Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry Letters 13 (2003) 2607–2610

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

# Synthesis and Activity of Novel Benzoxazole Derivatives of Mannopeptimycin Glycopeptide Antibiotics

Phaik-Eng Sum,[a,*] David How,[a] Nancy Torres,[a] Howard Newman,[a] Peter J. Petersen[b] and Tarek S. Mansour[a]

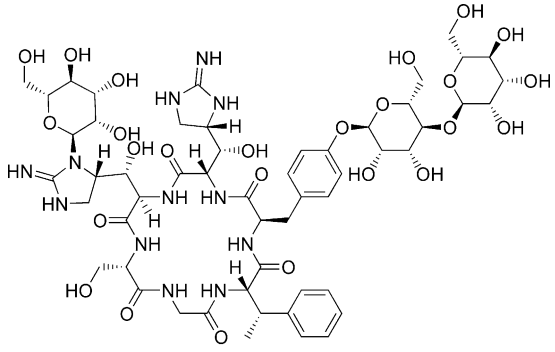
[a]*Chemical Sciences, Wyeth Research, Pearl River, NY 10965, USA*
[b]*Infectious Disease Research, Wyeth Research, Pearl River, NY 10965, USA*

Received 2 January 2003; accepted 24 March 2003

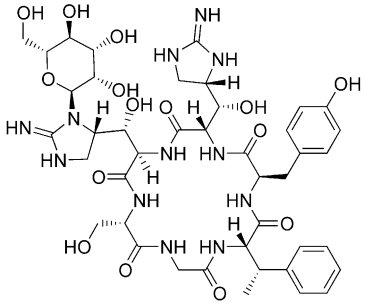
**Abstract**—A series of benzoxazole derivatives of the mannopeptimycin glycopeptide antibiotics was synthesized via a novel benzoxazole formation reaction by treating aminophenol of mannopeptimycin-β with an aldehyde and DDQ in DMF. Some of these derivatives (e.g., **5b**, **5d**, **5m**, and **7b**) showed good activity against Gram-(+) bacteria when compared to the parent compound mannopeptimycin-β.


The need for new antibacterial agents to combat resistance problems has rekindled our interest in anti-infective research, especially in the natural product area. Previously, we reported the synthesis and activity of a series of ether derivatives of the mannopeptimycin glycopeptide antibiotics.[1] These semi-synthetic ether derivatives helped clarify the structure–activity relationship of the substitutions at various positions of the terminal mannosyl disaccharide of the natural product, mannopeptimycin-α (**1**).[2–4] Mannopeptimycin-β (**2**) was one of the components isolated from the mannopeptimycin complex; it could also be obtained from selective removal of the mannosyl disaccharide (Fig. 1).[3b] In continuation of the research to identify compounds with improved biological activity and pharmacokinetic properties, the synthesis of a series of benzoxazole derivatives of mannopeptimycin-β (**2**) was investigated. Our strategy was to introduce an amino group α to the tyrosine hydroxyl group, then investigate the formation of an oxazole ring using this aminophenol. Herein, we describe the synthesis and antibacterial activities of 2-substituted benzoxazole mannopeptimycins.

Introduction of the key amino functionality was accomplished as shown in Scheme 1. Treatment of mannopeptimycin-β with $KNO_3$ in TFA gave nitro compound **3**, catalytic hydrogenation of **3** gave the desired aminophenol **4** in good yield. Though numerous methods to generate benzoxazoles have been reported in the literature, most involved reaction conditions that were not suitable for our application.[5] Therefore we developed milder and more convenient conditions for



**1** Mannopeptimycin-α



**2** Mannopeptimycin-β

**Figure 1.** Structures of mannopeptimycin-α and mannopeptimycin-β.

*Corresponding author. Tel.: +1-845-602-3431; fax: +1-845-602-5561; e-mail: sump@wyeth.com

0960-894X/03/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0960-894X(03)00512-2

benzoxazole formation, which involved treatment of one equivalent of aminophenol **4** with excess aldehyde and DDQ in DMF (Scheme 1).[6]

Aldehydes with different lipophilicity and steric bulk were selected for the preparation of benzoxazoles **5a**–**p** (Fig. 2). Compound **5p** with its sugar moiety was designed to mimic the natural product. We found that aldehydes with electron withdrawing groups such as **5a**, **5c**, **5d**, and electron donating groups such as **5b**, **5e**, **5h**, and **5m** readily underwent this transformation. Reaction with alkenyl aldehyde such as **5j** also proceeded smoothly with good yields. The reactions were monitored by ES/MS and most were completed in 1–3 h rt. All final products reported herein were purified by reverse-phase HPLC (acetonitrile–water–0.02% trifluoroacetic acid).

