

Synthesis and SAR of Aziridinylquinoline-5,8-diones as Agents against Malignant Tumor Cells

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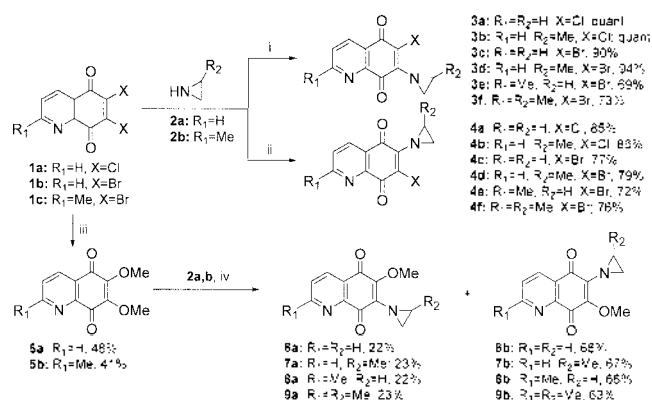
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It has been proven that the elemental pharmacophore of the naturally occurring antitumor antibiotics, streptonigrin and lavendamycin, is quinoline-5,8-dione nucleus.¹ Actually, the quinoline-5,8-dione derivatives show a wide spectrum of biological activities such as antitumor, antifungal and anti-malarial agents.² As shown already, the plausible mechanism of antitumor activity of these quinone type compounds is derived from the oxidative cleavage of single-stranded DNA by oxygen free radicals, which are generated by biological oxidoreduction.³ Since the antitumor activity of these quinoid compounds is not sufficient, the introduction of aziridinyl group sometimes is carried out to enhance the activity.⁴ This effect might be caused by covalent bindings of aziridinyl substituent with biological nucleophiles, such as proteins and DNA. There have been few reports on the structure-activity relationship of mono-aziridinylquinolinedione derivatives. Herein, we wish to disclose the synthesis and antitumor activities of mono-aziridinylquinolinedione derivatives.

Based on an established procedure,⁵ regioselective conversion of 6,7-dihaloquinoline-5,8-diones **1a-c** to 7- and 6-aziridinylquinoline-5,8-diones **3a-f** and **4a-f** was accom-

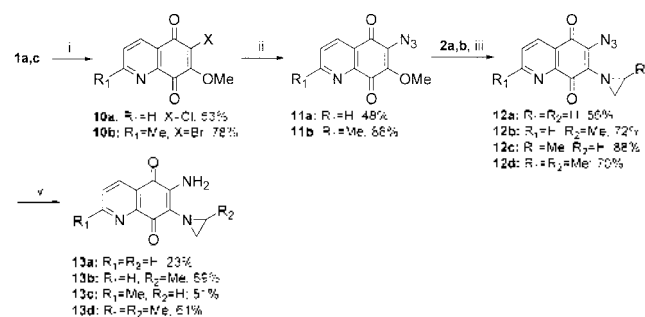


Scheme 1. Reagents and reaction conditions: (i) Et₃N, C₆H₆, 0 °C to rt, 2 h; (ii) Et₃N, CeCl₃·7H₂O, 2-PrOH, rt, 1 h; (iii) NaOMe, MeOH, rt, 4 h; (iv) Et₃N, MeOH, 0 °C to rt, 24 h.

plished (Scheme 1). In another series of reactions, treatment of **1a-c** with sodium methoxide followed by amination of resultant **5a, b** with aziridines **2a, b** led to a 1 : 3 mixture of 7-aziridinylquinoline-5,8-diones **6a-9a** and 6-aziridinylquinoline-5,8-diones **6b-9b**, respectively, which were separated by column chromatography. The regiochemistry of these isomers could be assigned on the basis of their IR spectra in which a significant difference was observed in the absorption range of the carbonyl groups.⁵

