

Corrole dimers – synthetic, spectroscopic and antimicrobial activity studies

Paula S. S. Lacerda^{1,2}, Maria Bartolomeu³, Adelaide Almeida³,
M. Amparo F. Faustino², M. Graça P. M. S. Neves², Joana F. B. Barata¹

¹ CESAM, University of Aveiro, 3010-193 Aveiro, Portugal;

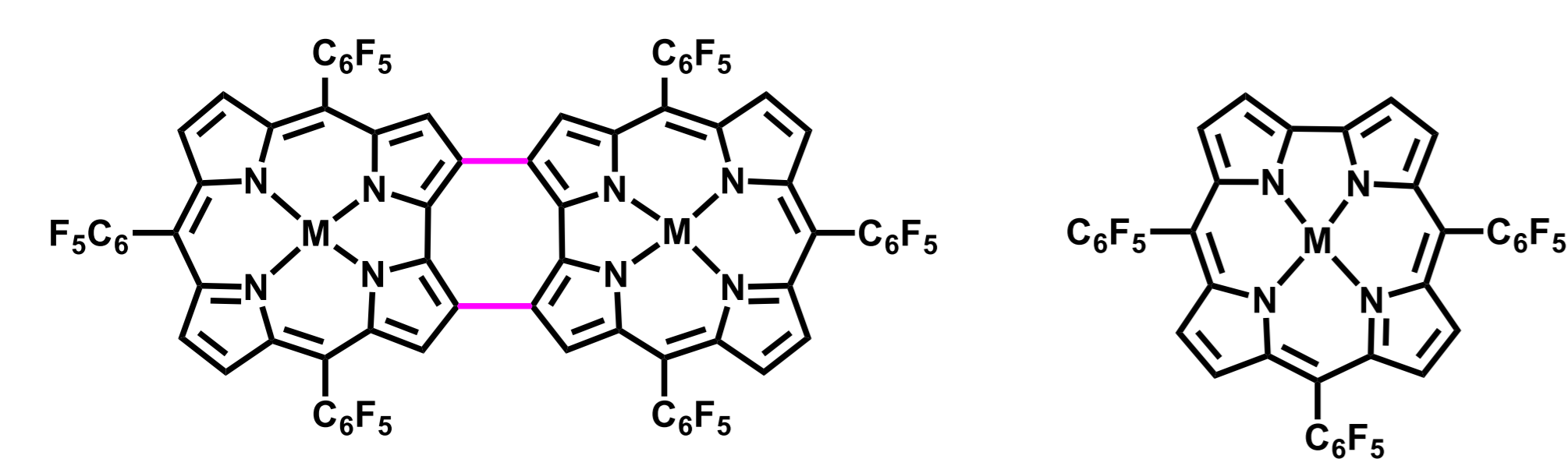
² LAQV-Requimte and Department of Chemistry, University of Aveiro, 3010-193 Aveiro, Portugal;

³ CESAM and Department of Biology, University of Aveiro, 3010-193 Aveiro, Portugal

Introduction

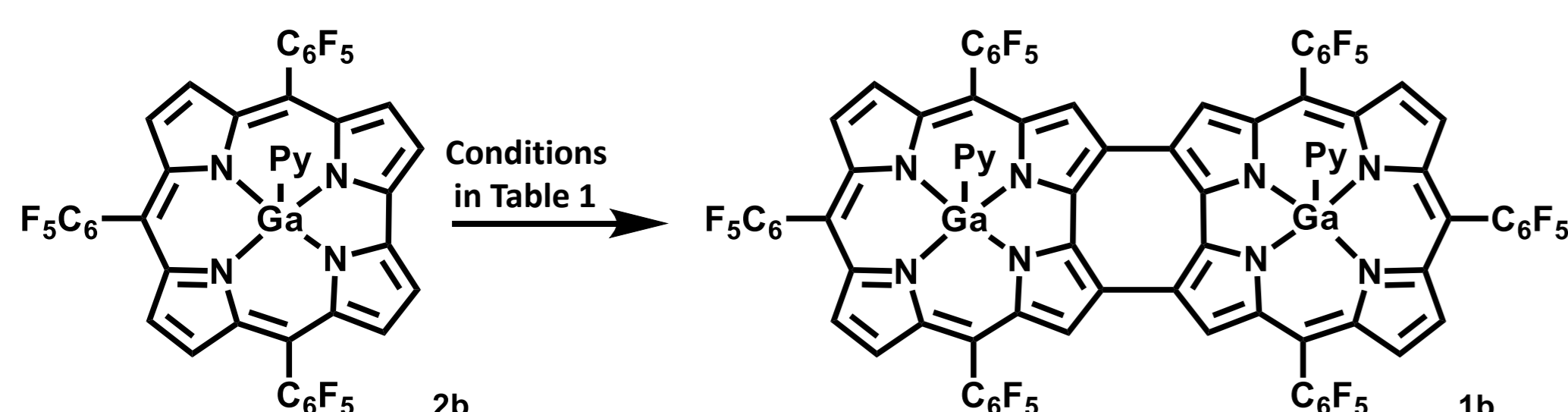
Corroles are aromatic contracted tetrapyrrolic macrocycles with unique physicochemical features.¹ These compounds possess key photophysical/photochemical properties as high excitation molar coefficients, fluorescence quantum yields, phosphorescence and photostability to be used in several therapeutic applications namely as photosensitizers (Ps) in PhotoDynamic Therapy (PDT).² One of the main advantages of these macrocycles is their large delocalized π -electronic conjugation and their stability under the PDT conditions. Additionally, conjugated macrocycles corrole-based **1** (Scheme 1) demonstrated that their absorption spectra fall within the therapeutic window of 600 – 800 nm which make them promising candidates to be used as photosensitizers.³