Reaction of **4** with 1,1-thiocarbonyldiimidazole gave compound **6** which served as a key intermediate for subsequent alkylation reactions. Thus, alkylation with bromides such as **7a**, **7b**, **7c**, and **7d** produced regioselectively a series of novel 2-thiosubstituted benzoxazoles **7a**–**d** (Scheme 2).[7]

Reaction of **4** with 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl isothiocyanate gave thiourea **8** which underwent

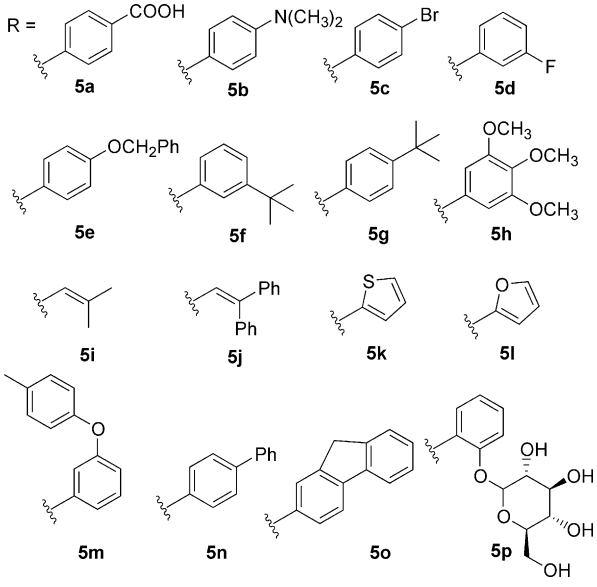
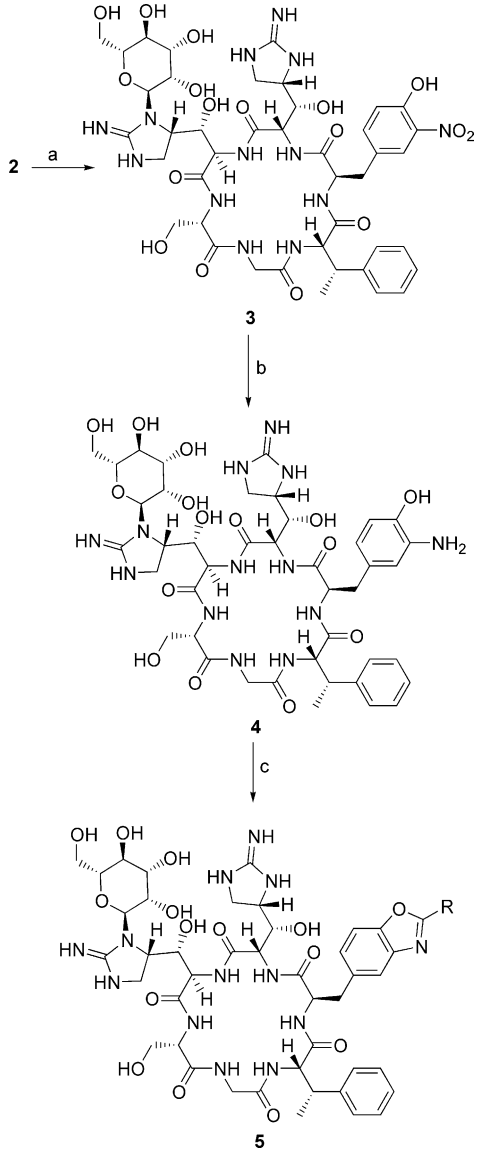
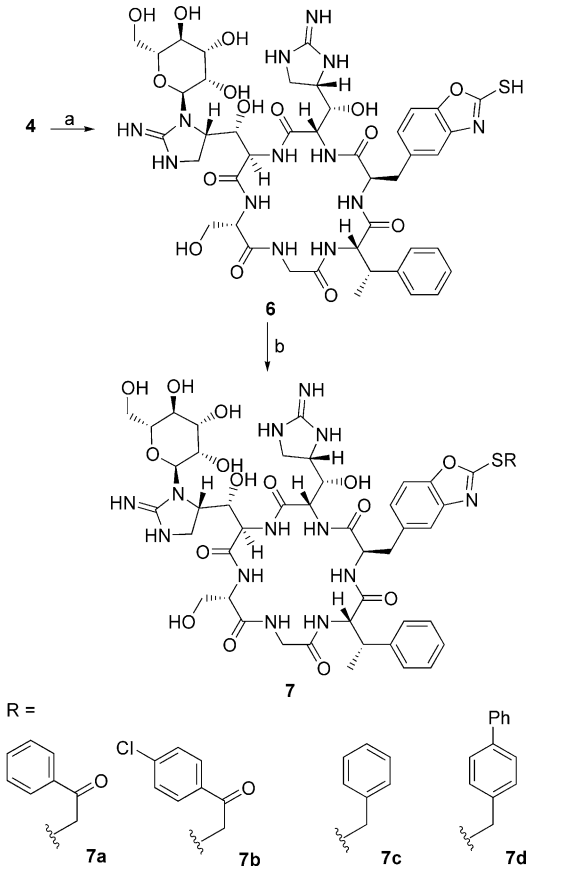


