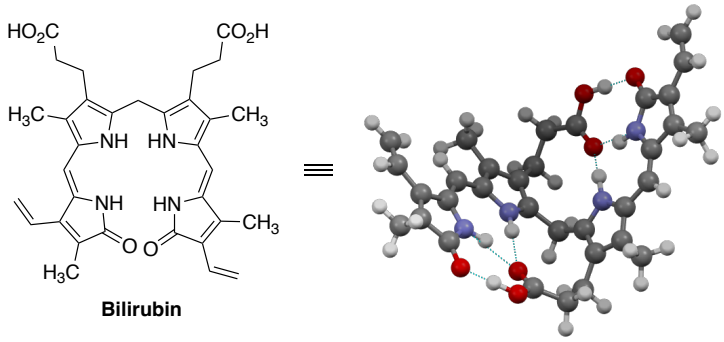
Synthesis of Small-Molecule Probes of Bilirubin Photochemistry and Biology

Taufiqueahmed Mujawar [a]; Petr Sevelda [a]; Jakub Švenda* [a, b]

[a] *Masaryk University, Faculty of Science, Department of Chemistry, Kamenice 5/A8, 623 00 Brno, Czech Republic*

[b] *International Clinical Research Center, St. Anne's University Hospital Brno, Pekařská 53, 656 91 Brno, Czech Republic*

mtaufiqueahmed@sci.muni.cz; svenda@chemi.muni.cz



Yellow pigment bilirubin is the well-known primary product of heme catabolism.[1] It is a powerful antioxidant and a potent signaling molecule with multiple speculated biological functions. When exceeding safe levels in the blood, particularly during the neonatal period, severe hyperbilirubinemia can result and lead to neurotoxicity accounting for some instances of neonatal morbidity and mortality.[2,3] Despite the worldwide use of phototherapy and numerous scientific studies thereof, there remain important unanswered questions about the photochemistry, the biology, and the clinical aspects of the therapy. Bilirubin gives rise to various molecular fragments formed through (photo)oxidative transformations.[4] Standards of such bilirubin-derived products are essential for studies of their bioactivities and mechanisms of formation in the context of hyperbilirubinemia phototherapy. Unfortunately, accessing these in the analytically pure form is in many cases problematic. The main objective of our work is to formulate a flexible synthetic strategy that will deliver pure samples of bilirubin and the oxidative degradation products as analytical standards or isotope-labeled probes. Our approach pursues a convergent and flexible strategy featuring pre-functionalized and easily varied cyclic building blocks. Through a series of metal-catalyzed annulations and cross-coupling reactions, we have been able to rapidly prepare subunits of bilirubin and selected degradation products. The approach also permits late-stage ^{15}N labeling of selected rings of bilirubin or fragments thereof.

Ref.:

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