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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 5-THIOABBEYMYCIN: LIMITATIONS OF THE IMINOTHIOETHER APPROACH TO CARBINOLAMINE-CONTAINING PYRROLOBENZODIAZEPINES

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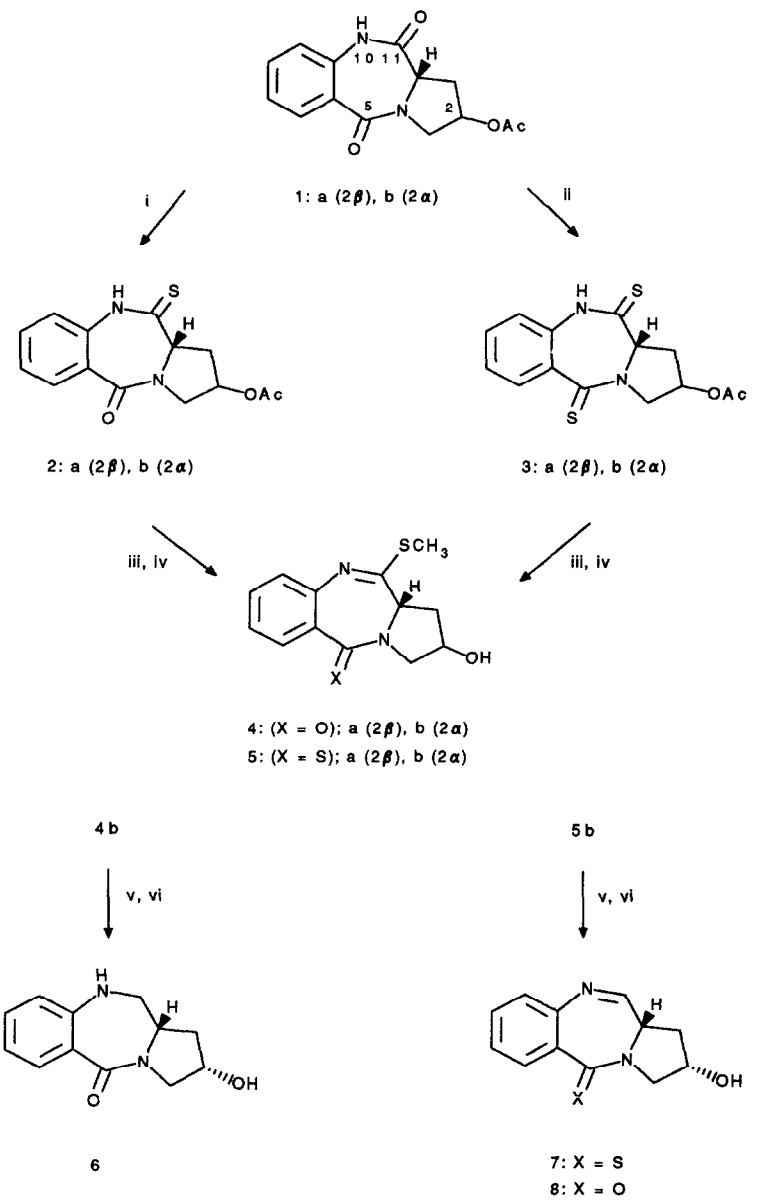
Abstract: The synthesis of 5-thioabbeymycin (**7**) by a modified iminothioether route is described. This analog of abbeymycin exhibits potent antimicrobial activity. Attempts to synthesize the natural product abbeymycin (**8**) by reduction of 2(S)-hydroxy-11-S-methylpyrrolobenzodiazepine **4b** with Al-Hg amalgam gave the over-reduction product (**6**) as the only isolable product.

The carbinolamine-containing pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) are a group of naturally-occurring antitumour antibiotics with DNA-binding properties. Well known members of the group include anthramycin, tomaymycin, sibiromycin, and the neothramycins A and B[1]. A key feature of these molecules with respect to their mechanism of action is the N10-C11 carbinolamine (or imine equivalent) that generates an electrophilic centre at C11. Nucleophilic attack by the N2 of a guanine base forms a covalent adduct in the minor groove of DNA[1]. Furthermore, they bind to DNA sequence-selectively[2] and have potential not only as antitumour agents but as gene regulators and probes of DNA structure[3].

A number of synthetic approaches have been reported for the preparation of carbinolamine-containing PBDs[1a,4]. One of the methods, introduced by Kaneko and co-workers[5,6a,6b], involves regioselective conversion of 5,11-diones of type **1** to 5-one-11-thiones of type **2**, followed by conversion to the corresponding iminothioethers (**4**). Reduction with Al-Hg amalgam then gives the carbinolamines or their imine equivalents (i.e. **8**). There is one other report of the successful use of this method[6c]. While using this approach, we observed that the reaction of **1a** and **1b** with Lawesson's reagent in benzene gave the 5,11-dithiones **3a** and **3b** (17%, 14%) in addition to the anticipated 5-one-11-thiones **2a** and **2b** (65%, 68%). Furthermore, we found that regioselectivity between the C5 and C11 carbonyls could be further reduced by raising the temperature, and that



i. (p-CH_3O-C_6H_4-$PS_2)_2$/C_6H_6/80°C/1h; ii. (p-CH_3O-C_6H_4-$PS_2)_2$/toluene/110°C/3h; iii. CH_3I/K_2CO_3/THF/15h; iv. K_2CO_3/CH_3OH/0°C; v. Al-Hg/aq.THF/0-5°C/20h; vi. $HgCl_2$/CH_3OH/0°C

3a and **3b** could be obtained in quantitative yield[7] if toluene was used as solvent instead of benzene with one molar equivalent of Lawesson's reagent. This provided the opportunity to synthesize a new class of C5-sulfone-containing PBDs with DNA-binding potential. We report here preparation of the novel abbeymycin analog (2S,11aS)-2-hydroxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine-5-thione (**7**) and describe its antimicrobial activity.

