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Synthesis, structural anticancer activity relationship, and docking study of novel 5-deazaflavin analogs

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In attempting to improve the efficacy of 5-deazaflavin derivatives as antitumor agents, novel 2-(N-substituted amino, hydrazino and heterocyclic amino), 2,2'-(piperazine-1,4-diyl)-bis(10-alkyl)-, and 2[(E)-2-(substituted) benzylidene hydrazino] derivatives were designed. These compounds were prepared by nucleophilic substitution of C2-methylthio group. The 10-aryl-2-thioxo- and 2-(substituted amino)-10-aryl derivatives were prepared by condensation reaction of 6-anilino-2-thioxopyrimidin-4(1H)-one analogs with o-bromobenzaldehyde and 2-(substituted amino)-10-aryl analogs with different amines and hydrazine, respectively. Many compounds revealed promising IC_{50} of nanomolar range against MCF-7 and Hela tumor cell lines. The potential antiproliferative activity against MCF-7 cells was detected for 5-deazflavin analogs with the following structural features: 2-(o-bromo-, o-chloro-, or unsubstituted) benzylidene hydrazine, 2-benzylamine, 2-morpholine, 2-hydrazine, 10-small alkyl, and the 2,2'-dimeric structure linked by piprazine ring. The selectivity towards MCF-7 over HeLa cells was revealed by 2-hydrazino-10-ethyl, 2-morpholino-10-ethyl, 2-(2-chlorobenzylidene) hydrazino]-10-methyl, and 2-(2-bromobenzylidene) hydrazino]-10-ethyl compounds. Whereas, selectivity towards HeLa cells was shown for 2-thioxo-10-(o-tolyl) and 2-benzylamino-10-(p-chlorophenyl) analogs. In this study, we got derivatives with IC50 of nanomolar range more than our earlier reported studies of micromolar ranges. Over the above, the molecular docking of many compounds showed good affinities into c-kit PTK domain with low binding free energies. Substitution with phenyl rings at the 2- or 10-position results in better fitting into PTK and enhancing their antiproliferative potency. Many of these 5-deazflavins exhibited a good correlation between their IC50 and their AutoDock binding free energies (ΔGb) and inhibitions (Ki). Therefore, they represent new classes of promising candidates as potential antitumor agents and PTK inhibitors.

Biography

Hamed I. Ali got his PhD in medicinal chemistry from Okayama University, Japan. Currently, he is an Assistant Professor at Texas A&M Rangel College of Pharmacy. He has devoted his research career to design, synthesize, and biological screening of antitumor agents against different tumor cell lines. Recently, his ongoing research focuses on SAR and synthesis with optimization of chemical functionalities of Iindole-2-carboxamides to improve their allostery for the CB1as potent AM for the CB1 cannabinoid receptors, and virtual screening for hits to get lead compounds.

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