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Design and Synthesis of Isoindoloquinoline Derivatives as Potential Antitumor Agents

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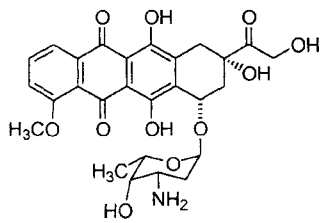
A series of isoindoloquinoline derivatives was synthesized and evaluated *in vitro* cytotoxicity against four human cancer cell lines (HCT15, SK-OV-3, MDA-MB-468 and T-47D).

Key words: Antitumor agents, Isoindoloquinolinedione, Cytotoxic activity, Doxorubicin

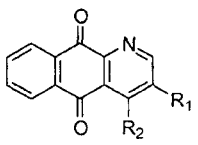
INTRODUCTION

The anthracycline antibiotics are commonly used intercalating agents in the treatment of cancer (Wakelin and Waring, 1990). A number of studies have identified anthracyclines as intercalating agents, all indications being that their biological activity are attributable to their DNA-binding properties. DNA intercalation and interference with the DNA-topoisomerase II activity resulting in protein-associated DNA strand breaks have been proposed as critical events that lead to anthracycline-induced cell death (Wakelin and Waring, 1990). Doxorubicin (Fig. 1.) is the best known member of the anthracyclines and particularly efficacious against solid tumors. However its cardiotoxicity limits the clinical usefulness (Priebe, 1995; Surato *et al.*, 1990). The search for new analogues having better therapeutic efficacy without undesirable side effects of the anthracycline analogues is of extreme interest and numerous analogues have been reported (Priebe, 1995).

We recently reported the synthesis and *in vitro* evaluation of various 1-azaanthraquinones 1 (Fig. 1.) (Lee *et al.*, 1996; 1998; 1999) and continued our effort to search for better antitumor intercalating agents that can overcome the shortcomings of the anthracycline analogues. In the present study, we report the synthesis and *in vitro* evaluation of isoindoloquinoline derivatives 2. The target compounds were designed to probe the effect of the incorporation of additional pyrrolidinedione ring to the azaanthraquinone system. Considering the factor that may be needed to potentiate the antitumor activity of the intercalating agents, we designed the target compounds bearing the alkyl or substituted aryl group. The aryl substituent would be in perpendicular position to the isoindolo-quinoline chromophore. After the isoindolo-quinoline ring intercalates between base pairs of DNA, the substituents would contribute to the increase of the residence time of the target compounds 2 within DNA through additional hydrophobic interaction possibly in the minor groove.

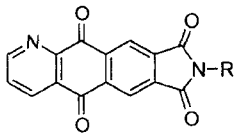


Doxorubicin



1

R_1,R_2: -NR_2 or -$CH_2OCONHR$ or CONHR



2

R:alkyl or aryl
Target Compounds

Fig. 1. Strnctmes of doxorubicin, **1** and **2**

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MATERIALS AND METHODS

Melting points were recorded on a Electrothermal IA9100 digital melting point apparatus and are uncorrected. IR spectra were determined with a Jasco FT/IR-300E spectrophotometer and reported in cm^{-1}. ^1H-NMR spectra were recorded on Bruker DPS300 NMR spectrometer using TMS as an internal standard and chemical shifts are reported as δ ppm units. Thin-layer chromatography was performed on E. Merck silica gel GF-254 precoated plates and the identification was done with UV light and colorization with spray of concentrated sulfuric acid followed by heating. Column chromatography was carried out on silica gel 60 (230-400mesh ASTM). Commercially available regents and solvents were used without additional purification unless otherwise stated. RPMI1640 media was obtained form Gibco BRL. Dimethyl sulfoxide(DMSO) and other chemicals were purchased from Sigma.

