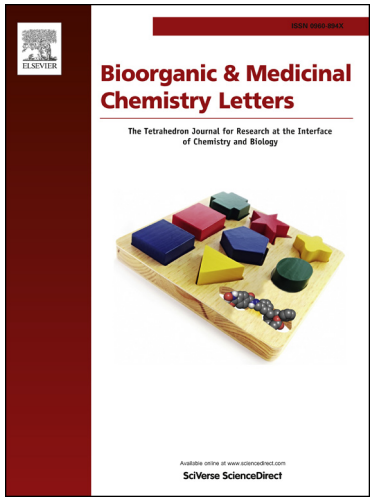

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Synthesis and Evaluation of a Bis-3-chloropiperidine Derivative Incorporating an Anthraquinone Pharmacophore

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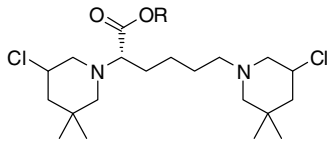
Abstract: With the aim to attain an alkylating agent with enhanced DNA-affinity, we have successfully synthesised lysine-linked bis-3-chloropiperidine **1** bearing an anthraquinone moiety known to bind double-stranded DNA. Consistent with our expectations, compound **1** appears to intercalate into the DNA double helix, which can be observed by conformational changes of plasmid DNA suggesting alkylation and intercalation-induced DNA unwinding. The results of this work can provide a meaningful starting point for investigating the molecular mechanism of action of this novel DNA alkylating conjugate **1** with improved affinity for DNA.

Keywords: Alkylating agents • Nitrogen mustard • Anthraquinone • DNA cleavage • Intercalation

Alkylating and intercalating agents are important classes of DNA-interactive drugs that are used clinically in the field of chemotherapy.[1] The nitrogen mustard alkylators were among the earliest synthetic anticancer agents.[2] They react covalently with nucleophilic sites on DNA bases forming DNA adducts which contribute to their cytotoxic effects. On the other hand, the intercalators bind to DNA through non-covalent interaction by inserting their planar chromophore units between adjacent base pairs of the DNA duplex. The intercalation process causes conformational changes in DNA leading to the unwinding of the double helix.[3] In many instances, the DNA-binding abilities of intercalating drugs have been shown to correlate well to their respective biological properties.[4] However, several unpleasant side-effects and the emergence of drug resistance limit the clinical use of alkylating as well as intercalating agents.[5]

A valuable approach to improve affinity towards DNA and circumvent resistance mechanisms involves the design of DNA-directed alkylating agents by attaching the alkylators to DNA-affinic molecules.[6] Several lines of evidence have indicated that nitrogen mustards conjugated with intercalating carriers can exhibit up to 100-fold increase in potency and activity compared to the corresponding parent mustard.[7] In this context, the anthraquinone pharmacophore, which is present in a range of antitumour drugs such as the anthracycline antibiotic doxorubicin and its synthetic analogue mitoxantrone, can be an effective structural feature for the development of novel DNA-targeted agents.[8,9]

In our previous studies on the synthesis and biological evaluation of nitrogen-linked bis-3-chloropiperidines as DNA alkylating agents, we have demonstrated that these mustard-like compounds alkylate DNA very effectively.[10,11] The reaction with DNA proceeds through a bicyclic aziridinium ion intermediate, followed by attack of nucleophilic centers on DNA.[12] Our results revealed that the investigated alkylators were capable of inducing DNA strand cleavage preferentially at guanine sites, which is in accord with the observed alkylation patterns of conventional nitrogen mustards.[13] In addition, we have shown that the incorporation of a DNA-affinic naphthalene chromophore to the side chain carboxylate of lysine-bridged bis-3-chloropiperidines can provide favourable DNA interactions (compare compounds **B1a** and **B1b** in Figure 1).[11] These findings suggest that the attachment of a stacking moiety to the linker structure might reinforce the DNA recognition properties of these alkylators.



B1a: R = -1-naphthyl
B1b: R = -1-naphthyl-4-OCH_3
1: R = -2-methylanthraquinone

Figure 1. Chemical structures of lysine-bridged bis-3-chloropiperidines containing naphthalene chromophores (**B1a** and **B1b** were previously evaluated)[11] and of the presently investigated conjugate **1** incorporating an intercalating anthraquinone moiety.

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