N-GLYCOSYL DERIVATIVES OF POLYENE MACROLIDE ANTIBIOTICS

Sir:

The polyene macrolides are known as potent antifungal agents. However their use in therapy is limited by considerable toxicity and very poor water solubility. Many efforts had been taken to obvert these undesirable properties[1~5]. We report now a new group of derivatives of polyene macrolides exhibiting improved solubility in water and organic solvents and retaining the biological activity of parent compounds.

These derivatives are prepared in the reaction of an antibiotic, containing a free aliphatic amino group, with a carbohydrate or its appropriate derivative. Optimal conditions of the reaction are the following: dimethyl formamide as solvent, temperature range 35~40°C and 0.5 molar excess of carbohydrate. The course of the reaction can be followed by thin-layer chromatography on silica gel with the solvent system, ethyl acetate - acetic acid - water (4 : 1 : 1, v/v). The reaction is completed within 12~40 hours, depending on the polyene macrolide and carbohydrate used. The products are isolated by precipitation and washing with ethyl ether, followed by drying under vacuum. The yields are almost quantitative. The derivatives can be purified by counter-current distribution (chloroform - methanol - water, 2 : 2 : 1, v/v) or butanol - ethyl acetate - methanol - water (20 : 10 : 5 : 35, v/v) or by partition chromatography on silica gel or Sephadex LH-20 (chloroform - methanol - water, 20 : 10 : 1, v/v).

Derivatives of polyene macrolides representing major structural groups (pimaricin, nystatin, amphotericin B, mycoheptin, candicidin, levorin and trichomycin) with various carbohydrates (such as glucose, mannose, fructose, ribose, maltose and glucuronic acid) were synthesised and characterised. In an exampler synthesis, 1 g of amphotericin B ($E^{1\%}_{1cm}$ 1480 at 382 nm) and 0.3 g of glucose were dispersed in 15 ml of DMF and left for 16 hours at 37°C. The product was precipitated with 300 ml of ethyl ether, centrifuged, washed 3 times with ether and dried in vacuum to obtain 1.28 g of crude derivative ($E^{1\%}_{1cm}$ 1120 at 382 nm). Crystallization from methanol-butanol mixture, followed by washing with acetone yielded 0.65 g of derivative exhibiting $E^{1\%}_{1cm}$ 1350 at 382 nm. The minimum inhibitory concentration (MIC) against *Saccharomyces cerevisiae* determined in liquid SABOURAUD medium was 0.1 mcg/ml (MIC for parent amphotericin B, 0.08 mcg/ml).

In the ultraviolet spectrum of the derivative the positions of the absorption maxima and their relative intensities are identical with those of the parent antibiotic. The decrease of the $E^{1\%}_{1cm}$ values is in accordance with the increase of the molecular weight.

In the reaction of amphotericin B with glucose the substitution occurred on the amino group of mycosamine moiety. The derivative treated with 1 % hydrogen chloride in methylene chloride afforded N-(1-deoxyfructose-1-yl)-mycosamine. The structure of this compound follows from the mass spectral data of its peracetylated dimethoxime.

The N-glycosyl derivatives of polyene macrolides containing a free carboxyl group form salts at pH values close to neutrality with inorganic and organic bases. The salts are readily soluble in water. The degree of their dispersion in aqueous solutions can be estimated by comparing the electronic absorption spectra measured in water and in methanol[6].

The antifungal activities of N-glycosyl derivatives are similar to those of the parent polyene macrolides.[7] Simultaneously they exhibit lower haemolytic activity, lower toxicity and are effective in experimental candidiasis in mice when administered intraperitoneally.[7,8]

The encouraging biological properties of these compounds, along with their water solubility indicate that N-glycosyl derivatives of polyene macrolides are interesting novel antifungal chemotherapeutic agents. The simplicity of their preparation is an additional positive factor.

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