7,8-Dimethyl-5,10-dihydrobenzo[*g*]quinoline-5,10-dione (6)

To a solution of quinoline-5,8-dione (**3**, 1000mg, 6.28 mmol) in anhydrous toluene (50 mL) was added 2,3-dimethyl-1,3-butadiene (**4**, 1430 μL, 12.56mmol). The reaction mixture was stirred at reflux for 12 h under nitrogen atmosphere. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. To the residue was added a solution of 5*N*-potassium hydroxide solution (20 mL) and ethanol (30 mL) and stirred at reflux for 4 h. The resulting mixture was cooled to room temperature and diluted with water (200 mL). The mixture was extracted with dichloromethane (50 mL × 3). The organic phase was washed with brine (30 mL × 3) and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated *in vacuo* to give a crude product. The crude product was crystallized from n-hexane and methanol to give the compound **6** (1109 mg, 74.3%); mp 259.0~259.2°C (needle from n-hexane and methanol); IR(KBr) 3068, 2922, 1677 cm^{-1}; ^1H-NMR($CDCl_3$/TMS) δ 9.33 (dd, *J*=4.7Hz, 1.7Hz, 1H, Ar-H), 8.69 (dd, *J*=7.9Hz, 1.7Hz, 1H, Ar-H), 8.11 (s, 1H, Ar-H), 8.07 (s, 1H, Ar-H), 7.83 (dd, *J*=7.9Hz, 4.7Hz, 1H, Ar-H), 2.57 (s, 6H, Ar-CH_3).

5,10-Dioxo-5,10-dihydrobenzo[*g*]quinoline-7,8-dicarboxylic acid (7)

A solution of 7,8-Dimethyl-5,10-dihydrobenzo[*g*]quinoline-5,10-dione (**6**, 800mg, 3.37 mmol) in 18% nitric acid (50 mL) was heated at 185-190°C in a titanium autoclave for 2 h. After cooling the precipitate was collected by suction and washed with water. After drying the compound **7** (614 mg, 61%) was obtained as a yellow solid: mp 259.0~261.0°C; IR(KBr) 3520-2720(br), 3079, 2920, 1740, 1690 cm^{-1}; ^1H-NMR($CDCl_3$/TMS) 9.12 (dd, *J*=4.7Hz, 1.7Hz, 1H, Ar-H), 8.60 (dd, *J*=7.9Hz, 1.7Hz, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 8.36 (s, 1H, Ar-H), 7.94 (dd, *J*=7.9Hz, 4.7Hz, 1H, Ar-H).

8-Propyl-7,8,9,10-tetrahydro-5*H*-isoindolo[5,6-*g*]quinoline-5,7,9,11-tetraone (2a)

5,10-Dioxo-5,10-dihydrobenzo[*g*]quinoline-7,8-dicarboxylic acid (**7**, 200 mg, 0.67 mmol) was dissolved in $SOCl_2$ (10 mL) and stirred at reflux for 5 h under nitrogen atmosphere. The mixture was cooled to room temperature and concentrated *in vacuo* to give the acid anhydride **8**; IR(KBr) 2920, 1778, 1690 cm^{-1}. The crude compound **8** was suspended in anhydrous tetrahydrofuran (10 mL) and stirred under nitrogen atmosphere. To the mixture was added dropwise a solution of 1-propylamine (61 μL, 0.74mmol) in anhydrous THF (3 mL). The mixture was stirred for additional 2 h under nitrogen atmosphere. The reaction mixture was concentrated *in vacuo*. To the residue was added acetic anhydride (1 mL, 2.89 mmol) and sodium acetate (26 mg, 0.32 mmol). The mixture was stirred for 1 h at 60~70°C. The mixture was cooled to room temperature and ice-water (2 mL) was added. The precipitates were filtered by suction and washed with water (10 mL × 3) and petroleum ether (10 mL) to give brown solid. The crude product was purified by flash column chromatograpy (dichloromethane) to give the compound **2a** (33 mg, 15.3%) as yellow solid; mp 292 dec; IR (KBr) 3044, 2926, 1708, 1674 cm^{-1}; ^1H-NMR($CDCl_3$/TMS) δ 9.21 (dd, *J*=4.6Hz, 1.7Hz, 1H, Ar-H), 8.91 (s, 1H, Ar-H), 8.81 (s, 1H, Ar-H), 8.72 (dd, *J*=7.9Hz, 1.7Hz, 1H, Ar-H), 7.84 (dd, *J*=7.9Hz, 4.6Hz, 1H, Ar-H), 3.75 (t, *J*=7.4Hz, 2H, -NCH_2), 1.75 (m, 2H, -$NCH_2\underline{CH_2}CH_3$), 0.99 (t, *J*=7.4Hz, 3H, $CH_2\underline{CH_3}$).

