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Biological studies of unsaturated aliphatic-heterocyclic polyamides

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Two polyamides were synthesized by polycondensation using modified Higashi's method of phosphorylation from maleic and fumaric acid with 2,6-diaminopyridine. They were characterized by inherent viscosities and spectral studies like IR, UV-Visible spectra. Antimicrobial studies were studied in detail for both the polyamides and the results compared to study the effect of *cis-trans* isomerism.

Keywords: Cytotoxicity, cell death, cell viability, IC_{50}.

Introduction

Natural as well as synthetic five member heterocyclic compounds are biologically important[1,2]. In particular pyrrole derivatives are important in pharmacological activity such as cytotoxicity, antiviral, *in vitro* cytotoxic activity against a solid tumor models, hyperlipidemias, antibiotic, anticancer and antimicrobial activity. 1,4-Dihydropyridine derivatives have important biological activity such as anti-inflammatory agent, anti-hypoxic and anti-ischemic activities and 1,4-dihydropyri-dine based calcium channel modulator of the nefidipine type, antimicrobial and anti-brest cancer activity. These characteristics served as the main rationales for the cytotoxic studies of our unsaturated polyamides.

Experimental

The polymer was prepared by modified phosphorylation method employing Higashi's conditions. A solution of NMP (65 ml), pyridine (10 ml), LiCl (l g) and $CaCl_2$ (3 g) was added to a mixture of 2,6-diaminopyridine (0.005 ml), diacid maleic acid or fumaric acid (0.005 ml) and triphenyl phosphite (0.01 mol). Mixture was stirred for 4 h at 110°C until a viscous solution was obtained[3,4]. The resulting mixture was poured into hot aqueous methanol. The precipitated polymer was filtered and washed with dil. HCl, aqueous solution of Na_2CO_3, water and methanol. The polymer (PY-MA or PY-FU) obtained was dried in vacuum at 100°C over P_2O_5 for 24 h.

Antibacterial activity assay was performed by agar disc diffusion method. Antifungal extracts was determined by disc diffusion method on Sabouraud Dextrose Agar (SDA) medium. For anticancer activity assay MCF-7 cell line and VERO cell line was obtained from National Centre for Cell Sciences Pune (NCCS).

Results and discussion

The unsaturated polyamides were characterized by viscosity measurements, UV spectroscopy and IR studies and the results are published by the author in the previous papers.

The antibacterial activity was screened against *Staphylococcus aureus*, *Bacillus subtilis* (Gram-positive bacteria) and *Escherichia coli* (Gram-negative bacteria), *Pseudomonas aeroginosa*, *Aeromonas spp.,* on nutrient agar plates at 37°C for 24 h using amphotericin as reference drug.

In the present study it was observed that both the polyamides were generally active against Gram-negative bacteria like *E. coli*. Both the polyamides exhibited equipotent antibacterial activity against *E. coli* when compared with standard amphotericin. Of the three microorganism *E. coli* was found to be the bacterial most influenced by polyamide where as *Bacillus spp.*, *Salmonella spp.* and *Pseudomonas aeroginosa* were the most resistant bacterium.

Anti-fungal activity:

In the present study it was observed that both the polyamides showed moderate antifungal activity against *Candida albicans* and *Aspergillus niger* as evident from zone of inhibition values. The polyamides PY-FU showed equipotent antifungal activity against *Trichoderma viride* when compared

to standard Amphotericin.

On the MCF-7 cell line different concentration of the compound were chosen for determining the cytotoxicity of the polyamides. The concentration tested are 1000 (μg/ml), 500 (μg/ml), 125 (μg/ml), 62.5 (μg/ml), 31.2 (μg/ml), 15.6 (μg/ml) and 7.08 (μg/ml). The absorbance values were measured at 570 nm. The cell survival at different concentration were calculated using the formula.

$$\% \text{ of viability} = \frac{\text{mean OD of durg exposed}}{\text{mean OD of control}} \times 100$$

It was observed that there is a complete loss in morphology in all the cells. It was also observed that there was complete cell death in all the wells that were treated with 1000 (μg/ml) concentration of the test sample. The % of cell death was calculated using the OD values and was found to be 87.50 for PY-MA and 85.72 for PY-FU. Hence, the most effective concentration for both the polymers against MCF-7 cell line was found to be 1000 (μg/ml). Among the two polyamides PY-MA and PY-FU, PY-FU was found to be more potent as evident by low concentration at which 50% of cancer cell death occurred. IC_{50} value for PY-FU was found more efficient for anti-breast cancer activity. Thus % of cell death decreases with decrease in the concentration of the sample.

Cell death was observed by viewing the 24 well plates under a phase contract with microscope. It correlated with the OD observed and it was also found that the cell death was maximum in 1000 (μg/ml).To evaluate the cytotoxic effect of polyamides against African green monkey kidney cell lines (VERO), samples were incubated in different doses (1000 to 7.8 (μg/ml)). After 24 h of incubation cell viability was determined by the MTT assay. Polyamides induced cell toxicity in a concentration dependent manner. PY-MA and PY-FU showed low to moderate activity on VERO cell line as seen by high conc. (1000 mg/ml) at which 50% death occurs.

Conclusions

In the present study it was observed that both the polyamides were generally active against Gram-negative bacteria like *E. coli*. Both the polyamides exhibited equipotent antibacterial activity against *E. coil* when compared with standard amphotericin. It was also observed that both the polyamides showed moderate antifungal activity against *Candida albicans* and *Aspergillus niger* as evident from zone of inhibition values. The polyamide PY-FU showed equipotnent antifungal activity against *Trichoderma viride* when compared to standard amphotericin. The unsaturated polyamide PY-FU showed good anti-breast cancer activity in MCF-7 cell line.

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