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Letter

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Synthesis of 8-Hydroxyquinoline Derivatives as Novel Antitumor Agents

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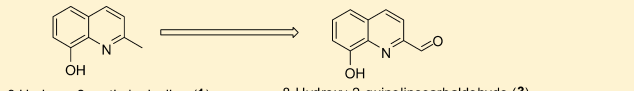
Supporting Information

ABSTRACT: This letter describes the preparation of quinoline derivatives and their cytotoxic potentials toward human carcinoma cell lines. Among the selected compounds, 8-hydroxy-2-quinolinecarbaldehyde (**3**) showed the best *in vitro* cytotoxicity against the human cancer cell lines, including MDA231, T-47D, Hs578t, SaoS2, K562, SKHep1 (with a MTS_{50} range of 12.5−25 μg/mL) and Hep3B (with a MTS_{50} range of 6.25±0.034 μg/mL). The *in vivo* antitumor activity of compound **3** on subcutenaous Hep3B hepatocellular carcinoma xenograft in athymic nude mice was then studied. The results showed that the dose of 10 mg/kg/day of compound **3** with intraperitoneal injection for 9 days totally abolished the growth of the xenograft tumor of Hep3B with no histological damage on vital organs as compared with the control. The experimental results suggested that compound **3** has a good potential as an antitumor agent.



KEYWORDS: *quinoline derivatives, 8-hydroxy-2-quinolinecarbaldehyde, antitumor, hepatocellular carcinoma*

Cancer is a life-threatening disease worldwide,[1] and the development of anticancer drugs with high efficacy and minimal side effects remains to be a challenge. The nitrogen-containing alkaloids, which were discovered in natural plants, are usually basic in nature and bear biological activities.[2−8] Quinoline-bearing structures are well-known due to their broad biological activities,[9] such as antifungal,[10] antibacterial,[11] and HIV-1 replication inhibitors[12] that have been used in traditional medicine as a remedy. Recently, quinoline-based azolylalkylquinolines bearing different azole groups, such as benzothiazole (SRA-HX-1), tetrazole (SRA-HX-2), and 1,2,4-triazole (SRA-HX-3), have been synthesized and reported as potent antitumor agents for breast cancer cells *in vitro*.[13]

More recently, Serda and co-workers reported that quinoline-based thiosemicarbazones showed antitumor efficacy involving iron chelation mechanism.[14] With reference to 5-FU, Ai and co-workers reported the synthesis of a series of pyrimido[5,4-*c*]quinoline-4-(3*H*)-one derivatives, which exhibited moderate antitumor activity against several selected human cancer cell lines including KB, CNE2, MGC-803, GLC-82, MDA-MB-453, and MCF-7.[15] Palit and co-workers reported the one-pot synthesis of bis-quinolines using phase transfer catalysis and 8-hydroxy quinoline derivatives as substrates. The *in vitro* and *in vivo* studies showed that the synthesized derivatives exhibited antileishmanial activity, especially including 1,1-bis-[(8-quinolyl)oxy]methane and (1,5-bis-[(2-methyl-9-quinolyl)-oxy]pentane. They also discovered that 1,1-bis-[(5-chloro-8-quinolyl)oxy]methane was a potential lead for leishmanicidal drug development.[11] Zhang and co-workers reported the design and synthesis of a series of quinoline-3-carbonitrile derivatives, and most of them showed excellent selective cytotoxicity toward SMMC-7721 cell line in comparison to Gefitinb in MTT assay.[16] Kumar and co-workers reported the Cu(I)-catalyzed synthesis of quinoline coupled 1,2,3-triazoles compounds using inexpensive azidomethyl quinoline and alkynes. These compounds were reported to inhibit anti-tuberculosis activities.[17]

8-Hydroxyquinoline derivatives had been prepared and studied for the treatment of neurodegenerative diseases such

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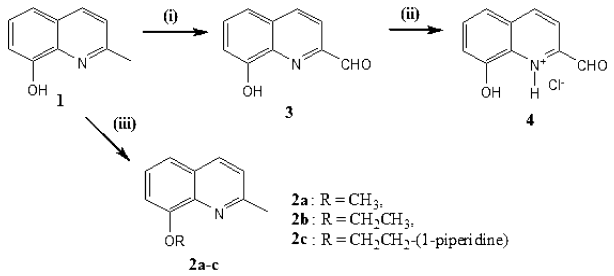
as Alzheimer's disease.[18] In addition, the derivatives had been reported to possess biological activities on the proliferation of rat mesenchymal stem cells (rMSCs).[19] The antitumor applications of quinoline-based analogues were also reported.[20−23]

The quinoline compounds have raised our interest for investigating their antitumor activities.[24,25] In this paper, we further reported the effective quinoline compounds, which exhibited strong antitumor activities against human cancer cell lines and hepatocellular carcinoma Hep3B xenograft in athymic nude mice model, and there was no observable damage on the vital organs at histological level.