8-Phenyl-7,8,9,10-tetrahydro-5*H*-isoindolo[5,6-*g*]quinoline-5,7,9,11-tetraone (2b)

The product was obtained in 14.9% yield; mp 326°C dec; IR(KBr) 3047, 1720, 1680 cm^{-1}; ^1H-NMR($CDCl_3$/TMS) δ 9.23 (dd, *J*=4.6Hz, 1.7Hz, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 8.93 (s, 1H, Ar-H), 8.74 (dd, *J*=7.9Hz, 1.7Hz, 1H, Ar-H), 7.86 (dd, *J*=7.9Hz, 4.6Hz, 1H, Ar-H), 7.52 (m, 5H, Ar-H).

8-(2-Hydroxyphenyl)-7,8,9,10-tetrahydro-5*H*-isoindolo[5,6-*g*]quinoline-5,7,9,11-tetraone (2c)

The product was obtained in 37.8% yield; mp 258.6~259.0°C IR(KBr) 3445, 3072, 1727, 1688 cm^{-1}; ^1H-NMR($CDCl_3$/TMS) δ 9.23 (dd, *J*=4.5Hz, 1.3Hz, 1H, Ar-H),

9.02 (s, 1H, Ar-H), 8.93 (s, 1H, Ar-H), 8.75 (dd, *J*=7.9Hz, 1.3Hz, 1H, Ar-H), 7.86 (dd, *J*=7.9Hz, 4.5Hz, 1H, Ar-H), 7.54 (m, 1H, Ar-H), 7.43 (m, 3H, Ar-H).

8-(2-Methoxyphenyl)-7,8,9,10-tetrahydro-5*H*-isoindolo[5,6-*g*]quinoline-5,7,9,11-tetraone (2d)

The product was obtained in 24.0% yield; mp 278°C dec; IR(KBr) 3050, 2923, 1727, 1686 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ 9.22 (dd, *J*=4.6Hz, 1.8Hz, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 8.93 (s, 1H, Ar-H), 8.74 (dd, *J*=7.9Hz, 1.8Hz, 1H, Ar-H), 7.86 (dd, *J*=7.9Hz, 4.6Hz, 1H, Ar-H), 7.49 (m, 1H, Ar-H), 7.31 (m, 1H, Ar-H), 7.11 (m, 2H, Ar-H), 3.82 (s, 3H, -OCH_3).

8-(2-Nitrophenyl)-7,8,9,10-tetrahydro-5*H*-isoindolo [5,6-*g*]quinoline-5,7,9,11-tetraone (2e)

The product was obtained in 12.0% yield; mp 255°C dec; IR(KBr) 3090, 1727, 1683, 1531 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ 9.23 (dd, *J*=4.6Hz, 1.7Hz, 1H, Ar-H), 9.04 (s, 1H, Ar-H), 8.95 (s, 1H, Ar-H), 8.75 (dd, *J*=7.9Hz, 1.7Hz, 1H, Ar-H), 7.86 (dd, *J*=7.9Hz, 4.6Hz, 1H, Ar-H), 7.84 (d, *J*=1.5Hz, 1H, Ar-H), 7.79 (d, *J*=8.9Hz, 1H, Ar-H), 7.72 (dd, *J*=8.0Hz, 1.2Hz, 1H, Ar-H), 7.59 (dd, *J*=8.0Hz, 1.2Hz, 1H, Ar-H).

8-(3-Chlorophenyl)-7,8,9,10-tetrahydro-5*H*-isoindolo[5,6-*g*]quinoline-5,7,9,11-tetraone (2f)

The product was obtained in 13.6% yield; mp 348°C dec; IR(KBr) 3084, 1726, 1679 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ 9.23 (dd, *J*=4.6Hz, 1.7Hz, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 8.93 (s, 1H, Ar-H), 8.75 (dd, *J*=7.9Hz, 1.7Hz, 1H, Ar-H), 7.86 (dd, *J*=7.9Hz, 4.6Hz, 1H, Ar-H), 7.72 - 7.47 (m, 4H, Ar-H).

