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FERROCENE-PEPTIDE CONJUGATES WITH POTENTIAL ANTITUMOR ACTIVITY

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INTRODUCTION

New anticancer therapies are currently much needed. Our contribution aims at synthesizing and studying ferrocene(Fc)-peptide conjugates to be tested as anti-tumor agents. The peptide is intended to selectively address over-expressed integrins of cancer cells, whereas ferrocene is expected to display anti-proliferative activity through the production of reactive oxygen species (ROS) [1]. A concentration of ROS higher than normal favors carcinogenesis, but if this exceeds a certain value then a cytotoxic effect is observed. The exogenous production of ROS, consequently, represents a possible strategy to induce apoptosis in diseased cells.

SYNTHESIS

Inspired by previous contributions [2-7], we synthesized conjugates made up of four components (Figures 1 and 2):

i) an Fc unit as the electroactive element;
ii) an aromatic moiety to modulate the oxidation potential of Fc and thus to favor its oxidation under physiological conditions;
iii) an alkyl spacer to increase flexibility and, consequently, to improve integrins affinity, cellular uptake and antitumor activity [6];
iv) an oligopeptide, including the well-known RGD, able to interact with over-expressed receptors of the cancer cells.

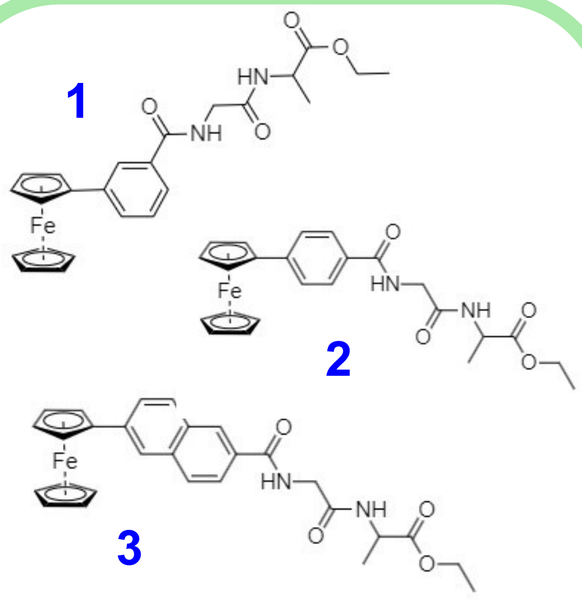

Figure 1. Known Fc-aromatic-peptide conjugates [3-6] synthesized as reference compounds.

