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Synthesis and in vitro evaluation of 7-dialkylaminomethylbenzo[*g*]quinoxaline-5,10-diones

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Abstract—A series of benzo[*g*]quinoxaline-5,10-dione derivatives carrying a 7-dialkylaminomethyl substituent was synthesized and their in vitro cytotoxic activities were evaluated against four human cancer cell lines (HCT-15, SK-OV-3, MD-MB-468 and T-47D). The most active compound **9d** showed cytotoxic activity comparable to that of doxorubicin against HCT-15 cancer cell line.
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Doxorubicin (**1**) is a well-known member of the anthracycline antibiotics and the most commonly prescribed intercalating agents for the treatment of cancer.[1] Doxorubicin has a broad spectrum of activity, being particularly efficacious against solid tumors. However, its clinical usefulness is limited due to the cardiotoxicity developed upon extended therapy, and the appearance of an acquired resistance.[2,3]

The azaanthraquinones are a new class of antitumor agents that exhibit promising in vitro and in vivo activity against a wide spectrum of tumor cell lines.[4–6] These are the chromophore-modified analogues of mitoxantrone, a synthetic analogue of doxorubicin. In an effort to develop novel antitumor agents that could overcome the shortcomings of anthracyclines, we recently reported the synthesis and biological evaluation of a series of mono-(**2**)[7–9] and diazaanthraquinone derivatives (**3**)[10,11] (Fig. 1). The previous study revealed that the diazaanthraquinone derivatives were more potent than the monoazaanthraquinone derivatives. Herein, we report the synthesis and biological evaluation of benzo[g]quinoxaline-5,10-dione derivatives bearing 7-dialkylaminomethyl substituent. These analogues (**4**) were designed to explore the effect of changing the position of the nitrogen of the diazaanthraquinone derivatives from 1,8- to 1,4- position on their cytotoxic activities. The side chain of the target compounds was designed to have a basic nitrogen based on the previous study.

The general synthetic strategy employed to prepare the target compounds was based on the Diels–Alder reaction of quinoxaline-5,8-dione (**5**) with isoprene (**6**) and outlined in Scheme 1. Quinoxaline-5,8-dione (**5**) was prepared by the reported procedure.[12] The starting

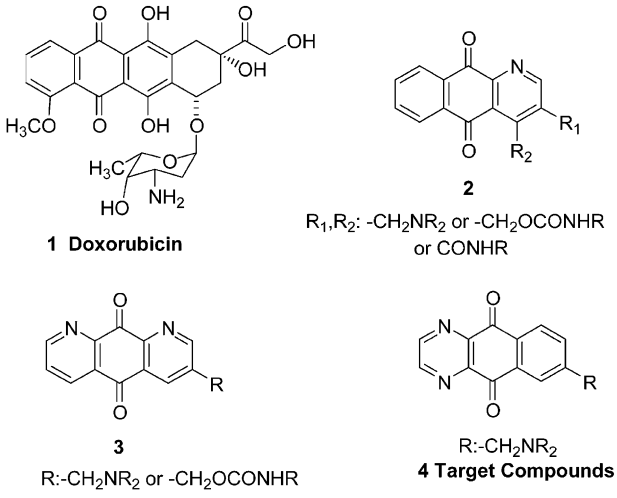

Figure 1. Structure of doxorubicin (**1**), azaanthraquinone derivatives **2**, **3** and target compounds **4**.

Keywords: Benzo[*g*]quinoxaline-5,10-dione; Antitumor agents; Azaanthraquinones.
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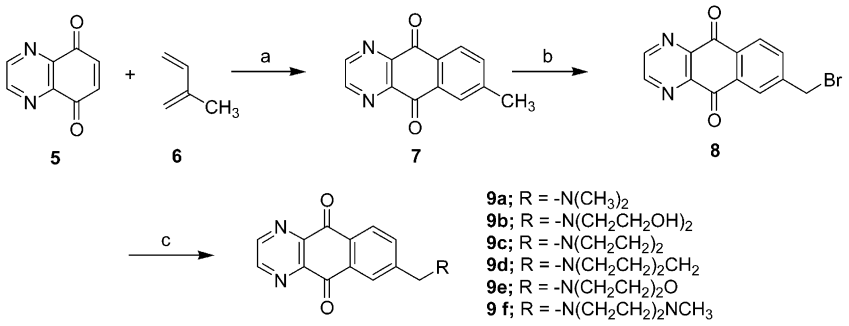

Scheme 1. Synthesis of 7-dialkylaminomethylbenzo[*g*]quinoxaline-5,10-diones: (a) (i) toluene, reflux; (ii) 5N-KOH/EtOH, reflux; (b) NBS, benzoylperoxide, $ClCH_2CH_2Cl$, reflux; (c) RH, DMF.

material **5** was treated with isoprene (**6**) to give the cycloaddition adduct which was directly aromatized by aerial oxidation in 5*N*-ethanolic KOH at reflux to give the 7-methylbenzo[g]quinoxaline-5,10-dione (**7**). Having obtained the required intermediate **7**, it was treated with *N*-bromosuccinimide (NBS) and a catalytic amount of benzoylperoxide in anhydrous 1,2-dichloroethane at reflux for 48 h with the irradiation of tungsten lamp to give the bromomethyl product **8** in 30% yield.

