Scientific and technical report

Project title: he synthesis and evaluation of some tribenzotriquinacene-flavonoids tripodal antibacterial agents

Project code: PN-III-P1-1.1-PD-2016-1117

Objectives:

1. The synthesis, characterization and antibacterial evaluation of some new tribenzotriquinacene-flavonoid derivatives.
2. Conducting a structure-activity study in order to optimize the structure of the new compounds.
3. Cytotoxicity evaluation of the synthesized antibacterial agents.
4. Diseminating the results by publishing them in Web of Science indexed journals and by participating at national and international conferences.

Current stage objectives: The synthesis of the tripodal antibacterial agents.

The synthesis of tripodal antibacterial agents

The aim of the current stage of the project was to obtained the desired antibacterial agents, whose structure consists of three 1,3-dithiolium flavonoid moieties, bound together by a common cenral core (Figure 1a).

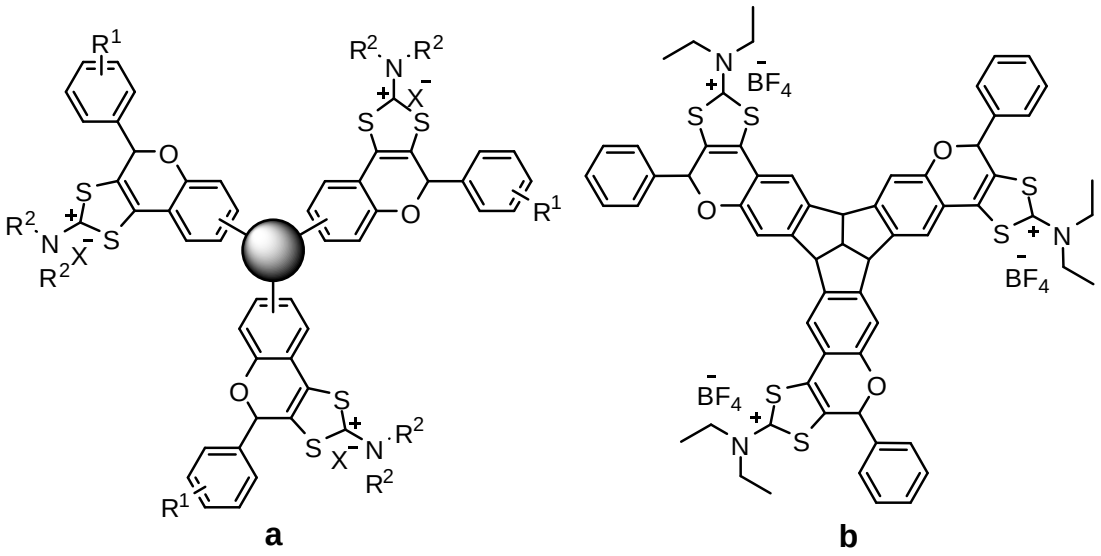
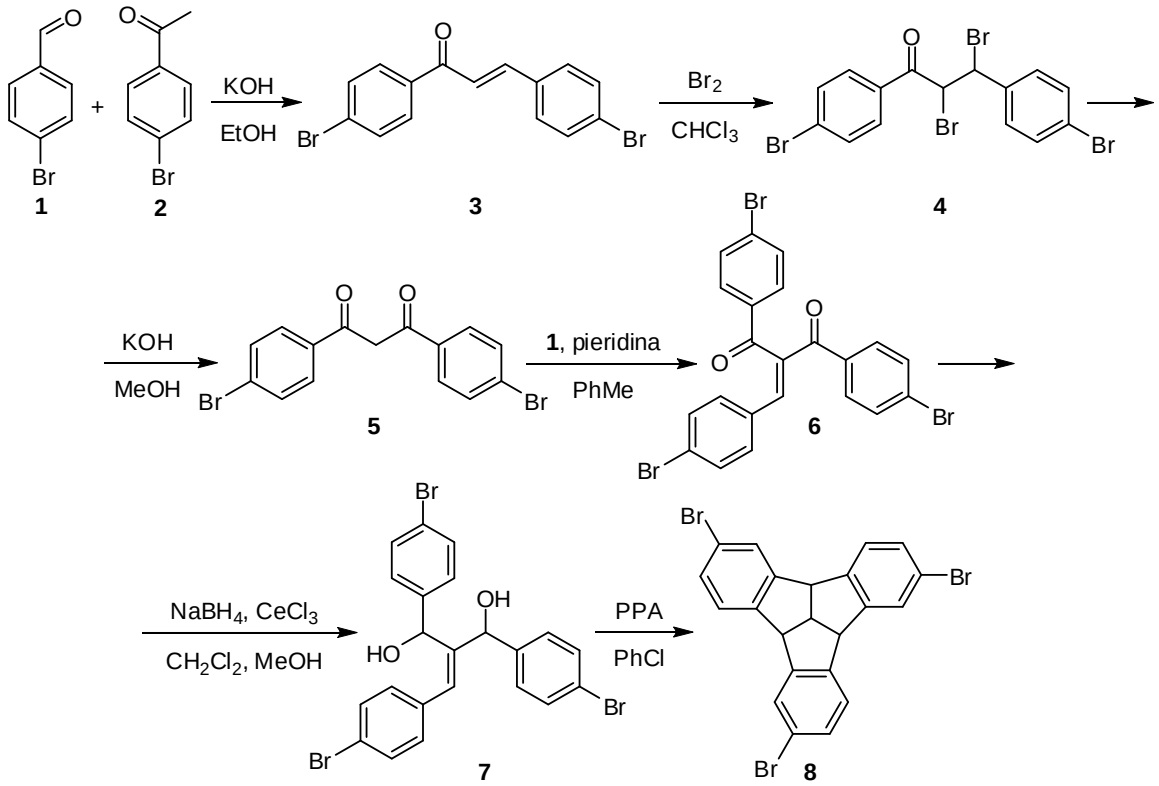


