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Synthesis and radioiodination of some daunorubicin and doxorubicin derivatives

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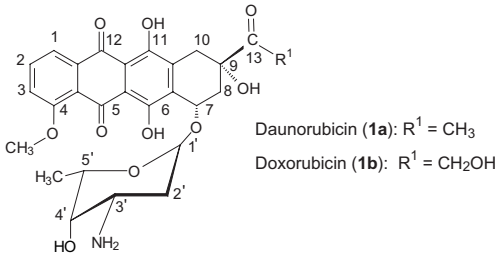
Abstract—Daunorubicin and doxorubicin are efficient agents for cancer treatment. Their clinical efficacy is, however, hampered by their indiscriminant toxicity. This problem may be circumvented by encapsulating the drugs in liposomes and selectively targeting the tumor cells using tumor targeting agents. Furthermore, the antitumor effect could be enhanced by attaching the Auger electron emitter, ^{125}I, to daunorubicin and doxorubicin derivatives. In this context a number of ester, amide, and amine derivatives of daunorubicin and doxorubicin were synthesized. Benzoic acid ester derivatives of daunorubicin were synthesized by nucleophilic esterification of the 14-bromodaunorubicin with the potassium salt of the corresponding benzoic acid, resulting in good yields. Nicotinic acids and benzoic acids, activated with a succinimidyl group, were coupled to the amino group of daunorubicin to give the corresponding amide derivatives. Amine derivatives were obtained by the reductive amination of aromatic aldehydes with daunorubicin hydrochloride. The stannylated ester and amide derivatives were used as precursors for radioiodination. Radiolabeling with ^{125}I was performed using chloramine-T as an oxidant. The optimized labeling resulted in high radiolabeling yields (85–95%) of the radioiodinated daunorubicin and doxorubicin derivatives. Radioiodination of the amines was conducted at the *ortho* position of the activated phenyl rings providing moderate radiochemical yields (55–75%).

Keywords: Daunorubicin; Doxorubicin; Radioiodination; ^{125}I; Chloramine-T

1. Introduction

Daunorubicin (**1a**) and doxorubicin (**1b**) are the most extensively used anthracycline antitumor antibiotics. Daunorubicin was the first antibiotic of this class to show activity against acute leukemia in humans. Later studies have shown that it also has activity against solid tumors.[1,2] The substitution of one hydrogen atom in the daunorubicin acetyl side chain with an hydroxyl group gives doxorubicin. Doxorubicin exhibits antitumor activity against solid tumors, such as breast and lung cancers, and is generally known to be more potent than daunorubicin. Both compounds are known for their effective intercalation to DNA.



The generation of free radicals following microsomal or chemical activation of the quinone moiety of the anthracyclines is believed to contribute to either their cytotoxicity or cardiotoxicity.[3] Many derivatives of these compounds have therefore been synthesized to improve their cytotoxicity and decrease their cardiotoxicity.[4–10] The mechanism of the antibiotic action of these molecules is related to their ability to intercalate between adjacent

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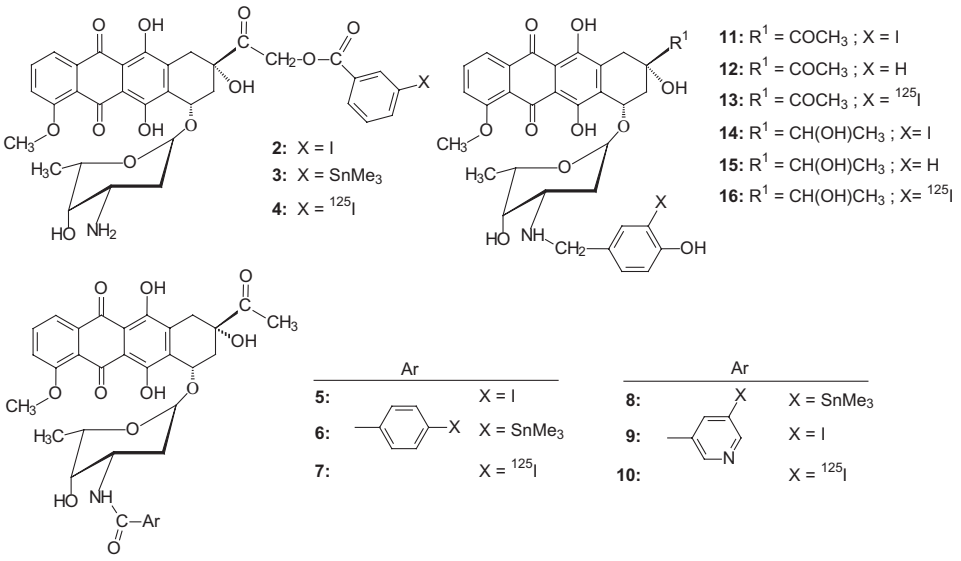

