Abstracts

Oral Session I

Design of Antiviral Agents

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4'-Azidothymidine: Synthesis and *in vitro* anti-HIV activity. H. Maag, N. Chu, D. Crawford-Ruth, E. Eugui, M.J. McRoberts, A. Mirkovich, M. Pettibone, E.J. Prisbe, R.M. Rydzewski and J.P.H. Verheyden.
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The majority of the clinically investigated anti-HIV nucleosides, such as AZT, ddC and ddI, belong to the 2',3'-dideoxy class. We report here on a novel class of potent anti-HIV 2'-deoxynucleosides which, while retaining a 3'-hydroxy group, derive their inhibitory properties from a 4'-azido substituent. The synthesis of these compounds was accomplished starting with the addition of iodine azide to the exocyclic double bond of 2',5'-dideoxynucleosid-4'-enes **1**, which provided, in a regio- and stereoselective manner, the 4'-azido-2',5'-dideoxy-5'-iodo derivatives **2**. Acylation of the 3'-hydroxy group followed by a novel oxidative iodine displacement reaction and a deprotection step furnished the 4'-azido-2'-deoxynucleosides **3**. *In vitro* evaluation of this series of compounds identified the thymidine analog, 4'-azidothymidine (ADRT), as one of the most active and the most selective anti-HIV compounds. ADRT proved to be as potent as AZT in inhibiting HIV replication in several cell lines while displaying reduced toxicity to hematopoetic progenitor cells *in vitro*. Anti-HIV activity is retained against clinical isolates insensitive to AZT. ADRT has excellent oral bioavailability in rats, dogs and monkeys. In monkeys and rats, ADRT has a longer half life than AZT following oral or IV administration. Only very low levels of glucuronides can be detected, with the majority of the drug being excreted in urine unchanged. Thus ADRT holds promise for the treatment of HIV infections in man. The synthesis and the *in vitro* structure activity relationships in this series of compounds will be discussed.