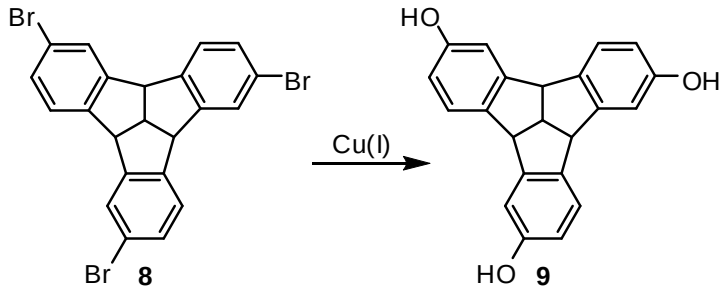
Figure 1 – The general structure of the desired compounds (**a**); the structure of the envisioned tribenzotriquinacene-containing antibacterial agents (**b**).

The first attempts targeted the synthesis of derivatives similar to those presented in Figure 1b. The method used to obtain the tribenzotriquinacene (TBTQ) core is presented in Scheme 1.



Scheme 1 – The synthesis of tribenzotriquinacene **8**.

Once derivative **8** became available, the goal was to convert it to the trihydroxilated TBTQ **9** (Scheme 2), which would be used in the synthesis of the targeted compounds.

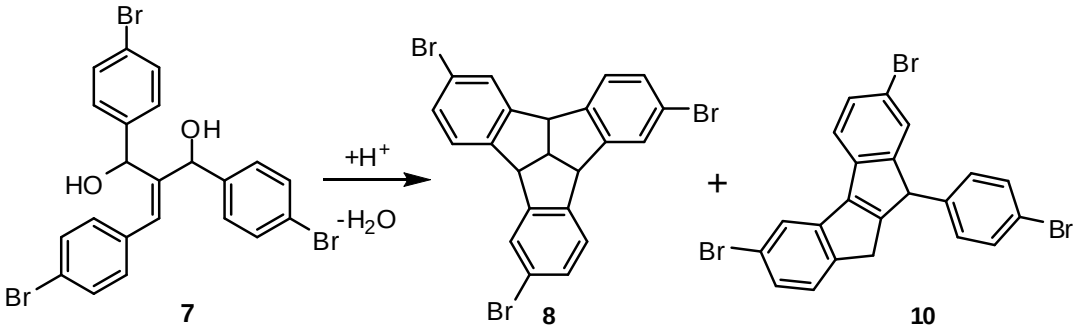


Schema 2 – The synthesis of trihydroxilated TBTQ **9**.