The starting PBD-11-thiones (**2**) and 5,11-dithiones[7] (**3**) were prepared by reaction of the corresponding 5,11-diones[4b,8] (**1**) with Lawesson's reagent. Methylation and deacetylation of **2a,b** and **3a,b** gave the corresponding 2-hydroxy-11-S-methyl PBDs (**4a,b**[9] and **5a**[9],**b**[9,10]) in good yield. In an attempt to synthesize abbeymycin[11], **4b** was reduced with Al-Hg amalgam followed by treatment with $HgCl_2$ in methanol but gave the over-reduced compound **6**[12] (25% yield) as the only isolable product. Reduction of **5b** with Al-Hg amalgam followed by treatment with $HgCl_2$ in methanol under similar conditions gave a residue which was subjected to column chromatography (silica gel, CH_2Cl_2-EtOAc-CH_3OH, 10:9:1) to afford the 5-thio analog of abbeymycin **7**[13] (28% yield) as the only isolable product. This compound exhibited potent antimicrobial activity[14] against *Staphylococcus aureus* (MIC 2-4 μg cm^{-3}, MBC 2-8 μg cm^{-3}) and *Pseudomonas aeruginosa* (MIC 2-4 μg cm^{-3}, MBC 2-4 μg cm^{-3}).

In conclusion, the modified iminothioether methodology described here has allowed us to produce the first example of a new class of carbinolamine-containing 5-thio PBDs with interesting antibacterial activity. In our hands, the iminothioether approach was not successful for the synthesis of abbeymycin, leading mainly to the over-reduction product (**6**). In view of recent interest in DNA-interactive ligands as potential gene regulators, 5-thio analogs of this type are attractive synthetic targets due to a likely improvement in lipophilicity compared to existing PBD antitumour antibiotics.

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9. **4a**, **4b**, **5a** and **5b** were obtained in 72%, 78%, 68% and 65% yields, respectively. Satisfactory spectral data were obtained for all compounds.

10. **5b**: R (KBr): 3450, 1675, 1600, 1480, 1420 cm^{-1}; ^{1}H-NMR (270MHz, $CDCl_3$ + DMSO-d_6, δ): 2.23 (m, 4H), 2.95 (m, 1H), 3.91-4.38 (m, 3H), 4.76 (br, 1H), 7.08-7.45 (m, 3H), 8.27 (d, 1H, J=7.9Hz); ^{13}C-NMR (δ): 20.4, 34.9, 55.0, 57.9, 60.9, 124.3, 126.0, 131.6, 132.9, 133.5, 141.7, 159.6, 193.2; MS (EI): 278 ($M^{+\cdot}$, 91).

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12. **6**: m.p. 242-243°C; ^{1}H-NMR (270MHz, DMSO-d_6, δ): 1.69 (dt, 1H, J=13.2, 4.7Hz), 2.36 (m, 1H), 3.3-3.5 (m, 3H), 3.61 (dd, 1H, J=12.4, 5.1Hz), 3.74 (br, 1H), 4.21 (br, 1H), 5.07 (d, 1H, J=3.3Hz), 6.53 (m, 2H), 6.65 (d, 1H, J=3.3Hz), 7.31 (dd, 1H, J=7.0, 1.3Hz), 7.71 (d, 1H, J=7.0Hz); ^{13}C-NMR (δ): 38.6, 52.5, 55.5, 55.7, 66.5, 114.9, 117.7, 131.3, 132.4, 146.5, 165.9; MS (EI): 218 ($M^{+\cdot}$, 61); HRMS (EI): observed 218.1064, calcd for $C_{12}H_{14}O_2N_2$ 218.1073.

13. **7**: ^{1}H-NMR (270MHz, DMSO-d_6, δ): 2.17 (ddd, 1H, J=13.7, 1.6Hz), 2.50 (m, 1H), 3.32 (br d, 1H, J=12.5Hz with fine coupling), 3.75 (dd, 1H, J=12.5, 5.3Hz), 4.14 (dd, 1H, J=9.0, 1.6Hz), 4.29 (br, 1H), 4.87 (d, 1H, J=3.8Hz), 7.13-7.55 (m, 4H), 7.80 (dd, 1H, J=7.7, 1.6Hz); ^{13}C-NMR (δ): 37.8, 60.9, 61.1, 62.6, 121.2, 123.5, 126.3, 129.5, 131.7, 142.3, 158.6, 190.9; MS (EI): 232 ($M^{+\cdot}$, 76); HRMS (EI): observed 232.0707, calcd for $C_{12}H_{12}O_2S$ 232.0720.

14. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were determined by nutrient broth dilution and by subculture after 48h onto nutrient agar, respectively.