NEW SOLUBLE GUANYLYL CYCLASE (sGC) AGONISTS: DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION

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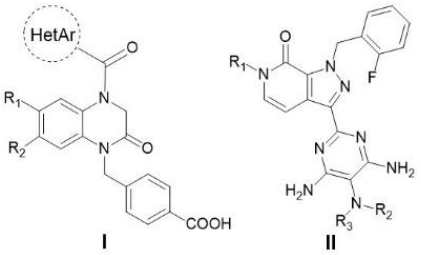
Soluble guanylyl cyclase (sGC), a α/β-heterodimeric enzyme, is the primary receptor of endogenously produced nitric oxide (NO). The prosthetic heme moiety, located in the regulatory β_1 Heme-NO OXygen (H-NOX) domain, binds NO with high affinity, triggering an increase of catalytic activity and, thus, leading to the conversion of guanosine triphosphate (GTP) to the crucial second messenger cyclic guanosine monophosphate (cGMP). Dysregulation of NO/sCG/cGMP pathway, either by impaired NO bioavailability or by heme oxidation and conversion of sGC to its NO-unresponsive apo-enzyme state in oxidative stress conditions, contributes to various cardiovascular, renal and CNS disorders.[1] Novel treatments of these diseases have targeted the NO-insensitive forms of sGC, aiming to restore or augment enzymatic activity in a heme-dependent (sGC stimulators) or heme-independent (sGC activators) manner.[2]



Our studies focus on the discovery of new chemotypes which can act as sGC agonists. In particular, applying rational drug design approaches, we built two distinct libraries of compounds containing 3,4-dihydroquinoxalin-2(1*H*)-one (**I**) and 1*H*-pyrazolo[3,4-c]pyridin-7(6*H*)-one derivatives (**II**). Efficient synthetic routes were developed for the synthesis of the designed derivatives **I** and **II**. A series of newly synthesized compounds was assessed for their effect on sGC activity by utilizing enzyme- and cell-based assays. Certain derivatives induced enzymatic activity acting either as activators or stimulators of sGC and may serve as promising hits for further optimization. Herein, our endeavors towards the design, synthesis and biological evaluation of these new sGC agonists will be presented.

References:

1. Friebe A., Sandner P., Schmidtko A. *Naunyn-Schmiedeberg's Archives of Pharmacology* **2020**, *393*, 287–302.
2. Sandner P., Follmann M., Becker-Pelster E., Hahn M.G., Meier C., Freitas C., Roessig L., Stasch J.-P. *Br. J. Pharmacol*. **2021**, 1–22.