

Summary of the Ph.D. thesis

Selective modification of cobyrinic acid derivatives – new sGC regulators

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Soluble guanylyl cyclase (sGC) is an enzyme which catalyse transformation of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which triggers further biochemical effects that ultimately result in vasodilatation of blood vessels. Preliminary experiments made in E. Martin group showed that cobinamide, a derivative of vitamin B₁₂, activates sGC.

The main aim of my work was to develop new methodologies for the selective synthesis of novel cobyrinic acid derivatives and examine their influence on sGC enzyme.

During my work the synthesis of mono- and diamide derivatives, including the spirolactone intermediate, was achieved *via c*-lactone opening using various primary amines. This is the first known example of selective *d*-position modification (*Org. Lett.* **2010**, *12*, 4674-4677).

Furthermore, selective *meso*-functionalized cobyrinic acid derivative, *meso*-amine **5**, was synthesized. This allowed for reactions with carboxylic acids, anhydrides and acid chlorides. In coupling reactions a lactam **302** by-product was isolated and analyzed. Manipulation of this compound led to selective *d*-/*meso*- modifications (*Eur. J. Org. Chem.* **2012**, *1*, 154-159).

During attempts to directly arylate heptaester cobryinate **3** at the *meso*- position it was discovered that in the presence of oxygen and a palladium catalyst it transformed into cobryketone **313**. The method was fully optimized and allowed for the synthesis of *d*-nor-*c*-amides (*J. Org. Chem.* **2013**, *78*, 4115-4122).

Obtained compounds were submitted for biological tests to the E. Martin group at University of Texas, Health Science Center, Houston. The results showed that *c,d*-diisopropylamide activates sGC better than cobinamide. Furthermore, modification of the *meso*-position showed a dramatic decline in sGC activation. This is also true when the *d*-position is elimination, highlighting its importance.