Synthesis of Dopamine Analogues and Analysis in Human Cytosolic Sulfotransferase and Catechol-*O*-methyltransferase Enzymes

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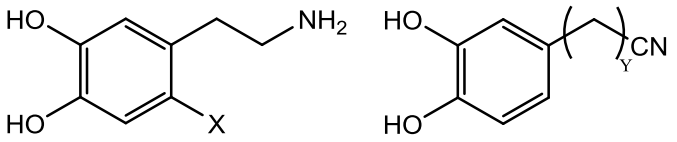
The neurotransmitter dopamine is a natural substrate of both human sulfotransferases and catechol-*O*-methyltransferase in the body. Human cytosolic sulfotransferases (SULTs) are enzymes that catalyze the transfer of a sulfate group from 3'-phosphoadenosine-5'-phosphosulfate to many endogenous substances and xenobiotic compounds, thereby regulating metabolism and aiding in excretion. The SULT1A1 sub-family targets phenolic compounds, like *p*-nitrophenol, while SULT1A3 sulfates catecholamines, including dopamine and serotonin. Despite structural similarities, the reasons for the enzymes' substrate specificity are poorly understood. Catechol-*O*-methyltransferase (COMT), on the other hand, catalyzes *O*-methylation, or the transfer of a methyl group of S-adenosyl-L-methionine to a phenolic group of the catechol substrate in the presence of Mg^{2+}. COMT targets catecholic compounds, including physiological catecholamines and their hydroxylated metabolites. COMT inhibitors have an application in the treatment of Parkinson's disease symptoms. To better understand the stereoelectronic factors that influence SULT1A1 and SULT1A3's substrate selectivity and to potentially inhibit COMT, a suite of dopamine analogues (Fig. 1) were designed and synthesized. Analogues have substituents at the 6-position with varying sizes and degrees of electron withdrawing and donating capabilities or different tail moieties. The design and synthesis of these analogues will be discussed.

Fig. 1: The structures of dopamine analogues synthesized for this study.



X = OH, Br, I, NO_2, CO_2H, CN, $CHCH_2$

Y = 0, 1