH_2Cl_2, 0 °C, 92%; (vii) NaI, acetone, 60 °C, 2 h, 87%.



Scheme 3. (i) **2a**–**k**, K_2CO_3, acetone, 60 °C, 3 h, 83–98%; (ii) 1*N* NaOH, MeOH, 0 °C, 20 min, 90–100%.



Scheme 4. (i) **3a**–**k**, *i*-Pr $_2$EtN, CH_3CN, 0 °C, 5 h, 45–60%; (ii) $Pd(PPh_3)_4$, *n*-Bu_3SnH, CH_2Cl_2, 0 °C, 1 h, 26–49%; (iii) MeI, acetone, rt, 24 h, quant.

Gram-negative organisms, especially against *Pseudomonas*. Compound **1c** which has the smallest alkyl group among the title compounds exhibited enhanced antibacterial activity against Gram-positive organisms and similar antibacterial spectrum against Gram-negative strains compared to meropenem. Compounds **1d** and **1k** which possess hydroxyethyl and dimethylaminoethyl group at *N*-1 position of tetrazole, respectively showed slightly better antibacterial activity against Gram-positive organisms than meropenem. However, **1d** and **1k** were inferior to meropenem against Gram-negative organisms. Interestingly, compounds **1e**–**j** bearing the electron withdrawing groups exhibited similar activity against all of bacteria when compared to **1d** and **1k** which have the electron donating groups. Quaternized compound **1l** showed a pronounced effect on the activity against *Pseudomonas* and enhanced stability to DHP-I, whereas it had a reduction in activity against Gram-positive and Gram-negative bacteria compared to the parent compound **1k**.

Among these series of compounds, as **1c** showed the best antibacterial activity against Gram-positive and Gram-negative bacteria, it was selected for further evaluation. Table 2 describes the pharmacokinetics of **1c** in rat together with those of imipenem and meropenem.

It demonstrated that the half-life of **1c** was 3-fold longer than that of imipenem and meropenem. And also, **1c** displayed approximately 3 times higher value in AUC and 3 times lower value in clearance than imipenem and meropenem.

In summary, the title new carbapenems exhibited the potent antibacterial activity, especially against

Table 1. In vitro antibacterial activity and DHP-I stability of carbapenem compounds **1a–l**

Organism	MIC (μg/mL)[a]							
	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**IPM[b]**	**MPM[c]**
S. pyogenes 308A	0.007	0.007	0.004	0.007	0.007	0.007	0.007	0.013
S. aureus SG 511	0.049	0.049	0.025	0.098	0.098	0.098	0.025	0.195
S. aureus 285	0.049	0.098	0.049	0.098	0.098	0.098	0.025	0.195
S. aureus 503	0.025	0.049	0.025	0.049	0.025	0.025	0.013	0.098
E. coli 078	0.195	0.098	0.025	0.025	0.025	0.025	0.098	0.025
E. coli 1507E	0.391	0.195	0.025	0.025	0.025	0.025	0.195	0.025
P. aeruginosa 9027	50	50	0.781	1.563	3.125	6.25	0.781	0.195
P. aeruginosa 1592E	50	50	0.781	1.563	3.125	12.5	1.563	0.195
P. aeruginosa 1771M	3.125	0.781	0.195	0.195	0.391	0.391	0.195	0.049
S. typhymurium	0.098	0.049	0.025	0.049	0.049	0.049	0.781	0.049
K. aerogenes 1522E	0.391	0.195	0.025	0.049	0.049	0.049	0.391	0.049
E. cloacae 1321E	0.098	0.098	0.025	0.049	0.025	0.025	0.195	0.025
DHP-I stability[d]	NT[e]	0.98	0.88	0.96	NT[e]	0.72	0.19	1.00

Organism	MIC (μg/mL)[a]							
	1g	**1h**	**1i**	**1j**	**1k**	**1l**	**IPM[b]**	**MPM[c]**
S. pyogenes 308A	0.013	0.013	0.013	0.007	0.013	0.025	0.007	0.013
S. aureus SG 511	0.195	0.195	0.098	0.098	0.049	0.098	0.025	0.195
S. aureus 285	0.195	0.195	0.098	0.098	0.098	0.195	0.025	0.195
S. aureus 503	0.098	0.049	0.025	0.049	0.025	0.049	0.013	0.098
E. coli 078	0.025	0.025	0.025	0.025	0.025	0.049	0.098	0.025
E. coli 1507E	0.049	0.049	0.025	0.025	0.049	0.098	0.195	0.025
P. aeruginosa 9027	1.563	3.125	1.563	1.563	3.125	0.781	0.781	0.195
P. aeruginosa 1592E	1.563	3.125	0.781	1.563	3.125	0.781	1.563	0.195
P. aeruginosa 1771M	0.391	0.391	0.195	0.391	0.195	0.195	0.195	0.049
S. typhymurium	0.098	0.049	0.049	0.049	0.098	0.195	0.781	0.049
K. aerogenes 1522E	0.098	0.098	0.049	0.049	0.098	0.195	0.391	0.049
E. cloacae 1321E	0.049	0.049	0.025	0.025	0.049	0.098	0.195	0.025
DHP-I stability[d]	0.86	0.86	0.92	0.91	0.88	1.35	0.19	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.
[e]NT = Not tested.