8-(3-Hydroxyphenyl)-7,8,9,10-tetrahydro-5*H*-isoindolo[5,6-*g*]quinoline-5,7,9,11-tetraone (2g)

The product was obtained in 14.0% yield; mp 283°C dec; IR(KBr) 3370, 3060, 1725, 1682 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ 9.22 (dd, *J*=4.6Hz, 1.7Hz, 1H, Ar-H), 9.01 (s, 1H, Ar-H), 8.92 (s, 1H, Ar-H), 8.74 (dd, *J*=7.9Hz, 1.7Hz, 1H, Ar-H), 7.86 (dd, *J*=7.9Hz, 4.6Hz, 1H, Ar-H), 7.56 - 7.22 (m, 4H, Ar-H).

8-(3-Methoxyphenyl)-7,8,9,10-tetrahydro-5*H*-isoindolo[5,6-*g*]quinoline-5,7,9,11-tetraone (2h)

The product was obtained in 14.7% yield; mp 318°C dec; IR(KBr) 3044, 2925, 1726, 1679 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ 9.22 (dd, *J*=4.6Hz, 1.7Hz, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 8.92 (s, 1H, Ar-H), 8.74 (dd, *J*=7.9Hz, 1.7Hz, 1H, Ar-H), 7.86 (dd, *J*=7.9Hz, 4.6Hz, 1H, Ar-H), 7.46 (t, *J*=7.9Hz, 1H, Ar-H), 7.04 (m, 3H, Ar-H), 3.86 (s, 3H, -OCH_3).

8-(3-Nitrophenyl)-7,8,9,10-tetrahydro-5*H*-isoindolo[5,6-*g*]quinoline-5,7,9,11-tetraone (2i)

The product was obtained in 14.0% yield; mp 348°C dec; IR(KBr) 3090, 1728, 1687, 1533 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ 9.24 (dd, *J*=4.6Hz, 1.7Hz, 1H, Ar-H), 9.06 (s, 1H, Ar-H), 8.97 (s, 1H, Ar-H), 8.76 (dd, *J*=7.9Hz, 1.7Hz, 1H, Ar-H), 7.87 (dd, *J*=7.9Hz, 4.6Hz, 1H, Ar-H), 7.71 (m, 1H, Ar-H), 7.54 (m, 3H, Ar-H).

8-(4-Chlorophenyl)-7,8,9,10-tetrahydro-5*H*-isoindolo[5,6-*g*]quinoline-5,7,9,11-tetraone (2j)

The product was obtained in 16.7% yield; mp 346°C dec; IR(KBr) 3050, 1713, 1690, 1499 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ 9.23 (dd, *J*=4.6Hz, 1.7Hz, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 8.93 (s, 1H, Ar-H), 8.75 (dd, *J*=7.9Hz, 1.7Hz, 1H, Ar-H), 7.86 (dd, *J*=7.9Hz, 4.6Hz, 1H, Ar-H), 7.51 (m, 4H, Ar-H).

8-(4-Hydroxyphenyl)-7,8,9,10-tetrahydro-5*H*-isoindolo[5,6-*g*]quinoline-5,7,9,11-tetraone (2k)

The product was obtained in 20.5% yield; mp 348°C dec; IR(KBr) 3414, 3077, 1725, 1680, 1515 cm^{-1}; ^{1}H-NMR(CD_3OD/TMS) δ 9.18 (dd, *J*=4.6Hz, 1.7Hz, 1H, Ar-H), 8.97 (s, 1H, Ar-H), 8.91 (s, 1H, Ar-H), 8.80 (dd, *J*=7.9Hz, 1.7Hz, 1H, Ar-H), 7.96 (dd, *J*=7.9Hz, 4.6Hz, 1H, Ar-H), 7.59 (d, *J*=9Hz, 2H, Ar-H), 7.26 (d, *J*=9Hz, 2H, Ar-H).

8-(4-Methoxyphenyl)-7,8,9,10-tetrahydro-5*H*-isoindolo[5,6-*g*]quinoline-5,7,9,11-tetraone (2l)

