

Ribonucleotide reductase potential inhibitors: Design, synthesis and activity of bioisosters of ribofuranosylnucleoside diphosphates

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RNR inhibitors are a class of potent antiviral/antineoplastic agents. With the purpose of verifying both substrate specificity and contribution to biological activity of potential diphosphate mimicking moieties, we have prepared 5'-phosphono acetic acid, amide and ester analogs of adenosine, uridine and cytidine. These moieties were designed on the basis of molecular modeling studies conducted on the RNR R1 subunit, and obtained by a new synthetic route. The degree of inhibition of these bio-isosters on recombinant murine RNR R1 subunit ranged from 350 microM of the UDP amide analog to 600 microM of the CDP ester analog. None of these compounds were cytostatic at 100-500 microM, whereas ADP amide analogs showed a moderate activity (48 microM) against HSV2, and a very modest but interesting activity (110 microM) against HIV-1, respectively. The main difference between the activity behavior in vitro and in vivo can sensibly ascribed to a poor cellular uptake.