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Abstract

Synthesis, Biological Evaluation and Modeling Studies of New Pyrido[3,4-b] indole Derivatives as Broad-Spectrum Potent Anticancer Agents

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Abstract:

Objective: There is an urgent need drugs against particularly difficult to treat solid tumors such as pancreatic, triple negative breast, lung, colon, metastatic prostate cancers and melanoma. Thus, the objective of this study was to synthesize compounds based computational modeling that indicated the pyrido[3,4-b]indole class bind to MDM2, a new cancer target for which there are still no drug on the market.

Methods: Compounds were synthesized by established methods and tested for antiproliferative activity against a broad range of human cancer cell lines, comprising HCT116 colon, HPAC, MIA PaCa-2 and Panc-1 pancreatic, MCF-7 and MDA-MB-468 breast, A375 and WM164 melanoma, A549 lung, and LNCaP, DU145 and PC3 prostate cancer lines. Computational docking was also undertaken. Results: The novel pyrido[3,4-b]indoles synthesized exhibited a clear SAR with regards to antiproliferative activity, with potent broad-spectrum anticancer activity with IC50s down to 80, 130, 130 and 200 nM for breast, colon, melanoma and pancreatic cancer cells, respectively. 1-Naphthyl at C1 combined with methoxy at C6 provided the best antiproliferative activity. Thus, compound 11 (1-naphthyl-6-methoxy-9H-pyrido[3,4-b]indole) showed the highest potency. A mechanistic feature of the compounds as a group is a strongly selective G2/M cell cycle phase arrest. Docking at on MDM2 suggested a hydrogen bond interaction between the 6-methoxy Tyr106, hydrophobic interaction with Val93, pi-pi stacking interactions with Tyr100 and His96 and hydrophobic interactions with Leu54 and Ile99. An N9-methyl group disrupted binding interactions, such as H-bond interactions involving the N9 hydrogen.

Conclusion: We have identified a novel series of pyrido[3,4-b]indoles with potent broad spectrum anticancer activity towards the most aggressive and difficult to treat cancers including metastatic pancreatic cancer, non-small cell lung cancer, triple negative breast cancers, and BRAFV600E mutant melanoma, as well as metastatic colon and prostate cancers. There was also evidence of selectivity towards cancer cells relative to normal cells. These compounds will serve as new leads from which novel therapeutics and molecular tools can be developed for a wide variety of cancers.

Biography:

Shivaputra A Patil, Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee Health Science Center, USA is Submitted his abstract on the Webinar on Drug Design Techniques and Pharmacology; September 22, 2020; Paris, France.

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