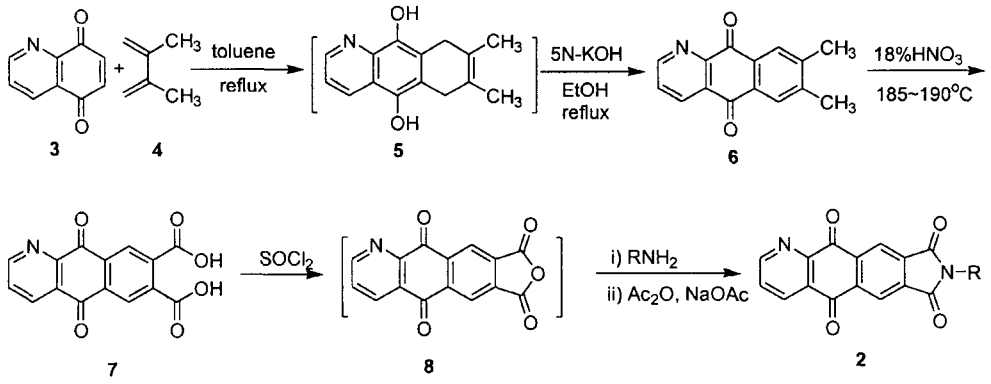
The product was obtained in 18.3% yield; mp 310°C dec; IR(KBr) 3078, 2924, 1725, 1677, 1510 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS) δ 9.22 (dd, *J*=4.6Hz, 1.7Hz, 1H, Ar-H), 9.00 (s, 1H, Ar-H), 8.91 (s, 1H, Ar-H), 8.74 (dd, *J*=7.9Hz, 1.7Hz, 1H, Ar-H), 7.85 (dd, *J*=7.9Hz, 4.6Hz, 1H, Ar-H), 7.39 (d, *J*=8.6Hz, 2H, Ar-H), 7.06 (d, *J*=8.6Hz, 2H, Ar-H), 3.88 (s, 3H, -OCH_3).

Cells

Four human cancer cell lines, HCT15, SK-OV-3, MDA-MB-468 and T-47D were used in this study. SK-OV-3 and HCT15 were obtained from national cancer institute, U.S.A. MDA-MB-468 and T-47D were purchased from American Type Culture Collection. These cells were maintained in Dulbecco's modified eagle media supplemented with 10% fetal calf serum at 37 under a humidified atmosphere of 5% CO_2.

In vitro cytotoxicity assay

Cell numbers were measured indirectly by sulforhodamine B (SRB) method according to the NCI (USA)'s protocol (Skehan *et al.*, 1990). Briefly, cells were



Cpd	R	Yield(%)	Cpd	R	Yield(%)
2a	-propyl	15.3	2g	-3-hydroxyphenyl	14.0
2b	-phenyl	14.9	2h	-3-methoxyphenyl	14.7
2c	-2-hydroxyphenyl	37.8	2i	-3-nitrophenyl	14.0
2d	-2-methoxyphenyl	24.0	2j	-4-chlorophenyl	16.7
2e	-2-nitrophenyl	12.0	2k	-4-hydroxyphenyl	20.5
2f	-3-chlorophenyl	13.6	2l	-4-methoxyphenyl	18.3

Scheme 1. Synthesis of 8-substituted-7,8,9,10-tetrahydro-5*H*-isoindolo[5,6-*g*]quinoline--5,7,9,11-tetraones

plated into 96 well plate at a density of 2 x 10^3 cells per well. Next day (day 0), compounds of interest dissolved in DMSO/media were added in quadriplicate. The final concentrations of each compound were 1 nM - 10 μM and the final concentration of DMSO was <0.1%. 72 hours later, cells were fixed with 10% trichloroacetic acid (TCA) for overnight at 4°C. The TCA-treated cells were extensively washed with distilled water and dried in the air. Then, SRB solution (0.4% in 1% acetic acid) was added to the well at room temperature for one hour. Bound dye was solubilized with 10 mM Tris after washing the wells with 1% acetic acid, and absorbances at 690 nm were measured using a microplate reader. The absorbance value of day 0 was subtracted from the absorbance values of day 3.