Table 2. Pharmacokinetics of carbapenem **1c** after a single intravenous administration of 20 mg/kg dose in rat

Compounds	Phamacokinetic parameters		
	$t_{1/2}$ (min)	AUC (μg.min/ml)	CL (ml/min/kg)
1c	11.02±0.94	955±131	21.81±3.20
Imipenem	3.46±0.10	330±23	61.50±3.65
Meropenem	3.99±0.24	383±36	54.16±5.27

Gram-positive bacteria, showing 2–4-fold superior to meropenem. In particular, **1c** possessed well-balanced antibacterial activity and showed better pharmacokinetics in rat than those of imipenem and meropenem.

Acknowledgement

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9. **1c**: IR (KBr) 3390, 1760, 1574 cm^{-1}; ^1H NMR (D_2O) δ 4.30–4.20 (m, 3H), 4.19–4.06 (m, 1H), 4.05 (s, 3H, CH_3), 3.90–3.68 (m, 3H), 3.52–3.47 (m, 2H), 3.45–3.35 (m, 1H), 2.96–2.85 (m, 1H), 1.98–1.91 (m, 1H), 1.32 (d, 3H, $J=6.4$ Hz, CH_3), 1.25 (d, 3H, $J=7.2$ Hz, CH_3); ^{13}C NMR (D_2O) δ 171.99, 163.00, 149.23, 133.29, 129.27, 60.46, 54.44, 54.21, 51.30, 47.76, 37.78, 35.08, 30.16, 29.24, 29.00, 15.50, 11.19; MS (FAB) m/z (relative intensity) 441 $(M+H)^+$ (40), 311 (9), 286 (9), 232 (14), 198 (28), 158 (32), 114 (52), 82 (base peak), 68 (90), 43 (24), 30 (23); HRMS calcd for $C_{17}H_{25}N_6O_4S_2$ $(M+H)^+$ 441.1379, found 441.1368. **1d**: IR (KBr) 3406, 1752, 1586 cm^{-1}; ^1H NMR (D_2O) δ 4.56 (t, 2H, $J=4.7$ Hz), 4.30–4.18 (m, 3H), 4.11–4.04 (m, 3H), 3.90–3.69 (m, 3H), 3.52–3.46 (m, 2H), 3.45–3.34 (m, 1H), 2.94–2.85 (m, 1H), 1.97–1.89 (m, 1H), 1.32 (d, 3H, $J=6.3$ Hz, CH_3), 1.24 (d, 3H, $J=7.2$ Hz, CH_3); ^{13}C NMR (D_2O) δ 171.02, 163.01, 148.78, 133.29, 129.31, 60.50, 54.70, 54.52, 54.25, 51.34, 47.79, 45.63, 37.83, 35.10, 30.20, 29.28, 15.53, 11.23; MS (FAB) m/z (relative intensity) 471 $(M+H)^+$ (30), 307 (21), 289 (11), 228 (7), 154 (base peak), 136 (65), 107 (20), 89 (17), 68 (12), 39 (7); HRMS calcd for $C_{18}H_{27}N_6O_5S_2$ $(M+H)^+$ 471.1484, found 471.1484. **1i**: IR (KBr) 3420, 1752, 1676 cm^{-1}; ^1H NMR (D_2O) δ 4.65 (t, 2H, $J=6.5$ Hz), 4.31–4.08 (m, 4H), 3.92–3.70 (m, 3H), 3.52–3.48 (m, 2H), 3.43–3.38 (m, 1H), 3.03 (t, 2H, $J=6.5$ Hz), 2.96–2.86 (m, 1H), 1.98–1.90 (m, 1H), 1.33 (d, 3H, $J=6.4$ Hz), 1.26 (d, 3H, $J=7.2$ Hz, CH_3); ^{13}C NMR (D_2O) δ 172.05, 170.18, 163.08, 143.38, 133.25, 129.39, 60.51, 54.54, 54.28, 51.35, 47.81, 39.29, 37.83, 35.13, 30.23, 29.27, 28.90, 15.53, 11.23; MS (FAB) m/z (relative intensity) 498 $(M+H)^+$ (62), 307 (16), 289 (12), 256 (9), 255 (8), 154 (base peak), 136 (64), 114 (23), 107 (20), 89 (18), 68 (26); HRMS calcd for $C_{19}H_{28}N_7O_5S_2$ $(M+H)^+$ 498.1593, found 498.1595.