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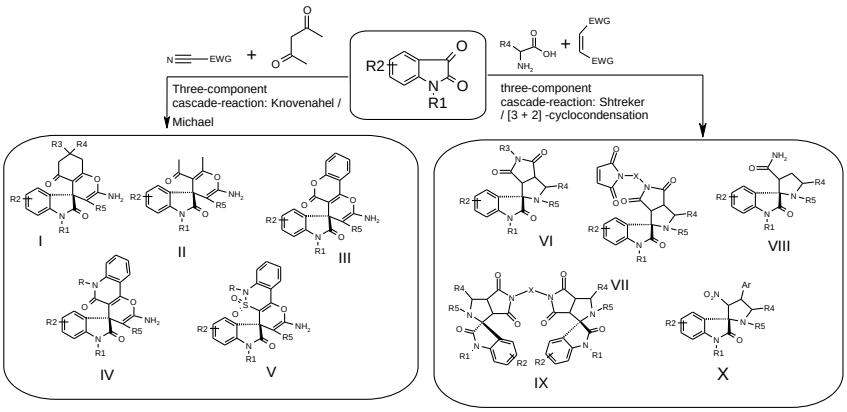
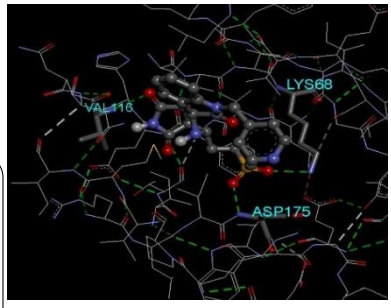
Synthesis and Molecular Diversity of Spirooxindoles in a Search for Potential Inhibitors of Protein Kinases: Convergence of Ligand-based and Structure-based Approaches

Redkin R.G., Shemchuk L.A., Chernykh V.P.
The National University of Pharmacy, Kharkiv, Ukraine,
e-mail: ruslan.red.chem@gmail.com

Identification of protein kinase inhibitors is an urgent task in the field of present-day medicinal chemistry, pharmacology and experimental medicine in general. The overwhelming majority kinase inhibitors known by now are flat or flattened structure, resulting in the presence of specific cavities either above or below the plane of the inhibitor can not be used to create selective molecules. There was a target-oriented search (*in silico* and *in vitro*) for drug-like molecules and potential anticancer agents being CK2 and FGFR1 kinase inhibitors among 1000 structures I-X of spiro-2-oxindoles focus-library (Fig.), which was synthesized by diversity-oriented synthesis MCRs way [1,2].





The complex of a ligand to the ATP-binding site of the protein kinase CK2

The study algorithm comprises three stages: 1) calculation and analysis of structure molecular descriptors using the *Molinspiration* software complex (chemoinformatics method); 2) molecular modeling of binding a collection of compounds with CK2 and FGFR1 protein kinases *in silico* and selection candidates for biochemical tests based on the binding energy (bioinformatics method); docking was carried out in ATP binding sites of CK2 protein kinases (RCSB code: 3NSZ – 1.30 Å) and FGFR1 (RCSB code: 3GQI – 2.50 Å) using the Autodock4 software; 3) *in vitro* screening the selected compounds relative to CK2 and FGFR1. Accordingly, to the *in silico/in vitro* screening results CK2 inhibitors is {VIII, 1 active compound with rest of kinase activity, 49% (33μM)} and FGFR1 compound inhibits only {VII, 1 active compound with rest of kinase activity, 53% (33μM)}.

[1] *Tetrahedron. – 2014. – Vol. 70. – P. 8348-8353.*
[2] *Mol. Divers. – September 2015. – P. 1-46.*