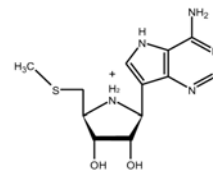


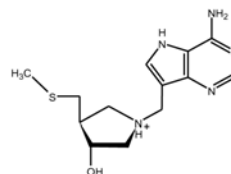
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**Pico- and Femtomolar Transition State Inhibitor-complexes of MTA/AdoHcy Nucleosidase.** JE Lee<sup>1</sup>, V Singh<sup>2</sup>, VL Schramm<sup>2</sup>, GB Evans<sup>3</sup>, PC Tyler<sup>3</sup>, RH Furneaux<sup>3</sup>, PL Howell<sup>1</sup> <sup>1</sup>Hospital for Sick Children and Univ. of Toronto, Toronto, ON; <sup>2</sup>Albert Einstein College of Medicine, Bronx, NY; <sup>3</sup>Industrial Research Ltd, Lower Hutt, NZ.

5'-Methylthioadenosine (MTA) /S-adenosylmethionine (AdoHcy) nucleosidase (MTAN) deurinates MTA or AdoHcy to adenine and its corresponding thioribose. MTAN is found in many microbes but not mammals, and its critical role in a number of biological processes including quorum sensing, biological methylation, polyamine biosynthesis and methionine recycling make it an ideal target for drug design. The crystal structures of *E. coli* MTAN complexed with the picomolar and femtomolar transition state (TS) analogues, MT-ImmA and MTDADMe-ImmA have both been solved to 2.2Å resolution. Comparison of MTAN-MT-ImmA and MTAN-MTDADMe-ImmA with structures of other available nucleosidase-inhibitor complexes reveals that improved stabilization of the oxocarbenium TS by the nucleophilic water accounts for the tight binding affinities. Distance analysis of the nucleophile and leaving group show that MT-ImmA and MTDADMe-ImmA are inhibitors mimicking the substrate and product side of the TS energy barriers, respectively. The MTAN-MT-ImmA and MTAN-MTDADMe-ImmA complexed structures provide insight into the future design of more potent and specific transition state mimics.



**MT-ImmA ( $K_i^*=26$  pM)**



**MTDADMe-ImmA ( $K_i^*=160$  fM)**