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Three-dimensional structure of moenomycin A--a potent inhibitor of penicillin-binding protein 1b

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The first three-dimensional structure of moenomycin A in aqueous solution based on NMR-derived distance constraints and molecular dynamics simulations is presented. The antibiotic moenomycin A was obtained from the FlavomycinR complex by ultrafiltration, chromatography on a DEAE-cellulose ion exchanger and reverse-phase chromatography in 98% purity. In contrast to the previously reported behaviour, the compound gave rise to well-resolved NMR spectra in standard solvents. Using several two-dimensional experiments, a complete assignment of proton and carbon chemical shifts was achieved in (CD3)2SO, CD3OD and H2O/D2O (9:1, pH 7.3). A total of 175 interproton distances were determined from 600-MHz rotating-frame NOE (ROE) spectra and were used as restraints in molecular dynamics calculations. These restraints included 84 ROEs between protons of the moenocinol part leading to a very well-defined structure of the lipid part of the molecule. The relative orientation of the subunits was determined by 66 ROEs among different sugar rings and between the sugar rings and moenocinol. As a result of the molecular dynamics calculation, rings D, E, and F as well as the moenocinol part are very well-defined (average rms deviation over all heavy atoms 0.48 Å) whereas rings A, B and C display a higher degree of conformational flexibility which might be an artefact due to the lower number of ROEs in this part of the molecule. A three-dimensional pharmacophore hypothesis comprising functional groups of rings E and F and the carboxyl group of glyceric acid is presented on the basis of the degradation and derivatization studies of Welzel and coworkers [Welzel, P., Kunisch, F., Kruggel, F., Stein, H., Scherkenbeck, J., Hiltmann, A., Duddeck, H., Muller, D., Maggio, J. E., Fehlhaber, H.-W., Seibert, G., van Heijenoort, Y. & van Heijenoort, J. (1987) Moenomycin A: Minimum structural requirements for biological activity, Tetrahedron 43, 585-598; Welzel, P. (1993) Transglycosylase inhibition, in Antibiotics and antiviral compounds--Chemical synthesis and modifications (Krohn, K., Kirst, H. A. & Maag, H., eds) pp. 373-378, VCH Weinheim].

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