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Combretastatin A-4 inspired novel 2-aryl-3-arylamino-imidazo-pyridines/pyrazines as tubulin polymerization inhibitors, antimitotic and anticancer agents

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Based on the pharmacophoric features of the natural product, combretastatin A-4 (CA-4) and its synthetic analogues that inhibit tubulin polymerization, a series of novel 2-aryl-3-arylamino-imidazo-pyridines/pyrazines as potential antitubulin anticancer agents were designed. They were synthesized by a one-pot method involving preparation of isocyanides from the anilines via formylation and subsequent dehydration followed by their reactions with heterocyclic-2-amidines and aldehydes. Compounds 1, 2, 14, and 15 were found to exhibit significant tubulin polymerization inhibition and disruption of tubulin–microtubule dynamics similar to that of CA-4. They showed potent anticancer activities in kidney, breast and cervical cancer cell lines, and relatively low toxicity to normal cells, compared to CA-4. The compounds induced DNA and chromosomal damage, and apoptosis via cell cycle arrest in the G2/M phase. The molecular docking and molecular dynamics (MD) simulation studies revealed that disruption of microtubule dynamics might occur by interaction of the compounds at the colchicine binding site at the a,b-tubulin heterodimer interface, similar to that of CA-4. Molecular modelling analysis showed that two of the three methoxy groups at ring A of all four potent compounds (1, 2, 14, and 15) were involved in bifurcated hydrogen bonding with Cysb241, an important molecular recognition interaction to show tubulin inhibitory activity. In comparison to CA-4, the bridging NH and the imidazo-pyridine/pyrazine moieties in the title compounds provide flexibility for attaining the required dihedral relationship of two aryls and additional pharmacophoric features required for the interaction with the key residues of the colchicine binding site.

Biography

Sarita Das has completed her MSc in Biotechnology from KIIT University, India and is currently pursuing PhD in Cancer Biology from KIIT University, India. She has published 3 research papers in international journals.

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