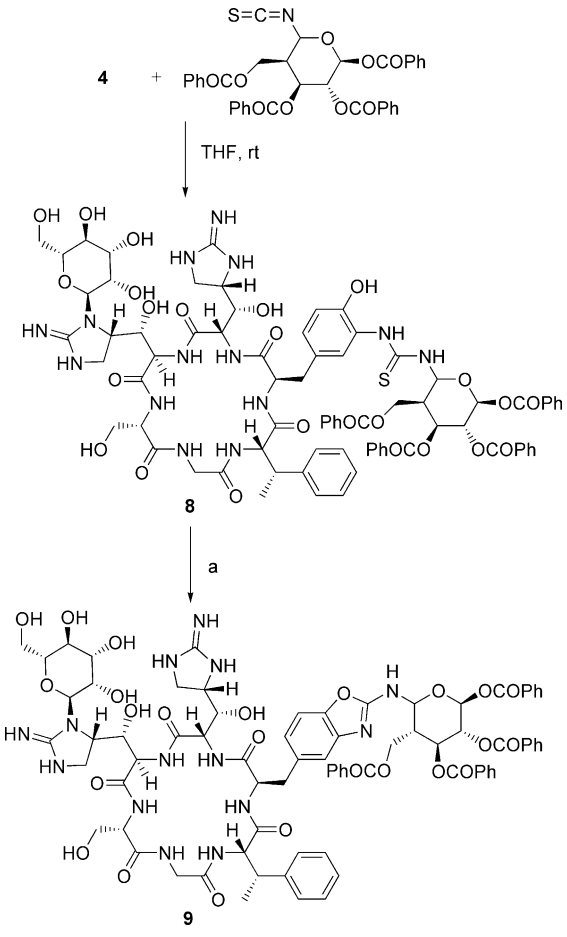

**Figure 2.** Benzoxazole derivatives synthesized.



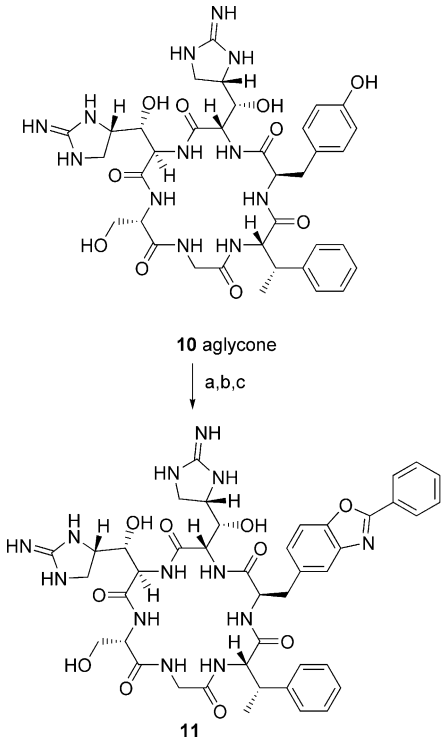

**Scheme 1.** (a) $KNO_3$/TFA, rt, 2 h; (b) 10% Pd/C, $H_2$, MeOH; (c) RCHO, DDQ/DMF.




**Scheme 2.** (a) 1,1-Thiocarbonyldiimidazole/DMPU, rt, 2 h; (b) Diisopropylethylamine, RBr.




**Scheme 3.** (a) $HgCl_2$/MeOH, rt.




**Scheme 4.** Benzoxazole derivative of aglycone: (a) $KNO_3$/TFA; (b) 10% Pd/C, $H_2$, MeOH; (c) PhCHO, DDQ, DMF.

cyclization upon treatment with mercury (II) chloride ($HgCl_2$) to give benzoxazole **9** (Scheme 3).[8]

To determine the effect of the guanidine sugar moiety of mannopeptimycin-β on the biological activity, benzoxazole derivative **11** was prepared from the aglycone **10**[3b] via a similar route previously described for the preparation of **5** (Scheme 4).

The in vitro testing results of the benzoxazole derivatives described above together with vancomycin and piperacillin are summarized in Table 1. Most of the benzoxazole derivatives showed good to moderate activities against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. Many compounds showed better activity than the parent compound mannopeptimycin-β (**2**). Compound **11**, a benzoxazole derivative of aglycone, was much less active than the derivatives of the mannopeptimycin-β series. The most active compound of the thio-alkylated analogues was **7b**, which was significantly more potent than **2**. More extensive in vitro activities (MICs) of selected compounds are shown in Table 2. The benzoxazole derivatives **5b**, **5d**, and **5m** demonstrated moderate to good overall activity and are about three dilutions (MIC) more potent than the parent compound **2**.