In this communication, it will be discussed a simple and peculiar alternative to the synthesis of fused corrole dimer **1b** (Scheme 2), mediated by acidic conditions using a mixture of common laboratory acids. It has been previously reported the synthesis of fused dimer **1b** by bis-gallium(III) complexation of dimer **1a** prepared via thermic oxidation cyclisation of **2a**.⁴ The structural and optical characterizations of these doubly linked dimers as well as their antimicrobial activity studies, namely dark toxicity and photoactivity under irradiation using the Gram-positive bacterium *Staphylococcus aureus* will also be presented.



Scheme 1. Structures of doubly linked corrole dimers **1a** and **1b** and parent corroles (**2a** and **2b**).

Synthesis of dimer 1b



Scheme 2. Synthetic route to doubly linked corrole dimer **1b**.

Table 1 - Experimental reaction conditions (solvent, temperature and time) and its effect on the yield of obtained dimer **1b**.

Solvent	Temperature (°C)	Time (h)	Yield dimer 1b (%)
AcOH / TFA / 5% H ₂ SO ₄	100	2	18
AcOH / 5% H ₂ SO ₄	100	1	12 (27)*
H ₂ SO ₄	100	0.5	minor
AcOH	100	2	vestigial
AcOH / 5% H ₂ SO ₄	40	2	vestigial

* Number in brackets correspond to yield obtained considering parent corrole **2b** recovered.

