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DEOXYPSEUDOPHRYNAMINOL: A NOVEL ANTIBACTERIAL ALKALOID

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Abstract. Deoxypseudophrynaminol, **1**, is a potent antibacterial agent that inhibits the *in vitro* growth of vancomycin-resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus* with MIC values ≤40 μg/mL.

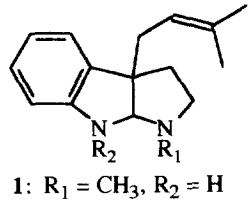
Nosocomial infections caused by vancomycin-resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus* are serious health problems for the hospitalized and immunocompromised patient.[1,2] Thus, the discovery of clinically useful agents against these multidrug-resistant pathogens is of paramount importance.

In this study, we have discovered that deoxypseudophrynaminol, **1**,[3] inhibits the *in vitro* growth of patient-isolated vancomycin-resistant *Enterococcus faecium* (VRE_1), vancomycin-resistant *Enterococcus faecalis* ATCC 51299 (VRE_2), and two patient isolates of methicillin-resistant *Staphylococcus aureus* ($MRSA_1$ and $MRSA_2$) with MIC (minimum inhibitory concentration) values ≤ 40 μg/mL (see Table). For comparison, vancomycin has an MIC of 2 μg/mL vs. MRSA isolates,[4] and teicoplanin has an MIC of 8 μg/mL vs. VRE isolates.[5] In our study, both Gram positive and Gram negative bacteria were tested. However, Gram negative bacteria were only marginally affected by **1**. For example, with *E. coli* ATCC 25922, the MIC value was 160 μg/mL. MIC values were also obtained for 3a, 8-di (3-methyl-2-butenyl)-1-formyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole, **2**.[6] At up to 320 μg/mL, compound **2** had no effect on the growth of both Gram positive and Gram negative bacteria. The only conclusion that may be drawn from this data is that the antibacterial potency of **1** depends on the nature of N-1 and/or N-8 substitution and is not simply a function of having a 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole skeleton with a 3-methyl-2-butenyl group at C-3a.

Table. MIC Values for **1** and **2** (μg/mL)**

Bacteria	1	2
VRE_1	20	---
VRE_2	40	n. i.
$MRSA_1$	40	---
$MRSA_2$	40	n. i.

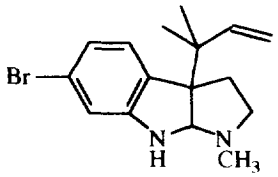
** All MIC values were obtained in duplicate.
n.i. = no inhibition



1: $R_1 = CH_3$, $R_2 = H$

2: $R_1 = CHO$, $R_2 = CH_2CH{=}C(CH_3)_2$

Interestingly, there are two other known hexahydropyrrolo[2,3-b]indole antibiotics. Dihydroflustramine C, **3**, inhibits the growth of the Gram positive soil bacterium *Bacillus subtilis*,[7] and flustramine E , **4**, inhibits the growth of the pathogenic plant fungi *Rhizotonia solani* and *Botrytis cinerea*.[8] Also, based on our work, pseudophrynaminol, **5**,[9] is a strong candidate for an antibacterial agent.



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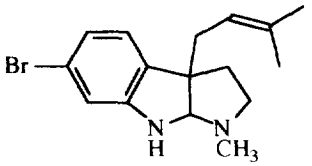

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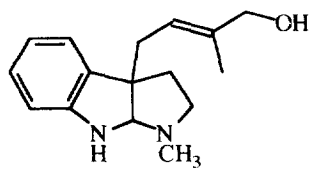

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Antibiotic assay: Bacteria were grown on 5% sheep blood agar plates for 24 hours. The colonies were inoculated into 0.45% saline solution (O.D.: 0.5 MacFarland measured by Vitek colorimeter). The bacterial suspension was further diluted 1:100 to achieve a working suspension of 10^6 colony-forming units (CFU)/mL. Antibiotic stock solutions in 2% ethanolic, sterile Mueller-Hinton broth were serially diluted in 96-well microtiter plates (Corning) using sterile broth diluent. 150 μL of bacteria were added to each well after serial dilution of antibiotic (total volume: 250 μL). Bacteria in wells were incubated for 48 hours. Then the microtiter dilution trays were read with a MicroScan microtiter reader.

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6. Synthesis of **2**: N_b-formyltryptamine (3.4 mmol), triethylamine (3.4 mmol), and 4-bromo-2-methyl-2-butene (3.4 mmol) were combined in 10 mL ethyl acetate and reacted for 1.5 hours. The reaction mixture was quenched with 2 M HCl. Then the reaction mixture was extracted with 3x10 mL ethyl acetate. The combined extracts were dried over magnesium sulfate and filtered. Solvent was removed *in vacuo*. The residue was purified by flash chromatography (eluent: 10:1 ethyl acetate/triethylamine). Yield: 3.7% (optimized). ^{1}H-NMR ($CDCl_3$, TMS reference): δ1.52-1.80 (m, 12H), 1.96-2.16 (m, 2H), 2.36-2.50 (t, 2H), 2.80-3.00 (m, 1H), 3.10-3.25 (m, 1H), 3.55-4.20 (m, 2H), 4.90-5.20 (m+s, 3H), 6.30-6.44 (t, 1H), 6.60-6.76 (m, 1H), 6.98-7.16 (m, 2H), 8.2 (s, 1H). EI-MS: 324 (M+.), 255.

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