Synthesis of selected porphyrins for NO-free regulation of sGC enzyme

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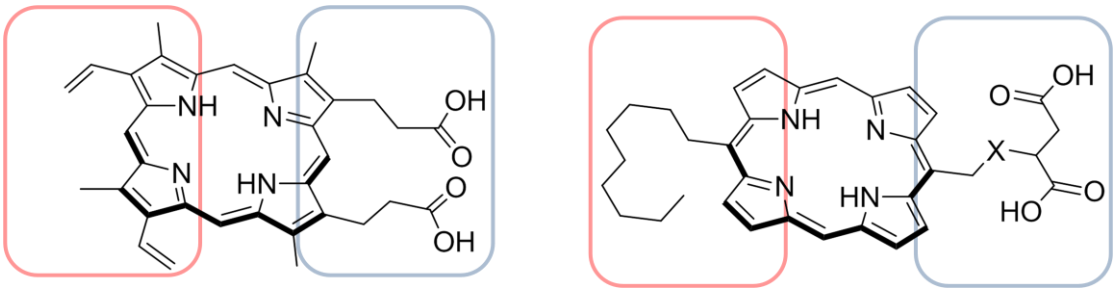
Nitroglicerin and other organic nitrates have been used for the treatment of heart diseases for more than century.[1] These compounds form nitric oxide (NO), a molecule which acts as a biological messenger, activating the soluble guanylyl cyclase (sGC) enzyme.[2] By activating sGC relaxation of the vascular smooth muscle occurs. However, over the years it has been documented that long term exposure to such nitrates causes the body to build up a tolerance thus decreasing their effectiveness.[3] Therefore, a NO-free activation of sGC is of great importance.

Protoporphyrin IX (PPIX) has been found to activate sGC in vitro, in a kinetically similar way to NO.[4] Unfortunately, it was discovered that it is a poor activator of enzyme in vivo. Our research focuses on the synthesis of new porphyrin derivatives – potential sGC activators. With the goal to increase bioavailability, PPIX was modified by attachment of various amino acids and alcohols.[5,6] Furthermore, a synthetic trans-AB-porphyrins with hydrophobic and hydrophilic groups, mimicking the system of substituents in PPIX, were obtained. The synthesis involved of suitable building blocks starting from hydroxy/aminodiacids, aldehydes and followed by acid catalyzed [2+2]-dipyrromethane condensation.



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