Synthesis of porphyrins with ABAB symmetry from dipyrromethanes as potential phototherapeutic

Milena B. Boarini[1], María E. Pérez[1], María E. Milanesio[1] and Edgardo N. Durantini[1],*

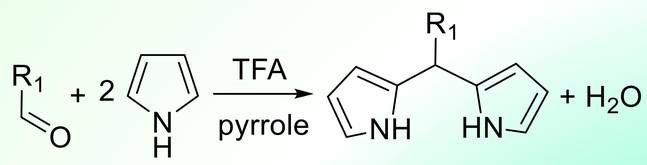
[1]*IDAS-CONICET, Departamento de Química, Facultad de Ciencias Exactas, Físico-Químicas y Naturales, Universidad Nacional de Río Cuarto, Ruta Nacional 36 Km 601, X5804BYA Río Cuarto, Córdoba, Argentina.*

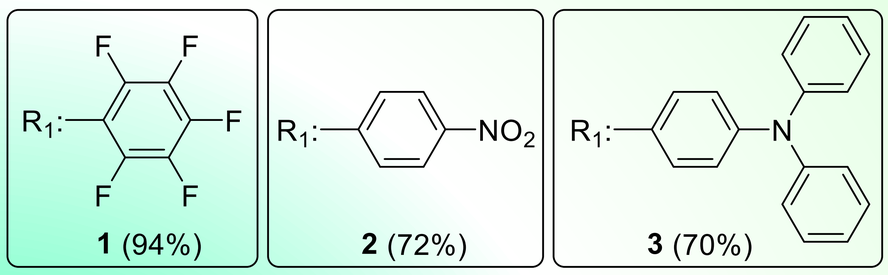
**Correspondence: edurantini@exa.unrc.edu.ar; Tel.: +54 358 4676157.*

Porphyrin derivatives have been proposed as photosensitizers in the photodynamic inactivation of microorganisms [1,2]. However, depending on the substituents on the periphery of the tetrapyrrolic macrocycle, these molecules tend to aggregate, producing a loss of photodynamic activity. Thus, to achieve effective photoinactivation, these compounds can bind to different supports forming photoactive materials [3,4]. In this sense, it is interesting to develop porphyrins asymmetrically substituted in the meso positions by two different structures (A and B). In these compounds, structure A has a functional group that allows covalent attachment to other molecules, while B is substituted by groups that allows changing the properties of the tetrapyrrolic macrocycle [5,6]. A major limitation of available methods to synthesize tetrapyrrole macrocycles concerns the ability to place different substituents at the four meso-positions of the porphyrin. Thus, porphyrins bearing two different types of meso-substituents can be prepared by a binary mixed aldehyde condensation. However, this approach is statistical in nature and usually multiple porphyrin products are obtained [7]. Often, six porphyrins are formed, the work up is no simple because the tar present. The isolate requires slowly chromatographic separation and no pure porphyrin is always possible, resulting in low yields of the desired product. More direct approaches to obtain trans-substituted porphyrins (ABAB-porphyrins) are provided by condensation of dipyrromethanes with aldehydes. These porphyrins require access to meso-substituted dipyrromethane, which can be synthesized from the reaction of aldehyde with excess of pyrrole catalyzed by acid [8].

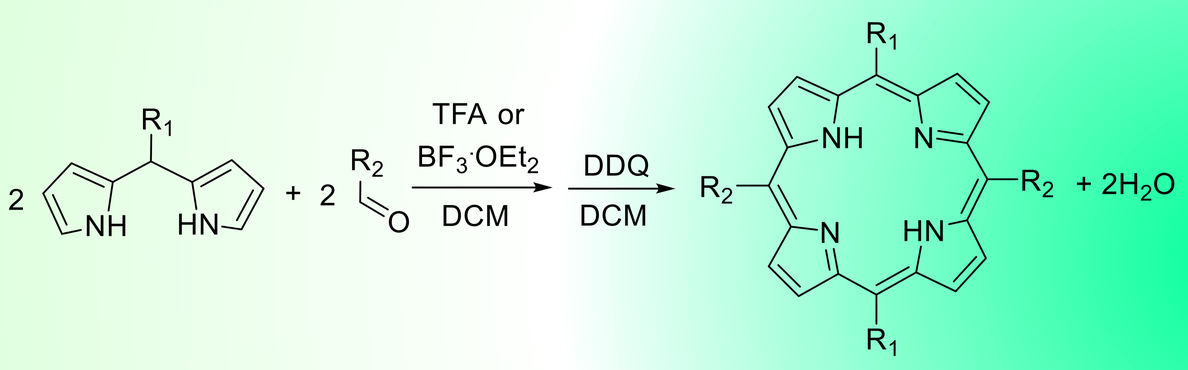
In the present work, ABAB-porphyrins were synthesized from the condensation of meso-(substituted)dipyrromethanes with benzaldehyde derivatives catalyzed by acid. These porphyrins are interesting starting materials to obtain photoactive molecular structures as potential phototherapeutic agents.