The thio-alkylated compound **7b** showed good in vitro activity (MIC) against staphylococcal isolates, including methicillin-resistant *S. aureus* (MIC 1–8 μg/mL) and methicillin-resistant Coagulase-negative *Staphylococci* (MIC 1–4 μg/mL). Against the enterococcal strains,

**Table 1.** In vitro activity of oxazole derivatives[a]

| Compd | Minimum inhibitory concentration (MIC), μg/mL | | |
|---|---|---|---|
| | *S. aureus* | *Streptococcus spp.* | *Enterococcus spp.* |
| **5a** | >128 | 128 | 128 |
| **5b** | 8 | 16–32 | 8–64 |
| **5c** | 8–16 | 4–8 | 8–64 |
| **5d** | 8–16 | 4–16 | 16– |
| **5e** | 8–16 | 8–64 | 4–128 |
| **5f** | 16–32 | 8–32 | 8–64 |
| **5g** | 2–4 | 8–16 | 2–8 |
| **5h** | 8–32 | 8–32 | 8–64 |
| **5i** | 32–64 | 32–128 | 16–128 |
| **5j** | 8–16 | 4–16 | 8–32 |
| **5k** | 8–32 | 16–32 | 16–128 |
| **5l** | 16–64 | 32–64 | 32–128 |
| **5m** | 4–8 | 1–4 | 4–8 |
| **5n** | 4–16 | 16–64 | 4–64 |
| **5o** | 8–16 | 4–32 | 4–16 |
| **5p** | >128 | 128→128 | 128→128 |
| **7a** | 8–16 | 8–32 | 4–64 |
| **7b** | 2–8 | 2–8 | 2–16 |
| **7c** | 4–16 | 4–16 | 4–32 |
| **7d** | 8–32 | 2–4 | 2–64 |
| **9** | 32–64 | 4–32 | 4–32 |
| **11** | 32–64 | 32–64 | 32–64 |
| **2** | 64–128 | ND | 32–128 |
| **Vanco** | 1–4 | 0.25–0.5 | 05→64 |
| **Piper** | 0.5–128 | ≤0.12–2 | 0.25→128 |

[a]Range of MICs (minimum inhibitory concentration) for *Staph.* (10 strains, including MRSA); *Strep.* Species (5 strains, including PRSP); Enterococcus species (11 strains, including VRE); Vanco (vancomycin); Piper (piperacillin).

