Pyridine based antitumor compounds acting at the colchicine site

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Tubulin inhibitors are amongst the most successful anti-cancer, anti-parasitic and herbicidal agents. Their vascular disrupting activity has recently attracted research focus as it elicits anti-cancer effects at doses well below that of other toxic agents. The colchicine site of tubulin is located in a hydrophobic region at the interface of the tubulin α,β-dimer.

Ligands binding at the colchicine site occupy different pockets and make different types of interactions with the protein. Colchicine site agents are structurally simple, and synthetically accessible anti-tubulin agents are in active development. But these agents suffer from poor pharmacokinetics. The incorporation of pyridines and related nitrogenated heterocycles in the structures of colchicine site agents has resulted in new active scaffolds, improved potencies and pharmacokinetic improvements for binding with colchicine site ligands.

This article critically reviews the impact of such modifications in the field and in the future perspectives of this class of clinically successful agents. The colchicine binding drugs have been classified according to their described or presumed binding modes and the impact of the pyridine and related moieties on the activity for each compound class is discussed based on structure - property and structure - activity relationships, and on X-ray structures when available. Special emphasis has been made on drugs advancing to clinical trials and on proof of concept modifications.

From this analysis, a new insight into tubulin targeting is highlighted

along with future perspectives for the development of similar site-specific agents.

More information: R. Álvarez et al, Pyridine Based Antitumour Compounds Acting at the Colchicine Site, *Current Medicinal Chemistry* (2016). DOI: 10.2174/0929867323111604201048 23