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Title : SYNTHESIS, BIOACTIVITY EVALUATION AND COMPUTATIONAL STUDIES OF BISINDOLYLMETHANE AND FLAVONE DERIVATIVES

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Bisindolylmethane and flavone are well-known natural product scaffolds having important pharmacophores and they have gained tremendous interest owing to their remarkable potency and activity profile towards various target diseases. In this study novel bisindolylmethanes and flavones were synthesized to identify potential inhibitors for bacterial infection, cancer, and diabetes. One hundred twenty-nine (129) bisindolylmethane derivatives (Schiff base, thiourea, sulfonamide, and hydrazone) and 43 flavone derivatives (hydrazone and ether) were synthesized, evaluated for various in vitro bioactivities, and analyzed through computational studies to identify possible inhibition mechanisms. Antibacterial activity of bisindolylmethane Schiff bases showed that most compounds moderately inhibit *Salmonella typhi, S. paratyphi* A and *S. paratyphi* B bacterial strains. The results also reveals that compounds having halides and nitro substituents showed best antibacterial activity. Bisindolylmethane thioureas and sulfonamides were tested for carbonic anhydrase II inhibition activity. Molecular docking results suggest that nitro substituent at *para* position interacts well with Zn^{2+} ion and interferes with the Zn-OH-Thr199-Glu106 hydrogen bond network. Bisindole hydrazone in this study were synthesized through a three-step reaction. β-Glucuronidase inhibitory property of some derivatives were found to be very potent (0.1-83.5 μM). Docking studies showed that active compounds should have two or more hydroxyl groups substituted on carbon adjacent to each other for good interactions to take place. Hydroxyl group at *meta* position of **269** was found to interact with important amino acids Glu450 and Glu540. With regards to flavone hydrazones and α-glucosidase inhibitory activity, thirty derivatives (**288-317**) were found to be active (0.7-30.7 μM). Compound **288** (0.7 ± 0.2 μM) was the most active compound in the series. QSAR model developed using Discovery Studio (DS) 2.5 had successfully predicted the pIC_{50}. Molecular docking on α-glucosidase was able to identify possible binding modes responsible for the inhibitory activity. Benzohydrazone linkage enhances rotatability and allows *N*-benzylidene moiety to interact with residues like Glu276, His348, and Asp349. In the final part of this thesis, 155 synthesized derivatives consisting of bisindolylmethanes (anilines, Schiff bases, thioureas and sulfonamides) and flavones (hydrazones and ethers) were evaluated for their antiproliferative activity against lung, breast, colon, nasopharyngeal, and endometrial cancer cell lines followed by molecular docking studies. Docking results suggest that bisindolylmethane thiourea and sulfonamide adopt different inhibition mechanisms. Thiourea derivative **191** was able to fit in the S1' hydrophobic pocket of MMP-2 protein, while sulfonamide **224** , which was too bulky for MMP-2 protein, was able to fit into DDX3 protein. Molecular docking for Schiff base and thiourea derivatives of bisindolylmethane suggest that they inhibit through the same mechanism by targeting HER2 protein. Schiff base and thiourea interact with residues in the phosphate binding pocket and also hinge region of HER2 protein. In general, the synthesized compounds represent potential leads for future drug discovery.