The synthesis of quinoline compounds was described in Scheme 1. 8-Alkoxy-substituted quinaldine (**2a−c**) was

Scheme 1. Synthesis of Quinoline Derivatives[a]



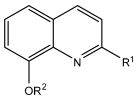
[a]Reagents and conditions: (i) SeO_2, dioxane, H_2O, reflux. (ii) HCl(g), DCM. (iii) RX (X = Cl or Br), K_2CO_3, DMF.

prepared by simple alkyl halide substitution of the commercially available 8-hydroxy-2-methylquinoline (**1**) in DMF under basic condition.[26] The reaction was run at room temperature and monitored by TLC until the reaction was completed. The crude products were extracted and purified by silica gel column chromatography to give pure products in good yield (>80%). 8-Hydroxy-2-quinolinecarbaldehyde (**3**) can be prepared by oxidation of 8-hydroxy-2-methylquinoline (**1**) with selenium dioxide in dioxane/water mixture at reflux.[24,25] 2-Formyl-8-hydroxyquinolinium chloride (**4**) was prepared by bubbling hydrochloride gas in a dichloromethane solution of 8-hydroxy-2-quinolinecarbaldehyde (**3**).[26]

A number of easily available substituted quinolines were prepared to initialize the study of their antitumor effects on various types of cancer cell lines (K562, T47D, and Hep3B) *in vitro* (Scheme 1). The preliminary screening with MTS ([3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium]) assay, in comparison with cisplatinum (CDDP) as a positive reference, showed that purely 2-substituted quinoline moieties, such as 2-methylquinoline, did not constitute any significant anticancer effect.

The introduction of hydroxyl group at position 8 (**1**) (Table 1, compound **1**) showed a prominent positive antitumor effect against K562 and T47D cancer cell lines *in vitro*. Commercially available compounds with a hydroxyl group on position 4, 6, and 7 were also studied, but they only showed little activities. As for compound **1**, the replacement of the hydroxyl group by various alkoxyl groups (Table 1, compound **2a−c**) led to an increase in cytotoxicity against K562 cell line. Compounds having a hydroxyl group at position 8 and various functional groups at position 2 (**3**, **5**, and **6**) were also studied, and different anticancer effects were detected (Table 1). For compound **3**, which bears a carboxyaldehyde group on position 2 together with a hydroxyl group on position 8, the cytotoxicity

Table 1. Cytotoxicity Assay for the Tested Quinoline Compounds[a]



			activities	
compd	R_1	R_2	T-47D	K562
control			100 ± 6.49	100 ± 5.96
1	CH_3	H	46.54 ± 9.40	34.46 ± 5.67
2a	CH_3	CH_3	37.92 ± 3.57	27.15 ± 2.46
2b	CH_3	CH_2CH_3	63.43 ± 4.81	21.38 ± 3.79
2c	CH_3	CH_2CH_2-(1-piperidine)	69.20 ± 13.36	27.43 ± 2.84
3	CHO	H	8.37 ± 3.46	7.00 ± 1.95
5	CN	H	72.92 ± 12.01	23.08 ± 1.00
6	H	H	52.60 ± 2.36	26.66 ± 6.28
CDDP			30.50 ± 4.83	4.17 ± 1.10

[a]All of the testing compounds were at a concentration of 50 μg/mL. Results are shown as means ± standard derivations (SDs) from triplicated experiments.

was increased by nearly 4-fold in comparison to CDDP against T-47D cells.

To further demonstrate the anticancer effect of compound **3**, we studied the cytotoxic activity by MTS assay against various cancer cell lines together with a nontumor cell line NIH3T3. As shown in Table 2 (entries 1−8), compound **3** showed very

Table 2. In Vitro Antitumor Activity (MTS_{50}) of Compound 3

entry	cell lines	MTS_{50} (μg/mL) range
1	A549	>50
2	MDA231	12.5−25
3	T-47D	12.5−25
4	Hs578t	12.5−25
5	SaoS2	12.5−25
6	K562	12.5−25
7	SKHep1	12.5−25
8	Hep3B	6.25 ± 0.034
9	NIH3T3	7.00 ± 0.051

promising MTS_{50} activity (50% reduction of MTS assay signal in the treated cells as compared with the control), especially for Hep3B cells (entry 8), which was about 11% more sensitive to the cytotoxicity effect of compound **3** than the NIH3T3 cells (entry 9). Figure 1 shows the dose-dependent cytotoxicity of compound **3** against T47D, Hs578t, and K562 as other examples.

