Master Thesis

Towards an AURKA-targeting PROTAC: Route Development and Synthetic Optimization

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SUMMARY

Proteolysis-targeting chimeras (PROTACs) represent an innovative therapeutic modality that induces selective protein degradation by recruiting a protein of interest (POI) to an E3 ubiquitin ligase. This may allow to target previously undruggable proteins, yet pharmacokinetic limitations of PROTACs, such as metabolic instability and poor solubility, remain a major challenge in clinical translation.

Previous work in the Laboratory of Medicinal Chemistry at Ghent University (LMC) has yielded potent Aurora kinase A (AURKA) degraders capable of inducing MYCN destabilization in neuroblastoma models. However, despite strong initial degradation, limited metabolic stability resulted in a rebound of AURKA levels over time.

This Master thesis focused on the synthesis of the AURKA-targeting PROTAC B-81, as reported in patent literature, with the aim of reproducing the synthetic route to enable future biological evaluation in neuroblastoma cells, following its previous testing in breast cancer cells. The synthesis proved challenging, and several key transformations could not be reproduced under the reported conditions.

Efforts were directed towards the optimization of both the AURKA and the E3 ligase ligand syntheses, involving systematic variation of reaction conditions and detailed LC-MS and NMR analyses to monitor reaction outcomes and identify side products. Mechanistic studies revealed competing deprotonation pathways and undesired side products, especially in the C-alkylation step of the AURKA ligand, which ultimately required redesign of the synthetic strategy.

Although the full synthesis of B-81 was not achieved, this work provided important insights into the limitations of the reported route and the reactivity of key intermediates. The findings contribute to a better understanding of the synthetic challenges associated with AURKA-targeting PROTACs and may support future optimization and synthetic efforts.