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Kinase bypass: A new strategy for anti-HIV drug design.

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As part of our effort to deliver masked phosphates inside living cells we have discovered that some phosphate triester derivatives of inactive (non-azido) nucleoside analogues are active inhibitors of HIV replication. This discovery underlies the importance of the masked phosphate approach, and has significant implications for the future design of chemotherapeutic nucleoside analogues. If highly modified nucleoside analogues are found to be active without the intervention of nucleoside kinase enzymes, major advantage may accrue in terms of low toxicity, enhanced selectivity, and reduced likelihood of resistance. Indeed, these derivatives are fully active against AZT-resistant strains of HIV-1. The concept we describe as "kinase-bypass" may thus stimulate the discovery of a new generation of antiviral agents.

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INTRACELLULAR DELIVERY OF ANTI-HIV NUCLEOTIDES

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Most nucleoside analogues require intracellular transformations by kinases to their free nucleotides so as to exert an antiviral or antitumor activity. Unfortunately, bio-active nucleotides cannot be clinically used because of their poor penetration into cell membranes and rapid dephosphorylation to nucleosides.

In order to overcome these problems various nucleosidic phosphotriesters have been developped (ie corresponding to ddU, AzT, PMEA...) and it will be shown that such derivatives deliver intracellularly the corresponding nucleotides. In addition, the decomposition pathway of these compounds in biological milieu (culture medium, cellular extracts...) will be commented.