SYNTHETIC STUDIES ON AN ANTITUMOR ANTIBIOTIC BLEOMYCIN. A SYNTHETIC ANALOGUE EQUIVALENT TO BLEOMYCIN IN ACTIVATING MOLECULAR OXYGEN

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Bleomycin(BLM) is an antitumor antibiotic clinically used in the treatment of squamous cell carcinoma and malignant lymphoma. In addition to its medicinal importance, BLM has attracted a great deal of structural and synthetic studies because of the unique structure and interesting biological activity. The mechanism by which the drug exhibits antitumor activity is currently under active investigation, and two important capabilities of BLM are considered essential. BLM is capable of producing strand breaks in DNA and binding Fe(II) to yield an oxygen-sensitive complex, BLM-Fe(II). The synthetic approach has been considered to provide the most reliable evidence for the controversial transition-metal binding sites of BLM and now extended to the synthesis of the analogues of the pyrimidine moiety of BLM. The key features of the present approach include (1) simplification of the pyrimidine nucleus of BLM to 4-substituted pyridine nucleus (PYML), (2) use of a simplified side chain, (3) use of β-t-butyloxyhistidine for sugar-substituted β-hydroxyhistidine of BLM and (4) the assembly of such fragments to provide simplified analogues possessing different environmental factors. Thus, PYML-6-Fe(II) complex has been found to be almost equivalent to natural BLM-Fe(II) complex in activating molecular oxygen. The present study is considered to be the essential step for the synthesis of man-designed bleomycins.