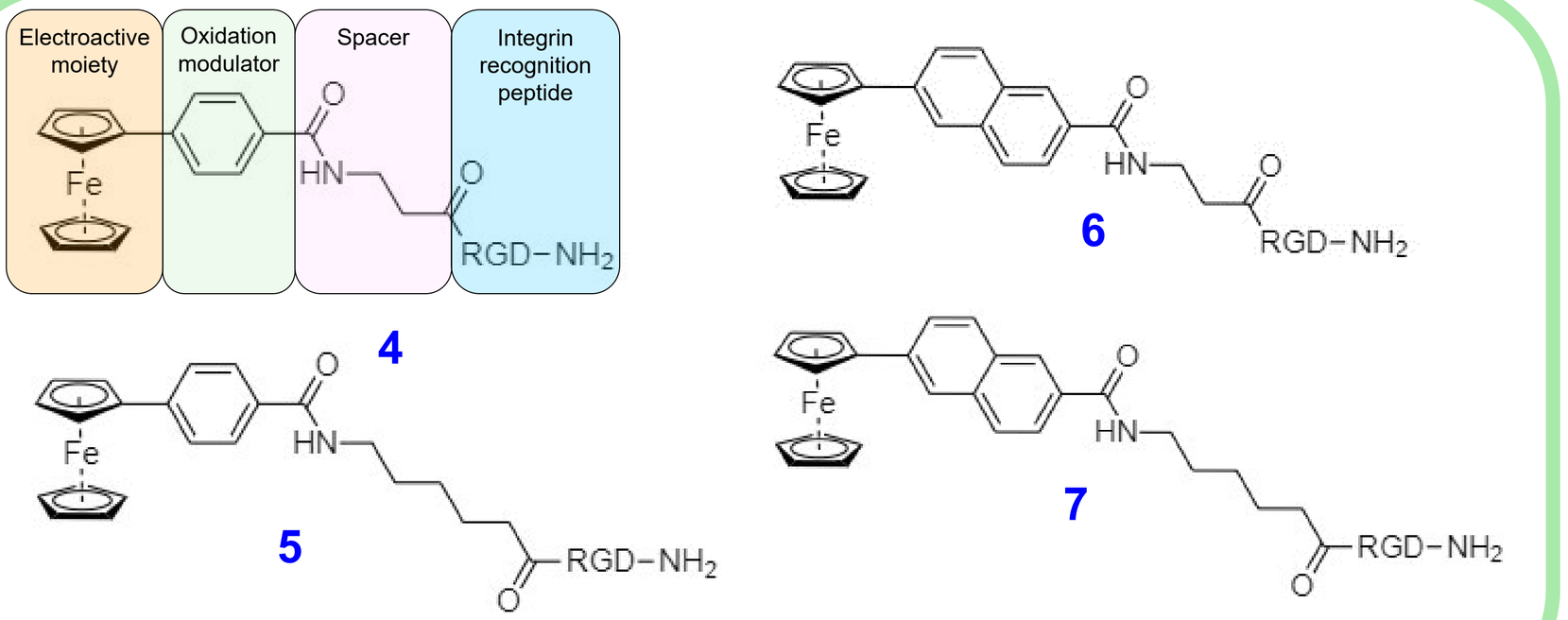

Figure 2. New Fc-aromatic-spacer-peptide conjugates synthesized in this work.

CONFORMATION in methanol

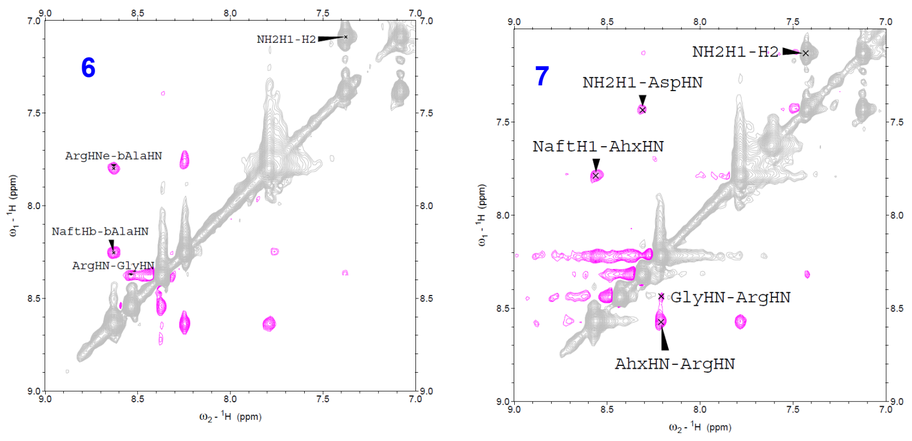

Figure 3. Amide region of the NOESY spectra of **6** and **7**. The sequential $NH_{i} \rightarrow_{i+1}$ connectivities indicate a helical conformation.

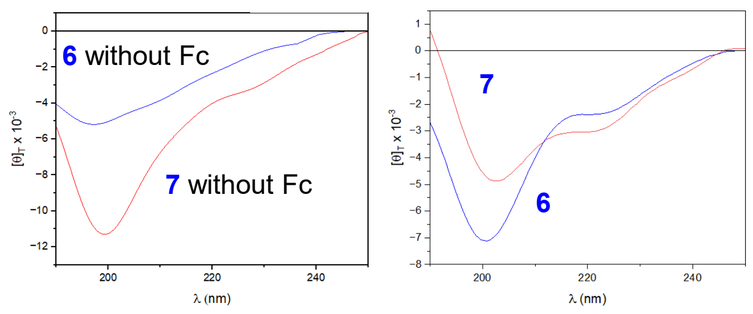

Figure 4. CD spectra in the amide absorption region of **6** and **7** (right panel) and of the same two conjugates missing the Fc-aromatic moieties (left panel).

ENZYMATIC STABILITY

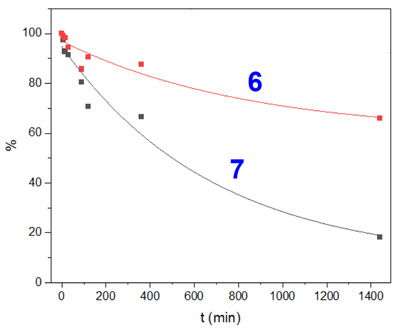

Figure 5. Conjugates **6** and **7** incubated for 24 hr in human serum.

CONCLUSIONS

- Conjugates 6 and 7 display a significant α-helical content, not observed when the Fc-aromatic moiety is removed.
- The Fc moiety prevents peptide degradation in human serum. After a 24 hours treatment, significant amounts of 6 and 7 are still detected. The shortest spacer gives the best results as Fc is closer to the peptide.
- Cyclic voltammetry measurements indicate a relevant influence of the aromatic groups on the Fc oxidation potentials.
- The anticancer activity of our conjugates is currently under scrutiny.

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