Characterization

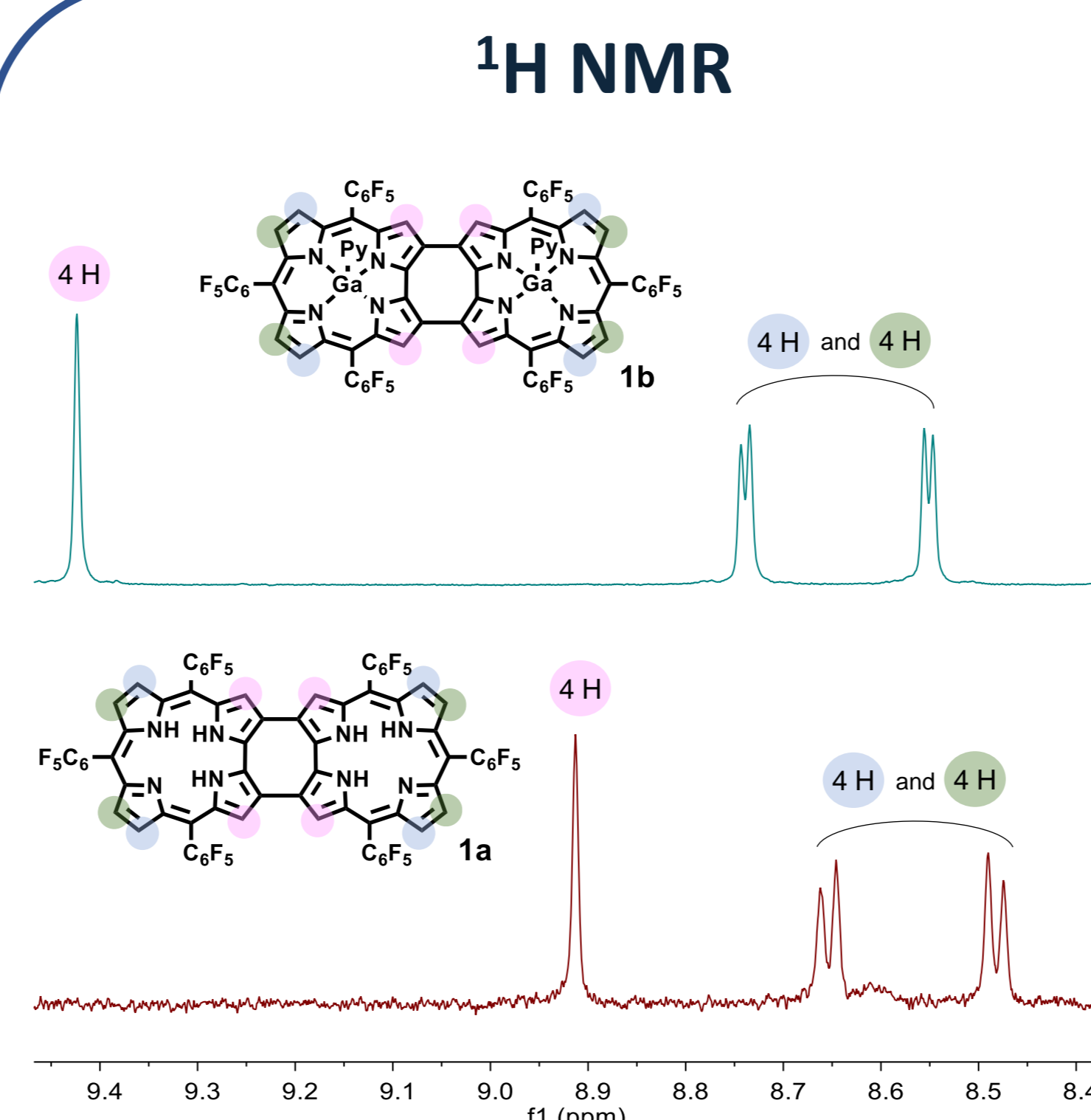


Figure 1. ¹H NMR spectra of dimers **1a** and **1b**, in CDCl₃.

Optical Properties

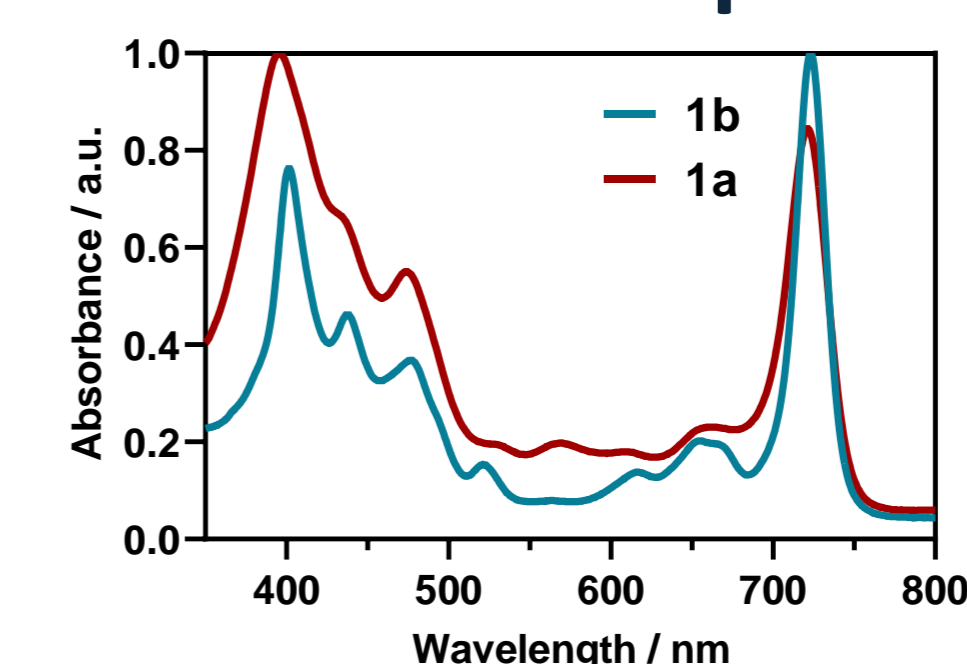


Figure 2. Absorption spectra of **1a** and **1b** in CH₂Cl₂.

