DISCOVERY OF NOVEL BIOLOGICALLY ACTIVE SUBSTANCES AMONG AZOLES WITH *IN SILICO* APPROACHES APPLICATION

Klenina O.V., Chaban T.I.
Danylo Halytsky Lviv National Medical University, Lviv, Ukraine
olena_klenina@yahoo.com

Nowadays computer-aided drug discovery (CADD) approaches have been developed and integrated in all stages of novel drug candidates discovering. The field of CADD is rapidly advancing, and techniques and methods are under active development. Thiazolidine core is a powerful and effective pattern for rational design of "drug-like" molecules.

Traditional organic synthesis protocols, pharmacological screening methodologies and *in silico* techniques including molecular modeling and virtual screening were used to discover novel drug-like compounds. Flexible molecular docking as a powerful virtual screening tool was applied for a series of the investigated compounds as potential anti-inflammatory agents *via* structure-based approach. Organic synthesis including [3+3]-cyclocondensation, cyanethylation, hydrolysis, acylation, [2+3]-cyclocondensation and alkylation reactions were used, elemental analysis and ^{1}H-NMR spectroscopy have been applied to prove the structures of synthesized compounds. Pharmacological *in vivo* screening of anti-exudative effect of novel compounds was performed.

A series of 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-ones were evaluated for their anti-inflammatory activity and subjected to virtual screening procedure.Flexible molecular docking studies were performed with MOE software using high resolution crystallographic structures of α-methyl-4-biphenylacetic acid:COX-1complex (pdb code 1Q4G), naproxen:COX-2 complex (pdb entry 3NT1), and glutathione:mPGES-1 complex (pdb code 4AL0). Minimized complexes as the docking studies outcome were scored by four scoring functions available in MOE revealing the synthesized compounds moderate potency as non-selective COX-1 and COX-2 inhibitors and were evaluated to form energetically favourable ligand-receptor complexes with the receptors. The binding modes in the complexes were realized on account of pyridine ring nitrogen atom or oxygen of acetamide moiety of the compounds with Arg120 or Tyr355 side chains of COX-2 isoform. Active dock poses inspection of thiazolo[4,5-*b*]pyridines within the binding pocket of mPGES-1 ensured the acceptor-ligand interaction possibility *via* hydrogen binding confirmed with the effective docking scores.

The next stage provided synthesis of some novel anti-inflammatory drug candidates *via* a structural modification of early obtained 5,7-dimethyl-2-oxo-3*H*-thiazolo[4,5-*b*]pyridine-3-acetic acid hydrazide. The acylation reaction approach was introduced for its functionalization. The synthetic potential of the basic scaffold hydrazine group was utilized by its interaction with a series of carboxylic acid chlorides. A series of 8 novel compounds was obtained as of N-acylation products of 5,7-dimethyl-2-oxo-2,3-dihydrothiazolo [4,5-b] pyridine-3-acetic acid hydrazide. The composition and structure of the synthesized compounds were confirmed by elemental analysis and ^{1}H NMR spectroscopy. Pharmacological *in vivo* screening of their anti-inflammatory activity was performed which allowed identifying one compound with moderate anti-exudative activity and one highly active lead-compound.

The anti-inflammatory activity evaluation and virtual structure-based screening for a series of N^3 substituted 3*H*-thiazolo[4,5-*b*]pyridine-2-one derivatives were carried out. The proposed virtual screening results provide an excellent starting point for rational design thiazolo[4,5-*b*]pyridine-2-one scaffold based potential drug candidates. The synthetic protocol for thiazolo[4,5-*b*]pyridine system functionalization in fused heterocycle N^3 position were utilized for a series of novel N^3 substituted 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one derivatives obtaining as potential anti-inflammatory drug candidates.