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Journal Article: Design and Synthesis of Novel Piperidine analogues as anti-colon cancer agents.

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Abstract: Aurora A kinase, a serine/threonine kinase that is overexpressed in various cancers, is a promising target for anticancer drugs. This study developed a robust ligand-based pharmacophore model using HypoGen to identify the key features of Aurora A kinase inhibition. The optimal hypothesis (Hypo-1), with one hydrogen bond acceptor, one hydrophobic aliphatic, and two aromatic ring features, showed excellent statistical validation (correlation coefficient = 0.94, RMSD = 1.30, cost difference = 58 bits). Model validation with known inhibitors yielded high enrichment (GH score = 0.65), confirming its reliability. A comparative model integrating HypoGen and GLIDE docking scores was constructed using multiple linear regression ($r^2 = 0.843$), enhancing predictive accuracy. A virtual library of 10,000 compounds was constructed using fragment- and knowledge-based design principles, incorporating pharmacophore-aligned scaffolds. PASS prediction prioritized molecules with a high probability of activity against colorectal cancer (Pa > 0.5). Based on these criteria, 29 hits bearing aminopyrimidine-substituted piperidine-4-ones were synthesized and characterized using IR, ^{1}Hsingle bondNMR, ^{13}Csingle bondNMR, mass spectrometry, and elemental analysis. The synthesized compounds were screened in vitro against HCT-15 colorectal cancer cells. Notably, compounds 21A and 25A exhibited potent antiproliferative activity, with IC_{50} values of 0.01 μM. Structure–activity relationship analysis revealed that electronegative substituents, such as –F, –Cl, and $–NO_2$, on aromatic rings significantly enhanced the anticancer activity. This study established a rational strategy combining

pharmacophore modeling, PASS prediction, and synthetic validation to develop selective Aurora A kinase inhibitors with potential therapeutic relevance in colorectal cancer.

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