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Design, synthesis and biological evaluations of Antitumor 6,11-dihydro-indolizino[8,7-b]indole-1,2-diyl) dimethanol having multi-functions, inhibition of Topoisomerase I/II and DNA cross-linking

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Our previous study demonstrated that derivatives of bis(hydroxymethyl)- indolizino[6,7-b]indole, a hybrid molecule consisting β-carboline (topoisomerase inhibition moiety) and bis(hydroxymethyl)pyrrole (DNA cross-linking moiety), exhibited multiple modes of action including DNA interstrand cross-linking and inhibition of topoisomerase I and II. To continue the investigation of hybrid molecules bearing multiple modes of action, we synthesized a series of 6,11-dihydro-5H-indolizino[8,7-b]indole-1,2-diyl)dimethanol for antitumor studies. These agents were also designed as a hybrid molecules of β-carboline and bis(hydroxymethyl)pyrrole. The target compounds were synthesized starting from the reaction of tryptamine with glyoxalic acid to give the intermediate pyrido[3,4-b]indole-1-carboxylic acid, which was then converted into the desired target compounds via esterification, N-acylation by treating with various acyl chloride, condensation with DMAD in acetic anhydride to give indolizino[8,7-b]indole-1,2-dicarboxylate derivatives and reduction. The preliminary antitumor studies revealed that these new compounds exhibited significant cytotoxicity against the cell growth of a variety of human tumor cell lines *in vitro*. Remarkably, we found that the newly synthesized compounds also possessed multiple modes of action comprising induction of DNA interstrand cross-linking and inhibition of topoisomerase I and II. In addition, cell-cycle arrest at the G2/M phase and subG1phase and apoptosis in human lung H460 tumor cells were observed. The present studies suggest that a lead compound having potent antitumor activity and multiple modes of action may be generated for further clinical development.

Biography

Sue-Ming Chang has completed his PhD from National Taiwan University in 2013 and currently postdoctoral studies from the Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan. Research field: medicinal chemistry; carbohydrate chemistry; natural product chemistry; chemical biology.

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