Computer-assisted design of isoflavanone derivatives as novel inhibitors of the enzyme aromatase, an anti-breast cancer target

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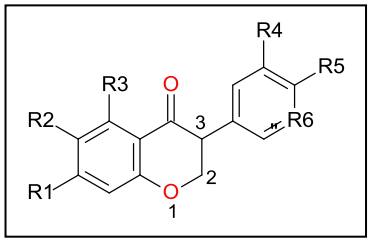
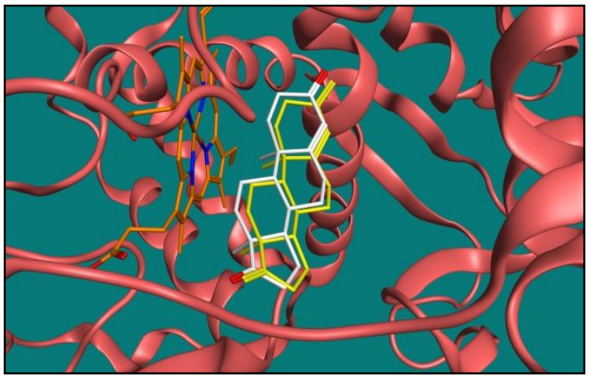
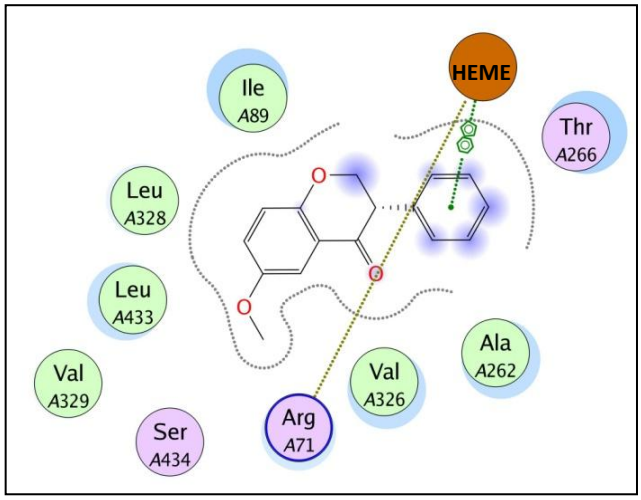
The medicinal value of inhibitors of the enzyme aromatase stems from their potential as drugs against hormone-dependent breast cancer. Currently used drugs such as tamoxifen target the estrogen receptor and can cause undesirable and sometimes severe side effects. Therefore, the development of aromatase inhibitors that interfere with estrogen synthesis has been pursued as an alternative. Among these inhibitors, isohydrocoumarins and isoflavanones have shown promise in preliminary studies. In order to elucidate the intermolecular interactions responsible for inhibitor binding and to guide future synthetic efforts, we computationally docked the structures of 15 synthesized isoflavanones into the X-ray crystal structure of human aromatase. Three different docking programs (Gold, Surflex Dock, MOE) with various scoring functions were evaluated. Criteria for the accuracy of a given docking protocol were its ability to correctly reproduce the pose of the original ligand, 4-androstene-3,17-dione, and the correlation between docking score and bioactivity. So far, best results were obtained with Gold in conjunction with the scoring function GoldScore. Analysis of the docking results identified hydrophobic interactions along with arene-arene interactions as the main driving forces for inhibitor binding by aromatase. Docking runs with a conformationally flexible binding site were conducted also. Future work aimed at improving the binding affinity of inhibitors for their target will address the size and nature of the aromatic substituent at carbon 3.



General structure of isoflavanone derivatives used for inhibition of aromatase



Androstenedione, GOLD docked pose (white) against crystal structure pose (yellow) in aromatase (red ribbon)



Two-dimensional representation of crucial enzyme inhibitor interactions