The method selected for the synthesis of TBTQ **8** was developed by G. Markopoulos, under the supervision of Prof. H. Hopf.[1] Briefly, it is based on the polyphosphoric acid induced cyclization of 1,3-diols such as **7**. The latter was obtained through a sequence of two reactions, a Knoevenagel condenstation that leads to diketone **6** and its Luche reduction to the desired precursor. The advantage of this method is that it yields only

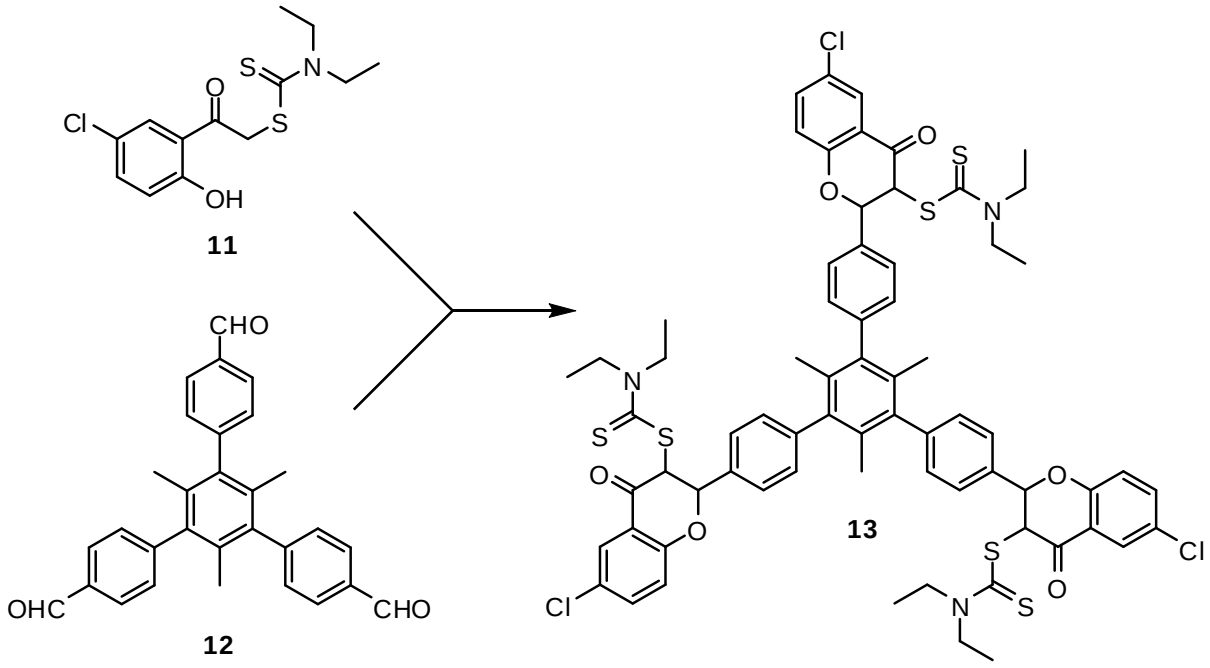
[1]. Markopoulos, G., Henneicke, L., Shen, J., Okamoto, Y., Jones, P. G., Hopf, H., *Angew. Chem. Int. Ed.*, **2012**, *51*, 12884–12887.

2,6,10 substituted TBTQs, as opposed to the method used by Prof. Kuck, which leads to a mixture of 2,6,10 and 2,6,11 substituted TBTQs.[2] On performing the cyclization of **7**, it was found that the desired TBTQ **8** was obtained with a very small yield (<1%), while the major product of this reaction was alkene **10** (Scheme 3).



Scheme 3 – The two products obtained through the cyclization of **7**.

Because of the small yield of **8**, other synthetic pathways are currently under investigation. Moreover, the replacement of the TBTQ core was also considered. One such alternative is the mesitylene core, which was used to link three dithiocarbamic flavonoids together, as presented in Scheme 4.



Scheme 4 – The synthesis of dithiocarbamate **13**, a precursor for tripodal antibacterial agents.

[2]. Xu, W. R., Chow, H. F., Cao, X. P., Kuck, D., *J. Org. Chem*. **2014**, *79*, 9335−9346.

Further, derivatives such as **13** can be converted to their corresponding 1,3-dithiolium salts, which can then be tested for antibacterial properties.