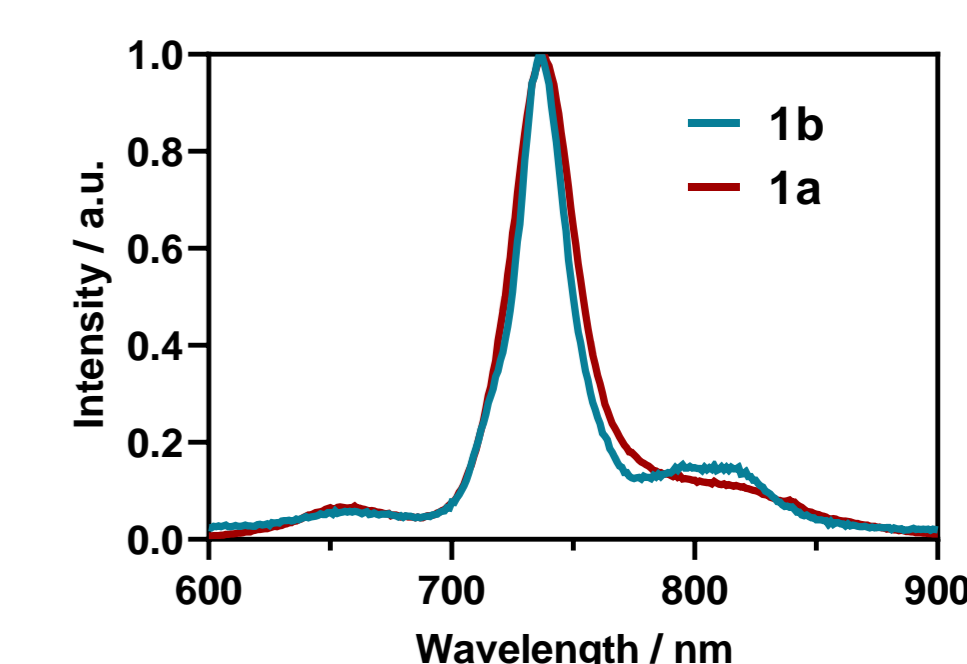


Figure 3. Emission spectra of **1a** and **1b** in CH₂Cl₂ ($\lambda_{exc} = 420$ nm)

Effects on singlet oxygen generation

Table 2 - Photo-oxidation of 9,10-dimethylanthracene after 10 min of blue light irradiation

Photosensitiser	DMA Decay (%)*
Dimer 1a	88
Dimer 1b	78
TPP	71

* Photo-oxidation of 9,10-dimethylanthracene (DMA, 30 μ M), by ¹O₂ generated by the Ps when exposed to blue light irradiation (420 nm) for 600 s in toluene. The DMA absorbance was recorded at 378 nm.