Then, various cancer cells were treated with compound **3** as presented in Table 2, and after 48 h, morphological changes including cell rounding, cell shrinkage, and loss of adherent property (for solid tumor cell lines) were recorded under phase contrast microscope, indicating the antitumor effect of the compound **3**. Seven out of the eight cancer cell lines showed cell shrinkage including the breast carcinoma cell lines (T47D, MDAMB-231, and Hs578t), which also lost the adherent property and showed cell rounding (Figure 2). Normal growth was observed from the DMSO controls. The A549 lung cancer cells were least affected. Moreover, compound **3** could exhibit its antitumor effect by inhibiting the anchorage-dependent

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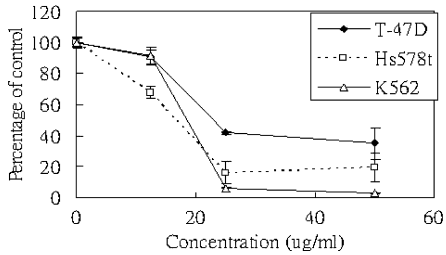


Figure 1. Dose-dependent cytotoxicity of compound **3** on three human cancer cell lines including breast carcinoma T47D, Hs578t, and chronic myelogenous leukemia K562. Triplicated tests were performed, and three independent experiments were done. Results are shown as means ± SDs when compared with vehicle control.

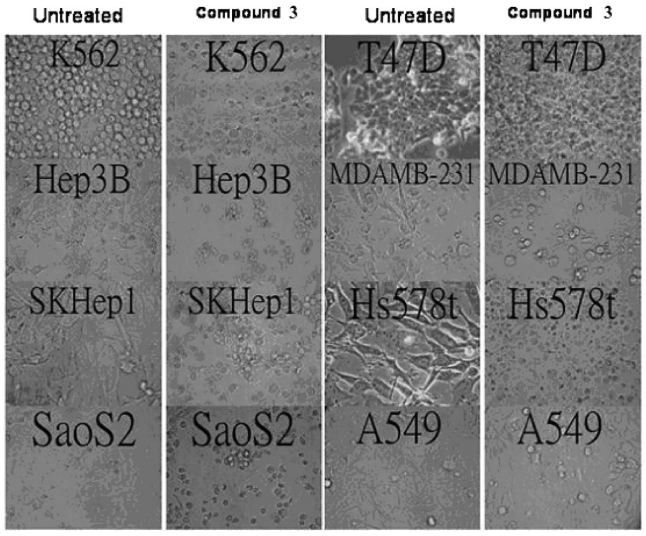


Figure 2. Morphological study for the cytotoxic action of compound **3** (50 μg/mL) on human cancer cell lines. All of the tumor cell lines showed cell shrinkage, cell rounding, and loss of adherent property (for solid tumor cell lines) after treatment with compound **3** except the lung cancer cell line A549.

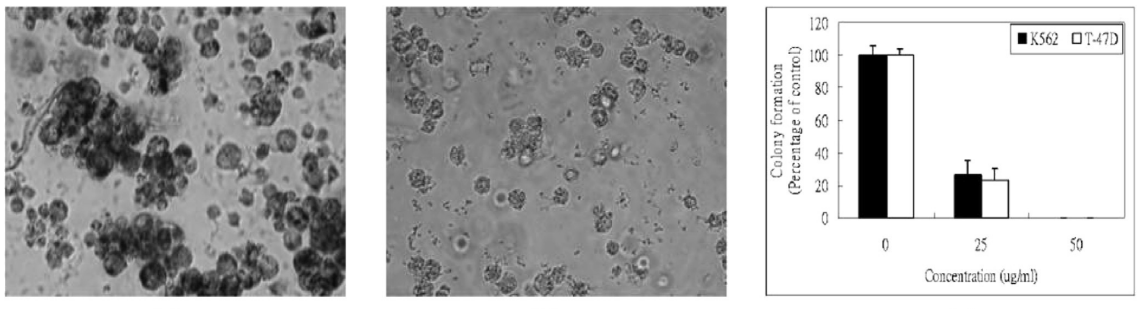
clonogenicity potential of K562 and T47D cells in a dose-dependent manner (Figure 3).

