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# Synthesis and Biological Properties of New 1β-Methylcarbapenems Containing Heteroaromatic Thioether Moiety

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**Abstract**—The synthesis and biological activities of a series of new 1β-methylcarbapenems **1a**–**h** having heteroaromatic thioether moiety at C-5 position of pyrrolidine were described. Among these compounds, 1,2,3-thiadiazole derivative **1h** showed the most potent antibacterial activity and advanced pharmacokinetics in comparison with meropenem. 

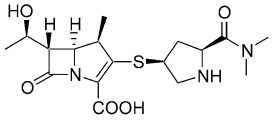
In our previous work,[1] we described the synthesis and biological properties of a novel series of 1β-methylcarbapenems containing tetrazolothioether moiety at C-5 position of pyrrolidine. These compounds showed the pronounced antibacterial activity against Gram-positive bacteria compared to meropenem[2] without the loss of activity against Gram-negative bacteria. We conceived that the improvement of antibacterial activity and pharmacokinetic profiles were responsible for the tetrazolothioether moiety to be introduced in pyrrolidine nucleus.[3]

On the basis of these results, we further investigated the effect of other heteroaromatic thioether moiety on the antimicrobial activity, stability to DHP-I and pharmacokinetics. The new carbapenems **1a**–**h** displayed the activity ranging from excellent to moderate depending on the heteroaromatic substituents.

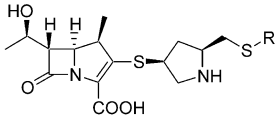
## Chemistry

The title compounds **1a**–**1h** were synthesized through the general procedure described in Scheme 1.

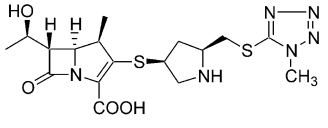
It contains coupling reaction of enol phosphate **3** with appropriate pyrrolidinethiols **5a**–**h** to give the protected 1β-methylcarbapenems **4a**–**h**, and the following



Meropenem



1a~h



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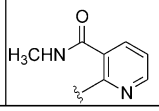
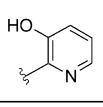
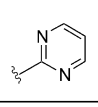
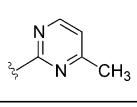
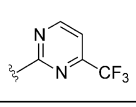
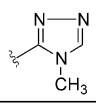
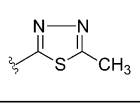
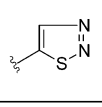
| | a | b | c | d | e | f | g | h |
|---|---|---|---|---|---|---|---|---|
| R |  |  |  |  |  |  |  |  |

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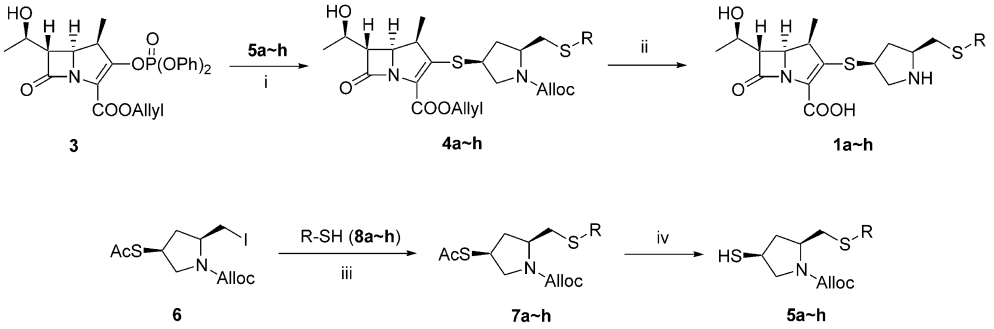


**Scheme 1.** (i) *i*-Pr $_2$EtN, $CH_3CN$, 0 °C, 5 h, 48–72%; (ii) $Pd(PPh_3)_4$, *n*-$Bu_3SnH$, $CH_2Cl_2$, 0 °C, 1 h, 32–48%; (iii) $K_2CO_3$, acetone, 60 °C, 3 h, 78–98%; (iv) 1 N NaOH, MeOH, 0 °C, 20 min, 90–100%.

deprotection of allyl group with $Bu_3SnH$ in the presence of catalytic amount of $Pd(PPh_3)_4$ (5 mol%). The resulting carbapenem derivatives **1a**–**h** were purified by the column chromatography on Diaion HP-20 and lyophilized as free forms. The pyrrolidinethiols **5a**–**h** were prepared by the substitution reaction of common intermediate, iodo compound **6**, with mercaptoheteroaromatic compounds **8a**–**h** and deacetylation according to similar method depicted in literature.[1] The mercaptoheteroaromatic compounds **7a**–**g** were commercially available and **8h** was synthesized by a known procedure.[4]

## Biological Properties

The title new carbapenems **1a**–**h** were evaluated for the antibacterial activity and the stability to porcine DHP-I relative to meropenem and **2** as shown in Table 1.

