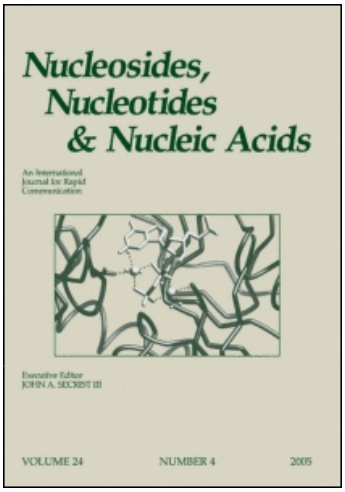

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DESIGN AND BIOLOGICAL EVALUATION OF NEW MECHANISM-BASED INHIBITORS OF *S*-ADENOSYL-L-HOMOCYSTEINE HYDROLASE

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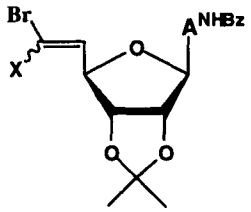
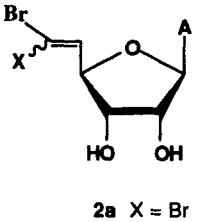
ABSTRACT: Geminal dihalohomovinyl **2** and haloacetylenic **4** analogs derived from adenosine were prepared. These compounds exhibited type II (covalent) mechanism-based inactivation of *S*-adenosyl-L-homocysteine hydrolase.

The cellular enzyme *S*-adenosyl-L-homocysteine hydrolase effects hydrolytic cleavage of *S*-adenosyl-L-homocysteine, a potent inhibitor of crucial transmethylation enzymes, to adenosine and L-homocysteine. A number of inhibitors which function as substrates for the "3'-oxidative activity" of the enzyme and convert the enzyme from its active form (NAD^+) to its inactive form (NADH, type I inhibition) have been prepared.[1] Inhibitors which function as substrates for the "5'/6'-hydrolytic activity" were also synthesized[2] which included oxime derivatives of adenosine 5'-carboxaldehydes and their 2'- and 3'-deoxy analogues.[3]

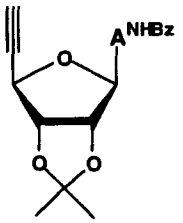
Geminal (dihalohomovinyl)adenosines **2** were designed as putative new substrates for the hydrolytic activity of AdoHcy hydrolase.[4] Analogues **2** have been synthesized from protected Ado-5'-carboxaldehyde with the Corey-Fuchs procedure[5] [CBr_3X (X = Br or F)/PPh_3/Zn] and successive deprotections of **1**.[4a] Treatment of **1** (X = Br) with excess BuLi gave the acetylenic derivative **3** (53%).[6,7]



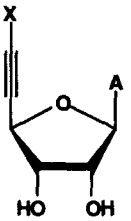
1



2a X = Br
2b X = F



3



4a X = I
4b X = Br

Treatment of **3** with *N*-iodosuccinimide and catalytic $AgNO_3$[8] resulted in efficient 6'-iodination. Sequential removal of the 6-*N*-benzoyl (NH_3/MeOH) and isopropylidene [CF_3CO_2H/H_2O] groups gave the iodoacetylene derivative **4a** (42% from **3**). Analogously, treatment of **3** with *N*-bromosuccinimide gave bromoacetylene derivative **4d**.

Addition of an enzyme-sequestered water molecule across the 5',6'-double bond of bromo(fluoro)homovinyl analogue **2b** followed by loss of bromide could result in the formation of a reactive homoAdo 6'-carboxyl fluoride at the active site of AdoHcy hydrolase.[4b] Nucleophilic attack by proximal amino acid functionalities causes type II (covalent binding) inhibition of the AdoHcy hydrolase. Similarly, addition of water across the 5',6'-triple bond of haloacetylenes **4** followed by tautomerization of the hydroxyvinyl intermediates could generate acyl halides (C6' hydroxyl attack) and/or α-halomethyl ketones (C5' hydroxyl attack) at the enzyme active site. Compound **2** and **4** are the first examples of type II inhibitors that are activated by the "hydrolytic activity" of the enzyme without prior oxidation at C3'.

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