A Dramatic Side Chain Movement in Adrenaline-Synthesising PNMT: Implications for Drug Design

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Phenylethanolamine N-methyltransferase (PNMT) catalyses the methylation of noradrenaline to form adrenaline using S-adenosyl-L-methionine as the methyl donor. Adrenaline is produced in the adrenal medulla (hormone), and in selected neurons in the CNS (neurotransmitter). The role of adrenaline in the CNS is poorly understood, though it has been implicated in blood pressure control and Alzheimer's disease.

Classic inhibitors of PNMT also act on the α2-adrenoreceptor, or are unable to cross the blood brain barrier. Therefore we are using the crystal structure of PNMT to design potent selective CNS-active PNMT inhibitors. The structure of PNMT with 7-SO_2NH_2-THIQ[1] revealed room in the binding pocket for bulkier 7 substituents so these were designed and tested for PNMT inhibition. Some inhibited with high potency despite predicted steric clashes. A co-crystal structure revealed a dramatic conformational change in a lysine residue to accommodate the substituent, indicating that drug design strategies must address large conformational changes at active sites.

[1] Martin J.L., Begun J., McLeish M.J., Caine J.M., Grunewald G.L., *Structure*, 2001, **9**, 1.

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