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With a little help from computer-aided drug design – new antitumor agents as tubulin polymerization inhibitors

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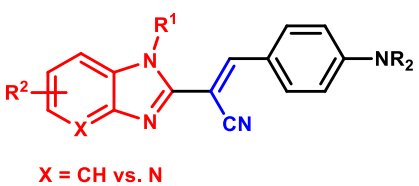
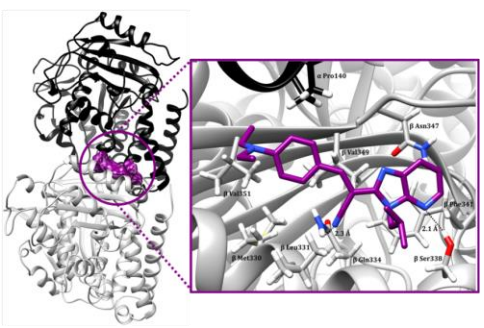
Due to their widespread applications and interesting chemical and biological features, nitrogen heterocycles are still playing a significant role in the modern medicinal chemistry by extensively contributing to the rational design of novel biologically active molecules.[1] Benzazole scaffold has become a fundamental building block widely incorporated in the structure of numerous natural and synthetic molecules, while displaying a whole range of versatile biological activities.[1] The structural similarity of the benzimidazole core with natural purines, allowed its optimization towards more efficient and selective ligands, being of particular interest for the pharmaceutical industry.

Here, we are presenting the design, synthesis and *in vitro* antiproliferative activity of several antitumor agents. Our research was initiated with variously substituted benzimidazole derived acrylonitriles,[2] which were tested for the tubulin polymerization inhibition as a possible mechanism of their biological activity. Immunofluorescence staining and tubulin polymerization assays confirmed tubulin as the main target, with several compounds highlighted as very selective, non-cytotoxic and promissing antitumoral agents. Computational analysis supported the measured activities by identifying binding preferences and affinities, while elucidating precise protein-ligand interactions governing the binding. The obtained insight underlined a simple idea to replace the benzimidazole phenyl ring with pyridine, which led us to prepare several imidazo[4,5-*b*]pyridine derivatives[3] with tubulin polymerization inhibition potencies significantly surpassing those of the initial benzimidazole analogues.





[1] A Kumar *et al.* (2023) *Pharmaceuticals* 16, 299; L-S Feng *et al.* (2022) *Arch Pharm* 355, 2200051.
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