قطاع الدراسات الصيدلية (٩٤)
اللجنة العلمية للكيمياء الصيدلية والحيوية
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باللغة الانجليزية: (٢)

Design, synthesis, anticancer evaluation, and molecular modeling studies of novel tolmetin derivatives as potential VEGFR-2 inhibitors and apoptosis inducers

Novel tolmetin derivatives **5a–f** to **8a–c** were designed, synthesized, and evaluated for antiproliferative activity by NCI (USA) against a panel of 60 tumor cell lines. The cytotoxic activity of the most active tolmetin derivatives **5b** and **5c** was examined against HL-60, HCT-15, and UO-31 tumor cell lines. Compound **5b** was found to be the most potent derivative against HL-60, HCT-15, and UO-31 cell lines with IC_{50} values of 10.32 ± 0.55, 6.62 ± 0.35, and 7.69 ± 0.41 μM, respectively. Molecular modeling studies of derivative **5b** towards the VEGFR-2 active site were performed. Compound **5b** displayed high inhibitory activity against VEGFR-2 (IC_{50} = 0.20 μM). It extremely reduced the HUVECs migration potential exhibiting deeply reduced wound healing patterns after 72 h. It induced apoptosis in HCT-15 cells (52.72-fold). This evidence was supported by an increase in the level of apoptotic caspases-3, -8, and -9 by 7.808-, 1.867-, and 7.622-fold, respectively. Compound **5b** arrested the cell cycle in the G0/G1 phase. Furthermore, the ADME studies showed that compound **5b** possessed promising pharmacokinetic properties.