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Biodegradable Polymer-Drug Conjugates for pH-Sensitive Anti-Cancer Drug Delivery

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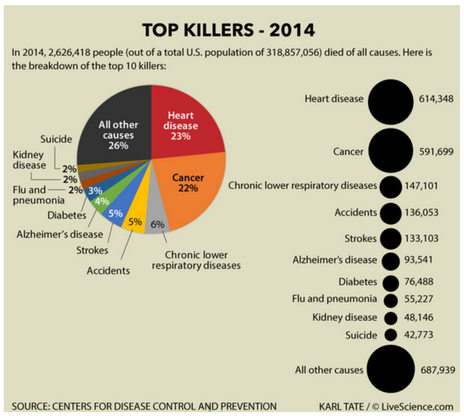
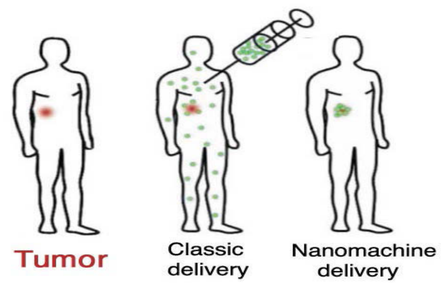
Abstract

Polymer-drug conjugates represent a selective and novel chemotherapy approach for cancer treatment. Polycaprolactone and polylactide were chosen as the building blocks for drug delivery systems because of their biodegradability. Accordingly, two ester-based monomers with an acetylene or allyl group were designed to allow for the attachment of anti-cancer drugs and solubility-enhancing zwitterionic groups with the resulting polymers. The anti-cancer drugs, doxorubicin and paclitaxel, were conjugated with the polymer chains using pH-sensitive linkages. Novel "click chemistries" were utilized throughout the synthesis of the polymer-drug conjugates. Precursors of the conjugates have been obtained with sufficient yields and characterized using nuclear magnetic resonance spectroscopy (NMR) and gel permeation chromatography (GPC).

Introduction

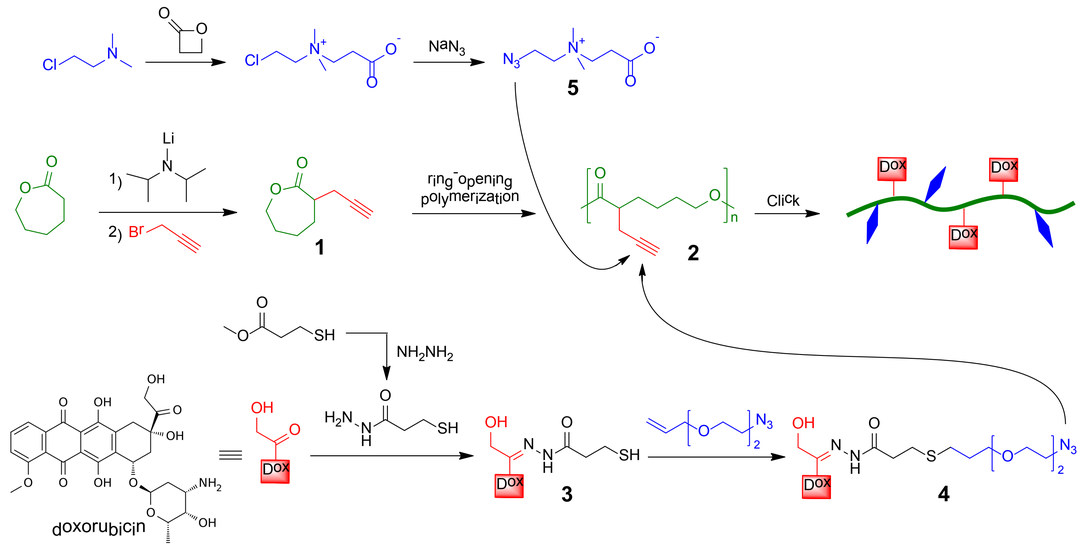


Many anti-cancer drugs are hydrophobic small molecules that are poorly dissolved but can be excreted quickly by the kidneys. Conjugating the drugs with polymers can prevent the kidneys from eliminating the drug, and functionalization of the systems with hydrophilic groups can promote drug solubility. The polymer-drug conjugates can accumulate at tumor sites due to the enhanced permeability and retention (EPR) effect. The pH-sensitive linkages in the conjugates further enable the selective drug release in tumor tissues for effective treatment and to prevent adverse side effects on healthy tissues. Therefore, the overall approach allows greater selectivity and lower side effects.

