Design of Potent and Drug-like Non-phenolic Inhibitors for Catechol O-Methyltransferase

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For the first time nonphenolic and small low nanomolar potent, SAM competitive COMT inhibitors are reported. Initial fragments with high ligand efficiency, were identified in a fragment screening approach designed to target specifically the *S*-adenosyl-L-methionine pocket of catechol *O*-methyl transferase. By use of a reliable enzymatic assay together with X-ray crystallography as guidance, a series of fragment modifications revealed an SAR and, after several expansions, potent lead compounds could be obtained.

[1] Christian Lerner, Roland Jakob-Roetne, Bernd Buettelmann, Andreas Ehler, Markus G. Rudolph and Rosa María Rodríguez Sarmiento*, *J. Med: Chem.* **2016**, 59, 10163-10175