The heteroaromatic thioether carbapenem derivatives **1a**–**h** exhibited potent antibacterial activity against Gram-positive and Gram-negative organisms and good DHP-I stability. In particular, they showed improved antibacterial activity against Gram-positive bacteria compared to meropenem. However, their antipseudomonal activity was inferior to those of meropenem and **2**. In the series of N-containing six-membered heteroaromatic compounds **1a**–**e**, pyridine and pyrimidine derivatives were not beneficial to antibacterial activity, although antimicrobial activity against Gram-positive strains was superior to that of meropenem and similar to parent compound **2**. Also, they did not show the difference in activity related to aromatic substituents which were attached to pyridine and pyrimidine. On the other hand, the introduction of five-membered heteroaromatic groups showed better antibacterial activity in comparison with six-membered heteroaromatic compounds. In this class of analogues, sulfur containing heteroaromatic compounds **1g** and **1h** showed more potent antibacterial activity and higher DHP-I stability than triazole derivative **1f**. Thiadiazole derivatives **1g** and **1h** had similar antibacterial spectrum against Gram-positive and Gram-negative organisms, but 1,2,3-thiadiazole derivative **1h**[5] surpassed 1,3,4-thiadiazole compound **1g** in DHP-I stability. Accordingly, **1h** was chosen for further evaluation in view of well-balanced antibacterial activity and DHP-I stability. Table 2 described the pharmacokinetics of **1h** in rat together with those of imipenem, meropenem and **2**.

It showed that **1h** had 10 times longer half-life and 6 times higher AUC value than meropenem. It also displayed 5 times lower value in clearance than

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

| Organism | MIC (μg/mL)[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **1a** | **1b** | **1c** | **1d** | **1e** | **1f** | **1g** | **1h** | **2** | MPM[b] |
| *S. pyogenes* 308A | <0.002 | <0.002 | <0.002 | 0.007 | 0.007 | 0.013 | 0.004 | 0.007 | 0.004 | 0.013 |
| *S. aureus* SG 511 | 0.049 | 0.025 | 0.025 | 0.049 | 0.098 | 0.049 | 0.025 | 0.025 | 0.025 | 0.195 |
| *S. aureus* 285 | 0.049 | 0.049 | 0.049 | 0.098 | 0.098 | 0.098 | 0.025 | 0.049 | 0.049 | 0.195 |
| *S. aureus* 503 | 0.025 | 0.195 | 0.025 | 0.025 | 0.025 | 0.025 | 0.007 | 0.013 | 0.025 | 0.098 |
| *E. coli* 078 | 0.049 | 0.195 | 0.049 | 0.049 | 0.025 | 0.025 | 0.007 | 0.013 | 0.025 | 0.025 |
| *E. coli* 1507E | 0.098 | 0.195 | 0.049 | 0.098 | 0.025 | 0.049 | 0.007 | 0.013 | 0.025 | 0.025 |
| *P. aeruginosa* 9027 | 12.5 | 25 | 3.125 | 25 | 50 | 1.563 | 3.125 | 1.563 | 0.781 | 0.195 |
| *P. aeruginosa* 1771M | 1.563 | 6.25 | 0.391 | 6.25 | 0.781 | 0.195 | 0.195 | 0.195 | 0.195 | 0.049 |
| *S. typhymurium* | 0.098 | 0.195 | 0.098 | 0.098 | 0.049 | 0.098 | 0.025 | 0.025 | 0.025 | 0.049 |
| *K. aerogenes* 1522E | 0.098 | 0.195 | 0.098 | 0.098 | 0.049 | 0.098 | 0.025 | 0.025 | 0.025 | 0.049 |
| *E. cloacae* 1321E | 0.049 | 0.098 | 0.049 | 0.098 | 0.025 | 0.049 | 0.013 | 0.013 | 0.025 | 0.025 |
| DHP-I stability[c] | NT[d] | NT | 0.89 | 1.22 | NT | 0.93 | 1.08 | 1.67 | 0.88 | 1 |

[a]MIC was determined by agar dilution method using Mueller–Hinton.
[b]MPM, meropenem.
[c]Relative $t_{1/2}$ of hydrolysis to meropenem by partially purified porcine renal DHP-I.
[d]NT, not tested.

**Table 2.** Pharmacokinetics of carbapenem **1h** 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) |
| **1h** | 43.13±7.69 | 2212±522 | 10.15±2.42 |
| **2** | 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 |

meropenem. As can be seen from the above data, the introduction of appropriate heteroaromatic thioether group into pyrrolidine could exert a profound influence on antibacterial activity and pharmacokinetics. Among these compounds, sulfur containing heteroaromatic compound **1h** possessed well-balanced antibacterial activity and showed remarkably advanced pharmacokinetics in rat.

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5. **1h**: IR (KBr) 3388, 1754, 1592 $cm^{-1}$; $^1H$ NMR ($D_2O$) δ 8.87 (s, 1H), 4.35–4.27 (m, 2H), 4.14–4.01 (m, 3H), 3.81–3.60 (m, 3H), 3.54–3.38 (m, 3H), 2.96–2.85 (m, 1H, C4′-H), 1.96–1.85 (m, 1H), 1.35 (d, 3H, $J=6.3$ Hz), 1.27 (d, 3H, $J=7.2$ Hz); MS (FAB) $m/z$ 443 $(M+1)^+$ 415, 383, 329, 307, 289, 246, 200, 154, 136, 107, 89, 68, 39, 23; HR-MS calcd for $C_{17}H_{23}N_4O_4S_3$ $(M+1)^+$ 443.0881, found 443.0878.