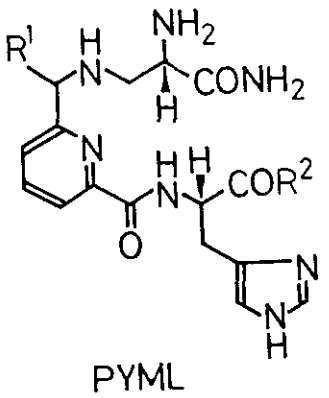
A SYNTHETIC APPROACH TO THE MECHANISM OF DNA-CLEAVAGE BY BLEOMYCIN-Fe(II)-O_2 COMPLEX

M. Otsuka[a], A. Kittaka[a], Y. Sugano[a], S. Kobayashi[a], Y. Sugiura[b], T. Takita[c], H. Umezawa[c] and M. Ohno[a]

a) Faculty of Pharmaceutical Sciences, University of Tokyo, Bunkyo-ku, Tokyo 113, Japan b) Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto 606, Japan c) Institute of Microbial Chemistry, Kamiosaki, Shinagawa-ku, Tokyo 141, Japan

The base-sequence specific DNA-cleavage by an antitumor antibiotic bleomycin (BLM) is considered to be due to (i) selective DNA-binding by the bithiazole-terminal amine portion and (ii) metal-chelation and oxygen-activation by the pyrimidine moiety. In the present study, the molecular mechanism of the DNA-cleavage by BLM was investigated using synthetic homologues and it was demonstrated that (i) molecular oxygen was activated by the ferrous complex of PYML, a model corresponding to the controversial metal binding site, (ii) certain substrates were oxygenated by the PYML-iron complex in the presence of relevant oxygen donor, and (iii) DNA was cleaved by a combination of PYML and a DNA-interacting site consisting of 1-methylpyrrole systems. Based on these results, the role of each functional group of BLM is to be discussed in relation to effective oxygen activation leading to DNA-cleavage.



PYML