Photocyclization of Mono- and Bis-styrylazaheterocycles. A Straightforward Way to DNA-Binding Benzo[c]quinolizinium Derivatives

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Benzo[c]quinolizinium derivatives represent a pharmacologically important class of heteroaromatic compounds that is applied in clinical practice. In particular, benzo[c]quinolizinium drugs are used as pharmacological chaperonsthat promote folding and channel activation of the mutant CFTR protein in the treatment of mucoviscidosis.[1] In addition, DNA-binding properties of benzo[c]quinolizinium ions[2] make them promising lead structures for the development of novel anticancer chemotherapeutic agents.

Recently, we reported that regioselective C−N photocyclization of 2-styrylpyridine[3] and 2-styrylquinolines[4] lead to the efficient formation of benzo[c]quinolizinium derivatives. We assumed that such photochemical reactivity may be a general property of *ortho*-styryl-substituted *N*-hetarenes containing donor substituents in the styryl residue. The photocyclization reactions of a series of monostyryl derivatives were carried out to prove our hypothesis (Fig 1). Benzo[c]quinolizinium derivatives **2a-c** were isolated as perchlorates and fully characterized.

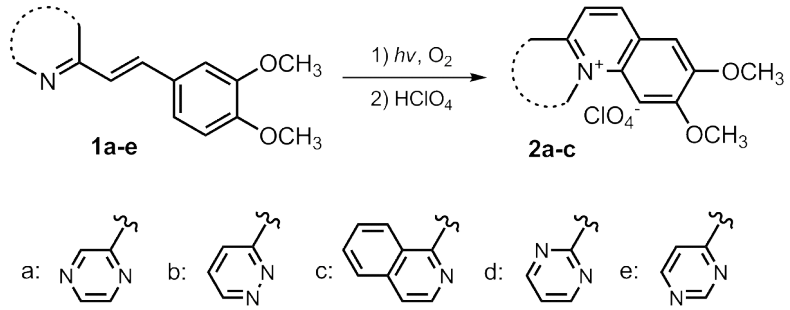

Figure 1. Photocyclization of monostyryl derivatives **1a-e**.

In case of bis-styryl derivatives **3a,b** solely the products of monocyclization **4a,b** were isolated (Fig. 2).

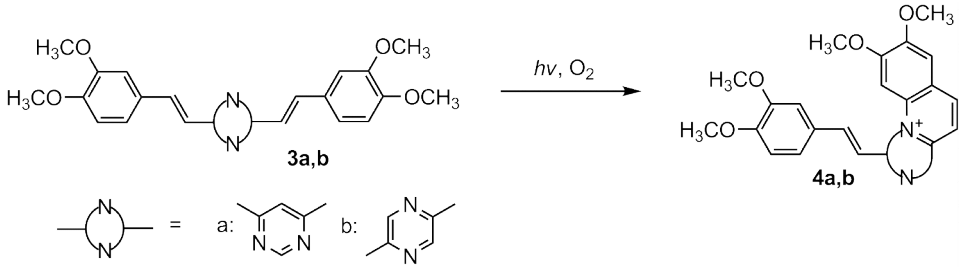

Figure 2. Photocyclization of bisstyryl derivatives **3a,b**.

Photoproducts **2a-c**, **4a,b** possess characteristic features of DNA-intercalators, namely, planar heteroaromatic structure with a permanent positive charge.[5] To estimate the DNA-binding activity

and binding modes of these compounds, their interactions with calf thymus DNA (ctDNA) were examined. In case of ligands **2a-c** intercalation was stated as a single binding mode, whereas ligands **4a,b** demonstrated mixed binding mode comprising intercalation and non-specific aggregation along DNA phosphate backbone.
Thus we demonstrated, that photocyclization of *ortho*-styryl-substituted *N*-hetarenes may be a simple route to highly DNA-affinite (aza)benzo[c]quinolizinium derivatives.

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References:

[1] (a) C. Marivingt-Mounir, C. Norez et. al. *J. Med. Chem*. **2004**, 47, 962. (b) C. Norez, F. Bilan, et. al. *J. Pharmacol. Exp. Ther*. **2008**, 325, 89.

[2] (a) H. Ihmels, K. Faulhaber et. al. *Photochem. Photobiol.* **2005**, 81, 1107. (b) K. Benner, H. Ihmels et. al. *Org. Biomol. Chem*. **2014**, 12, 1725.

[3] D. V. Berdnikova, T. M. Aliyeu et. al. *Chem. Commun*. **2015**, 51, 4906.

[4] E. N. Gulakova, D. V. Berdnikova et. al. *J. Org. Chem.* **2014**, 79, 5533.

[5] (a) A. Rescifina, C. Zagni et. al. *Eur. J. Med. Chem*. **2014**, 74, 95. (b) S. Banerjee, E. B. Veale et. al. *Chem. Soc. Rev*. **2013**, 42, 1601. (c) A. Mukherjee, W. D. Sasikala. *Adv. Protein Chem. Struct. Biol.* **2013**, 92, 1. (d) X. Wang, Z. Guo. *Chem. Soc. Rev*. **2013**, 42, 202.