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Plant based analogues possessing selective toxicity against resistant colorectal cancer

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Current modes of treatment, is less effective in aggressive colon cancer due to development of resistance, indicating novel targeted therapies for colon cancer are much needed. Harnessing beneficial effects of plant based molecules, we designed and developed molecules that retain the beneficial cytotoxic potential but have fewer side effects and can bypass drug resistance. We designed and synthesized severalnovel polycyclic heterocycles, with pyrimido[1,2:1,5]-pyrazolo[3,4-b]quinoline framework and evaluated them for anticancer activity against colon, breast, ovarian and hepatocellular carcinoma cell lines and non-cancer cells. The results of the screening studies revealed compound 5, a 4-chloro-2-methyl pyrimido[1",2":1,5]pyrazolo[3,4-b]quinoline to exhibit ten to fifteen times more selectivity and potent cytotoxic activity against seven colon cell lines at sub-nanomolar concentrations compared to other cell lines. This was also confirmed by changes in morphological status of the cells. Moreover, we found concentration dependent changes in mitochondrial membrane potential of HCT-116 with compound 5 leading to apoptosis and chromosomal DNA damage. Additionally, all the pyrimido[1,2:1,5]-pyrazolo[3,4-b]quinoline derivatives were found to-not-to be a substrate of MDR1/ABCB1/P-glycoprotein and/or ABCG2 transporters. Gene-chip analysis revealed that Compound 5 produces significant change in key signaling pathways leading to cell survival and progression. In sum, this work has led to the discovery of a novel 4-chloro-2-methyl pyrimido[1",2":1,5]pyrazolo[3,4-b]quinoline with potent cytotoxic and apoptosis- inducing properties on colon cancer cells, without being a substrate of ABCB1 or ABCG2 drug resistance factors. More mechanistic and pharmacokinetic-pharmacodynamic [PK-PD] directed studies integrated with rigorous toxicity studies would be conducted to bring Compound 5 or similar molecules in the clinics.

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