gratefully acknowledged for the financial support of the LC-MS/MS measurements at the Proteomics Core Facility. The work was co-funded by the MEYS project CEITEC 2020 (LQ1601).

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doi: http://dx.doi.org/10.7124/bc.0009EC

L-3. Design and development of new thiazolidinone-based drug-like molecules

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4-Thiazolidinones as privileged heterocycles are in focus since 60th. Main achievements are related to glitazones and set of drug-candidates with antidiabetic, antimicrobial, antiviral and anticancer activities. They are confirmed ligands toward various biotargets as well as compounds with unknown mechanism of actions. Combination of several reactive centers of main core and variety of its synthetic routs led do different 4-thiazolidinone subtypes. Among them 5-ene-thiazolidinones are of special interest due to chemical properties and pharmacological profiles. While, they are considered as frequent hitters or PAINS, which are useless because of possible low selectivity. This is argued by Michael acceptor property of 5-ene-4-thiazolidinones. Such thesis is discussed, and requires further investigation following the usefulness properties of Michael acceptors. The main goal of the project is the search for new 4-thiazolidinone-based drug-candidates. Methods: Drug design; synthesis; biological activity assays; SAR. Results and conclusions: The diverse in-house library have been designed and synthesized. Biological assays were focused on the search for anticancer, anti-inflammatory, antiparasitic/antimicrobial agents. Following polypharmacological approach and the multi-target drugs concept, the compound with several pharmacological effects were regarded as an advantage. Thus, the main directions for 4-thiazolidinones optimization were outlined: complication of C5 and modification of N3 positions; isosteric replacement; combination with other scaffolds; thiazolidinones-based synthesis of thiopyrano[2,3-d]thiazoles, thiazolo[4,5-b]pyridines, isothiocoumarines, *etc* and "simplified" derivatives. It was shown that thiopyranothiazoles are fixed "biomimetics" of starting 5-substituted-4-thiazolidiones without Michael acceptor properties. Study of the active anticancer thiazolidinones reveled the PPAR-mediated, ROS-dependent and pro-apoptotic mechanisms of action. Based on the biological activity data, 4-thiazolidinones can be considered as pro-drugs with efficient characteristics. The similarity of 4-thiazolidinones with H2S donors and preliminary results open new oportunities to design of new 4-thiazolidinone-based H2S releasing agents. Additionally, Michael functionality of thiazolidinones should be used in the useful way – search for Nrf2-modulatos, covalent inhibitors, ROS modulators.

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