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Inhibitory action of phenothiazine derivatives of substituted phenothiazine on the phenothiazine N-methyltransferase in rat liver. A molecular model of phenothiazine N-methyltransferase (PNMT) from rat liver homogenates was first developed by cysteamine hydrochloride induced denaturation of the enzyme in 0.5% SDS. This was followed by reduction of the disulfide bonds of the enzyme with dithiothreitol. The PNMT was then synthesized by partial alkylation of the reduced enzyme with iodoacetamide. Thus the synthetic PNMT was monomeric and catalytically active. Phenothiazine derivatives inhibited the catalytic activity of the synthetic enzyme in a competitive manner. The inhibition was linear with the concentrations of the inhibitor. The inhibition by various phenothiazine derivatives was also independent of substrate concentration but did depend on the inhibitor concentration. The K_i values of different phenothiazine derivatives were in a good agreement with the K_m values estimated from their inhibition patterns. It was suggested from kinetic parameters that N,N-dimethylated analogues of substituted phenothiazines were preferable

competitive inhibitors of rat PNMT

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