Cis-Trans photodynamics of benzodiazopyrrole derivatives in view of biomedical applications

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Benzodiazopyrrole derivatives have been reported as microtubules targeting agents on colon cancer cells. Their irradiation at 435 nm is related to trans/cis isomerization and degree of cell growth inhibition. An investigation of their photo-responsive behaviour at different pH is reported.
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1. Introduction

Recently, some benzodiazopyrrole derivatives have shown a photo-responsive antiproliferative activity against colon cancer cells (HCT 116 p53-/-, Figure 1) [1]. Colorimetric tests performed on this cancer cell line treated with the synthesized molecules, with and without LED irradiation at 435 nm, showed that the occurrence of the *trans-cis* isomerization is correlated with the degree of cell growth inhibition [1]. The obtained data suggested that the *cis* isomers showed the greatest antiproliferative activities. Two of these molecules forming the diastereomeric mixture (**1a** in Figure 1), exhibited the most interesting biological properties with a consistent inhibition of HCT 116 p53 -/- cell under 435 nm irradiation. In addition, an *in vitro* tubulin polymerization test also evidenced that, under LED irradiation, the two stereomers, **1RR** and **1RS** (see Figure 1), differently inhibited the tubulin aggregation into cell microtubules [1].

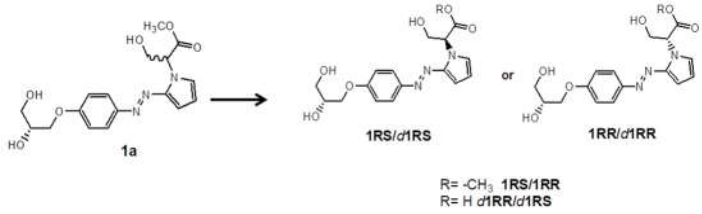

Fig. 1 Structure of the studied benzodiazopyrrole derivatives (the diastereomeric mixture and its pure stereomers **1RR** and **1RS**), and the water soluble deprotected *d***1RR** and *d***1RS** herein explored for their photo-responsive properties.

2. Results and Conclusions

With the aim to better understand the behavior of the **1a** compound and its specific biological properties, and considering that the tumor aggressiveness is correlated with the lowering of the pH around the membrane of cancer cells (see for instance [2]), we have performed UV time-resolved spectroscopy of *d***1RR** and *d***1RS** (the free carboxylic acids of **1RR** and **1RS,** Figure 1) in the 8.0-5.7 pH range (see an example reported in Figure 2). Results were analyzed based on computational simulations and by liquid chromatography high resolution mass spectrometry. Our investigation on *d***1RR**/*d***1RS** photo-responsive properties [3] showed that *d***1RR**, but not *d***1RS**, underwent a photo-transformation under prolonged irradiation.

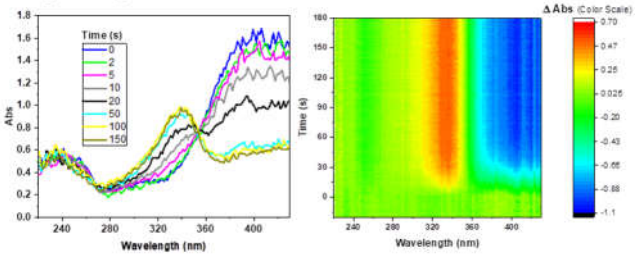

Fig. 2 **Left.** Time-dependent absorption spectra of *d***1RR**. **Right**. 2D graphical representation of the changes of absorbance of *d***1RR** plotted as a function of time.

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References

1. C. Imperatore, M. Scuotto, M. Valadan et al. *J. Photochem. Photobiol. A Chem*. **377**, 109-118 (2019).
2. M. Anderson, A. Moshnikova, D.M. Engelman et al. *PNAS* **113**, 8177-8181 (2016).
3. C. Altucci, C. Imperatore, M. Valadan et al. *Int. J. Mol. Sci*., in print (2020).