Antimicrobial activity studies

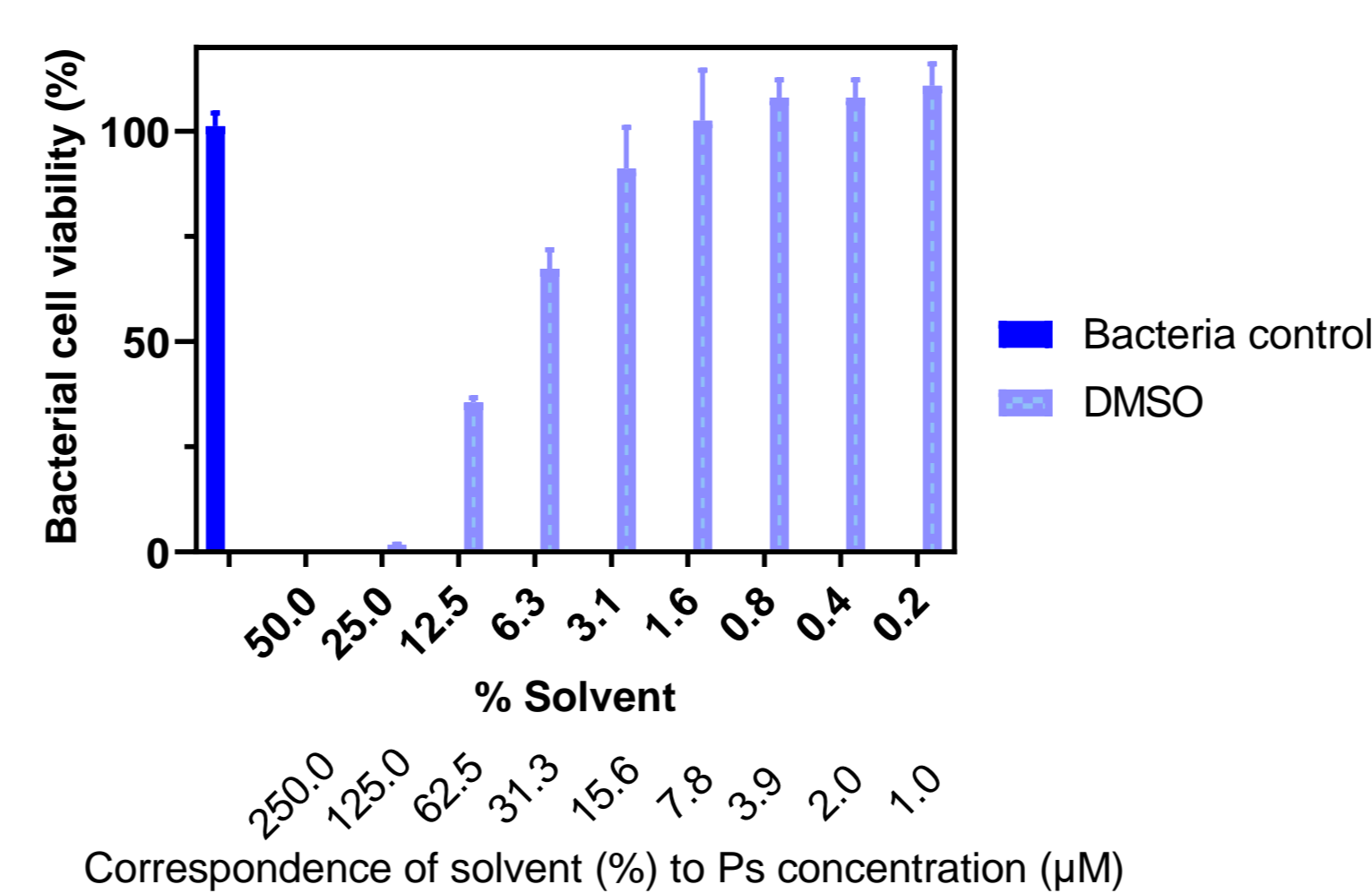


Figure 4. Toxicity evaluation of the solvent used (dimethyl sulfoxide, DMSO), in *S. aureus*. According to stock solution concentration (500 μ M) of the Ps, the correspondence between % solvent and Ps solution concentration is shown underneath the graph.

