

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

R. M. Rodríguez Sarmiento<sup>1</sup>, C. Lerner<sup>1</sup>, R. Jakob-Roetne<sup>1</sup>, B. Buettelmann<sup>1</sup>, A. Ehler<sup>1</sup>, M. G. Rudolph<sup>1</sup>

<sup>1</sup>Pharmaceutical Research and Early Development (pRED), Roche Innovation Center Basel, F.Hoffmann-La Roche

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