RESULTS AND DISCUSSION

The synthesis of the target compounds utilized Diels-Alder reaction of quinolinequinone and dimethylbutadiene as key step outlined in Scheme **1**. Dils-Alder cycloaddition of quinoline-5,8-dione (**3**) (Pratt *et al,* 1960) with 2,3-dimethyl-1,3-butadiene (**4**) at reflux in toluene resulted in a hydroquinone intermediate **5**. The intermediate **5** was identified by a typical IR band of phenolic hydroxy group shown at 3390 cm^{-1} and ^{1}H-NMR spectrum of the benzylic methylene (4H) appeared as two singlets (2H at 3.22 ppm and 2H at 3.20 ppm). Aerial oxidation of the intermediate **5** in 5*N* KOH solution and ethanol at reflux afforded the azaanthraquinone product **6** (Potts *et al,* 1986; Blanco *et al.*, 1996). 7,8-Dimethyl-5,10-dihydrobenzo[*g*]quinoline-5,10-dione (**6**) was oxidized to a dicarboxylic acid **7**. This reaction was carried out using 18% HNO_3 at 185-190 in a titanium autoclave (Iyengar *et al.* 1997; Lee *et al.*, 1999). The dicarboxylic acid **7** was then converted to the various isoindoloquinoline derivateves (**2a** - **2l**). The treatment of the compound **7** with $SOCl_2$ at reflux resulted in the intermediate acid anhydride **8** which was identified by typical cyclic acid anhydride carbonyl peak (1778 cm^{-1}). The crude compound **8** was directly treated with 1.1 equivalent of various amines (propylamine, aniline, 2-hydroxyaniline, 2-methoxyaniline, 2-nitroaniline, 3-chloroaniline, 3-hydroxyaniline, 3-methoxyaniline, 3-nitroaniline, 4-chloroaniline, 4-hydroxyaniline, and 4-methoxyaniline) followed by an acetic anhydride and sodium acetate in water bath to give the target compounds (**2a** - **2l**) in 12 - 38% yield (Scheme 1).

The evaluation of the biological activity for the compounds were performed *in vitro* following the protocols developed by the National Cancer Institute (Skehan *et al.*, 1990). The *in vitro* cytotoxic activities of the isoindoloquinolie derivatives **2a** - **2l** against human cancer cell lines originated from colon cancer (HCT15), ovarian carcinoma (SK-OV-3), breast adenocarcinoma (MDA-MB-468), and breast ductal carcinoma (T-47D) along with comparative data for doxorubicin and mitomycin C are listed in Table 1.

All of the isoindoloquinoline derivatives were less cytotoxic than doxorubicin and mitomycin-C. The most active compound **2d** showed good cytotoxic activity (0.6 - 3.2 μM) against four human cancer cells and the cytotoxicity against T-47D cancer cell was comparable to

Table I. *In vitro* Cytotoxic Activities of Isoindolo[5,6-*g*]quinoline Derivatives

Cpd	R	IC50[a] (mM) of cell lines[b]			
		HCT15	SK-OV-3	MDA-MB-468	T-47D
2a	-propyl	2.2	7.2	10	21
2b	-phenyl	16	50	22	24
2c	-2-hydroxyphenyl	20	>100	40	40
2d	-2-methoxyphenyl	0.6	3.2	3	3
2e	-2-nitrophenyl	3	32	21	30
2f	-3-chlorophenyl	22	>100	43	90
2g	-3-hydroxyphenyl	20	>100	>100	>100
2h	-3-methoxyphenyl	4.2	30	20	25
2i	-3-nitrophenyl	20	72	33	34
2j	-4-chlorophenyl	6	70	12	31
2k	-4-hydroxyphenyl	3	14	20	14
2l	-4-methoxyphenyl	3	30	20	10
	DOXORUBICIN	0.08	0.05	0.005	0.02
	Mito-C	0.13	0.52	0.1	2.1

[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: HCT15 (colon cancer cell), SK-OV-3 (ovarian carcinoma cell), MDA-MB-468 (human breast adenocarcinoma), T-47D (human breast ductal carcinoma)

that of mitomycin-C. Except for the compound **2d**, the compound with alkyl substituent (**2a**) was in general more potent than the compounds with aryl substituent (**2b** - **2l**). In the case of the compounds bearing methoxy (**2d**, **2h** and **2l**) and nitro group (**2e** and **2i**), 2-position showed more potent cytotoxicity than 3- or 4-position. On the other hand, in the case of the compounds bearing hydroxy (**2c**, **2g** and **2k**) and chloro group (**2f** and **2j**), 4-position was more motent than 2- or 3-position.

In summary, twelve isoindoloquinoline derivatives were designed and synthesized as potential antitumor agents. The most active compound **2d** may need further in depth biological evaluation. Work is in progress to design, synthesize, and evaluate additional compounds in this and related systems.

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