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In Vitro Antiviral Activity Studies of Poly r(A-U) and Intercalating Agents.
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Experiments have been designed to systematically examine the effects of intercalating agents induced perturbations on the antiviral activity of poly r(A-U) using the human foreskin fibroblast-vesicular stomatitis biossay system with NIH poly (rI).poly (rC) as a reference standard. Over 60 chemical agents including a wide range of minor, major, and minor/major groove intercalating agents have been tested in this study. These chemical agents represent 17 diverse classes including: acridines, anthraquinones, brasilins, carbolines, diesquiterpenes, divalent cations, flavins, flavonoids, indigos, methylxanthines, mono-azo dyes, phenanthridines, 6-H pyrido-carbazoles, 7-H pyridocarbazole dimers, quinolines, thiazines, vitamins and xanthenes. With the exception of apigenin, caffeine, daunomycin, kaempferol, ploxine B, quinacrine, quinine, theophylline and poly r(A-U), none of the test agents alone are efficacious agents. When poly r(A-U) is combined with representatives of the amino acids, acridines, anthraquinones, selected flavonoids, phenanthridines, quinolines, thiazines, vitamins, xanthenes or xanthines with a test agent/nucleotide ratio of 1/4, the antiviral activity is enhanced 8- to 28-fold. Our experimental results suggest a synergism between the poly r(A-U) and the minor groove intercalating agent.

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Computer Assisted Molecular Design of Antisense Oligonucleotide-Intercalator Conjugates as Antiviral Agents. H.L. Weith, S.R.Byrn, M.S. Cushman, J. Stowell, B. Tobias, and D. Carlson. Departments of Biochemistry, and Medicinal Chemistry and Pharmacognosy, Purdue University, West Lafayette, Indiana 47907, U.S.A.

Application of software packages such as CHARMm and AMBER to the design of intercalators covalently attached to oligonucleotides by a linker arm will be illustrated. Particular emphasis will be placed on the linker arm. Progress toward the synthesis and characterization of the conjugates will also be described.