α-VINYLSERINE, AN AMINO ACID RATIONALLY DESIGNED TO INHIBIT SERINE HYDROXYMETHYLTRANSFERASE

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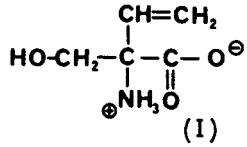
The enzyme serine hydroxymethyltransferase (SHMT) catalyses the interconversion of L-serine and glycine in the presence of pyridoxal phosphate (PLP) generating a one-carbon unit which may then be used for the de-novo synthesis of purines and thymine.

Many tumour cells, such as Jenson Sarcoma, have a nutritional requirement for L-serine although it is not essential (Kruse et al, 1967). On mitogenic stimulation of chronic lymphocytic leukaemia, a five fold elevation in SHMT levels was obtained (Thorndike et al, 1979). These results suggest that SHMT may be an apposite target for anti-proliferative therapy.



(I)

L-Alpha vinyl-serine (I) is a molecule that has been rationally designed to be an inhibitor of this enzyme. When bound to the PLP at the SHMT active site it may be de-hydroxymethylated to produce a Michael acceptor. This will rapidly react with active site nucleophiles irreversibly inhibiting the enzyme.

The racemic compound was synthesised by the general route of Greenlee et al, (1978). Chloromethyl acetate, prepared from acetyl chloride and paraformaldehyde in the presence of catalytic aluminium chloride, was used to introduce the hydroxymethyl group into the compound. The N-benzylidene-2-aminocrotonic acid alpha vinyl-amino acid framework was alkylated at -70°C with lithium hexamethyl-disilazide in THF/HMPA. Acid hydrolysis of the alkylated crotonic acid, followed by neutralisation gave the title compound in the zwitterionic form, in 11.6% yield. Spectroscopic evidence is in agreement with the proposed structure.

The structure was determined by X-ray crystallography on a CAD4 diffractometer using direct methods; the asymmetric unit is shown in figure 1. Biological testing showed the compound to be a competitive inhibitor of total human erythroid leukaemia cell SHMT, with an inhibitory constant of 15.2 mM.

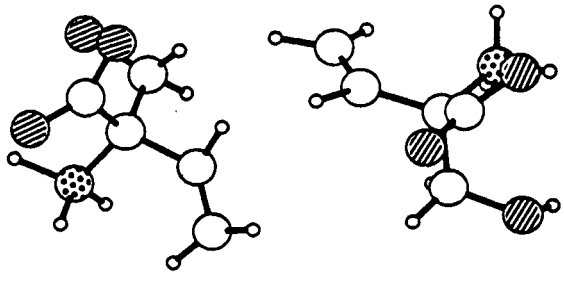


Figure 1.The asymmetric unit of α-vinyl serine

C O N

Greenlee, W J, et al, Tetrahedron Lett. (1978) 42, 3999.
Kruse, P F, et al, Biochem. (1967) 6, 949.
Thorndike, J, et al, Cancer Res. (1979) 39, 3455.