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A Comparison of the Cytotoxic and Physical Properties of Aziridinyl Quinone Derivatives Based on the Pyrrolo[1,2-*a*]benzimidazole and Pyrrolo[1,2-*a*]indole Ring Systems

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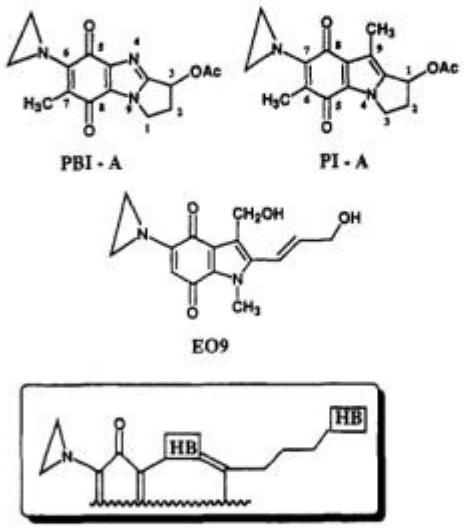
The cytotoxicity and physical properties of the pyrrolo[1,2-*a*]benzimidazole (PBI) and pyrrolo-[1,2-*a*]indole (PI) aziridinyl quinones were compared in order to assess the influence of the benzimidazole ring on antitumor activity and DNA reductive alkylation. Our studies show that the PI system possesses none of the cytotoxicity of the PBI systems. Unlike the PBIs, the PI system does not reductively alkylate DNA. Apparently, the benzimidazole ring favors reductive alkylation due to its electron deficient character compared to indole. In addition, the benzimidazole ring may provide the hydrogen bonding interactions required for the interaction with DNA. Our findings resulted in the elucidation of a PBI pharmacophore. Inspection of the literature revealed another drug sharing the PBI pharmacophore, 5-(1-aziridinyl)-3-(hydroxymethyl)-2-(3-hydroxy-1-propenyl)-1-methyl-1*H*-indole-4,7-dione (EO9), which remarkably has cytotoxic properties similar to those of the PBIs

Introduction

The pyrrolo[1,2-*a*]benzimidazoles (PBIs) represent a new class of antitumor agent recently discovered in this laboratory.[1-5] One of the most potent analogues, PBI-A, is shown in Chart 1. Although the PBI system resembles the mitomycin system (pyrrolo[1,2-*a*]indole), it possesses a unique spectrum of cytotoxicity and mechanism of action. Thus, PBIs show cytotoxicity toward solid tumors but not toward leukemia.[6] The mechanism of PBI cytotoxicity involves DNA cleavage presumably as a result of binding to the major groove followed by phosphate backbone alkylation.[6,7] The benzimidazole ring of the PBI system is thought to bind to the major groove as a result of Hoogsteen-type hydrogen bonds. In order to assess the role of the benzimidazole ring in PBI antitumor activity, we compared the cytotoxic and physical properties of PBI-A with the similarly functionalized pyrrolo[1,2-*a*]-indole system PI-A.

The results of this comparative study, which led to the elucidation of the pharmacophore shown in the inset of Chart 1, are presented herein. Since PI-A is completely noncytotoxic, we concluded that a heteroatom is required in the ring of the pharmacophore. This heteroatom may influence cytotoxicity by providing a hydrogen-bonding donor or acceptor and by exerting an electronic effect. In contrast, the 9-methyl of PI-A prevents any hydrogen-bonding donor or acceptor interactions. Ongoing studies have provided evidence that a side-chain hydrogen-bonding moiety also contributes to cytotoxicity. It is noteworthy that a recently discovered antitumor agent, 5-(1-aziridinyl)-3-(hydroxymethyl)-2-(3-hydroxy-1-propenyl)-1-methyl-1*H*-indole-4,7-dione (EO9),[8] possesses a structure which resembles the pharmacophore in the inset of Chart 1 and a spectrum of cytotoxicity similar to that of PBI-A. In additon, both EO9 and PBI-A have the unique property of not suppressing bone marrow.

Chart 1



Synthesis

The preparation of PI-A was carried out as outlined in Scheme 1. The synthetic steps leading to PI-A are based on previous reports from this laboratory[1] and elsewhere.[9-11]

In order to introduce a methyl group into the 9-position of the final product, the potassium salt **1**[9] was treated with methyl iodide. The presence of this methyl group in the final product was required in order to prevent hydrogen bonding interactions and thereby assess the role of these interactions in cytotoxicity. A 9-unsubstituted analogue was deemed unsuitable for this purpose since the 9-position is susceptible to electrophilic substitution. The methylated product was then reductively cyclized to afford **2**. Annelation of the pyrrolo ring was carried out by treatment of **2** with methyl acrylate in the presence of potassium *tert*-butoxide. The annelation product **3** was decarboxylated to **4**, which was then nitrated to afford **5**. Reduction of **5** and then Fremy oxidation of the reduction reaction mixture afforded three products: **6**, **7**, and **8**. The minor products (**7** and **8**) were formed as a result of methanolysis

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