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

R. M. Rodríguez Sarmiento[1], C. Lerner[1], R. Jakob-Roetne[1], B. Buettelmann[1], A. Ehler[1], M. G. Rudolph[1]

[1]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