SYNTHESIS OF HASPIN KINASE INHIBITORS AND DEVELOPMENT OF PROTACS CANDIDATES FOR CANCER THERAPY APPLICATIONS

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Due to their crucial role in regulating cell signaling pathways, protein kinases can be implicated in a variety of pathologies. For example, many kinases are overexpressed in cancer. Among them, Haspin stands out as an essential mitotic kinase and a potential therapeutic target, particularly for developing new therapeutic strategies against triple-negative breast cancer and pancreatic cancer, which are associated with poor prognosis.

In previous work, a structure-activity relationship study on a pyrroloisoquinoline backbone demonstrated the ability of various compounds to inhibit Haspin (Fig. 1A) [1].

In parallel, a novel therapeutic strategy has emerged: PROTACs (PRoteolysis TArgeting Chimeras), which induce degradation of the targeted protein rather than simply inhibiting it. This intracellular degradation is achieved by hijacking the cell's natural protein degradation system to target the protein of interest (Fig. 1B). PROTACs offer several advantages, including efficacy at low doses and a lasting effect even after the molecule has been eliminated from the body.

This work aims to integrate previously identified inhibitors with the PROTACs strategy to break down Haspin kinase, ultimately contributing to the development of novel anti-cancer therapies.

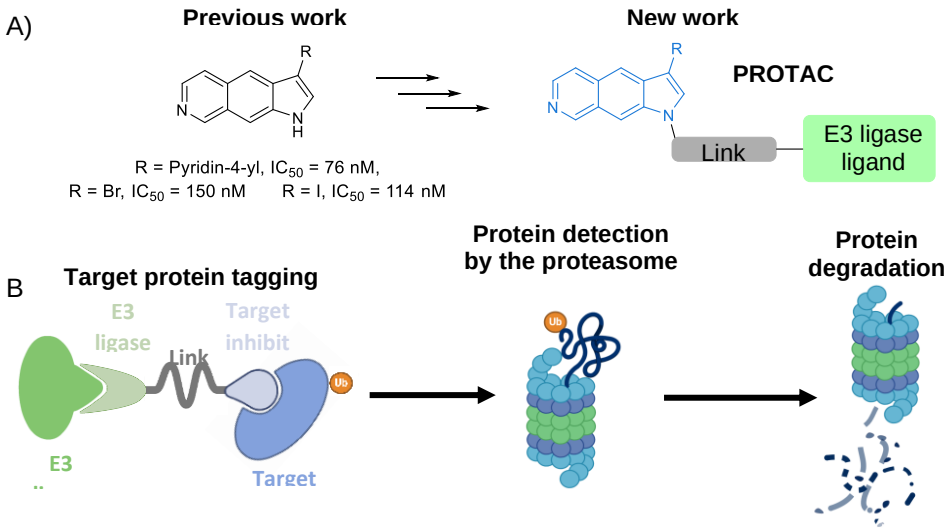

Figure 1: A) General structure of synthesized molecules.
B) Schematic representation of the PROTAC mechanism.

References:

[1] M. Defois, B. Josselin, P. Brindeau, A. Krämer, S. Knapp, F. Anizon, F. Giraud, S. Ruchaud, P. Moreau. Synthesis and biological evaluation of 1*H*-pyrrolo[2,3-*g*]isoquinolines. *Bioorg. Med. Chem*. **2024**, *100*, 117619.