OPTIMIZATION OF ADME-TOX PROPERTIES BY EXAMPLE OF DESIGN OF BUTYRYLCHOLINESTERASE AND NITRIC OXIDE SYNTHASE INHIBITORS AND TUBULIN TARGETED LIGANDS

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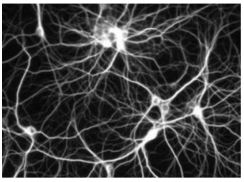
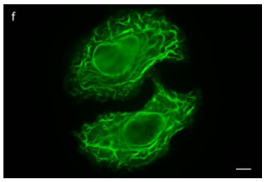
The ADME-Tox properties of a putative drug candidate should be good enough to enable its drug-like behavior in the human organism. Therefore, identified lead molecules are subjected to various chemical modifications with the purpose to improve their pharmacokinetic and safety profiles, while maintaining the potency and selectivity towards the aimed molecular target. The present report gives three examples of optimization of ADME-Tox properties fulfilled in our group.



Wistar rats with LPS stimulated acute vasodilatation shock:

Cpd causes strong and prolonged (> 90 min) antihypotensive effect



A series of conformationally restricted analogues of N,N-disubstituted 2–aminothiazolines were synthesized as selective butyrylcholinesterase inhibitors. One of the obtained cyclic isothioureas maintained the activity of the lead molecule, but was devoid of toxophoric group in the structure.

In a search of nitric oxide synthase inhibitors with prolonged vasoconstrictive activity, a series of lipophilic cyclohexa-fused 2-amino-2-thiazolines was obtained. One compound caused pronounced and prolonged vasoconstrictive effect after single injection to the Wystar rats with lipopolysaccharide induced acute endotoxic (vasodilatation) shock.

New analogues of anticancer agent tubuloclustin [N-(7-(adamant-1-yloxy)-7-heptanoyl)-N-deacetylcolchicine] were obtained with the aim to enhance the metabolic stability and to decrease lipophilicity of the parent molecule. One compound with ether moiety in the shortened linker was very effective in inhibition of the growth of carcinoma cells A549 (IC50 = 5 nM). Thus, it represents an active, but less lipophilic and metabolically more stable tubuloclustin analogue.