THE SYNTHESIS OF AMIDES OF POLYENE MACROLIDE ANTIBIOTICS

Sir:

Polyene macrolide antibiotics are commonly applied in therapy of fungal infections. A number of derivatives of these antibiotics exhibiting improved physico-chemical and biological properties have been described[1~6]. However the further development of new antifungal agents is still desired.

In the present paper we report the synthesis and properties of amides of polyene macrolides. These compounds were obtained in the reaction of amines with antibiotics containing carboxyl groups activated under the treatment with diphenyl phosphorazidate[7] and triethylamine or N,N'-dicyclohexylcarbodiimide and 1-hydroxy-1H-benzotriazole mixtures. The reaction was carried out in N,N-dimethylformamide or N,N-dimethylacetamide, at room temperature, using an excess of the reagents. The course of the reaction was followed by means of thin-layer chromatography on silica gel with the solvent system: chloroform - methanol - water in volume proportions depending on the antibiotic and amine applied.

Derivatives of polyene antibiotics representing different structural groups (pimaricin, polyfungin, amphotericin B and aureofacin) were synthesized and characterized. In the ultraviolet-visible spectra of the amides of polyene macrolides the position of the absorption maxima and their relative intensities are identical with those of the parent antibiotics. The presence of the amide bonds were confirmed by their IR spectra. Absorption maxima of the amide carbonyl ranged from 1600 cm^{-1} to 1675 cm^{-1}. The molecular weights of the synthesized derivatives were measured by means of field desorption mass spectrometry.

In an exampler synthesis, 665 mg of pimaricin ($E^{1\%}_{1cm}$ = 1,000 at 304 nm) was suspended in 20 ml of N,N-dimethylacetamide and 1 ml of butylamine, 2.15 ml of diphenyl phosphorazidate and 1.4 ml of triethylamine were added with stirring and the mixture was kept at room temperature for 4 hours in darkness. The product

Table 1. The antifungal and haemolytic activities of the amides of polyene macrolide antibiotics.

	Compound	IC_{50} (mcg/ml)	EH_{50} (mcg/ml)
Amphotericin B	Amphotericin B	0.03	1.35
	Amphotericin B 2-hydroxyethyl amide	0.034	3.16
	Amphotericin B 3-carbomethoxypropyl amide	0.071	7.22
	Amphotericin B cyclohexyl amide	0.085	5.48
	Amphotericin B *n*-decyl amide	1.12	4.89
Aureofacin*	Aureofacin	0.005	0.5
	Aureofacin *n*-butyl amide	0.01	2
Pimaricin	Pimaricin	0.8	40
	Pimaricin *n*-butyl amide	1.78	80
	Pimaricin benzyl amide	0.71	—
	Pimaricin morpholine amide	3.16	—
Polyfungin	Polyfungin	0.08	20
	Polyfungin *n*-butyl amide	0.08	120
	Polyfungin *n*-octyl amide	0.5	15
	Polyfungin 3-(N,N-dimethylamine)-propyl amide	0.13	180
	Polyfungin 3-(N-isopropylamine)-propyl amide	0.6	54

IC_{50} : the concentration of compound tested which inhibited by 50% the growth of *Saccharomyces cerevisiae* in SABOURAUD liquid medium as determined spectrophotometrically (λ=660 nm) after 24-hour incubation at 28°C.

EH_{50}: the concentration of compound tested causing 50% haemolysis of human erythrocytes under standard conditions.

*: isolated and characterized as derivatives of unresolved antibiotic complexes.

was precipitated with ethyl ether, centrifuged and dissolved in water-saturated *n*-butanol. The butanol layer was washed twice with water and concentrated under reduced pressure. Precipitation with ethyl ether followed by washing with ether and hexane and drying in vacuum yielded 520 mg of crude derivative ($E^{1\%}_{1cm}=800$ at 304 nm). The derivative was purified by partition chromatography on silica gel using solvent system: chloroform - methanol - water (50: 10: 1, v/v/v) affording 450 mg of pimaricin *n*-butylamide. The derivative exhibited electronic absorption maxima at: $\lambda=290$, 304 ($E^{1\%}_{1cm}=950$) and 318 nm, oscillation band at $\nu=1640$ cm^{-1} (–CONH–) and lack of 1590 cm^{-1} ($-COO^-$). The following ions in field desorption mass spectra were found: $m/e=743$ (M+Na, 27%), 721 (M+H, 100%), 703 ($M+H-H_2O$, 67%), 685 ($M+H-2\times H_2O$, 34%) and 667 ($M+H-3\times H_2O$, 25%).

The compounds obtained form with organic and inorganic acids salts which are soluble in water.

The antifungal and haemolytic activities of these derivatives are shown in Table 1.

The properties of the amides of polyene macrolides described above indicate them as a new group of potential therapeutical agents.

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