**Table 2.** In vitro antibacterial activity of selected benzoxazole derivatives

| Organism; (MIC) μg/mL | Compd | | | | |
|---|---|---|---|---|---|
| | Piper | **5b** | **5d** | **5m** | **7b** |
| *S. aureus* (GC 1131) MRSA | >64 | 8 | 8 | 8 | 4 |
| *S. aureus* (GC 4541) MRSA | >64 | 8 | 16 | 8 | 4 |
| *S. aureus* (GC 4542) MRSA | 64 | 8 | 8 | 8 | 4 |
| *S. aureus* (GC 4543) MSSA | 1 | 8 | 8 | 4 | 2 |
| *S. aureus* (GC 4544) MSSA | 4 | 8 | 8 | 8 | 4 |
| *S. aureus* (GC 4545) MSSA | 8 | 8 | 8 | 4 | 2 |
| *S. aureus* (GC 2216) MSSA | 4 | 8 | 8 | 8 | 8 |
| *Staphylococcus hemolyticus* (GC 4546) MRCNS | >64 | 4 | 4 | 4 | 1 |
| SCN (GC 4547) MRCNS | >64 | 4 | 8 | 8 | 4 |
| SCN (GC 4548) MRCNS | 16 | 4 | 4 | 4 | 2 |
| SCN (GC 4549) MSCNS | 32 | 2 | 16 | 4 | 1 |
| SCN (GC 6257) MSCNS | 4 | 4 | 4 | 2 | 1 |
| SCN (GC 4551) MSCNS | 4 | 8 | 8 | 4 | 4 |
| *Enterococcus faecalis* (GC 4552) VSE | 2 | 64 | 64 | 8 | 2 |
| *E. faecalis* (GC 4553) VSE | >64 | 16 | 16 | 4 | 4 |
| *E. faecalis* (GC 4554) VSE | 1 | 32 | 64 | 8 | 16 |
| *E. faecalis* (GC 2242) VRE | 2 | 32 | 32 | 4 | 16 |
| *E. faecalis* (GC 4555) VSE | 1 | 32 | 64 | 8 | 16 |
| *Enterococcus faecium* (GC 2243) VRE | 64 | 16 | 32 | 8 | 8 |
| *E. faecium* (GC 4556) VSE | 1 | 64 | 64 | 8 | 8 |
| *E. faecium* (GC 4557) VSE | 0.12 | 8 | 8 | 4 | 2 |
| *E. faecium* (GC 4558) VRE | >64 | 16 | 16 | 4 | 4 |
| *Streptococcus pyogenes* (GC 4563) | ≤0.06 | 16 | 4 | 1 | 2 |
| *Streptococcus agalactiae* (GC4564) | 0.12 | 32 | 8 | 4 | 4 |
| *Streptococcus pneumoniae* (GC 4565) PSSP | ≤0.06 | 32 | 16 | 4 | 8 |
| *Bacillus cereus* (GC 4561) assay organism | 1 | 32 | 64 | 8 | 1 |
| *Micrococcus lutea* (GC 4562) | ≤0.06 | 2 | 2 | 1 | 16 |
| *E. faecalis* (GC 2691) VSE | 2 | 32 | 32 | 8 | 16 |
| *E. faecalis* (GC 6189) VRE | 2 | 32 | 32 | 8 | 16 |
| *E. faecalis* (GC 3059) VRE | 2 | 64 | 64 | 8 | 32 |
| *S. pneumoniae* (GC 1894) PRSP | 2 | 32 | 16 | 4 | 8 |
| *S. pneumoniae* (GC 6242) PSSP | ≤0.06 | 32 | 8 | 4 | 8 |
| *S. aureus* (GC 3051) GISA | 64 | 8 | 16 | 4 | 4 |
| *S. aureus* (GC 3066) GISA | 0.5 | 8 | 16 | 4 | 4 |