The target compounds, **9a–f**, containing 7-dialkylaminomethyl substituent were synthesized by direct substitution reaction of the bromomethyl compound **8** with the corresponding dialkylamine as shown in Scheme 1. Treatment of the compound **8** with the appropriate secondary amines in anhydrous DMF afforded *N,N*-dimethylamino-**9a** (64%), *N,N*-diethanolamino-**9b** (40%), pyrrolidino-**9c** (68%), piperidino-**9d** (49%), morpholino-**9e** (50%), and (*N*-methyl)piperazino-**9f** (27%) methyl derivatives, respectively.

The in vitro cytotoxic activities of the newly synthesized 7 - dialkylaminomethylbenzo[*g*]quinoxaline - 5,10 - dione derivatives[13] were evaluated against human cancer cell lines: SK-OV-3 (ovarian carcinoma), HCT-15 (colon cancer), MD-MB-468 (breast cancer), T-47D (breast cancer) according to the protocols developed by the National Cancer Institute.[14] The concentrations of benzo[*g*]quinoxaline-5,10-dione derivatives (**7**, **8**, and **9a–f**) inhibiting cellular growth by 50%, IC_{50} values, are shown in Table 1. The comparative data for doxorubicin and mitomycin C are also shown for comparison.

All of the analogues tested in this study exhibited significant cytotoxic activity. Although all of the analogues were less potent than doxorubicin, the compounds **9a**, **c** and **d** exhibited cytotoxicity comparable to that of mitomycin-C against all human cancer cell lines tested. In particular, the compound **9d** exhibited cytotoxicity comparable to that of doxorubicin against HCT-15 cancer cell line. The compounds **9b**, **e** and **f** were 5–50 times less potent than the other analogues bearing dialkylaminomethyl substituents. This might be ascribed to the additional hetero atom incorporated into the side chain of the derivatives. 1,4-Diazaanthraquinone chromophore of the target compounds was designed to explore the effect of changing the position of the nitrogen of the diazaanthraquinone derivatives from 1,8- to 1,4-position on their cytotoxic activities. The target compounds (**9a–f**) having 1,4-diazaanthraquinone system were, in general, found to be less active than the 1,8-diazaanthraquinone derivatives.[11] This suggests that 1,8-diaza system might be more important for the cytotoxic acitivity than 1,4-diaza system.

In summary, eight benzo[*g*]quinoxaline-5,10-dione derivatives were designed and synthesized as potential antitumor agents. The compounds **9a**, **9c**, and **9d** may need further in depth biological evaluation. Work is in

Table 1. In vitro cytotoxic activity of 7-dialkylaminomethylbenzo[*g*]quinoxalinediones against human cancer cell lines

Compd	R	IC_{50} (μM)[a] of cell lines[b]			
		SK-OV-3	HCT15	MD-MB-468	T-47D
7	H	2.2	0.12	1.5	1.2
8	Br	1.6	0.4	0.3	0.5
9a	$N(CH_3)_2$	0.22	0.1	0.1	0.1
9b	$N(CH_2CH_2OH)_2$	1.2	0.18	0.9	0.9
9c	$N(CH_2CH_2)_2$	0.25	0.1	0.1	0.1
9d	$N(CH_2CH_2)_2CH_2$	0.4	0.05	0.2	0.08
9e	$N(CH_2CH_2)_2O$	7.0	1.3	3.2	1.3
9f	$N(CH_2CH_2)_2N\ CH_3$	10.0	1.2	3.0	3.0
Doxorubicin		0.02	0.025	0.007	0.007
Mitomycin C		0.18	0.07	0.27	0.4

[a] IC_{50} = Concentration of compound (μM) required to inhibit the cellular growth by 50% after 72 h of drug exposure, as determined by the SRB assay. Each experiment was run at least three times, and the results are presented as an average value.
[b] Human cancer cell lines: SK-OV-3 (ovarian carcinoma), HCT-15 (colon cancer), MD-MB-468 (breast cancer), T-47D (breast cancer).

progress to design, synthesize, and evaluate additional compounds in this and related systems.

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