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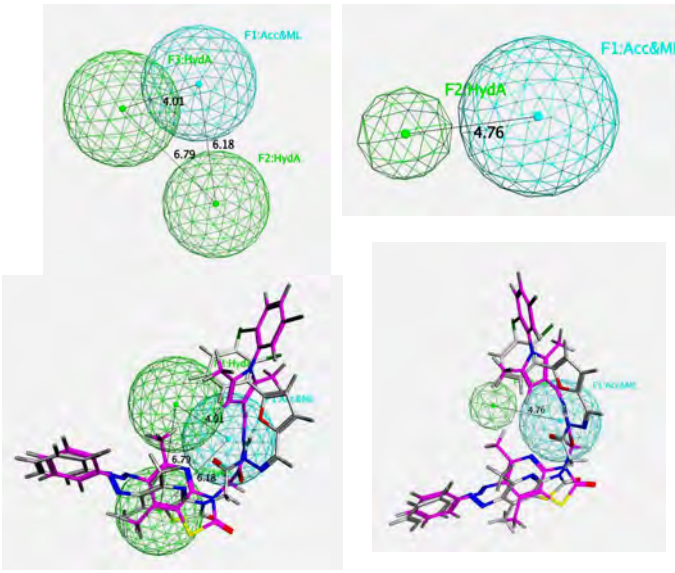
3D Pharmacophore modeling for thiazolo[4,5-b]pyridine-2-ones as novel potent mPGES-1inhibitors

Novel thiazolo[4,5-*b*]pyridine-2-one scaffold-based biologically active compounds design and their discovery as potential drug candidates using traditional organic synthesis protocols, pharmacological screening methodologies and *in silico* techniques is the nowadays drug design challenge.

A series of novel 5,7-dimethyl-6-phenylazo-3*H*-thiazolo[4,5-b]pyridine-2-one derivatives with alkyl, acetamide, phenylacetamide, hydrazide, phenylidene hydrazide moieties as N^3 position substituents were synthesized. Pharmacological screening of thiazolopyridines was performed for their anti-exudative response evaluation and a few compounds were disclosed as more potent anti-inflammatory agents than diclofenac which was used as a standard drug.

In order to identify novel compounds that can exhibit mPGES-1 inhibitory action flexible molecular docking studies of thiazolo[4,5-*b*]pyridin-2-ones were performed with MOE software using high resolution crystallographic structure of glutathione:mPGES-1 complex (pdb code 4AL0). Minimized complexes as the docking studies outcome were scored by the four scoring functions available in MOE revealing the synthesized compounds strong potency as mPGES-1 inhibitors most of them were evaluated to form more energetically favorable ligand-receptor complexes then that of Licofelone. Active dock poses of thiazolo[4,5-*b*]pyridines within the binding pocket of mPGES-1 analysis ensured the acceptor-ligand interaction possibility *via* hydrogen binding with oxygen of thiazole ring or acetamide moiety participation confirmed with the effective docking scores.

As a predictive tool for the design of more potent inhibitors development we performed 3*D* pharmacophore modeling for thiazolo[4,5-*b*]pyridines using protein-ligand interaction fingerprint (PLIF) tool implemented in MOE software. Receptor interaction fingerprints were generated from the docked poses of the virtual screening hits with mPGES-1 active sites coordinates depicting the interactions between researched compounds and the following receptor amino acids residues: Arg73, Asn74, Gln77, His113, Tyr117, Tyr117, Arg126, Ser127, Tyr130, and Thr131.



3*D* pharmacophore models were generated containing two and three points. Generated three-point pharmacophore query contains two hydrophobic atom features (with the radii of 2.768 Å and 2.893 Å) and hydrogen bond acceptor feature with the radius of 2.915 Å. The two-centered pharmacophore query contains hydrophobic atom feature with the radius of 2.678 Å and hydrogen bond acceptor feature with the radius of 2.880 Å.

The correctness of pharmacophore queries was confirmed in the way of pharmacophore search performing. The summary at 164 entries showed the absolute hits number as 71 (43.29 %) for the two-centered query and 91 (55.49 %) for the three-centered query with 21 (60.00 %) and 20 (57.14 %) of 36 structures, respectively. The proposed virtual screening results provide an excellent starting point for rational design and *de novo* synthesis of the novel thiazolo[4,5-*b*]pyridine-2-one scaffold based potential drug candidates.