ANTIPROLIFERATIVE AND ANTI-INFLAMMATORY PROPERTIES OF NOVEL 1*H*-PYRAZOLO[3,4-C]PYRIDIN-7(6*H*)-ONES AS SOLUBLE GUANYLYL CYCLASE (SGC) STIMULATORS

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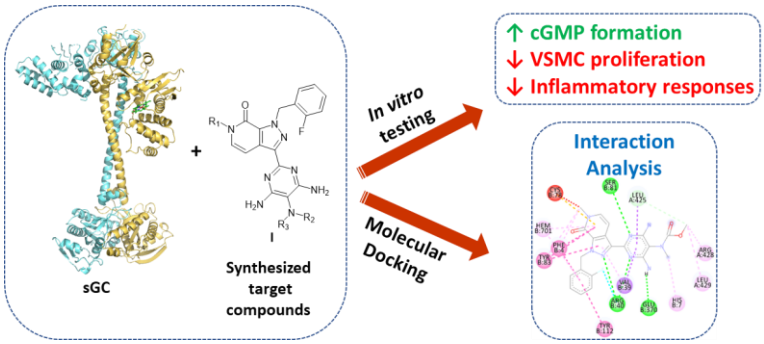
Vascular smooth muscle cell (VSMC) proliferation and inflammatory responses play a crucial role in the pathogenesis of various cardiopulmonary diseases, such as atherosclerosis, coronary artery disease and pulmonary hypertension. Accumulating evidence suggests that dysregulation of NO/sGC/cGMP pathway, mainly caused by impaired endothelial NO bioavailability, contributes to endothelial dysfunction.[1] This is one of the reasons why pharmacological agents targeting this pathway, especially acting as heme-dependent sGC stimulators, are used in clinical settings.[2]



In an effort to investigate the connection between stimulation of sGC and inhibition of VSMC proliferation and inflammation, we assessed selected, synthesized 1*H*-pyrazolo[3,4-c]pyridin-7(6*H*)-one derivatives (**I**), which elicit characteristic for sGC stimulators activity, on two different cell types (RAoSM and HUVEC cells) in the presence/absence of NO. Results indicate that these compounds reduce VSMC proliferation and proinflammatory responses, such as the expression of leukocyte adhesion molecules in HUVECs, to an equivalent level with reported sGC stimulators, such as BAY 41-2272. Furthermore, the designed molecules as well as known sGC stimulators were introduced into docking calculations on the cryo-EM structure of human sGC (*hs*GC) in NO-active state in order to gain useful information regarding the structural characteristics that could establish effective sGC binding and potent sGC stimulation. Herein, the results of our computational studies, synthetic efforts towards the target compounds and the evaluation of their biological activity will be presented.

References:

1. Thoonen R., Cauwels A., Decaluwe K. et al. *Nat. Commun*. **2015**, *6*, 8482.
2. Sandner P, Zimmer DP, Milne GT, Follmann M, Hobbs A, Stasch J-P. *Hand. Exp. Pharmacol.* **2021**, *264*, 355-394.