NOVEL CHK1 INHIBITOR MU380 EXHIBITS SIGNIFICANT SINGLE-AGENT ACTIVITY IN TP53-MUTATED CHRONIC LYMPHOCYTIC LEUKEMIA CELLS

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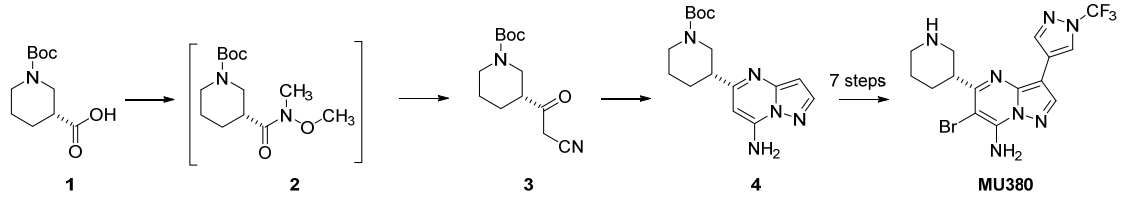
MU380 is a selective, potent and metabolically robust inhibitor of checkpoint kinase 1 (CHK1) [1]. Herein, we report enantioselective synthesis and anti-CLL single-agent activity of MU380 [2].



We first converted 1 to the Weinreb amide 2, whose treatment with deprotonated acetonitrile at low temperature afforded the required *β*-ketonitrile 3 with high optical purity (99% ee). Subsequent cyclization with 3-aminopyrazole in acetic acid afforded the desired pyrazolo[1,5-*a*]pyrimidine 4 in high yield (95%) and optical purity (96% ee). Of note, all three steps required extensive optimization of reaction conditions to avoid the loss of stereochemical integrity. Using the intermediate 4 in the synthetic sequence we previously reported for racemic MU380 [1] and final recrystallization from acetonitrile, we produced optically pure MU380 (> 99% ee) on gram scale (overall yield 33% over 10 steps).

MU380 manifested substantial single-agent activity in both *TP53*-wild type and *TP53*-mutated leukemia and lymphoma cell lines. Notably, MU380 also exhibited significant *in vivo* activity in a xenotransplant mouse model where it efficiently suppressed growth of subcutaneous tumors generated from MEC-1 cells [2].

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[1] P. Samadder et al. *Mol. Cancer Ther*. **2017**, 16, *9*, 1831-1842.

[2] M. Boudny et al. *Haematologica* **2019**, doi:10.3324/haematol.2018.203430.