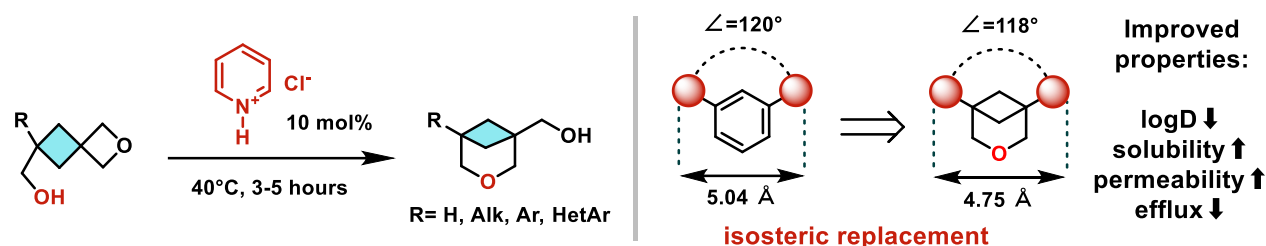


3-Oxabicyclo[3.1.1]heptanes as Isosteres of meta-Substituted Benzene Rings¹

Jennifer Morvan; Evelien Renders; Peter J.J.A. Buijnsters; **Pavel Ryabchuk**.

Johnson & Johnson Innovative Medicine, Janssen Research & Development, Janssen Pharmaceutica NV.
Turnhoutseweg 30, 2340, Beerse, Belgium,

Contact: Pavel Ryabchuk, pryabchu@its.jnj.com



Replacement of the aromatic rings in drug candidates with isosteric rigid sp^3 -rich scaffolds can improve physicochemical properties and increase the chance of progressing the molecule in the development and open new chemical space. Isosteres of meta-substituted benzenes remain challenging due to the difficulty of mimicking the exit vector angles and bond distances. Herein, we report the synthesis of 1,5-disubstituted 3-oxabicyclo[3.1.1]heptanes (oxa-BCHs), which can serve as saturated isosteres of meta-substituted phenyl rings, with similar geometric arrangement. This structural motif can be obtained under mild reaction conditions via acid-mediated isomerization of (2-oxaspiro[3.3]heptan-6-yl)methanols using catalytic quantities of pyridinium chloride (PyrHCl). We demonstrate the utility of this methodology by preparing various building blocks for use in medicinal chemistry and incorporating the 3-oxa-BCH into the anticancer drug Sonidegib, improving its physicochemical properties, such as permeability, metabolic stability and solubility.

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