Light-Activated counterion activation of Cell-Penetrating Peptide transport across synthetic membranes

Joana N. Martins[1]*, Javier Montenegro[2], João C. Lima[1], Nuno Basílio[1]

[1] Laboratório Associado para a Química Verde (LAQV), Rede de Química e Tecnologia (REQUIMTE), Departament of Chemistry, NOVA School of Science and Technology (FCT-NOVA), Caparica, Portugal

[2] Centro Singular de Investigación en Química Biológica y Materiales Moleculares (CIQUS), Organic Chemistry Department, Santiago de Compostela University, 1578 Santiago de Compostela, Spain

* jmn.martins@campus.fct.unl.pt

The study of peptides is of great interest, not only due to the variety of functions these molecules present in biological systems[1] but also as tools in biotechnology and as pharmacological agents, as is the case of antimicrobial cell-penetrating peptides.[2] Supramolecular receptors have had a rising application in the transport, modulation and sensing of these biomolecules, due to the strong interactions they can establish with affinities up to the nM range.[3] Our work focused on the development of a supramolecular amphiphilic counterion activator, SC6Azo (Figure 1), for the light-activated transport of polyarginines across phospholipidic membranes. This transporter is based on a modular amphiphilic system, with *p*-sulfonatocalix[4]arene as a receptor for cationic targets, monosubstituted in its lower rim with an aliphatic chain of 6 carbons, with a photo-active azobenzene moiety at its end. Not only was it shown that SC6Azo binds to polyarginines with comparable affinities to those of the *p*-sulfonatocalix[4]arene receptor, up to the nM range, but it was also shown that this molecule presents an efficient light induced isomerization, with quantitative photochemical conversion from trans to cis, when irradiated at 382 nm, and reaching 73% of maximum conversion for the reverse reaction, upon irradiation at 500 nm. This enabled a marked decrease in the EC50 for the peptide transport in phosphatidylcholine liposomes, when irradiating the cis isomer and converting it to the more hydrophobic trans isomer. Furthermore, a marked increase in peptide transport upon cis-trans isomerization was observed in a single dye-displacement assay, yielding an increase of release of, approximately, 15%.

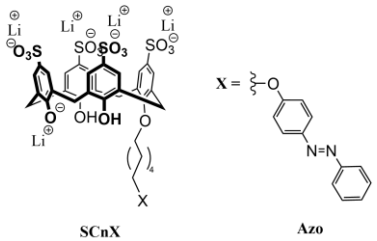

Figure 1. *Chemical Structure of the light-controlled counterion activator, SC6Azo.*

Acknowledgements: This work was supported by the Associate Laboratory for Green Chemistry - LAQV which is financed by national funds from FCT/MCTES (UIDB/50006/2020 and UIDP/50006/2020). FCT/MCTES is also acknowledged for the grants PTDC/QUI-COL/32351/2017 as well as for the financial support in the "Verão com Ciência" initiative in association with DGES – Direção Geral do Ensino Superior. N.B. also acknowledges the FCT/MCTES for a research contract CEECIND/00466/2017.

References:

[1] A. Voigt and H. F. Jelinek, *Physiol. Rep.,* **2016,** 4, 1–5.
[2] D. I. Chan, E. J. Prenner and H. J. Vogel, *Biochim. Biophys. Acta - Biomembr.,* **2006**, 1758, 1184–1202.
[3] J. N. Martins, J. C. Lima, N. Basílio, *Molecules*., 9, **2021,** 26(1), 106.