Atropisomerism by Design: Discovery of a Selective and Stable Phosphoinositide 3-Kinase (PI3K) β Inhibitor

**Significance:** The target molecule K is a phosphoinositide 3-kinase (PI3K) β inhibitor that is of interest for the treatment of various cancers. The restricted axis of rotation around a carbon–nitrogen bond of rac-K generated atropisomeric compounds (P)-K and (M)-K with significantly different pharmacological and pharmacokinetic profiles.

**Comment:** The metabolism of the inactive atropisomer (M)-K is the result of the action of the enzyme aldehyde oxidase (AO) whereas the active atropisomer (P)-K has lower affinity for AO resulting in better metabolic stability. The atropisomers (ΔErot = 35 kcal/mol) were separated by preparative chiral SFC chromatography.