THE ANTITUMOR EFFECTS OF 3'-*C*-METHYLADENOSINE MEDIATED BY INHIBITION OF RIBONUCLEOTIDE REDUCTASE

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Several *C*-branched nucleoside analogues emerged as promising therapeutical agents. As a part of our continued effort to identify nucleoside inhibitors of target enzymes in DNA/RNA biosynthesis as potential chemotherapeutic compounds, we have examined the antitumor activity of a series of adenosine derivatives substituted at the 1'-, 2'-, and 3'-*C*-position of the ribose ring with a methyl group. From this study 3'-*C*-methyladenosine (3'-Me-Ado) emerged as the most active compound showing activity against human leukemia and carcinoma cell lines. Structure-activity relationships studies showed that the structure of 3'-Me-Ado is crucial for the activity. The replacement of a hydrogen atom of N^6-amino group with small alkyl or cycloalkyl groups, the introduction of a chlorine in the 2-position of purine ring, or moving the methyl group from the ribose 3'-position to 1'- or 2'-positions brought about a decrease or loss of activity. The pronounced antiproliferative activity of 3'-Me-Ado, which makes this compound particularly interesting, appears to be related to its ability to deplete both intracellular purine and pyrimidine deoxynucleotides through ribonucleotide reductase (RR) inhibition.