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

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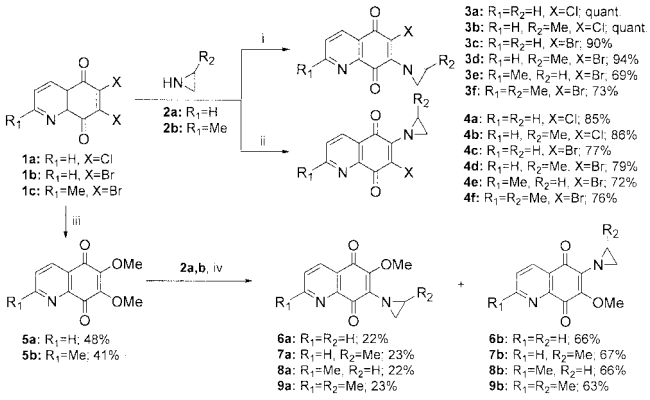
It has been proven that the elemental pharmacophore of the naturally occurring antitumor antibiotics, streptonigrin and lavendamycin, is quinoline-5,8-dione nucleus.[1] Actually, the quinoline-5,8-dione derivatives show a wide spectrum of biological activities such as antitumor, antifungal and antimalarial 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.

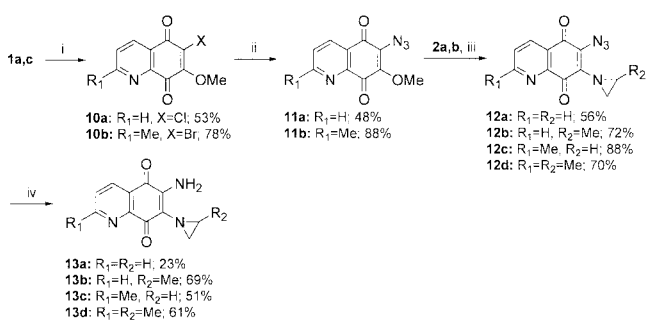
Based on an established procedure,[5] regioselective conversion of 6,7-dihaloquinoline-5,8-diones **1a-c** to 7- and 6-aziridinylquinoline-5,8-diones **3a-f** and **4a-f** was accomplished (Scheme 1). In another series of reactions, treatment of **1a-c** with sodium methoxide followed by amination of 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]



Scheme 1. *Reagents and reaction conditions:* (i) Et_3N, C_6H_6, 0 °C to rt, 2 h; (ii) Et_3N, $CeCl_3 \cdot 7H_2O$, 2-PrOH, rt, 1 h; (iii) NaOMe, MeOH, rt, 4 h; (iv) Et_3N, MeOH, 0 °C to rt, 24 h.

6-Amino-7-aziridinylquinoline-5,8-diones **13a-d** were prepared from 6,7-dihaloquinoline-5,8-diones **1a**, **c** by the multistep 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-H_2O (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, C_6H_6, 0 °C, 1 h; (ii) NaN_3, THF-H_2O (19:1), rt, 1 h; (iii) Et_3N, MeOH, rt, 1.5 h; (iv) $NaBH_4$, THF-MeOH (4:1), rt, 1.5 h.

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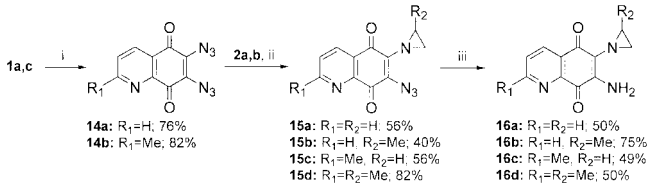

Scheme 3. *Reagents and reaction conditions:* (i) NaN_3, THF-H_2O (19:1), rt, 2 h; (ii) Et_3N, C_6H_6, rt, 4 h; (iii) $NaBH_4$, THF-MeOH (4:1), rt, 1 h.

