DIFFERENT BINDING MECHANISMS OF DOPAMINE TRANSPORTER INHIBITORS

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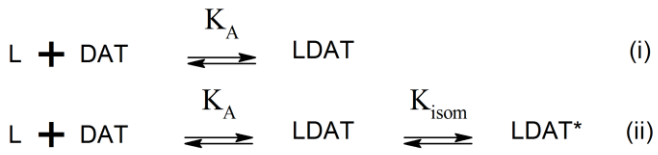
Dopamine transporter (DAT) is a 12-transmembrane protein responsible for the regulation of extracellular dopamine concentrations [1], and an important target for drugs and positron emission tomography ligands.

DAT inhibitors have at least two different binding mechanisms (Scheme 1): fast ligand binding following the conventional equilibrium scheme (i) and their binding effectiveness is described by the K_A values; two-step binding, after initial fast binding step the ligand induces protein conformation change (ii) [2]. This extra step consists of a slow protein conformational change, enhancing the apparent binding effectiveness of the ligand. Most of DAT inhibitors (e.g. cocaine) have shown the former binding mechanism (i), while very few (e.g. PE2I, GBR 12909) bind according to the latter (ii) [3]. This two-step binding mechanism of 7-transmembrane proteins has been reported before [4], in some cases the specificity factors which induce the change of the binding mechanism were discussed [5]. We search for similar interrelationships between binding mechanism and structure of DAT ligands that may have significant implication for drug development for this transporter system.



Scheme 1 Two binding mechanisms

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