قطاع الدراسات الصيدلية (٩٤)
اللجنة العلمية للكيمياء الصيدلية والحيوية
الدورة الثالثة عشر (٢٠١٩-٢٠٢٢)

باللغة الانجليزية: (٤)

Design, Synthesis and Mechanistic Study of New Benzenesulfonamide Derivatives as Anticancer and Antimicrobial Agents via Carbonic Anhydrase IX Inhibition

Changes in gene expression cause uncontrolled cell proliferation and consequently tumor hypoxia. The tumor cells shift their metabolism to anaerobic glycolysis with a significant modification in pH. Therefore, an over expression of carbonic anhydrase IX (CA IX) genes was detected in many solid tumors. Accordingly, selective inhibition of CA IX can be a useful target for discovering novel antiproliferative agents. The present study described the synthesis of new aryl thiazolone–benzenesulfonamides **4a–j** as well as their carbonic anhydrase IX inhibitory effect. All the designed derivatives were evaluated for their anti-proliferative activity against triple-negative breast cancer cell line (as MDA-MB-231) and another breast cancer cell line (MCF-7) in addition to normal breast cell line MCF-10A. Compounds **4b–c, 4e, 4g–h** showed significant inhibitory effect against both cancer cell lines at concentration ranges from 1.52–6.31 μM, with a high selectivity against breast cancer cell lines ranges from 5.5 to 17.5 times. Moreover, three sulfonamides derivatives **4e, 4g and 4h** showed excellent enzyme inhibition against CA IX with IC_{50} 10.93–25.06 nM and against CA II with IC_{50} 1.55–3.92 μM that revealed their remarkable selectivity for CA IX over CA II. Additionally, **4e** was able to induce apoptosis in MDA-MB-231 with a significant increase in the annexin V-FITC percent by 22 fold as compared with control. Cellular uptake on MDA-MB-231 cell lines were carried out using HPLC method on the three active compounds (**4e, 4g and 4h**). On the other hand inhibition of one or more CAs present in bacteria was reported to interfere with bacterial growth. So, the new benzenesulfonamides were evaluated against their antibacterial and anti-biofilm activities. Analogues **4e, 4g and 4h** exhibited significant inhibition at 50 mg mL^{-1} concentration with 80.69%, 69.74% and 68.30% against S. aureus compared to the positive control CIP which was 99.2%, while compounds **4g and 4h** showed potential anti-biofilm inhibition 79.46% and 77.52% against K. pneumonia. Furthermore, the designed compounds were docked into CA IX (human) protein (PDB ID: 5FL6) and molecular modeling studies revealed favorable binding interactions for the active inhibitors. Finally, the predictive ADMET studies showed that, compounds **4e, 4g and 4h** possessed promising pharmacokinetic properties.