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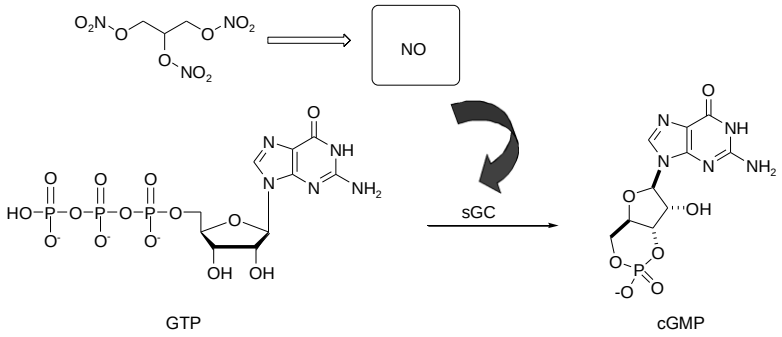
Novel approach towards NO-free activators of *sGC* enzyme for medical treatment of heart diseases

Cardiac patients learn very quickly and very well their symptoms and can easily assimilate the treatment and remember it. Nitroglycerin and its analogs are used as medicines for angina pectoris and heart failure.[i,ii] Doctors prescribe it and teach the patients that it should be taken only in case they feel an approaching angina attack. However many clinical studies, both of patients with angina pectoris and of patients with heart failure have demonstrated that continuous administration of organic nitrates leads to the development of nitroglycerine tolerance and decrease of its therapeutic efficiency.[iii] It is the goal of this project to design and prepare new **NO**-free functional mimics.

Nitro-compounds are used in heart diseases because of its vasodilatative property. Nitroglycerin and isosorbide nitrites dilate arterial blood vessels decreasing the cardiac preload and thus inducing a therapeutic effect on the cardiac muscle.[iv] It is established that after being absorbed the medicine is converted into nitric oxide. This molecule is known to be involved in the control of blood pressure, neurotransmission, and the immunedefense system of the body.[v] **NO** activates soluble guanylyl cycles (*sGC*),[vi] which catalyses the conversion of guanosine triphosphate (**GTP**) to cyclic guanosine monophosphate (**cGMP**), which triggers further biochemical effects that ultimately result in a physiological response (Scheme 1).[vii,viii,ix,x] Another mechanism of high-output *sGC* activation was described early on by Ignarro and co-workers who reported that protoporphyrin IX (**PPIX**) activated efficiently the *sGC* enzyme.[xi]



Scheme 1. Transformation of **GTP** into **cGMP** catalyzed by *sGC*

It is the goal of this project to produce new functional mimics for sGC regulation. We believe that chemically modified corrin compounds or other tetrapyrroles may be even more effective regulators of *sGC*. To test this hypothesis we will experimentally execute the following aims:

1) Elaborate new methods for the preparation of vitamin $\mathbf{B_{12}}$ and factor B derivatives as *sGC* regulators.

2) Prepare new porphyrin (especially **PPIX**) derivatives.

3) Prepare hybrid molecules with dual mode of action e.g. vitamin $\mathbf{B_{12}}$/factor B – porphyrinoid conjugates.

4) Investigate the cellular and cardiovascular effect of sGC activation by the new corrin derivative and hybrid molecules.

5) To assess the cellular toxicity of the new corrin derivatives and hybrid molecules.

References:

[i] L.J. Ignarro *J. Physiol. Pharm.* **2002**, *53*, 503 – 514.
[ii] L.J. Ignarro, C. Napoli, J. Loscalzo *Circ. Res.* **2002**, *90*, 21 – 28.
[iii] S. Ghio, S. de Servi, R. Perotti, E. Eleuteri, C. Montemartini, G. Specchia *Circulation* **1992**, *86*, 798 – 802.
[iv] L.J. Ignarro *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 7816 – 7817.
[v] L.I. Ingarro, C. Napoli Nit*ric Oxide: Biol. Chem.* **2001***, 5,* 88 – 97.
[vi] A. Pyriochou, A. Papapetropoulos *Cellular signaling* **2005**, *17*, 407 – 413.
[vii] W.P. Arnold, C.K. Mittal, S. Katsuki, F. Murad *Proc. Natl. Acad. Sci. USA* **1977**, *74*, 3203 – 3207.
[viii] Z. Chen, J. Zhang, J.S. Stamler *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 8306 – 8311.
[ix] L.J. Ignarro, H., Lippton, J.C. Edwards, W.H. Baricos, A.L. Hyman, P.J. Kadowitz, C.A. Gruetter *J. Pharmacol. Exp. Ther.* **1981**, *218*, 739 – 749.
[x] F. Murad, C.K. Mittal, W.P. Arnod,S. Katsuki, H. Kimura *Adv. Cyclic Nucleotide Res.* ***1978,*** 9*, 145 – 158.*
[xi] M.S. Wolin, K.S. Wood, L.J. Ignarro *J. Biol. Chem.* **1982***, 257,* 13312 – 13320.