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Synthesis and Evaluation of Hydrophilic Linkers for Antibody–Maytansinoid Conjugates

Robert Y. Zhao*, Sharon D. Wilhelm, Charlene Audette, Gregory Jones, Barbara A. Leece, Alexandru C. Lazar, Victor S. Goldmacher, Rajeeva Singh, Yelena Kovtun, Wayne C. Widdison, John M. Lambert, and Ravi V. J. Chari*

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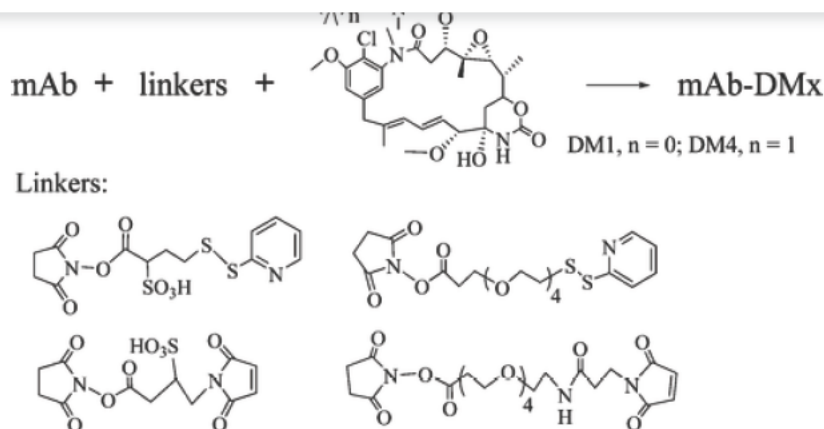
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The synthesis and biological evaluation of hydrophilic heterobifunctional cross-linkers for conjugation of antibodies with highly cytotoxic agents are described. These linkers contain either a negatively charged sulfonate group or a hydrophilic, noncharged PEG group in addition to an amine reactive *N* hydroxysuccinimide (NHS) ester and sulfhydryl reactive termini. These hydrophilic linkers enable conjugation of hydrophobic organic molecule drugs, such as a maytansinoid, at a higher drug/antibody ratio (DAR) than hydrophobic SPDB and SMCC linkers used earlier without triggering aggregation or loss of affinity of the resulting conjugate. Antibody–maytansinoid conjugates (AMCs) bearing these sulfonate- or PEG-containing hydrophilic linkers were, depending on the nature of the targeted cells, equally to more cytotoxic to antigen-positive cells and equally to less cytotoxic to antigen-negative cells than conjugates made with SPDB or SMCC linkers and thus typically displayed a wider selectivity window, particularly against multidrug resistant (MDR) cancer cell lines in vitro and tumor xenograft models in vivo.

Supporting Information

HPLC purity data and UV chromatographic profiles for target compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Conjugates

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Table of Content



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