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BOOK OF ABSTRACTS

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Designing novel spiropyrazoline oxindoles to dual target p53-MDM2/X PPIs

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Natural products (NPs) and their analogues have been historically a source of inspiration to pharmacotherapy, in particular drug discovery, as they cover unexplored chemical space that is not occupied by commercially available molecule libraries. Despite their limited application in drug discovery, the identification of biologically relevant fragments is a powerful strategy in the discovery and development of new drugs. NPs-derived spirooxindoles are privileged scaffolds and several analogues are undergoing clinical trials, as anticancer candidates [1]. In our research group, we have been focusing on the development of five-membered spirooxindoles to activate p53 tumor suppressor function [2].

The p53 protein is one of the most promising targets in cancer research since it is inactivated in cancer cells. Hence, the dual inhibition of p53 interactions with MDM2 and MDMX is an efficient approach to fully activate wild type p53 function. Despite several clinical candidates have entered clinical trials as MDM2 inhibitors, they all show toxicity and develop chemoresistance, and don't inhibit p53-MDMX protein-protein interaction (PPI). Currently, no small molecule is undergoing clinical trials as dual inhibitor of p53-MDM2/X PPIs. Therefore, it is imperative to develop new chemical families to inhibit both MDM2 and MDMX to consequently fully reactivate the p53 function [3].

Here, we report our recent results in the development of spiropyrazoline oxindoles as dual inhibitors of p53-MDM2/X PPIs. Structure-based optimization of the hit compound to mimic p53 pivotal amino acids was performed while introducing chemical diversity of substituents. The most promising compounds were synthesized and evaluated in cancer cell lines harboring wild type p53 and overexpressing MDM2 and/or MDMX. The most active compounds were also evaluated in an enzyme immunoassay for heterocomplexes p53-MDM2 and p53-MDMX. Four new

spiropyrazoline oxindole derivatives inhibited both p53-MDM2/X PPIs in the nanomolar range while one was highly selective disrupting p53-MDM2 PPI. These compounds are invaluable leads for developing new dual MDM2/X inhibitors [4].

References

[1] Atanasov, A, et al. *Nat. Rev. Drug Disc.* **2021,** 20(3): 200–216. doi: 10.1038/s41573-020-00114-z
[2] Zhu, H, et al. *J. Hemat. Onc.* **2022**, 15:91. doi: 10.1186/s13045-022-01314-3
[3] a) Ribeiro, C, et al. *Med Chem Comm* **2016**, 7, 420–425. doi: 10.1039/C5MD00450K
b) Nunes, R, et al. *Eur. J. Med. Chem.* **2017**, 139, 168–179. doi: 10.1016/j.ejmech.2017.07.057
c) Ribeiro, C, et al. *Eur. J. Med. Chem.* **2017**, 140, 494–509. doi: 10.1016/j.ejmech.2017.09.037
[4] Espadinha, M, et al. *Eur. J. Med. Chem.* **2022**, 241, 114637. doi: 10.1016/j.ejmech.2022.114637

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