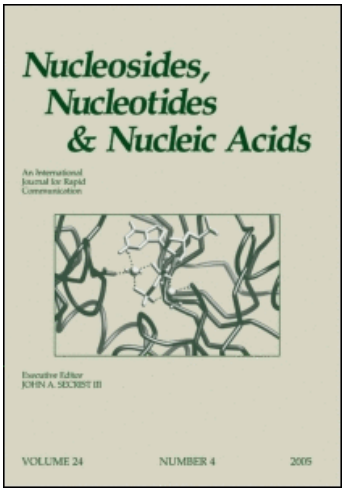


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

A New Series of Mechanism-Based Inhibitors of S-Adenosyl-L-Homocysteine Hydrolase from Beef Liver

Corinne Vandenplas[a]; Danielle Guillerm[a]; Georges Guillerm[a]
[a] UFR Sciences de Reims, Reims Cedex 2, France

To cite this Article Vandenplas, Corinne , Guillerm, Danielle and Guillerm, Georges(1999) 'A New Series of Mechanism-Based Inhibitors of S-Adenosyl-L-Homocysteine Hydrolase from Beef Liver', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 569 — 570
To link to this Article: DOI: 10.1080/15257779908041496
URL: http://dx.doi.org/10.1080/15257779908041496

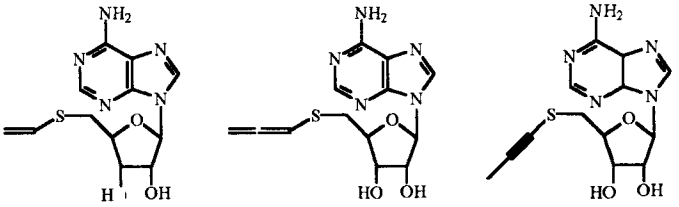
NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 569–570 (1999)

A NEW SERIES OF MECHANISM-BASED INHIBITORS OF S-ADENOSYL-L-HOMOCYSTEINE HYDROLASE FROM BEEF LIVER

Corinne Vandenplas, Danielle Guillerm, Georges Guillerm*
UMR 6519 CNRS - UFR Sciences de Reims
B.P. 1039 - 51687 Reims Cedex 2, France

ABSTRACT : Nucleosides I, II, III caused irreversible inactivation of AdoHcy hydrolase. A mechanism of inactivation is proposed.

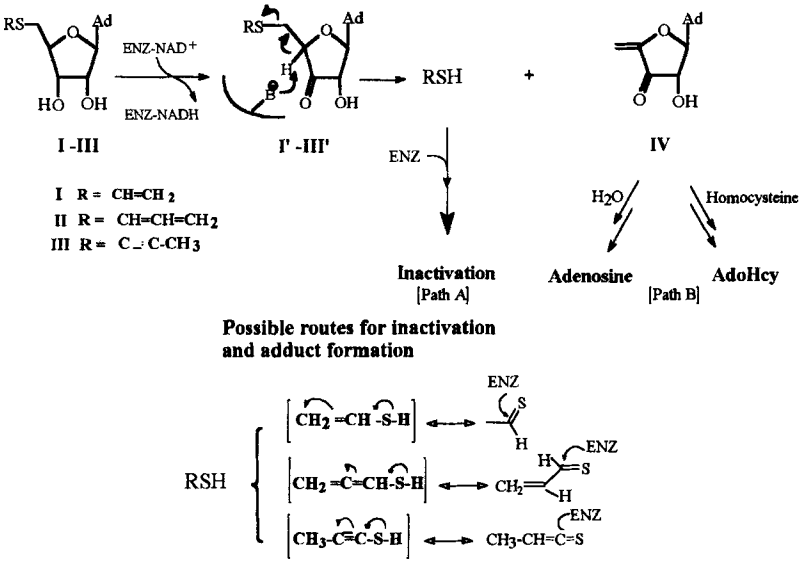
The importance of S-adenosyl-L-homocysteine (AdoHcy) hydrolase (EC 3.3.1.1) as a target for developing antiviral agents has been outlined[1] and the design and synthesis of mechanism based inhibitors have received considerable attention, since the mechanism of catalysis of AhoHcy hydrolase was elucidated by Palmer and Abeles[2]. Recent results from our laboratory[3] led us to hypothesis that a new series of thionucleosides (I, II, III) might serve as novel type of irreversible inhibitors of AdoHcy hydrolase.



I II III

Fig. 1

Based on the Palmer - Abeles mechanism of AdoHcy hydrolase, enzymatic oxidation of I, II, or III (Fig. 1) to the corresponding 3'-ketoderivatives (I', II', III'), if occuring, could be accompagnied by a β-elimination of a vinyl, allenyl or propynyl mercaptan



Scheme I

group (or their tautomeric forms). The latter could irreversibly acylate nucleophilic residus involved in the catalytic process within the enzyme cavity (Scheme 1 pathway A). I, II and III were tested on the activity of AdoHcy hydrolase, purified to homogeneity from beef liver. I, II and III cause potent time dependent and irreversible inactivation of the enzyme. The inactivation is concomitant with the formation of adenosine, or AdoHcy from I, II and III when the enzyme was incubated with inhibitors in the absence or in the presence of homocysteine (Scheme 1, pathway B).

Our results indicate that the inhibition process is largely predominant but the nature of the acylating agents by which inactivation of the enzyme proceeds has to be confirmed.

REFERENCES

1 Wolfe, M.S. ; Bochardt, R.T. *Med. Chem.* **1991**, *34*, 1521 and references therein.

2 Palmer, J.L. ; Abeles, R.H. *J. Biol. Chem.* **1979**, *254*, 1217.

3 Muzard, M. ; Guillerm, D. ; Vandenplas, C. ; Guillerm, G. *Bioorg. and Med. Chem. Lett.*. **1997**, *7*, 1037.