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N^2,N^9-Bis(Substituted benzyl)-β-Carbolineum Bromides as Potential Anticancer Therapeutics: Design, Synthesis, Cytotoxicity, Drug-DNA Intercalation and *In-Silico* Binding Properties

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Abstract

The present study reports a series of novel N^2,N^9-bis(substituted benzyl)-β-carbolineum bromides (**4a-f**) synthesized from L-tryptophan in three steps with excellent yields (>80%). The structures of synthesized compounds **4a-f** were confirmed by ^{1}H- and ^{13}C-NMR, FT-IR, LC-MS (ESI-MS) spectrum and elemental analysis. Meanwhile, the crystal structure for compound **4f** was determined by X-ray single-crystal diffraction. The crystal belongs in monoclinic space group in $P12_1/c_1$ space group with a = 13.253(6) Å, b = 20.809(10) Å, c = 9.116(6) Å, β = 107.215(13)°, V = 2401.4(19) Å^3 and Z = 4, F(000) = 1048, D_c = 1.403 Mg/m^3 and μ = 1.743 mm^{-1}. Compounds **4a-f** were evaluated for their *in-vitro* anticancer activity against selected human cancer cell lines, such as HT-29 (colorectal adenocarcinoma), HeLa (cervical carcinoma), HepG2 (hepatocellular carcinoma) and K562 (chronic myelogenous leukaemia, CML). Results showed that compounds **4a-f** exerted excellent cytotoxicity effect with IC_{50} values ranging from 0.36-1.08 μM against K562 human CML cell line. It was found that synthesized β-carbolines are much less toxic towards non-cancer cell lines BALB/c3T3 and Hs-27, in comparison to cisplatin and doxorubicin, which were employed as positive controls. To investigate the binding mode of these compounds against DNA, spectroscopic studies were conducted. Subsequent UV-Visible and *in-silico* (molecular docking) studies revealed that compound **4f** interacts with DNA through intercalation. Based on the present findings, it was suggested that compound **4f** has a great potential to be developed as a novel anticancer agent.