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Nucleoside HIV-antiviral agents incorporating degenerate bases.

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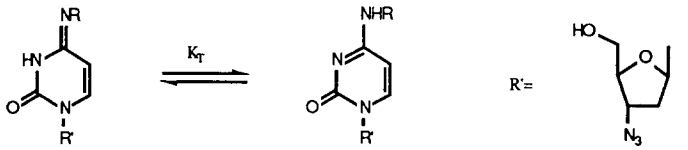
A number of 3'-azido-3'-deoxynucleosides (1) have been synthesized as reverse transcriptase inhibitors and tested against HIV-1. The natural pyrimidines have essentially fixed tautomeric states which define their hydrogen bonding potential, with tautomeric constants (K_T) of the order 10^4-10^6. The addition of substituents to N^4 of cytosine derivatives (e.g. (1), R=OH, OMe, NH_2, etc.) alter the K_T values to the range 0.1-100. This range in K_T is related to the electronegativity of the element (O or N) attached to N^4. These are designated as degenerate bases since they can hydrogen bond effectively with both adenine (A) and guanine (G), thus emulating a uracil (thymine) or cytosine at the demand of the system with which they interact. The chemical synthesis of these compounds and their biological activity compared with AZT, are described.



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Structural Design and Anti-HIV-1 Evaluation of Novel Naphthalenedisulfonic Acid Derivatives. P. Mohan[1] and M. Baba[2], [1]University of Illinois at Chicago, Chicago, Illinois, U.S.A., and [2]Fukushima Medical College, Fukushima, Japan.

Several naphthalenedisulfonic acid derivatives were rationally, designed, synthesized and evaluated for anti-HIV-1 activity measuring inhibition of HIV-1 induced cytopathogenesis in a clinical isolate and inhibition of purified recombinant reverse transcriptase activity. Structurally, these derivatives contained sulfonic acid units present in anti-HIV dyes, as well as simple acylated derivatives of other rationally selected naphthalenedisulfonic acid moieties. The results indicated that the naphthalenedisulfonic acid unit of Chicago Sky Blue was only active at toxic doses, indicating the need for a bis naphthalenedisulfonic acid unit for activity. Activity, at non-toxic doses, was demonstrated in bis derivatives of naphthalenedisulfonic acid containing a decamethylene spacer. However, the most potent activity, at non-toxic doses, was determined in the assay that measured inhibition of HIV-1 induced cytopathogenesis using a clinical isolate (HE strain) of HIV-1. In this assay, a small molecule, 4-acetylamino-5-hydroxy-2,7-naphthalenedisulfonic acid exhibited an EC_{50} value of 12.8 μM and an *in vitro* therapeutic index of >39. These agents may be considered as additional leads and contribute to the structure activity relationships in this new class of potential *non-nucleoside* anti-AIDS agents.