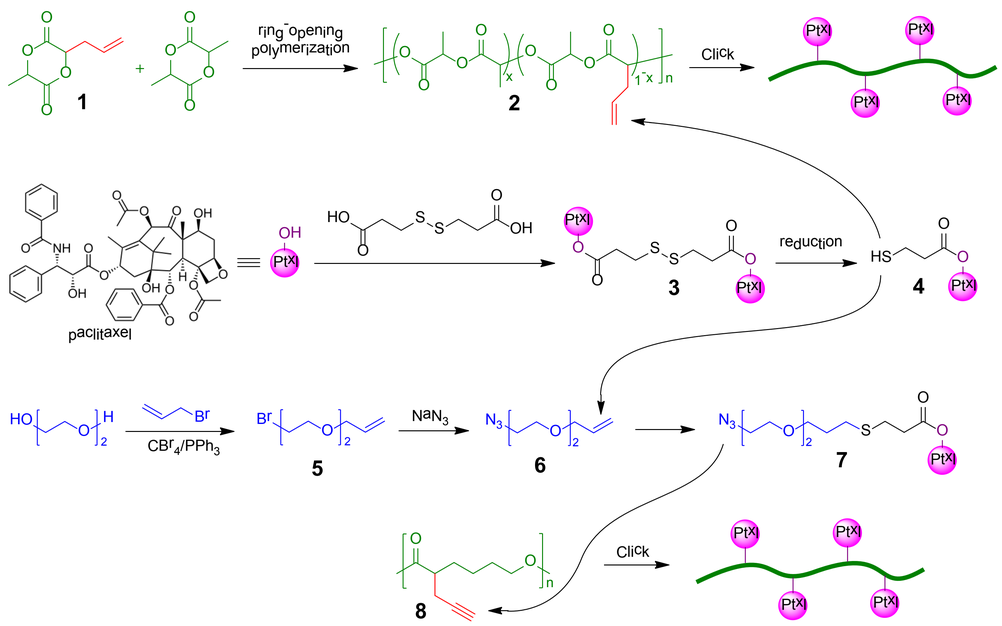


Methods

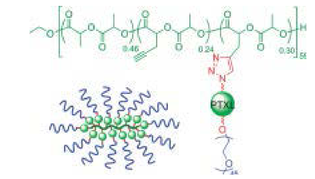
Scheme 1: Synthesis of Polycaprolactone-Doxorubicin Conjugates



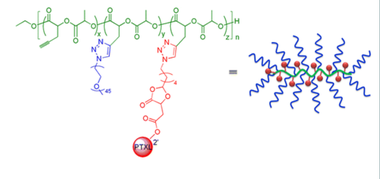
Scheme 2: Synthesis of Polylactide/Polycaprolactone-Paclitaxel Conjugates



Previous Work

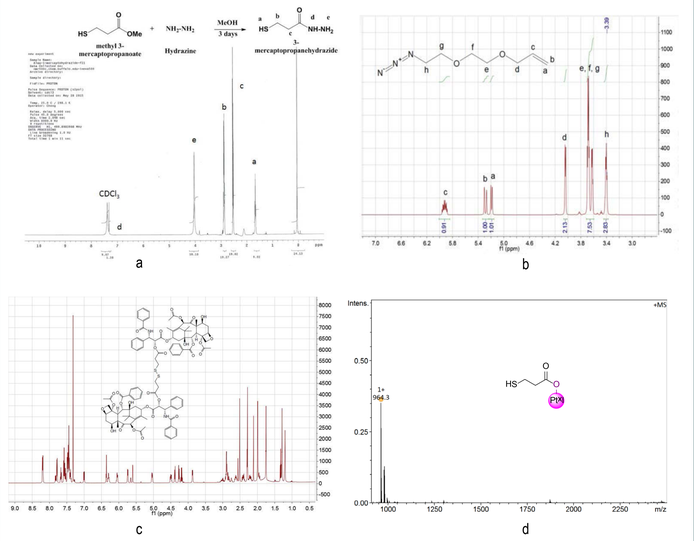


Functional Polylactide-g-Paclitaxel Poly(ethylene glycol) by Azide-Alkyne Click Chemistry



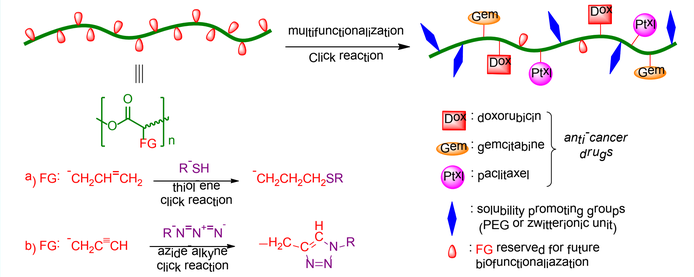
Degradable Brush Polymer–Drug Conjugates for Sustained Delivery of Paclitaxel

Sample Results



a) ^{1}H NMR spectrum of the precursor of pH-sensitive linkage with a hydrazone functionality. b) ^{1}H NMR spectrum of 1-azido-3,6-dioxanon-8-ene. c) ^{1}H NMR spectrum of disulfide-functionalized paclitaxel. d) MALDI spectrum of thiol-functionalized paclitaxel.

Desired Final Product



The ultimate goal is to create a multi-functionalized polymer-drug conjugate containing three anti-cancer drugs: doxorubicin, gemcitabine, and paclitaxel.

References

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Acknowledgements

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