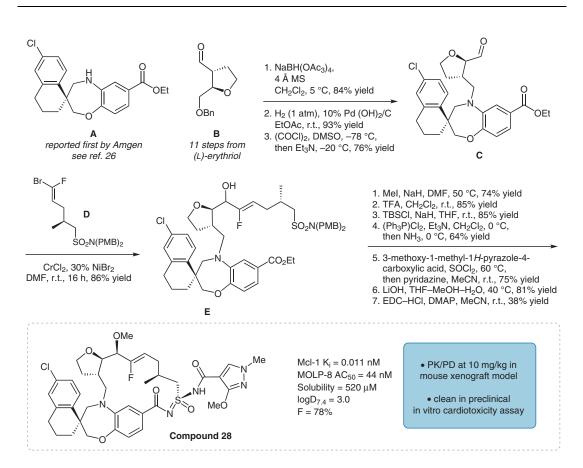
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Discovery of an Oral, Beyond-Rule-of-Five Mcl-1 Protein-Protein Interaction Modulator with the Potential of Treating Hematological Malignancies

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Toward Improved On-Target Safety: Discovery of Potent, Short Half-Life Macrocyclic Inhibitors of Mcl-1



Significance: Overexpression of the pro-survival and anti-apoptotic protein myeloid cell leukemia 1 (Mcl-1) is a hallmark of many human cancers. As Mcl-1 is also expressed in cardiomyocytes, there exists the potential for on-target cardiotoxicity. Jerhaoui and co-workers report the design of Mcl-1 inhibitor 28 that addresses the concern of on-target cardiotoxicity via a C_{max}-driven approach, achieving maximal concentration (C_{max}) quickly and pairing that with a short half-life to avoid prolonged systemic exposure. Excellent potency and oral bioavailability were achieved, and in vivo efficacy was observed in a mouse xenograft model. Also, the potential for off-target cardiotoxicity was de-risked through in vitro profiling in stem-cell-derived cardiomyocytes.

Comment: Compound 28 is constructed through key intermediate A (reported by Amgen for the synthesis of AMG176, ref. 26 of original article), tetrahydrofuran aldehyde B and (E)-bromo fluoroalkene D. Reductive amination between core A and aldehyde B followed by debenzylation and oxidation afforded intermediate C. A nickel/chromium-mediated Nozaki-Hiyama-Kishi (NHK) coupling of aldehyde C with alkene D afforded intermediate E which was poised to undergo macrocyclization followed by sulfonimidamide formation to afford compound 28.

SYNFACTS Contributors: Antonia F. Stepan (Roche), Danica A. Rankic (Pfizer) Synfacts 2023, 19(10), 1041 Published online: 14.09.2023 **DOI:** 10.1055/s-0042-1752786; **Reg-No.:** A04223SF