Peptide conjugates containing chlorambucil or tetradentate aminopyridine ligands for anticancer treatment

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Since drug administration is hampered by different physiological barriers, the development of novel delivery systems has attracted interest in the last decades.[1] Among different drug delivery approaches, the use of CPP-based delivery systems has been reported to enhance drug permeability, stability and solubility in anticancer therapies through prodrug strategies.[2-4] On the other hand, medicinal inorganic chemistry is a discipline of growing significance in both therapeutic and diagnostic medicine.[5,6] Particularly, redox active metal complexes and metal binding compounds are emerging as potential anticancer agents due to rich reactivity.[7] Within this context, metal-based drugs have been suggested to target biochemical alterations in cancer cells. In particular, since the alteration of redox environment through ROS species is directly correlated with oncogenic and metabolic dysregulations, pro-oxidant strategies are considered as emerging anticancer therapies due to their involvement in apoptosis and necrosis.[8]

Herein we report the development of an efficient CPP-based delivery system for the vectorization of redox-active N_4-based ligands into cancer cells. Bearing in mind this objective, first, we have studied the identification of a new non-toxic cell-penetrating sequence and its applicability in smart drug delivery approaches.[9,10] Next, a straightforward methodology to conjugate tetradentate aminopyridine ligands to different peptide derivatives has been developed. The cytotoxic activity, the cellular uptake behavior and the intracellular drug release of the resulting conjugates have been extensively explored.[11]

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