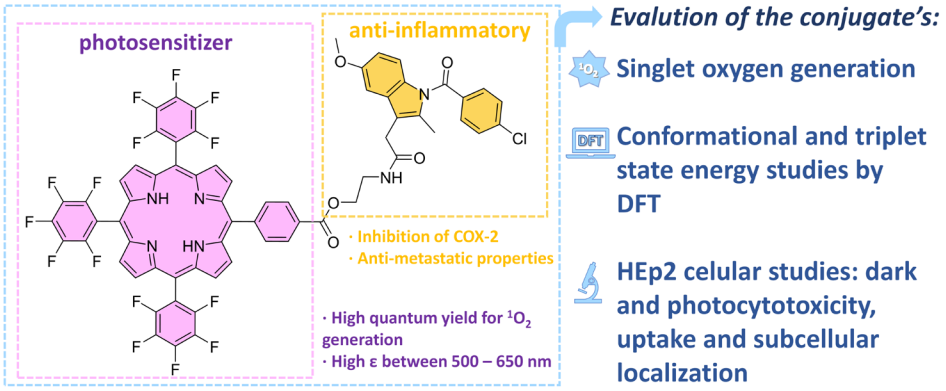
Study of Indomethacin–porphyrin conjugates as photosensitizers for photodynamic therapy of cancer

José Almeida[a], **Guanyu Zhang**[b], **Maodie Wang**[b], **Carla Queirós**[a], **Ana. F. R. Cerqueira**[c], **Augusto C. Tomé**[c], **Giampaolo Barone**[d], **M. Graça H. Vicente**[b], **Ana M. G. Silva**[a,*], **Maria Rangel**[e]

[a] *LAQV-REQUIMTE, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto 4169-007 Porto, Portugal; *ana.silva@fc.up.pt*
[b] *Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, USA*
[c] *LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal*
[d] *Dipartimento di Scienze e Tecnologie Biologiche, Chimiche e Farmaceutiche, Università di Palermo, Viale delle Scienze, Edificio 17, 90128 Palermo, Italy*
[e] *LAQV-REQUIMTE, Institute of Biomedical Sciences Abel Salazar, University of Porto, 4099-003 Porto, Portugal*

Indomethacin is a potent non-steroidal anti-inflammatory drug (NSAID) with a strong selective inhibitor activity towards cyclooxygenase-2 (COX-2), an enzyme that is highly overexpressed in various tumor cells, being involved in tumorigenesis.[1] Concomitantly, porphyrins have gained much attention as promising photosensitizers (PSs) for the non-invasive photodynamic therapy (PDT) of cancer.[2] Here, the design, singlet oxygen generation and theoretical studies of two indomethacin–porphyrin/chlorin conjugates are reported. Both conjugates were obtained in good yields and were characterized by ^{1}H, ^{19}F and ^{13}C NMR as well as by HRMS. Singlet oxygen generation properties were assessed by the 1,3-diphenylisobenzofuran trap method and DFT calculations were performed to determine the minimum energy conformation of the conjugates and their first excited triplet state structures. The conjugate's dark and photocytotoxicity in human HEp2 cells was investigated as well as the subcellular localization by fluorescence microscopy.



Acknowledgements: This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e a Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through the project UIDB/50006/2020 and PTDC/QUI-QOR/29426/2017 (X-Sensors). J. Almeida and A. F. R. Cerqueira acknowledge FCT and ESF (European Social Fund) through POCH (Programa Operacional Capital Humano) for their PhD grants (PD/BD/142868/2018 and SFRH/BD/135597/2018, respectively). J. Almeida is also grateful to the portuguese Fulbright Commission for the Fulbright-FCT research grant at LSU (USA). A. M. G. Silva thanks FCT for funding through program DL 57/2016 – Norma transitória. The research team would like to thank the valuable contribution from Nichole E. M. Kaufman and Philipp Stockmann and gratefully acknowledge COST Actions CM1302 (SIPs), CA18202 (NECTAR) and the "Cooperação Científica e Tecnológica FCT/DAAD-2017/2018"

REFERENCES

1. M. J. Uddin, B. C. Crews, S. Xu, K. Ghebreselasie, C. K. Daniel, P. J. Kingsley, S. Banerjee, L. J. Marnett, *ACS Chem. Biol.* 2016, *11*, 3052–3060.
2. M. Ethirajan, Y. Chen, P. Joshi, R. K. Pandey, *Chem. Soc. Rev.* 2011, *40*, 340–362.