Category

Innovative Drug Discovery and Development

Key words

YAP

TEAD

PPI inhibitors

virtual screening

structure-based design

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The First Class of Small Molecules Potently Disrupting the YAP-TEAD Interaction by Direct Competition

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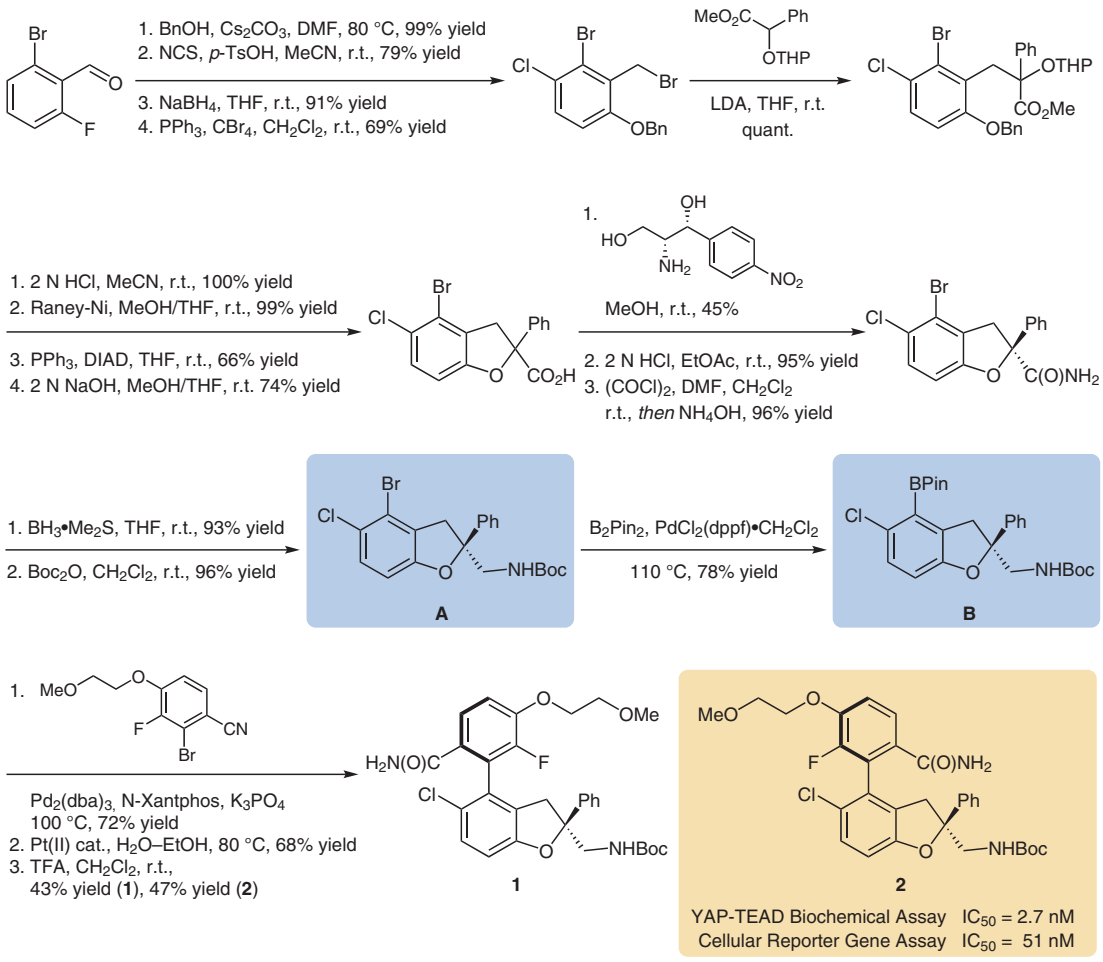
Small Molecule Inhibitors of the YAP-TEAD Interaction



Significance: Disruption of the YAP-TEAD protein–protein interaction (PPI) represents an opportunity to treat cancers associated with proliferation mediated by the Hippo signaling pathway. However, due to the extended and shallow surface that YAP and TEAD interact through, identification of efficient small-molecule inhibitors of the YAP-TEAD PPI has been challenging. Using virtual screening and structure-based drug design, Furet and co-workers have identified compound **2** which is a potent disruptor of the YAP-TEAD PPI both biochemically and in a cellular setting.

Comment: The single enantiomer dihydrobenzofuran present in intermediates **A** and **B** was installed through a key Mitsunobu reaction and salt resolution. Guided by structure, Furet and co-workers leveraged intermediates **A** and **B** to explore hydrophobic substitution at the 4-position of the dihydrobenzofuran scaffold through Suzuki coupling. Ultimately, compound **2** was synthesized in 47% yield via Suzuki coupling of compound **B**, followed by nitrile hydration, Boc deprotection and chromatographic separation from the undesired biaryl diastereomer **1**.

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