MRSA (methicillin-resistant *S. aureus*); MSSA (methicillin-susceptible *S. aureus*); MRCNS (methicillin-resistant Coagulase-negative *Staphylococci*); MSCNS (methicillin-susceptible Coagulase-negative *Staphylococci*); VRE (vancomycin-resistant *Enterococci*); PRSP (penicillinresistant *Strep. pneumoniae*); GISA (glycopeptide tntermediate *S. aureus*); Piper (piperacillin).

including vancomycin-resistant isolates, good activity was observed (MICs 2–16 μg/mL). The compound also demonstrated good streptococcal activity (MIC 2–8 μg/mL).

In summary, a series of benzoxazole derivatives of mannopeptimycin-β and its aglycone were synthesized to explore SAR. **5b**, **5d**, **5m**, and **7b** showed improved activity against a number of pathogens when compared to the parent compound **2**. The good activities demonstrated by these derivatives suggested that the mannosyl disaccharide moiety might not be essential for antibacterial activity.

## Acknowledgements

Analytical support provided by analytical group is gratefully acknowledged. We thank Drs. Jerry Skotnicki, Patricia Bradford, Russ Dushin, and Haiyin He for helpful discussion. We also thank Dr. Subas Sakya for exploring early nitration reactions.

## References and Notes

1. Sum, P.-E.; How, D.; Torres, N.; Petersen, P. J.; Lenoy, E.; Weiss, W. J.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1151.
2. De Voe, S. E.; Kunstmann, M. P. U.S. Patent 3,495,004, 1970: *Chem. Abstr.* **1970**, *72*, 131101
3. (a) He, H.; Bernan, V.; Williamson, R. T.; Graziani, E. I.; Shen, B.; Greenstein, M.; Carter, G. T. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, Dec 16–19, 2001; abstract F-1147. (b) He, H.; Williamson, R. T.; Shen, B.; Graziani, E. I.; Yang, H. Y.; Sakya, S. M.; Petersen, P. J.; Carter, G. T. *J. Am. Chem. Soc.* **2002**, *124*, 9729.
4. Petersen, P. J.; Weiss, W. J.; Lenoy, E. B.; He, H.; Testa, R. T.; Bradford, P. A. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, Dec 16–19, 2001; abstract F-1148.
5. (a) Kiselyov, A. S. *Tetrahedron Lett.* **1999**, *40*, 4119. (b) Bougrin, K.; Loupy, A.; Souflaoui, M. *Tetrahedron* **1998**, *54*, 8055.
6. A typical benzoxazole reaction is as follows: To a solution of 2TFA salt of **4** (0.121 g) in DMF was added 3-(4-methylphenoxy)benzaldehyde (0.106 g) and DDQ (0.057 g). The reaction was stirred at rt for 2 h and was triturated with acetonitrile and ether and the solid collected, purified by reverse-phase HPLC to give **5m**. MS (ES), $m/z$ 590 $(M+2H)^{2+}$.
7. Compound **6** was prepared as follows: To a solution of **4** in DMSO was added 1.10 equiv of 1,1-thiocarbonyldiimidazole. The reaction was stirred at rt for 1 h, triturated with diethyl ether and the solid filtered. To a stirred solution of crude compound **6** in DMF was added *N,N*-diisopropylethylamine (2 equiv) and benzyl bromide. The reaction mixture was stirred for 1 h and triturated with diethyl ether and the solid collected. The product was purified by reverse-phase HPLC to give **7c**. MS (ES), $m/z$ 560 $(M+2H)^{2+}$.
8. A suspension of **8** in THF was treated with 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl isothiocyanate (300 mg) and the mixture stirred at rt for several days (followed by ES/MS). The mixture was diluted with diethyl ether and solid collected. The solid then dissolved in MeOH and treated with mercuric chloride (350 mg). The reaction was stirred for 18 h and diluted with diethyl ether and the solid collected. The product was purified by reverse-phase HPLC to give **9**. MS (ES), $m/z$ 795.9 $(M+2H)^{2+}$.