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RNA-Intercalating Drug Interactions: In Vitro Antiviral Activity Studies.

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The role of adriamycin (ADR), ametantrone (HAQ), daunomycin (DMN), N-methyl-9-hydroxy-ellipticine (NMHE), N,N-dimethyl-9-hydroxy-ellipticine (DMHE), ethidium bromide (EB), mitoxantrone (DHAQ) and propidium iodide (PI) in modulating the antiviral and interferon-inducing activities of poly r(A-U) was examined using the human foreskin fibroblast-vesicular stomatitis virus (HSF-VSV) bioassay system in which the concentration of poly r(A-U) was fixed at 0.05 mM or 0.2 mM while the drug concentration was varied to produce variable drug/ribonucleotide ratios ranging from 1:16 to 2:1. None of the drugs alone or poly r(A-U) alone were efficacious antiviral agents. When poly r(A-U) was combined with the drugs at a drug/ribonucleotide ratio of 1/4, the 50% viral inhibitory doses (ID_{50}) of the poly r(A-U), ADR, DHAQ, DMHE, DMN, EB, HAQ, NMHE and PI decreased 18-, 60-, 125-, 274-, 61-, 154-, 113-, 251- and 299-fold, respectively. The interferon-inducing activity of the drug/poly r(A-U) combinations were equal to the sum of the interferon-inducing activities of their constituents. These results indicate that each of the drugs potentiate the antiviral activity of the poly r(A-U) without the superinduction of interferon. The direct viral inactivation studies demonstrate that the drugs alone, poly r(A-U) alone and the drug/poly r(A-U) combinations do not inactivate the VSV at concentrations near the viral 50% inhibitory dose. Photomicrographs of HSF cells incubated with NMHE alone or with a NMHE/poly (A-U) combination show that poly r(A-U) may affect the subcellular distribution of the NMHE by steering the NMHE to the nucleolus. These observations suggest that modulation of a nuclear process may be responsible for the enhanced antiviral activity.

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Synthesis and in Vitro Antiviral Activity of some Pyrazole-related Nucleosides.

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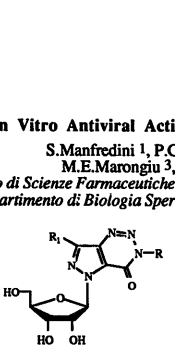

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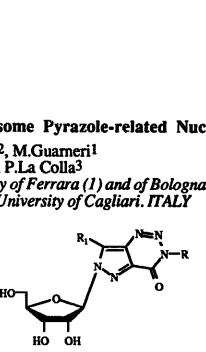

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Continuing our studies[1,2] on pyrazole related nucleosides we here describe the synthesis and in vitro antiviral activity of some substituted pyrazole[4,3-d]triazin-4-ones nucleosides ; while cyclisation to triazinones of the preformed N2-pyrazole-ribosides gave the N2 nucleoside (II), ribosilation of substituted pyrazolo[4,3-d]triazin-4-ones gave usually the N1 nucleoside. In vitro antiviral activities of the title compounds are also reported and discussed.

(1)a:Baraldi P.G.et al.*J.Med.Chem.* **1984, 27, 986.b:Baraldi P.G. et al. *Synthesis* 1988, 78.**
(2) Manfredini S.et al., poster comm., NATO advanced study institute, FEBS advanced course "Il Ciocco",Lucca, 1987.