SEQUENTIAL MULTI-BOND FORMING REACTIONS APPLIED TO THE SYNTHESIS OF CONFORMATIONALLY RESTRICTED MDM2-p53 INHIBITORS SUITABLE FOR INTERMITTENT DOSING

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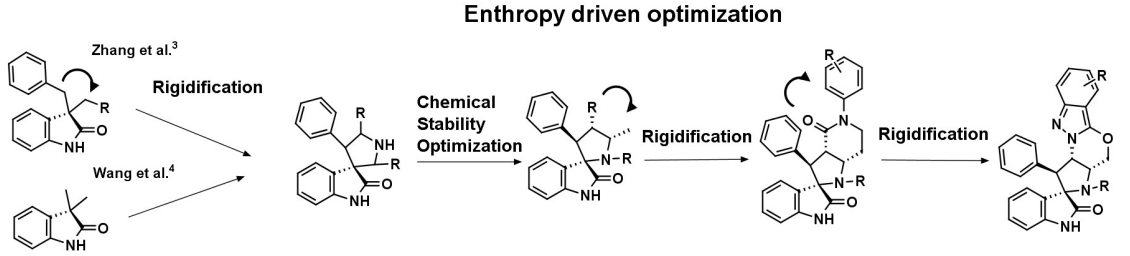
MDM2 is a main and direct inhibitor of the crucial tumor suppressor p53.[1] Reports from initial clinical trials showed that blocking this interaction with an inhibitor can be of great value in the treatment of p53 wild-type tumors. Dose-limiting hematological toxicities and drug-induced resistance have been identified as main issues in the clinic.[2] We aimed for an inhibitor with superior potency and pharmacokinetic properties to ultimately achieve full efficacy with less-frequent dosing schedules.



The discovery and optimization of novel, chemically stable spiro-oxindole compounds that are not prone to epimerization as observed for other MDM2-p53 inhibitors will be presented. Structure based optimization accompanied by conformational restriction served as guiding optimization principal and led to complex fused ring systems. The complex structures were prepared efficiently by the application of various multi-bond forming reactions (e.g.: cycloadditions, reductive cyclisation cascades, Davis-Beirut reactions) to enable accelerated optimization. *In vivo* efficacy in disease relevant xenograft models even when given as low single doses will be presented exemplified by the development candidate BI-0282.

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