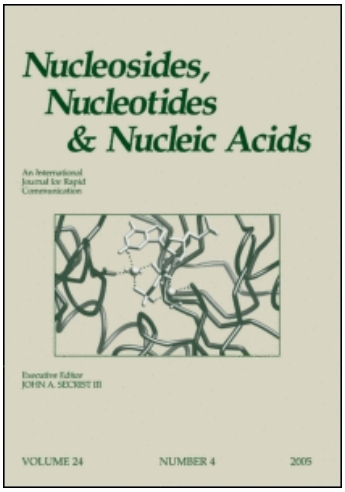

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Acycloadenosine Derivatives as Inhibitors of 5'-Deoxy-5'-Methylthioadenosine Phosphorylase (MesADo PASE)

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ACYCLOADENOSINE DERIVATIVES AS INHIBITORS OF 5'-DEOXY-5'-METHYL-THIOADENOSINE PHOSPHORYLASE (MeSADo PASE)

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Abstract: Four classes of acyclo analogs of 5'-methylthioadenosine were synthesized and tested as inhibitors of mammalian methylthioadenosine phosphorylase. Halogenated dihydroxypropyl acycloadenosines were most potent, i.e. K_i = 0.2 - 0.7 uM.

MeSAdo Pase is required to salvage the methionine and adenine components of MeSAdo generated during polyamine synthesis. Experimental tumors, e.g. L-1210 murine leukemia, that lack this enzyme are highly sensitive to the cytotoxicity of inhibitors of purine de novo biosynthesis, e.g. 6-methylthioinosine, folate antagonists; therefore, as proposed earlier[1] potent inhibitors of MeSAdo Pase might cause enzyme-containing cells to be more sensitive to inhibitors of purine de novo biosynthesis, e.g. glutamine antagonists, folate antagonists, etc. Initial tests of this concept with the MeSAdo Pase inhibitor, 5'-chloroformycin, increased the sensitivity of the L-5178Y leukemia (enzyme-containing) to methotrexate[2]. The present study explored various analogs of MeSAdo related to acyclovir and DHPG as inhibitors of MeSAdo Pase.

BIOLOGICAL ACTIVITY. Although acycloadenosine **(1)** itself was inactive (K_i > 170 uM), its 2-deoxy-2-halogenated congener's **(2)**, **(3)** and **(4)**, inhibited Sarcoma 180 MeSAdo Pase with K_i values in the range of 4 to 9 uM. The 2-deoxy analog of acycloadenosine, 9-(ethoxymethyl)adenine, was a weak inhibitor (K_i = 74 uM). The analogs of 9-(1,3-dihydroxy-2-propoxymethyl)adenine (DHPA), which possess the equivalent of the C(3')-OH of methylthioribose, were more potent inhibitors of MeSAdo Pase than their acycloadenosine-like congeners. While the parent compound, DHPA,

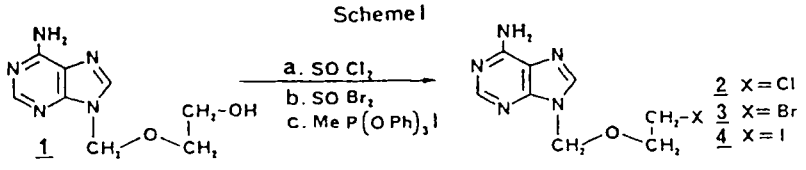
was inactive (K_i > 100 uM), replacement of a hydroxyl group by a halogen (Cl, Br, I) **(5)**, **(7)** and **(8)** gave K_i values in the range of 0.7 to 0.2 uM. 5'-Methylthio- and 5'-halogenated derivatives of 2'-deoxy-1',2'-seco-adenosine **(11-14)** had low activity. At low phosphate concentration (3.5 mM) the 9-(phosphonoalkyl)adenines **(16)** act as multisubstrate inhibitors of the enzyme. Compounds with longer (pentyl, hexyl, heptyl) acyclic tails bind more tightly (K_i values in the range of 70 to 15 uM) than those with shorter tails, i.e. propyl, butyl (K_i values >250 uM). At high (50 mM) potassium phosphate concentrations, the inhibitions were ablated, indicating interactions with the phosphate binding site of the enzyme.

These acyclic adenosines represent new classes of MeSAdo Pase inhibitors. In terms of SAR, the finding that many of these acyclic adenosine analogs bind as well or better than the natural substrate, MeSAdo (K_m = 2 uM), suggests that a flexible acyclic tail permits better orientation for enzyme binding than a relatively rigid pentose. The nearly 10 fold lower K_i values of the halogenated DHPA analogs as compared to the acycloadenosine analogs stress the importance of the C(3') hydroxyl group. Results with 9-(phosphonoalkyl)adenines suggest the design of potent multisubstrate inhibitors of MeSAdo Pase based on an acyclic adenosine structure.