base pairs causing topoisomerase II inhibition, which leads to the production of hydroxyl free radicals that are toxic to both normal and tumor cells.[11] The problems that limit the clinical efficacy of these agents are their cardiotoxicity and multidrug resistance.[12] One approach that possibly improves their therapeutic ability is targeting these molecules specifically to the cancer cells.[13]

In this report, we present the synthesis of some daunorubicin and doxorubicin derivatives as potential candidates for targeted nuclide therapy. The compounds are esters **2**–**4**, amides **5**–**10**, and amines **11**–**16**.

The precursor compounds are labeled with ^{125}I and will be loaded into liposomes. We plan to investigate their efficacy using a two-step targeting technique.[14] In the first step, stabilized liposomes conjugated with a targeting agent will be actively loaded with the labeled compounds and injected into blood circulation. After binding to cancer cells, the loaded liposomes will be internalized, and labeled daunorubicin and doxorubicin derivatives will be released into the cytoplasm. In the second step, the compounds, with the help of the DNA intercalating part, are supposed to bind to the DNA of the tumor cell. The ^{125}I nuclide emits Auger electrons that travel short distances, but are highly cytotoxic when emitted in close vicinity to DNA. In preliminary experiments, two of these compounds, **13** and **16**, were found to be taken up by a permeabilized cell line and transit into the cell nucleus. The biological experiments will be presented elsewhere.

2. Results and discussion

2.1. Synthesis

2.1.1. Synthesis of esters 2–4. Synthesis of compounds **2**–**4** was performed as shown in Scheme 1. Bromination of the hydrochloride of daunorubicin using bromine in the presence of trimethylorthoformate, as described in the literature,[15] gave 14-bromo-13-dimethyl acetal of daunorubicin, which upon being stirred in acetone provided 14-bromodaunorubicin (**17**), in high yield. The Stille coupling reaction of 3-iodobenzoic acid and hexamethylditin using a palladium(II) catalyst provided an 88% conversion to the corresponding stannyl compound **18**, as described in the literature.[16]

The reaction of 3-iodobenzoic acid with the bromo compound **17** and K_2CO_3 at room temperature produced a good (73%) yield of the ester, **2**. Similarly, synthesis of compound **3** was carried out with the stannylated compound **18**, providing a high yield of the target. Both esters were purified by flash chromatography. The purity and identity of the compounds were confirmed by LC/MS and NMR.

2.1.2. Synthesis of amides 5–10. The amides **5**–**7** were synthesized as outlined in Scheme 2. 4-Iodobenzoic acid and 4-(trimethylstannyl)benzoic acid were reacted with di-(*N*-succinimidyl)carbonate in pyridine to yield the corresponding *N*-succinimidyl-derivatives (**19** and **20**, respectively), as described previously.[16] These activated compounds, **19** and **20**, were reacted with daunorubicin hydrochloride in the presence of a 5-fold molar excess of triethylamine in DMF to give 74% and 86% yields of 3′-*N*-4-iodo-benzoyldaunorubicin, **5**, and 3′-*N*-4-trimethylstannylbenzoyldaunorubicin, **6**, respectively.

The syntheses of the amides **8**–**10** are outlined in Scheme 3. The previously known compound *N*-succinimidyl-5-bromo-nicotinic acid (**21**),[17] was synthesized by the same procedure as was used for **19**, except that 5-bromonicotinic acid was used as the starting material. The activated stannylated ester **22**[17] was obtained in a low yield from **21** using the same method as described for the preparation of **20**. *N*-Succinimidyl 5-(trimethylstannyl)nico-