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Novel C-3 and C-20 derived analogs of betulinic acid as potent cytotoxic agents: design, synthesis, *in vitro* and *in silico* studies†

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In this report, novel derivatives of betulinic acid were designed and synthesized by targeting the C-3-OH group and C-20 olefinic bond in an endeavour to develop potent antitumor agents. These analogs were screened for their anticancer activity against six different human cancer cell lines including breast cancer MCF-7, lung cancer A549, colon cancer HCT-116, leukemia MOLT-4, prostate carcinoma cell PC-3 and pancreatic cancer cell Miapaca-2 by MTT assay. Many derivatives displayed better cytotoxicity than the parent compound BA. More significantly compounds **9b**, **9e**, **10** and **11a** were found to have more promising activity than BA. Compound **11a** was the most potent analog with IC_{50} values of 7.15 (MCF-7), 8.0 (A549), 3.13 (HCT-116), 13.88 (MOLT-4), 8.0 (PC-3) and 6.96 (MiaPaCa-2) μM. In addition to experimental investigations, *in silico* aspects were evaluated for the parent compound, BA and **11a** derivative based on its potential bioactive behaviour. The representative compounds were optimized structurally using density functional theory (DFT). GaussView 6.1 graphical interface associated GAUSSIAN 09 (Revision C.01) software package was used for the calculations under 6-311g(d,p)/B3LYP formalism using under a SMD model (water as solvent) for the parent compound BA and **11a** to explain the respective bioactive behaviour. This was followed by molecular docking studies suggesting that compound **11a** binds efficiently with all the three proteins with the docking score of −7.2 kcal mol^{-1} in the case of matrix metalloproteinase-2 (PDB ID: 1HOV) and poly[ADP-ribose] polymerase-1 (PDB ID: 1UK0) and −6.7 kcal mol^{-1} in the case of TRAF2 (PDB ID: 2X7F). Further, molecular dynamics studies between **11a** and the three proteins were carried out using Desmond Maestro v11.3 to study protein–ligand interactions and protein stability.

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Introduction

Cancer is a leading cause of death worldwide. According to a WHO report, in 2020, ten million deaths were contributed by cancer alone, and the most common cancers responsible for this mortality include lung, colon, liver, stomach and breast.[1] Colon cancer was found to be the third most common cancer worldwide and is the second leading cause of cancer related deaths. By the end of 2040, it is expected that the colon cancer burden will increase to 3.2 million new cancer cases and 1.6 million deaths each year.[2] Available treatments for colon cancer including surgery, chemotherapy, radiation and targeted therapy have certain limitations associated with them such as adverse side effects, multidrug resistance and limited

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