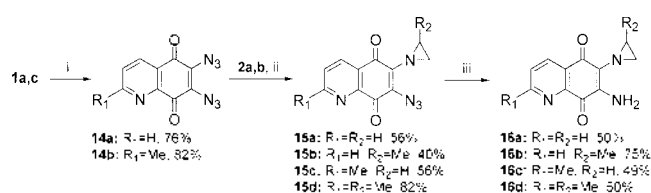
6-Amino-7-aziridinylquinoline-5,8-diones **13a-d** were prepared from 6,7-dihaloquinoline-5,8-diones **1a, c** by the multi-step procedure depicted in Scheme 2. As detailed in earlier work, direct 7-halogen displacement of **1a, c** with sodium methoxide in benzene at 0 °C gave 7-methoxyquinoline-5,8-diones **10a, b**. Treatment of **10a, b** with sodium azide in THF-H₂O (19 : 1) at room temperature yielded the 6-azide derivatives **11a, b**, possibly by addition of an azide ion at the 7-position followed by a triazole ring closure, loss of chloride or bromide, and synchronous ring opening at the 7-position.⁶ Subsequent treatment of **11a, b** with the appropriate aziridines **2a, b** afforded the corresponding 7-aziridinylquinoline-5,8-diones **12a-d**, which were converted into **13a-d** by reduction of the azide group with sodium borohydride in THF-MeOH (4 : 1).

The 6- and 7-halogen groups in compounds **1a, c** could be replaced by the azide groups by the treatment with excess



Scheme 2. Reagents and reaction conditions: (i) NaOMe, C₆H₆, 0 °C, 1 h; (ii) NaN₃, THF-H₂O (19:1), rt, 1 h; (iii) Et₃N, MeOH, rt, 1.5 h; (iv) NaBH₄, THF-MeOH (4:1), rt, 1.5 h.

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Scheme 3. Reagents and reaction conditions: (i) NaN₃, THF-H₂O (19:1), rt, 2 h; (ii) Et₃N, C₆H₆, rt, 4 h; (iii) NaBH₄, THF-MeOH (4:1), rt, 1 h.

sodium azide in THF-H₂O (19 : 1) to give 6,7-diazidoquinoline-5,8-diones **14a, b** (Scheme 3). Attempted replacement of 6-azide of **14a, b** with aziridinyl group in benzene provided 7-azido-6-aziridinylquinoline-5,8-diones **15a-d**, and subsequent reduction with sodium borohydride in THF-MeOH (4 : 1) afforded 7-amino-6-aziridinylquinoline-5,8-diones **16a-d**.

The *in vitro* cytotoxic activities were evaluated by SRB assay method⁷ using five human solid tumor cell lines. Data in Table 1 show that compounds synthesized are highly cytotoxic on all tested tumor cell lines, especially on HCT-15.

Some compounds were more active than mitomycin C and doxorubicin clinically used for the treatment of solid tumor. Aziridinylquinolinediones generally exhibited more potent cytotoxic activities than aziridinyl-2-methylquinolinediones on the most of tested cell lines. However, there appeared to be no clear structure-activity relationship between 6- and 7-aziridinyl substituents, or between aziridinyl and 2-methylaziridinyl substituents. The most active compounds were aminoaziridinylquinolinediones **13a** and **16a**.⁸ Especially, the activities of 7-amino-6-aziridinylquinolinedione **16a** were superior or comparable to those of bis-aziridinylquinolinedione against all the tested cell lines. This result means that bis-aziridinyl substitution on quinolinedione nuclei as alkylating groups is not a prerequisite to high cytotoxic activities.^{4b}

References and Notes

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- Selected data: **13a**: purple solid; mp 179-180 °C; IR (KBr) 3514, 3392, 1654, 1610, 1578, 1464, 1384, 1298, 1264 cm⁻¹; ¹H NMR (CDCl₃) δ 8.91 (dd, 1H, C₂-H), 8.27 (dd, 1H, C₄-H), 7.51 (dd, 1H, C₃-H), 5.04 (br s, 2H, NH₂), 2.32 (s, 4H, 2xCH₂); ¹³C NMR (CDCl₃) δ 179.8, 177.4, 154.2, 148.2, 138.1, 133.4, 132.9, 127.4, 126.3, 29.6. Anal. calcd for C₁₁H₉N₃O₂: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.34; H, 4.18; N, 19.58. **16a**: purple solid; mp > 250 °C; IR (KBr) 3482, 3368, 1618, 1562, 1388, 1280 cm⁻¹; ¹H NMR (CDCl₃) δ 8.83 (dd, 1H, C₂-H), 8.30 (dd, 1H, C₄-H), 7.55 (dd, 1H, C₃-H), 5.22 (br s, 2H, NH₂), 2.28 (s, 4H, 2xCH₂); ¹³C NMR (CDCl₃) δ 179.0, 177.9, 152.9, 146.9, 139.3, 133.8, 131.0, 129.4, 127.6, 29.3. Anal. calcd for C₁₁H₉N₃O₂: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.40; H, 4.11; N, 19.60.

