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Inside *c-kit* tyrosine kinase: molecular modeling and QSAR in the search of new inhibitors

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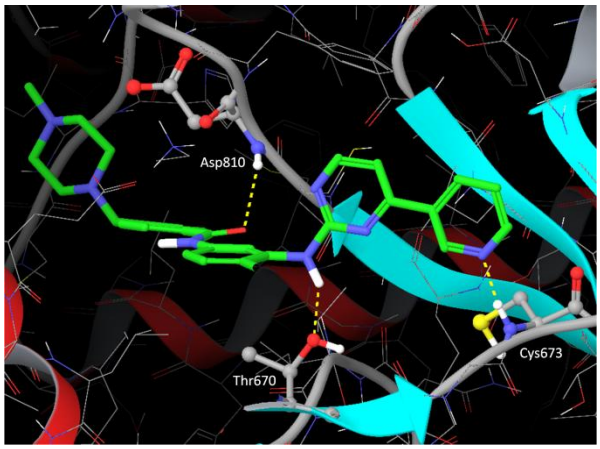
Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal tumors of the gastrointestinal tracts. Previously, they were effectively treated only with surgery that remains the mainstay of therapy for primary disease. Standard sarcoma chemotherapy and radiation have limited benefits against these tumors. The identification of *c-kit*, a receptor tyrosine kinase, that is commonly expressed by GISTs, provided a therapeutic target. Gleevec (also known as imatinib mesylate or STI-571) inhibits c-kit kinase and other kinases such as ABL, PDGFR, and is approved for the treatment of chronic myelogenous leukemia and GISTs[1].



Therapy suggested that certain mutations are likely to be responsive to imatinib, whereas others are less[2], therefore the search for new inhibitors is actual. Therefore, we tried to rationalize structure-activity relationships of four class of inhibitors (2-aminobenzoxazoles, thienopyrimidines, 3-aminobenzoisoxa(thi)azoles and 3-aminophtalazines) together with other promising inhibitors by means molecular modeling and 3D-QSAR. First, Induced Fit docking study was performed on these inhibitors and *c-kit* (wild type and mutants) revealing the involvement of different residues in H-bonding and the importance of aromatic features in correspondence of key residues. Obtained poses were used to create a ligand-based 3D-QSAR pharmacophore model with meaningful results (R^2=0.97; Q^2=0.73). Based on the identified features of the pharmacophore model, virtual screening was carried out over 8 million structures selecting some hits which are predicted as good inhibitors. Biological testing for the identified ligands will eventually allow to discover new lead compounds endowed with inhibitory activity against *c-kit*.

References:

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(2) Tarn C., Merkel E., Canutescu A. Shen W., Skorobogatko Y., Heslin M. J., Eisenberg B., Birbe R., Patchefsky A., Dunbrack R., Arnoletti J. P., von Mehren M., Godwin A. K. Analysis of KIT mutations in sporadic and familial gastrointestinal stromal tumors: therapeutic implication through protein modeling. Clin. Cancer Res. 2005, 11, 3668-3677.