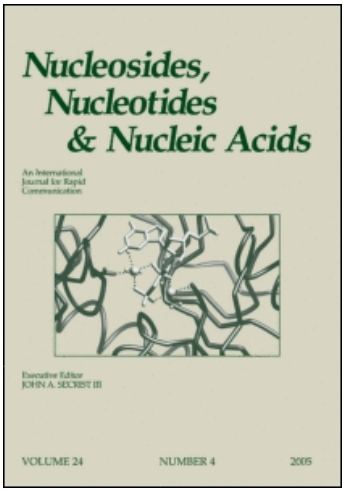

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UNSATURATED NUCLEOSIDE ANALOGUES: SYNTHESIS AND ANTITUMOR ACTIVITY

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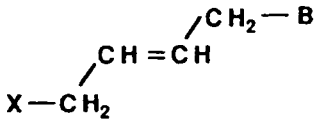
Abstract: Five classes of unsaturated nucleoside analogues were investigated as inhibitors of growth of murine leukemia L 1210 culture. The structural types include E-olefins 1, Z-olefins 2, acetylene derivatives 3, allenes 4 and oxacyclopentenes 5. Compounds of the type 1 - 3 (X = Cl) were obtained by alkylation of the respective nucleic acid bases or 2-amino-6-chloropurine with E- and Z-1,4-dichloro-2-butene or 1,4-dichloro-2-butyne. Acid hydrolysis of intermediates 1, 2 and 3 (X = Cl) led to the corresponding alcohols 1, 2 and 3 (X = OH). Chloroallene 4 (B = Ade, X = Cl) was obtained by chlorination of adenallene (B = Ade, X = OH). Compounds of the type 5 were obtained by base-catalyzed cyclization of the respective 2-butynes. A prolonged hydrolysis of compound 2 (B = 2-amino-6-chloropurine, X = Cl) gave tricyclic derivative 7. Similar cyclization of 2 (B = Ade, X = Cl) afforded a 3,9-bridged adenine 8. Alcohol 2 (B = Ade, X = OH) is a poor substrate for adenosine deaminase as contrasted with compounds 1, 3 and 4 (B = Ade, X = OH). 4-Hydroxybutyl derivative 6 (B = Ade, X = Cl) was completely inert.

Discovery of acyclovir, a powerful antiherpetic agent of clinical significance[1], led to extensive studies of related nucleoside analogues lacking the 2'- or both 2'- and 3'-carbon fragments of ribofuranose moiety. More recently, attention has centered on compounds derived from replacing the CH_2-O (ether) portion in the respective acyclic derivative with an olefinic bond CH=CH[2-7] (type 1 and 2) some of which exhibit interesting antiviral activity[3-5]. Other unsaturated analogues of nucleosides include acetylenic alcohols[3,8] (type 3) and isomeric allenols (type 4) which were first prepared in our laboratory[8]. Of the latter compounds, adenallene (4, B = Ade, X = OH) and

cytallene (4, B = Cyt, X = OH) are strong inhibitors of human immunodeficiency virus (HIV), an etiologic agent of acquired immunodeficiency syndrome (AIDS)[9]. It was also reported[6] that chloro olefin 1 (B = Ade, X = Cl) inhibited the growth of P 388 mouse lymphoid leukemia cells in culture.

All these reasons have led us to a more comprehensive study of chemistry and biology of unsaturated nucleoside analogues. We have also included in our investigations oxacyclopentenes 5, products of isomerization of allenes 4 (X = OH) in strong base[8].



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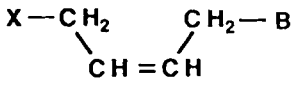

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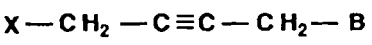

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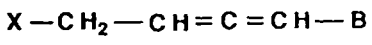

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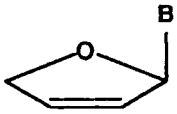

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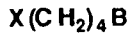

