7.043

Retinoic acid and its catabolic inhibitor, R75251, in human malignant glioma cells

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Retinoic acid is a natural intracellular retinoid able to induce differentiation in human malignant glioma cell lines. R75251, an initally antifungal imidazole, inhibits retinoic acid metabolism in-vivo, resulting in an increase of both natural or supplemented retinoic acid levels. We tested 13-cis retinoic acid and R75251 in-vitro on highly malignant glioblastoma cell cultures. The two substances seem to act synergistically, demonstrating effects not to be seen with either substance alone. ^{3}H-thymidine incorporation as well as cell size and appearance changed after incubation with RA plus R75251. We discuss these findings in the light of serum level measurements.

7.044

NEW SPIN LABELED NITROSOUREA

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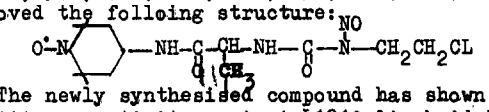
Nitrosoureas are one of the most important classes of antitumor agents but their application is limited because of the comparetively high toxicity.

It is well known that 1)nitroxyl groups present in biologically active compounds reduce the toxicity 2)the spin labeled biologically active compounds are suitable models for elucidation of the mechanism of action.

Bearing in mind the above facts we have synthesised spin labeled nitrosourea derivative of L-alanine(mp 53-55°C).Mass,ESR and IR spectra(cm^{-1} - 3300, 3080,2970,1710,1640,1525,1490,1350,1315,765), have proved the folloing structure:



The newly synthesised compound has shown a high antitumor activity against L1210 limphoid leukemia in BDF$_1$ mice. We established an 714,3% ILS and 100% cures when the nitrosourea was injected i.p. in the single dose 120,0 mg/kg.

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7.045

EGF RECEPTORS IN SENSITIVE AND MDR MCF7 CELLS. ACTION OF DIFFERENTIATING AGENTS AND VERAPAMIL.

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The expression of steroid and growth factor receptors was compared in sensitive and multidrug resistant (MDR) MCF_7 cell lines, then action of differentiating agents and of resistance revertants was studied.

Resistant MCF_7 cells exhibited typical features of MDR cells : amplification and surexpression of mdr, gene, cross resistance to cytotoxic drugs. Epidermal Growth Factor Receptors (EGF R) were determined on whole cell monolayers by a radio ligand assay. An immunocytochemical assay was made in parallel with a double immunostaining for estrogen receptors (ER) and EGF R.

Sensitive MCF_7 cells possessed ER but were devoid of EGF R. Results were strictly opposite for MDR-MCF_7 cells. The number of EGF R sites are 15 time higher in MDR-MCF_7 cells compared to sensitive cells : respectively 2,350 ± 870 and 151 ± 96 sites/cell. K_D was identical and close to 0,3 nM. Double immunostaining ER-EGFR of MDR cells was negative for ER in nuclei and positive for EGF R in cytoplasmic membranes.

Treatment by differentiating agents Retinoic Acid (RA 10^{-6}M) and Sodium Butyrate (NaBu 2.10^{-3}M) decreased the EGF R level of resistant cells and concomitantly increased that of sensitive cells. So the rate of EGF R expression of R/S is 15 for control cells, 8 for RA and 3 for NaBu treated cells.

Verapamil 5.10^{-6}M which reverses resistance of MCF_7 cells with an index of 100, decreased of almost 50 % the expression of MDR-MCF_7 cells without recovering the basal level of wild type MCF_7.

So differentiating agents and resistant revertants seemed decrease the number of EGF R sites.