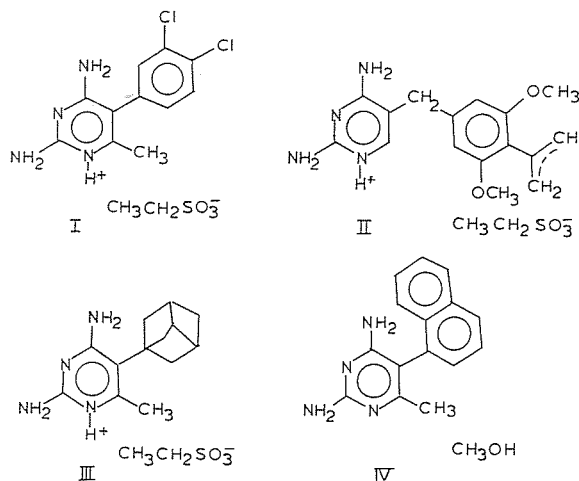


The binding of TMP is similar in each of the two molecules in the asymmetric unit; it lies in a prominent cleft, the face of the β -sheet closing the cleft at the rear. The 4-amino group, C2 and N3 of the pyrimidine group are all close to the first β -strand, in the region of residues 5, 6 and 7, and N1 and the 2-amino group of TMP are about 3\AA from the carboxyl oxygens of Asp 27. The other enzyme/drug interactions are largely hydrophobic in nature: the trimethoxybenzyl group of TMP is directed outwards from the enzyme cleft and is close to the side chains of Ile 50, Leu 28 and Phe 31.

The two analogues of TMP involve a substitution of N3 by CH and a substitution with methyl at C6. These modifications respectively affect the thermal vibration and conformation of the bound ligand.

The analysis of these data shows that all but IV are protonated at N1, all but III have coplanar 2,4-diaminopyrimidine rings and all have similar hydrogen bonding patterns with a base-pair hydrogen bond between N4...N3 of inversion-related molecules. The conformation of the 5-substituent in molecules I, III and IV is such that the two ring systems are rotated 108° , -8° , -87° , respectively. The torsion angles about the bridging carbon in (II) are $-153^\circ/-98^\circ$, respectively. The conformational and hydrogen bonding patterns exhibited by these structures may help explain binding affinity and dihydrofolate inhibition differences among these antifolates and distinguish structural features that control species specificity.



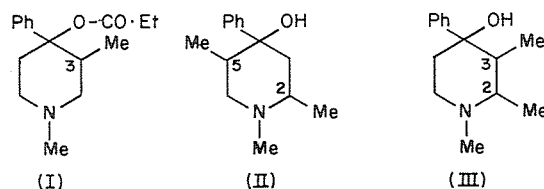
This research was supported by DHEW Grant No. RR-05716.

03.1-09 STRUCTURE-FUNCTION RELATIONSHIPS AMONG 2,4-DIAMINOPYRIMIDINE ANTIFOLATES. By Vivian Cody, Medical Foundation of Buffalo, Inc., Buffalo, NY 14203, U.S.A.

It has been shown that the essential features required for tight binding of antifolates to dihydrofolate reductase are a 2,4-diaminopyrimidine or s-triazine structure. In particular, those compounds with a lipophilic group at position five appear to act as antineoplastic agents while other compounds of this class have antibacterial or antimalarial activity. Some of these compounds also show species specificity in their antifolate activity. It has also been suggested that the enhanced binding of these antifolates compared to that of the natural folic acid substrates may be related to the activity of the 2,4-diaminopyrimidine (1) to achieve and maintain a specific hydrogen bonding pattern in the active site of the enzyme in contrast to the 2-amino, 4-oxo groups of folates, or (2) to contribute to electronic interactions such as charge-transfer or electron donation due to the increased basicity of N1 in the 2,4-diaminopyrimidines. Thus the crystal structures of the following lipophilic 5-substituted 2,4-diaminopyrimidines have been undertaken to investigate the conformational aspects of drug specificity. (I) 2,4-Diamino-5-(3,4-dichlorophenyl)-6-methyl pyrimidine ethyl sulfonate ($\text{C}_{13}\text{H}_{16}\text{N}_4\text{O}_2\text{Cl}_2\text{S}$; PI, $Z=2$, $a=10.6021(7)$, $b=12.7180(2)$, $c=7.5180(6)$ \AA , $\alpha=96.35(1)$, $\beta=103.59(7)$, $\gamma=117.57(1)^\circ$), (II) 2,4-diamino-5-((3,5-dimethoxy-4-propene)benzyl)pyrimidine ethyl sulfonate ($\text{C}_{16}\text{H}_{26}\text{N}_4\text{O}_5\text{S}$; PI, $Z=2$, $a=9.400(1)$, $b=19.563(2)$, $c=5.420(1)$ \AA , $\alpha=93.29(1)$, $\beta=94.11(1)$, $\gamma=103.95(1)^\circ$), (III) 2,4-diamino-5-(1-adamantyl)-6-methyl pyrimidine ethyl sulfonate ($\text{C}_{15}\text{H}_{22}\text{N}_4\text{O}_3\text{S}$; PI, $Z=2$, $a=10.309(1)$, $b=4.536(2)$, $c=6.486(1)$ \AA , $\alpha=91.76(2)$, $\beta=94.98(1)$, $\gamma=109.75(1)^\circ$), and (IV) 2,4-diamino-5-(1-naphthyl)-6-methyl pyrimidine methanol complex ($\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}$; C2/c, $Z=8$, $a=18.542(8)$, $b=10.990(4)$, $c=14.721(9)$ \AA , $\beta=91.91(5)^\circ$) [Cody & Zakrzewski; ACA Abstracts, 7, 13; 8, 35, 1980].

03.1-10 STRUCTURE-POTENCY RELATIONSHIPS FOR THE 2,3-DIMETHYL ANALOGS OF THE PROMEDOL ALCOHOLS. By M. Cygler and F.R. Ahmed, National Research Council of Canada, Ottawa K1A 0R6, Canada; A.F. Casy and F.O. Ogungbamila, University of Bath, Bath BA2 7AY, England.

The structure-potency relationships of the isomeric prodines (I) and the isomeric promedol alcohols (II) were summarized by Ahmed & De Camp (Acta Cryst. (1972), B28, 3489-3494), and a more general article on analgesics and their antagonists has been published by Casy (Progress in Drug Research. (1978) 22, 149-227). The present work extends these relationships to the three isomers of the 2,3-dimethyl analogs (III) of the prodine alcohols.



The isomers of (III) are confirmed to have the activity ranking $\gamma > \alpha > \beta$. The configurations of the α - and β -isomers have been determined from ^1H - and ^{13}C -NMR data and confirmed by the X-ray results. The configuration of the γ -isomer and the solid-state conformations of all three isomers have been elucidated from the crystal structures.

The potency-configuration relationships among the three isomers of (III) are found to follow the same pattern as for the isomers of (II), and are not affected by having a methyl substituent on C(3) instead of C(5). Only the isomers with the highest potency in (II) and in (III) crystallize in opposite conformations.