sodium azide in THF-H_2O (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 method[7] 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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8. Selected data: **13a**: purple solid; mp 179-180 °C; IR (KBr) 3514, 3392, 1654, 1610, 1578, 1464, 1384, 1298, 1264 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.91 (dd, 1H, C_2-H), 8.27 (dd, 1H, C_4-H), 7.51 (dd, 1H, C_3-H), 5.04 (br s, 2H, NH_2), 2.32 (s, 4H, 2xCH_2); ^{13}C NMR ($CDCl_3$) δ 179.8, 177.4, 154.2, 148.2, 138.1, 133.4, 132.9, 127.4; 126.3, 29.6. Anal. calcd for $C_{11}H_9N_3O_2$: 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 ($CDCl_3$) δ 8.83 (dd, 1H, C_2-H), 8.30 (dd, 1H, C_4-H), 7.55 (dd, 1H, C_3-H), 5.22 (br s, 2H, NH_2), 2.28 (s, 4H, 2xCH_2); ^{13}C NMR ($CDCl_3$) δ 179.0, 177.9, 152.9, 146.9, 139.3, 133.8, 131.0, 129.4, 127.6, 29.3. Anal. calcd for $C_{11}H_9N_3O_2$: 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)					Entry 2	6-	7-	Cytotoxicity IC_{50} (μg/mL)				
			A549[b]	SKOV3	SKMEL2	XF498	HCT15				A549	SKOV3	SKMEL2	XF498	HCT15
3a	Cl	Az[c]	0.97	0.42	0.30	0.68	0.47	**3e**	Br	Az	0.27	0.14	0.12	0.15	0.12
3b	Cl	MeAz[d]	0.92	0.48	0.18	0.40	0.29	**3f**	Br	MeAz	0.29	0.14	0.13	0.13	0.11
3c	Br	Az	1.14	0.30	0.16	1.39	0.14	**4e**	Az	Br	1.07	0.15	0.10	0.88	0.11
3d	Br	MeAz	0.77	0.29	0.16	0.58	0.17	**4f**	MeAz	Br	1.27	0.13	0.14	1.18	0.13
4a	Az	Cl	0.67	0.24	0.03	0.29	0.02	**9a**	OMe	MeAz	1.17	0.70	0.94	0.97	0.38
4b	MeAz	Cl	1.13	0.18	0.09	0.09	0.06	**9b**	MeAz	OMe	1.14	1.04	0.95	1.00	0.18
4c	Az	Br	1.06	0.69	0.16	1.71	0.08	**12c**	N_3	Az	0.25	0.96	0.48	0.18	0.15
4d	MeAz	Br	1.53	0.27	0.16	1.74	0.04	**12d**	N_3	MeAz	0.27	0.14	0.14	0.15	0.15
7a	OMe	MeAz	0.44	1.20	0.23	0.16	0.87	**13c**	NH_2	Az	0.93	1.74	1.64	1.47	0.31
7b	MeAz	OMe	0.27	0.35	0.21	0.12	0.37	**13d**	NH_2	MeAz	1.30	1.57	1.62	1.55	1.38
12a	N_3	Az	0.11	1.00	0.27	0.15	0.30	**15c**	Az	N_3	0.26	0.13	0.14	0.14	0.10
12b	N_3	MeAz	0.22	0.34	0.19	0.25	0.22	**15d**	MeAz	N_3	1.08	0.13	0.14	0.17	0.14
13a	NH_2	Az	0.07	0.34	0.12	0.09	0.09	**16c**	Az	NH_2	0.15	1.59	1.47	0.32	0.05
13b	NH_2	MeAz	0.22	0.87	0.25	0.17	0.97	**16d**	MeAz	NH_2	1.12	1.34	1.37	0.97	1.04
15a	Az	N_3	0.38	0.24	0.18	0.23	0.11	**Ref. Compd.**[e]			0.09	0.14	0.11	0.07	0.12
15b	MeAz	N_3	0.43	0.18	0.15	0.26	0.12	**Mitomycin C**			0.08	0.12	0.17	0.07	0.89
16a	Az	NH_2	0.02	0.17	0.09	0.03	0.02	**Doxorubicin**			0.11	0.16	0.15	0.18	0.24
16b	MeAz	NH_2	0.10	1.54	0.19	0.13	0.23								

[a]Cytotoxicity screening: SRB assay according to the National Cancer Institute (NCI) protocols. [b]Human 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. [c]Az=Aziridinyl. [d]MeAz=Methylaziridinyl. [e]6,7-Bisaziridinylquinoline-5,8-dione.