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Multi-target approach to anti-inflammatory drugs - *In silico* and medicinal chemistry

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The "one drug - one target - one disease"paradigm in drug discovery has been reconsidered during the last decade. This paradigm change was mainly caused by high attrition rates in drug approvals due to toxicity and lack of efficacy. Dual or multi-target ligands have several advantages compared with selective compounds, including improved efficacy and more simple pharmacokinetic and pharmacodynamic properties in comparison to the combination of several drugs. Unfortunately, the rational design of polypharmacological compounds is a rather hard task and not well established. Previous studies established a synergistic inflammatory effect resulting from inhibition of 5-lipoxygenase (5-LO) or cyclooxygenases in combination with soluble epoxide hydrolase (sEH). In this study we apply different design strategies to yield dual 5-LO/sEH inhibitors for treatment of inflammation. We present three methodic approaches to design dual inhibitors of 5-LO and sEH. In our first study, we connected previously pubished 5-LO and sEH pharmacophores, an imidazo-[1, 2a]-pyridine core with an aryl urea moiety via flexible propyl linker. The second study contains the discovery of a benzimidazole-based dual 5-LO/sEH inhibitor by means of *in silico* screening. The strategy of the virtual screening protocol was an exhaustive pairwise evaluation of pharmacophore models for both targets to obtain a dual-target pharmacophore model. Our last study deals with the development of a fragment based strategy for dual-target drug discovery. Here, we applied a modified self-organizing map algorithm for *in silico* recognition of molecular fragments binding both targets. The predicted properties were confirmed by complementary screening techniques: STD-NMR and enzyme assay. A variety of dual fragments active in both complementary assays could be obtained using self-organizing maps, which was optimized towards nanomolar inhibitory activity against both targets.

Biography

Eugen Proschak has completed his PhD in 2008 from Goethe-University of Frankfurt. He is Junior Professor of Drug Design in Frankfurt and is leading an interdisciplinary research group. He has published more than 60 papers in reputed journals. His main research interest is design of multi-target drugs supported by *in silico* and fragment-based drug discovery.

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