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Toward Dual Targeting of Catalytic and Gatekeeper Pockets in Cyclophilins Using a Macrocyclic Scaffold
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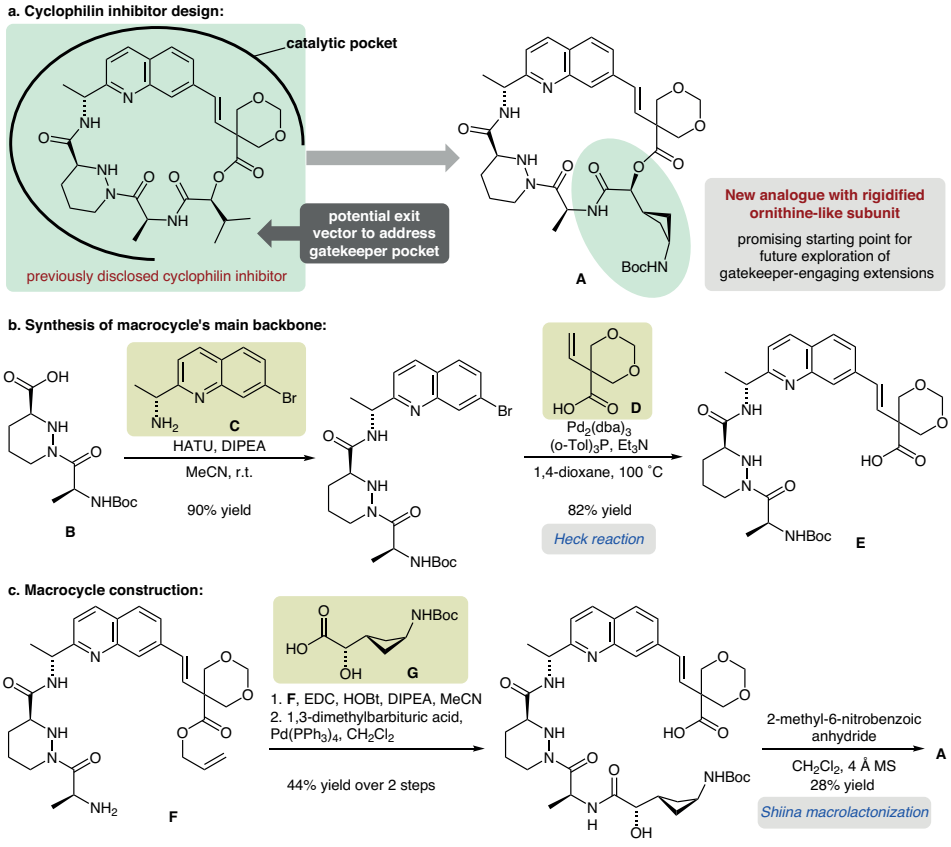
Gatekeeper Pocket as Auxiliary Interaction Site for Macrocyclic Cyclophilin Inhibitors



Significance: The cyclophilins are ubiquitous proteins that play important roles in the life cycles of various viruses. Cyclophilin inhibitors are therefore considered potential therapeutic agents for the treatment of viral infections. This work investigates a potential auxiliary binding site for macrocyclic peptide CyP inhibitors. These bind in the highly conserved catalytic pocket of the CyPs, which results in low subtype specificity. The authors suggest the neighboring variable gatekeeper pocket could be leveraged as interaction site for CyP inhibitors to increase specificity. They identified the branched sidechain as suitable exit-vector and synthesized a series of analogues including **A**, the rigid sidechain of which is thought to enable access to the gatekeeper pocket (**a**).

Comment: Hausch and co-workers' divergent synthetic approach relies on the rapid assembly of the core backbone of the macrocycle (intermediate **E**) from the three key building blocks **B**, **C** and **D** through a sequence of peptide coupling and Heck reaction (**b**). Intermediate **E** was advanced to **F**, from which the analogues investigated in this study were synthesized through sequential peptide coupling, ester deprotection and macrocyclization (**c**). For their rigid-sidechain analogue **A**, the authors established a synthesis of cyclobutane-containing amino acid **G**, which might be a valuable unnatural amino acid building block beyond the scope of this work.

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Category

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Key words

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macrocyclic (depsi) peptides

unnatural amino acids

Heck reaction

Shiina macrolactonization

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