CYP-Catalyzed Intramolecular C-N Cyclization in Antidepressant Duloxetine Metabolism

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The comprehensive characterization of drug metabolism is essential for assessing the efficacy and safety of therapeutic agents. In this study, we identify a rare and previously unrecognized metabolic transformation of duloxetine (DLX), a first-line antidepressant, catalyzed by cytochrome P450 1A2 and 2D6 (CYP1A2/2D6). We demonstrate that CYP1A2 converts DLX to 5-hydroxy-duloxetine (5-O-DLX), a primary metabolite. This metabolite is further transformed into an unusual cyclized product featuring a fused eight-membered nitrogen heterocycle linked to an ortho-quinone moiety via an intramolecular oxidative C-N bond-forming reaction. The mono- and di- ^{18}O incorporation into the quinone oxygens in the $H_2{}^{18}O$ enriched incubation of 5-O-DLX with CYP2D6 indicates that the quinone oxygens can be derived from the aqueous solvent. Both 5-O-DLX and 6-O-DLX readily underwent this cyclization, whereas 4-O-DLX did not, demonstrating regioselective requirements for the transformation. Studies in human liver and intestinal microsomes further confirmed the formation of this uncommon metabolite directly from DLX. Collectively, these findings expand the catalytic repertoire of CYP2D6 and uncover a rare oxidative cyclization pathway in drug metabolism. This intramolecular C-N bond-forming transformation represents an uncommon mode of CYP-mediated biotransformation.

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