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PII: S0040-4039(16)31609-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.11.118
Reference: TETL 48404

To appear in: *Tetrahedron Letters*

Received Date: 26 October 2016
Revised Date: 24 November 2016
Accepted Date: 28 November 2016

Please cite this article as: Piorecka, K., Stanczyk, W., Florczak, M., NMR analysis of antitumor drugs: Doxorubicin, daunorubicin and their functionalized derivatives, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.11.118

NMR analysis of antitumor drugs: doxorubicin, daunorubicin and their functionalized derivatives

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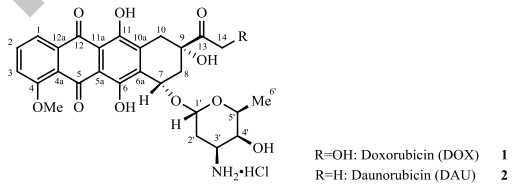
Abstract

^{1}H, ^{1}H-^{1}H COSY and ^{13}C NMR techniques were proven as effective methods for the analysis of functionalized doxorubicin (DOX) and daunorubicin (DAU) derivatives. These compounds represent important drug conjugate intermediates that can be coupled to a variety of nanocarriers. NMR spectroscopy was shown to be an efficient method for following the progress of drug modification and can also be useful for evaluation of the functionalized structures purity. Additionally, a correction of the chemical shifts reported in the literature for the relevant drugs e.g. DOX·HCl and DAU·HCl is presented.

Keywords: NMR analysis, anticancer drugs, modification of anthracyclines, doxorubicin and daunorubicin derivatives

Introduction

Doxorubicin (DOX) **1** and daunorubicin (DAU) **2** hydrochlorides (Scheme 1) are clinically important antibiotics currently used in anticancer chemotherapy. These anthracyclines intercalate with the DNA helix and form stable complexes, thus inhibiting the proliferation of cancer cells and consequently leading to their death.[1]



Scheme 1. Structures of doxorubicin and daunorubicin hydrochlorides.

Unfortunately, these compounds also have serious cardiovascular dose-dependent side-effects such as cardiomyopathy and congestive heart failure.[2,3] Thus, in order to limit the toxicity towards normal tissues, a number of chemical modifications of DOX·HCl and DAU·HCl have been examined involving both physical encapsulation in polymers[4] or solid lipids[5] and chemical conjugation with polymer nanoparticles,[6] fatty acids,[3,7] porous silicon,[8] gold[9] and graphene.[10] This type of nanomedical approach is expected to have a revolutionary impact on healthcare[11] and has been a focus of research. Recently, we reported the first conjugates of DOX·HCl and DAU·HCl with the polyhedral oligosilesquioxane cage, containing eight silicon atoms (T_8- POSS).[12] The POSS nanocarriers, due to their non-toxicity and nano-size, can be regarded as next generation materials in biomedical fields.[13] The synthesis of complex prodrug systems begins with simple modification of the anthracyclines allowing for their functionalization, such as the generation of a linker moiety to conjugate the drug with a suitable nano-carrier. Such transformations require significant care during both