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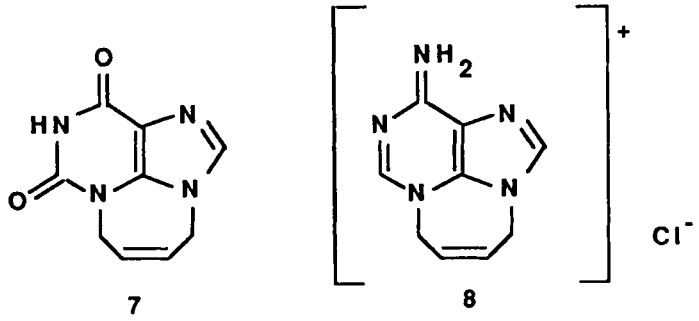
X = Cl or OH **B = Ade, Cyt, 5-MeCyt, Thy, Gua or 2-amino-6-chloropurine**

The syntheses of analogues of the structural type 3, 4 and 5 was reported earlier[8]. In preparation of 3 and 4 (X = Cl) the respective nucleic acid bases or 2-amino-6-chloropurine (guanine derivatives) were alkylated with suitable agents such as E- and Z-1,4-dichloro-2-butene or 1,4-dichloro-2-butyne employed in 4-fold excess by using K_2CO_3 in dimethylformamide (DMF) or tetrabutylammonium fluoride in tetrahydrofuran (THF). Similar procedures were adopted for the synthesis of Z-olefins 2 (X = Cl). Typical yields were ca. 50 %. Hydrolysis of intermediates 2, 3 and 4 (X = Cl) was then accomplished in 0.1 M HCl to give the desired alcohols of type 2, 3 and 4 (X = OH). Usually, reflux for 14 - 18 h is sufficient to afford the latter compounds in 60 - 70 % yields. In case of guanine derivative 2 (B = 2-amino-6-chloropurine, X = Cl) a prolonged reflux in 0.1 M HCl led to a formation of tricyclic compound 7 (Scheme 1) in almost 40 % yield. Nevertheless, when the reaction time was shortened to 3 h the re-



7 8

quisite compound 2 (B = Gua, X = OH) was obtained in 50 % yield. The latter analogue has a significant antiherpetic activity[3]. Our procedure thus constitutes an alternate and improved synthesis of this antiviral drug. Intermediate 2 (B = Ade, X = Cl) also underwent a ready cyclization in dimethylsulfoxide (DMSO, 48 h at room temperature) to give the 3,9-bridged adenine 8 in quantitative yield. Analogues 5 were obtained from the corresponding acetylenic precursors of the type 3 (X = OH) by reflux[8] in 1 M NaOH in 20 - 60 % yields. 5-Methylcytallene 4 (B = MeCyt, X = OH) was prepared following the procedure described for cytallene[8] 4 (B = Cyt, X = OH) but the yields were improved by using tBuOK in DMF at room temperature instead of refluxing with 0.1 M NaOH. 4'-Chloro-4'-deoxyadenallene was obtained by reaction of adenallene (B = Ade, X = OH) with CCl_4 and triphenylphosphine in DMF (see[10]). Compound 6 (B = Ade, X = Cl) was prepared by the described[11] procedure whereas alcohol 6 (B = Ade, X = OH) was obtained by hydrogenation[8] of adenallene (4, B = Ade, X = OH).

Inhibition of growth of murine leukemia L 1210 cells in culture and substrate activities of pertinent analogues toward adenosine deaminase were examined next. Compounds with antitumor activity can be divided in two groups - analogues of type 1 - 4 (X = Cl) containing a reactive allylic chlorine atom and pyrimidine derivatives 5. It is noteworthy that neither of analogues contains a phosphorylatable hydroxy group. Alcohols 1 - 4 (X = OH) as well as purines 5 have a much lower activity. In both groups the cytosine compounds are the most effective as seen in case of compounds 2 (B = Cyt, X = Cl), 3 (B = Cyt, X = Cl) and 5 (B = Cyt) active in the range of 2 - 5 μg/mL. Although all these analogues have a significantly lower inhibitory potency than cytarabine (araC) their efficacy is in the range of that of 5'-chloro-5'-deoxycytarabine[12].

Z-Olefin 2 (B = Ade, X = OH) is a substrate for adenosine deaminase albeit of low activity as compared with other unsaturated analogues such as 1, 3 and 4 (B = Ade, X = OH). This may be explained by a shorter distance between the purine ring and hydroxymethyl group in 2 (B = Ade, X = OH). The saturated compound 6 (B = Ade, (X = OH), the known inhibitor[13] of adenosine deaminase, is inactive as a substrate.

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