SYNTHESIS OF HALOGENATED ACYCLOADENOSINES

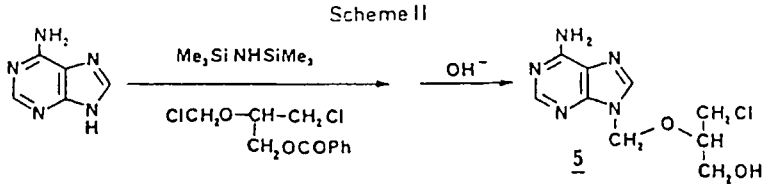
9-[(2-Chloroethoxy)methyl]adenine (2) and **9-[(2-bromoethoxy)methyl]adenine (3)** were synthesized by treating acycloadenine **(1)** in HMPA with $SOCl_2$ and $SOBr_2$, respectively. **(2)** 92% yield. m.p. 215°C(dec). UV(EtOH): λ_{max} 259 nm (14,000); **(3)** 81% yield m.p. 205°C; UV(EtOH): λ_{max} 259 nm (14,200); **9-[(2-iodoethoxy)methyl]adenine (4)** was iodinated smoothly by methyltriphenoxyphosphonium iodide in dry THF at -70°C. **(4)** 74% yield, m.p. 188°C; UV(EtOH): λ_{max} 259 nm (14,600).

Scheme I



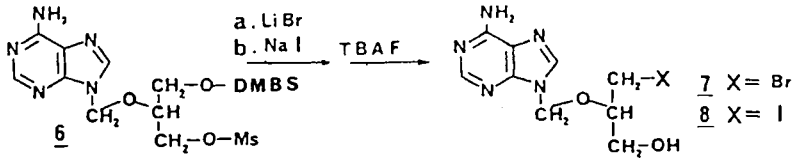
9-[(1-Chloromethyl-2-hydroxyethoxy)methyl]adenine (5) was synthesized by reacting adenine bis-trimethylsilyl ester with 1-chloro-3-benzyloxy-2-propoxymethyl chloride and deblocking with 0.1 N aqueous NaOH. m.p. 215°C; UV(EtOH): λ_{max} 259 nm (14,800).

Scheme II



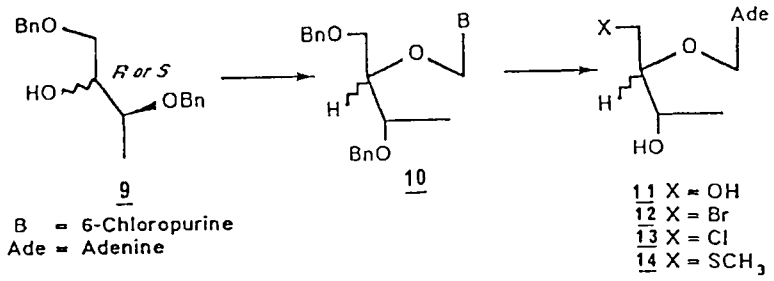
9-[(1-Bromomethyl-2-hydroxyethoxy)methyl]adenine (7) and **9-[(1-Iodomethyl-2-hydroxyethoxy)methyl]adenine (8)** were synthesized by halogenation of **(6)** by the method of Ogilvie el at.[6] using lithium bromide or sodium iodide respectively. **(7)** Yield 35% m.p. 194°C. UV(EtOH): λ_{max} 259 nm (14,700); **(8)** Yield 39% m.p. 200°C dec.; UV(EtOH): λ_{max} 259 nm (14,350).

Scheme III



5'-SUBSTITUTED 1',2' SECO-2'-DEOXYADENINE NUCLEOSIDES

Scheme IV

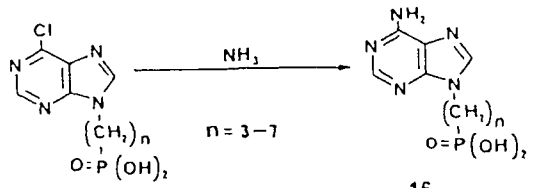


B = 6-Chloropurine
Ade = Adenine

The chloromethyl ethers prepared from (2R,3S) and (2S,3S) - 1,3-di-O-benzylbutane 1,2,3-triol[4] **(9)** were treated with the sodium salt of 6-chloropurine in acetonitrile[5] to give the 6-chloropurine analogs **(10)** as a mixture of N-7 and N-9 isomers. Chromatographic separation followed by heating with ammonia and subsequent debenzylation over Pd/C furnished the adenosine analogs **(11)**. The 5'-bromo **(12)** and 5'-chloro **(13)** substituents were added by treatment of **(10)** with triphenylphosphine and carbon tetrabromide or carbon tetrachloride respectively. This reaction was not totally selective necessitating the chromatographic separation of the 5'-halo from the 3',5'-dihalo derivatives. The 5'-methylthio compounds **(14)** were obtained by direct displacement of the 5'-bromides with potassium methyl mercaptide.

9-(PHOSPHONOALKYL)ADENINES. A series of 9-(phosphonoalkyl)adenines with carbon chains ranging from 3-7 C atoms was prepared from the respective 6-chloropurine analogs[6] by heating with ammonia.

Scheme V



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