Table 1. *In vitro* cytotoxic activity of quinoline-5,8-diones (Entry 1) and 2-methyl-quinoline-5,8-diones (Entry 2)

Entry 1	6-	7-	Cytotoxicity ^a IC ₅₀ (μg/mL)				
			A549 ^b	SKOV3	SKMEL2	XF498	HCT15
3a	Cl	Az ^c	0.97	0.42	0.30	0.68	0.47
3b	Cl	MeAz ^d	0.92	0.48	0.18	0.40	0.29
3c	Br	Az	1.14	0.30	0.16	1.39	0.14
3d	Br	MeAz	0.77	0.29	0.16	0.58	0.17
4a	Az	Cl	0.67	0.24	0.03	0.29	0.02
4b	MeAz	Cl	1.13	0.18	0.09	0.09	0.06
4c	Az	Br	1.06	0.69	0.16	1.71	0.08
4d	MeAz	Br	1.53	0.27	0.16	1.74	0.04
7a	OMe	MeAz	0.44	1.20	0.23	0.16	0.87
7b	MeAz	OMe	0.27	0.35	0.21	0.12	0.37
12a	N ₃	Az	0.11	1.00	0.27	0.15	0.30
12b	N ₃	MeAz	0.22	0.34	0.19	0.25	0.22
13a	NH ₂	Az	0.07	0.34	0.12	0.09	0.09
13b	NH ₂	MeAz	0.22	0.87	0.25	0.17	0.97
15a	Az	N ₃	0.38	0.24	0.18	0.23	0.11
15b	MeAz	N ₃	0.43	0.18	0.15	0.26	0.12
16a	Az	NH ₂	0.02	0.17	0.09	0.03	0.02
16b	MeAz	NH ₂	0.10	1.54	0.19	0.13	0.23

Entry 2	6-	7-	Cytotoxicity IC ₅₀ (μg/mL)				
			A549	SKOV3	SKMEL2	XF498	HCT15
3e	Br	Az	0.27	0.14	0.12	0.15	0.12
3f	Br	MeAz	0.29	0.14	0.13	0.13	0.11
4e	Az	Br	1.07	0.15	0.10	0.88	0.11
4f	MeAz	Br	1.27	0.13	0.14	1.18	0.13
9a	OMe	MeAz	1.17	0.70	0.94	0.97	0.38
9b	MeAz	OMe	1.14	1.04	0.95	1.00	0.18
12c	N ₃	Az	0.25	0.96	0.48	0.18	0.15
12d	N ₃	MeAz	0.27	0.14	0.14	0.15	0.15
13c	NH ₂	Az	0.93	1.74	1.64	1.47	0.31
13d	NH ₂	MeAz	1.30	1.57	1.62	1.55	1.38
15c	Az	N ₃	0.26	0.13	0.14	0.14	0.10
15d	MeAz	N ₃	1.08	0.13	0.14	0.17	0.14
16c	Az	NH ₂	0.15	1.59	1.47	0.32	0.05
16d	MeAz	NH ₂	1.12	1.34	1.37	0.97	1.04
Ref. Compd.^e			0.09	0.14	0.11	0.07	0.12
Mitomycin C			0.08	0.12	0.17	0.07	0.89
Doxorubicin			0.11	0.16	0.15	0.18	0.24

^aCytotoxicity screening: SRB assay according to the National Cancer Institute (NCI) protocols. ^bHuman solid tumor cell lines: A-549 (lung), SK-OV-3 (ovarian), SK-MEL-2 (melanoma), XF-498 (CNS) and HCT-15 (colon) from the NCI in USA. ^cAz=Aziridinyl. ^dMeAz=Methylaziridinyl. ^e6,7-Bisaziridinylquinoline-5,8-dione.