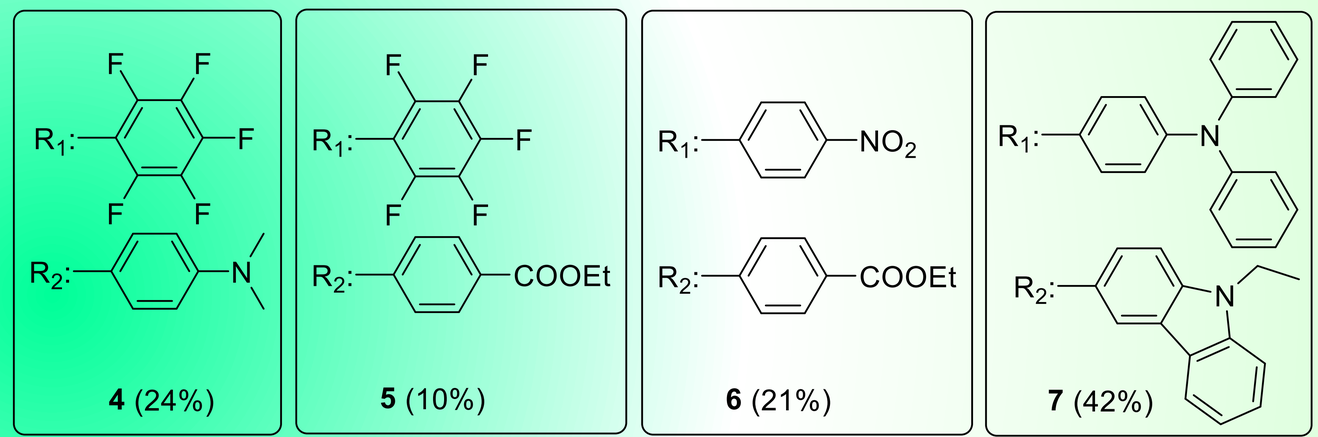
Synthesis of dipyrromethanes





Synthesis of ABAB-porphyrins





UV-visible absorption spectroscopic properties

PS	Absorption λ_{max} (nm)	$\varepsilon^{Soret\ a}$	Fluorescence λ_{max} (nm)	Φ_F [b]
4	418 510 542 589 647	4.67×10^5	651 712	0.063±0.003
5	420 512 543 590 648	4.72×10^5	652 712	0.054±0.002
6	421 516 551 591 647	4.72×10^5	652 717	0.10±0.01
7	428 520 563 596 653	3.15×10^5	668 729	0.12±0.01

[a] molar absorption coefficient ($Lmol^{-1}cm^{-1}$), [b] fluorescence quantum yield.

Conclusions

The following two basic steps were used sequentially in the synthesis of ABAB-porphyrin: 1) *meso*-(4-substituted) dipyrromethane was formed from correspondent benzaldehyde derivative and pyrrole catalyzed by acid, 2) condensation of dipyrromethane with appropriate benzaldehydes yields the ABAB-porphyrin, which was easily purified by flash chromatography. Thus, the desired ABAB-porphyrins 4-7, bearing different substituents were obtained with appreciable yields of 10-42%. Thus, the dipyrromethanes react with an aldehyde under the conditions of the two-step one-flask porphyrin synthesis, affording direct access to ABAB-porphyrins. Moreover, it has a relatively simple reaction work up and high yields. These trans-substituted porphyrins contain precursor groups of positive charges, which can be used to obtain cationic photosensitizers. Moreover, these tetrapyrrolic macrocycles can be covalently attached to molecular structures and be used to form polymeric materials. Therefore, these ABAB-porphyrins are interesting starting materials to obtain photoactive molecular structures as potential phototherapeutic agents.

References

1. A. Martinez de Pinillos Bayona, P. Mroz, C. Thunshelle, M.R. Hamblin, Chem. Biol. Drug. Des. 2017, 89, 192-206.
2. E. Alves, M.A.F. Faustino, M.G.P.M.S. Neves, Â. Cunha, H. Nadais, A. Almeida, J. Photochem. Photobiol. C: Photochem. Rev. 2015, 22, 34-57.
3. D. A. Heredia, S. R. Martínez, A. M. Durantini, M. E. Pérez, M. I. Mangione, J. E. Durantini, M. A. Gervaldo, L. A. Otero, E. N. Durantini, ACS Appl. Mater. Interfaces 2019, 11, 27574-27587.
4. A. C. Scanone, N. S. Gsponer, M. G. Alvarez, D. A. Heredia, A. M. Durantini, E. N. Durantini, ACS Appl. Bio Mater. 2020, 3, 5930-5940.
5. M. B. Ballatore, M. B. Spesia, M. E. Milanesio, E. N. Durantini, Eur. J. Med. Chem. 2014, 83, 685-694.
6. A. C. Scanone, N. S. Gsponer, M. G. Alvarez, E. N. Durantini, Photodiagn. Photodyn. Ther. 2018, 24, 220-227.
7. E. N. Durantini, J. J Silber, Synth. Commun. 1999, 29, 3353-3368.
8. J. S. Lindsey, Acc. Chem. Res. 2010, 43, 300-311.