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ACETAL PH-SENSITIVE LINKERS FOR GLYCO-PROTEIN CONJUGATION

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The environment of tumor tissue has a slightly lower pH compared to that of normal tissue. Cancer cells have high rates of converting glucose to lactate. Their intracellular pH is near to 5.0, while in the extracellular system the pH value is around 7.4. This difference can be exploited to design cleavable linker for drug conjugation to protein that are stable during circulation in the blood, while are activated to release the drug at more acidic pH. These drug delivery systems are at the base of a targeted therapy, since they are able to selectively distinguish between healthy and cancer cells by the use of cellular tags. In this way it is possible to reduce the unwanted, dose-limiting, and debilitating side effects of some chemotherapy agents.

Acetals are acid labile functional groups commonly employed as protecting groups for alcohols in organic synthesis. They have not been widely used in the design of pH-responsive linkers, even if they are appropriate for the conjugation of a drug containing free hydroxyl groups. So, acetals can be helpful in the design of bifunctional linkers, that are involved in the conjugation of a drug to a protein, since they are cleavable in biocompatible condition.

In this context, we have developed bifunctional linkers with a carboxylic function at one end and a dimethyl acetal at the other. The carboxylic group allows the conjugation to the protein through amide bonds with the lysine residues, while a transacetylation reaction on the dimethyl acetal is required to link the drug through an hydroxyl group. Herein, we will report the preparation of two linkers differing in the chain length, starting from γ-valerolactone. Furthermore, we will describe our results in the optimization of the transacetylation reaction for drug conjugation and on linker stability/solubility.