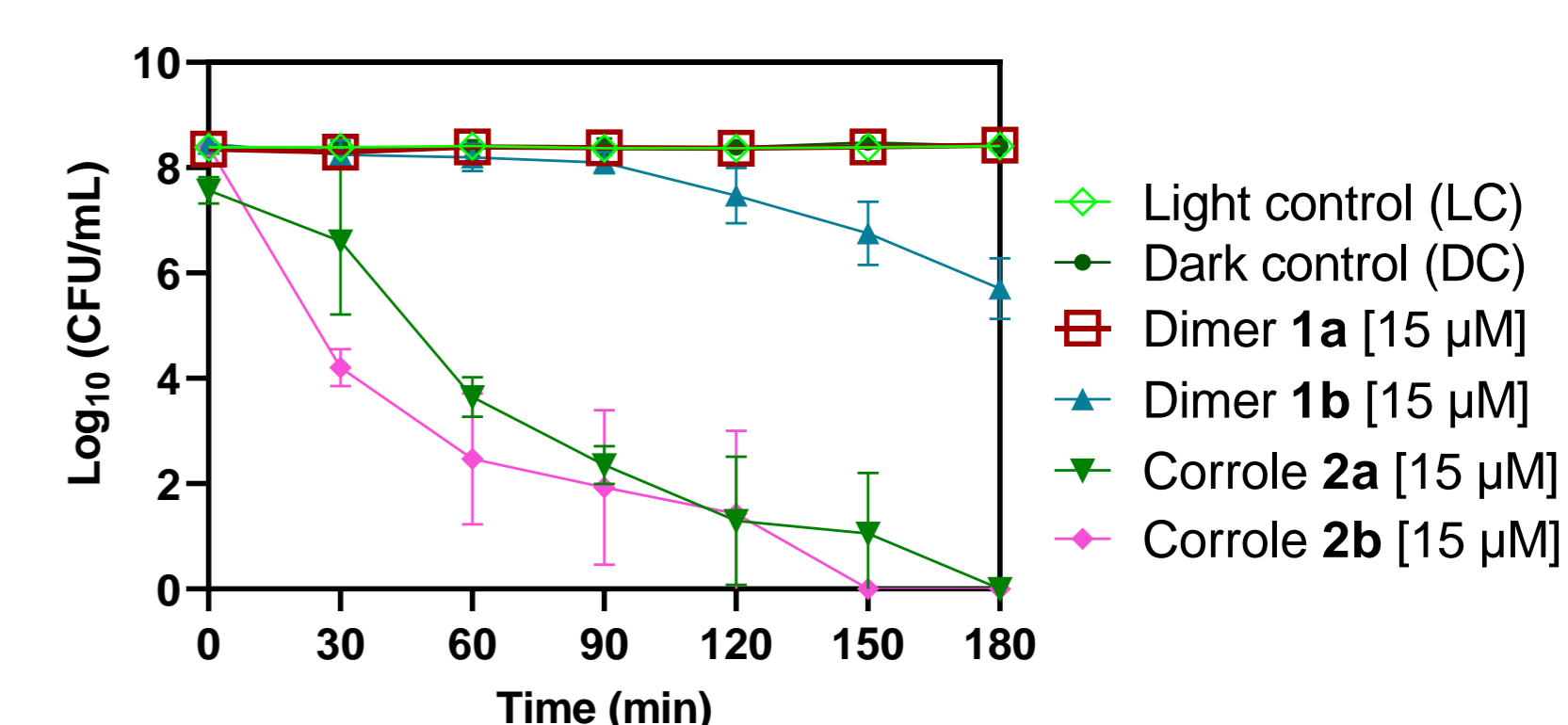


Figure 5. Inactivation of *S. aureus*, with tested Ps **1a**, **1b**, **2a** and **2b** at 15 μ M, for a total of 180 min of irradiation with white light (50 mW/cm²). LC corresponds to exposure of bacterial cells to irradiation, with no Ps added; DC corresponds to exposure of bacterial cells to Ps at the same concentration used in the samples, but without irradiation. Values are expressed as the mean of three independent experiments; error bars represent the standard deviation between the experiments.

Conclusions

✓ Bis-gallium(III) fused corrole dimer **1b** was successfully obtained from parent gallium corrole **2b** using a mixture of acids.

✓ The corrole precursors (**2a** and **2b**) showed an excellent photodynamic action against *S. aureus* at 15 μ M under white light irradiation. The dimerization step affected the antimicrobial activity of both derivatives although the gallium complex **1b** showed a better efficacy than **1a** which is probably related with its better performance to generate singlet oxygen.

References

- 1) J. F. B. Barata, M. G. P. M. S. Neves, et. al., Strategies for Corrole Functionalization. *Chem. Rev.*, 117, 3192, 2017.
- 2) M. Wainwright, T. Maisch, et. al., Photoantimicrobials—are we afraid of the light? *Lancet Infect. Dis.*, 17, e49, 2017.
- 3) J. F. B. Barata, A. M. G. Silva, et al., β, β' -Corrole Dimers. *Tetrahedron Lett.*, 47, 8171, 2006.
- 4) S. Bhowmik, M. Kosa, et al., The Planar Cyclooctatetraene Bridge in Bis-Metallic Macrocycles: Isolating or Conjugating? *Inorg. Chem.*, 56, 2287, 2017.

Acknowledgements:

Thanks are due to University of Aveiro and FCT/MCTES for the financial support to CESAM (UIDP/50017/2020 + UIDB/50017/2020), and LAQV-REQUIMTE (UIDB/50006/2020) through national funds and, where applicable, co-financed by the FEDER, within the PT2020 Partnership Agreement, and to the Portuguese NMR Network, which partially support the NMR spectrometers by Infrastructure Project N^o 022161 (co-financed by FEDER through COMPETE 2020, POCI and PORL and FCT through PIDDAC). This work was financially supported by the project Corlutna (POCI-01-0145-FEDER-031523) funded by FEDER, through COMPETE2020 - Programa Operacional Competitividade e Internacionalização (POCI), and by national funds (OE), through FCT/MCTES.