With a Little Help from Computer-Aided Drug Design: New Antitumor Agents as Tubulin Polymerization Inhibitors

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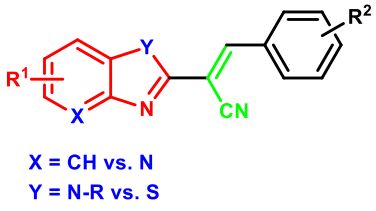
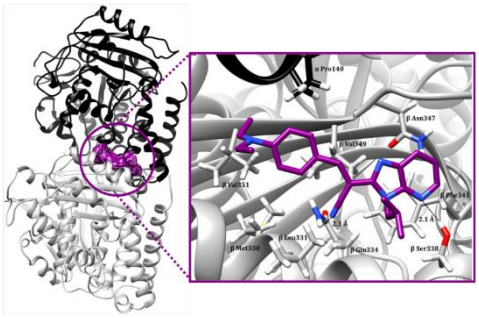
Nitrogen heterocycles, particularly benzazoles, are central to modern medicinal chemistry due to their versatile chemical and biological properties, serving as key scaffolds in designing novel bioactive molecules [1]. The benzimidazole core, resembling natural purines, has been refined to create selective and potent ligands, drawing significant pharmaceutical interest.

This study presents the design, synthesis, and *in vitro* antiproliferative activity of new antitumor agents. Starting with variously substituted benzimidazole-derived acrylonitriles [2], we evaluated their ability to inhibit tubulin polymerization as a possible mechanism of their biological activity. Immunofluorescence staining and tubulin polymerization assays confirmed tubulin as the primary target, with several compounds showing high selectivity, low cytotoxicity, and promising antitumor potential. Computational analysis revealed binding preferences, affinities, and critical protein-ligand interactions governing the binding. The obtained insight underlined a simple idea to replace the benzimidazole phenyl ring with pyridine, leading us to prepare several imidazo[4,5-*b*]pyridine derivatives [3] that exhibited markedly improved tubulin polymerization inhibition compared to the original benzimidazole analogues.





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