Synthesis of a Phosphoinositide 3-Kinase (PI3K) β Inhibitor

Category

Synthesis of Natural Products and Potential Drugs

Key words

phosphoinositide 3-kinase β inhibitor

aldehyde oxidase

atropisomers

benzimidazole ring formation

1,2,4-triazole ring formation

Suzuki–Miyaura coupling

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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 ($\Delta E_{\text{rot}} = 35 \text{ kcal/mol}$) were separated by preparative chiral SFC chromatography.

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