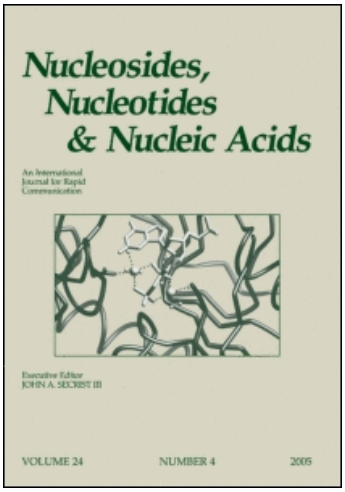

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Mechanistic Similarities Between Thymidylate Synthase and IMP Dehydrogenase: A Common Strategy of Catalysis

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To cite this Article Kalman, T. I.(1999) 'Mechanistic Similarities Between Thymidylate Synthase and IMP Dehydrogenase: A Common Strategy of Catalysis', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 845 — 846
To link to this Article: DOI: 10.1080/15257779908041577
URL: http://dx.doi.org/10.1080/15257779908041577

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 845–846 (1999)

MECHANISTIC SIMILARITIES BETWEEN THYMIDYLATE SYNTHASE AND IMP DEHYDROGENASE: A COMMON STRATEGY OF CATALYSIS

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Thymidylate synthase (TS) and inosine 5'-monophosphate dehydrogenase (IMPDH) are important targets of drug action and development. The two enzymes bear no structural resemblance to each other and they catalyze fundamentally different chemical reactions:

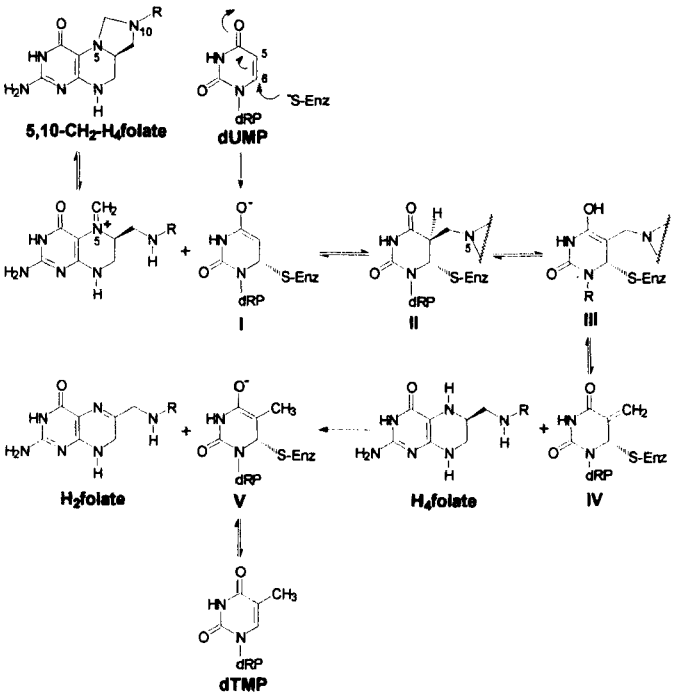
dUMP + 5,10-methylenetetrahydrofolate ===> dTMP + dihydrofolate (TS)

$IMP + NAD^+ + H_2O$ ===> XMP + NADPH + H^+ (IMPDH)

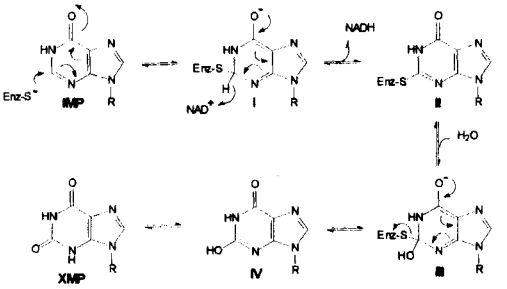
Therefore, it is surprising that TS and IMPDH appear to share many mechanistic features. Whereas TS has been studied extensively in many laboratories[1] and its mechanism described in detail[1,2], the information about the structure and mechanism of IMPDH is limited[3,4]. Nevertheless, there are sufficient data available that permitted the recognition of many striking mechanistic similarities: (1) both enzymes initiate catalysis by nucleophilic addition of the sulfhydryl group of an active site cysteine residue to the conjugated carbonyl system of the heterocyclic base of the substrate; (2) all chemical transformations are carried out while the nucleotide is covalently attached to the enzyme *via* a thioether linkage; (3) hydride transfer occurs between substrate and cofactor; (4) covalently bound enolate intermediates are involved; (5) sp^2 <==> sp^3 rehybridizations take place at the position of substitution of the substrate (C-5 for TS and C-2 for IMPDH), where a hydrogen is displaced during the reaction; (6) dehalogenations are catalyzed by both TS (5-bromo- and 5-iodo-dUMP) and IMPDH (2-chloro- and 2-fluoro-IMP); (7) the nucleotide substrate binds before the cofactor, which stacks on the purine or pyrimidine

ring in a parallel plane to facilitate hydride transfer; (8) a 'flap' covers the active site during catalysis requiring a large conformational change.

Interestingly, the similarities extend beyond the active sites: (1) both enzymes use



nucleoside 5'-monophosphates as substrates, which are converted to a unique purine or pyrimidine nucleotide, as part of *de novo* biosynthesis; (2) both enzymes utilize cofactors, which require regeneration by separate redox enzymes. Some of these similarities permit analogous rationales for inhibitor design, which should aid drug development.



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