

## **Non-nitrocatechol inhibitors of Catechol-O-methyltransferase**

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Catechol-O-methyltransferase (COMT) plays an important role in the termination of dopamine signaling in brain regions such as the prefrontal cortex and hippocampus, making it an important regulator of a number of cognitive and behavioral processes. Therefore, brain-penetrating inhibitors of COMT may be useful in treatment of a variety of conditions associated with dysregulated cortical dopaminergic function like schizophrenia, ADHD, and traumatic brain injury. COMT has two forms encoded from the same gene—a membrane-bound form (MB-COMT) and a soluble form (S-COMT). Genetic and pharmacological studies have demonstrated that the membrane-bound form is especially important in the human brain; however, the known brain penetrant COMT inhibitors nitrocatechol tolcapone has serious safety issues that preclude widespread use in psychiatric disorders. Therefore, we sought to determine if a potent and selective non-nitrocatechol COMT inhibitor would be useful for treatment of neurologic disorders. We chose to develop a relatively neglected quinoline lead from the literature. This strategy allowed us to avoid the potentially problematic nitrocatechol pharmacophore, although at the expense of robust initial potency. The initial fragment-like hit was optimized for potency, selectivity, pharmacokinetics, and brain penetration. A somewhat MB-COMT selective inhibitor was identified that had excellent bioavailability with consistent exposure in plasma and CSF upon oral administration. Assessment of dopamine metabolism in the brain via CSF monitoring of dopamine metabolites as well as microdialysis from cortex show the expected increases in biomarker DOPAC and decreases in biomarker HVA. Non-nitrocatechol inhibition of COMT produces biomarker changes consistent with those seen for the benchmark COMT inhibitor tolcapone, with the potential for greater safety and less frequent dosing.