The *in vivo* activity of compound **3** was also studied using athymic nude mice xenograft tumor model. As shown in the Figures 4 and 5, a near complete disappearance of Hep3B xenografts on the ninth day was observed in mice that received daily intraperitoneal (ip) injection of compound **3** in the dose of 10 mg/kg/day as compared with the vehicle control. None of the mice died during the treatment. It was noticed that a significant difference in the tumor volume was observed in the mice from the treatment and control groups. Representative examples are shown in Figure 4. Pathological investigation of vital organs from athymic nude mice treated with compound **3** stained with hematoxylin and eosin did not demonstrate any observable tissue damage. A representative example is shown in Figure 6.

We observed that the solubility of compound **3** was not optimal in physiological saline, which acts as the drug vehicle. To improve the solubility of compound **3**, compound **4** (salt of compound **3**) was also prepared (Scheme 1). The *in vitro* MTS assay was performed on the Hep3B cell line, and the antitumor activity of compound **4** is still comparable to compound **3** with the MTS_{50} range from 12.5 to 25 μg/mL.

The cytotoxicity effect of compound **3** against NIH3T3 cells (MTS_{50} = 7.00 ± 0.051 μg/mL) is about 11% less toxic than Hep3B (MTS_{50} = 6.25 ± 0.034 μg/mL)(Table 2). A similar observation was also reported recently for a panel of clinically used antitumor agents in which the *in vitro* cytotoxic effects of PKC412 and rapamycin, for examples, against cancer cells were higher than the normal cells also by only about 10%, with the *in vivo* antitumor effects being more prominent against cancer cells than normal tissues.[27] Such an observation could still bring about the clinical benefits to the cancer patients with the careful selection of the doses and types of the antitumor agents for determining the best therapeutic index.

Here, we reported the synthesized quinoline derivatives and their cytotoxic potentials against the tumor cells and nontumor cells. 8-Hydroxy-2-quinolinecarbaldehyde (compound **3**) and its salt (compound **4**) showed a remarkable cytotoxicity against the human tumor cell lines. Athymic nude mice tumor-xenograft experiments with subcutaneous Hep3B tumor confirmed its *in vivo* antitumor activity for abolishing the growth of the tumor at a dose of 10 mg/kg/day on day 9 when administrated intraperitoneally with no observable toxicity from the vital organs at histological level. To identify the most involved molecular pathways of the drug actions, a preliminary cDNA microarray analysis was performed in the Genome Research Centre of the University of Hong Kong using the Human Genome U133 Plus 2.0 arrays (Affymetrix) as previously described[28] to identify the differentially expressed genes in cancer cells after the treatment with compound **3**. Total RNA was extracted from the vehicle control and the esophageal cancer cell line KYSE150 treated with 8.5 μg/mL of compound **3** for 48 h with reference to the MTS_{50} value (6.25–12.5 μg/mL). The results indicated that the CCL5 [chemokine



(a) (b) (c)

Figure 3. (a) K562 colonies from vehicle control, (b) K562 treated with compound **3** (50 μg/mL) for 24 h, and (c) percentages of colony formation inhibition of compound **3** on the K562 and T47D cancer cells using the anchorage-dependent clonogenicity assay.

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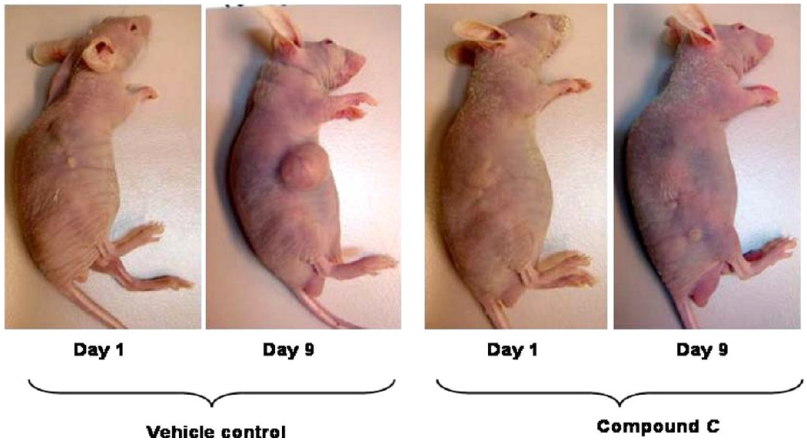

Figure 4. Athymic nude mice with Hep3B xenograft experiment for testing the *in vivo* anticancer effect of compound **3**. Arrows indicate the positions of the xenograft tumors. The tumor size was significantly reduced in the mice tested with compound **3**.

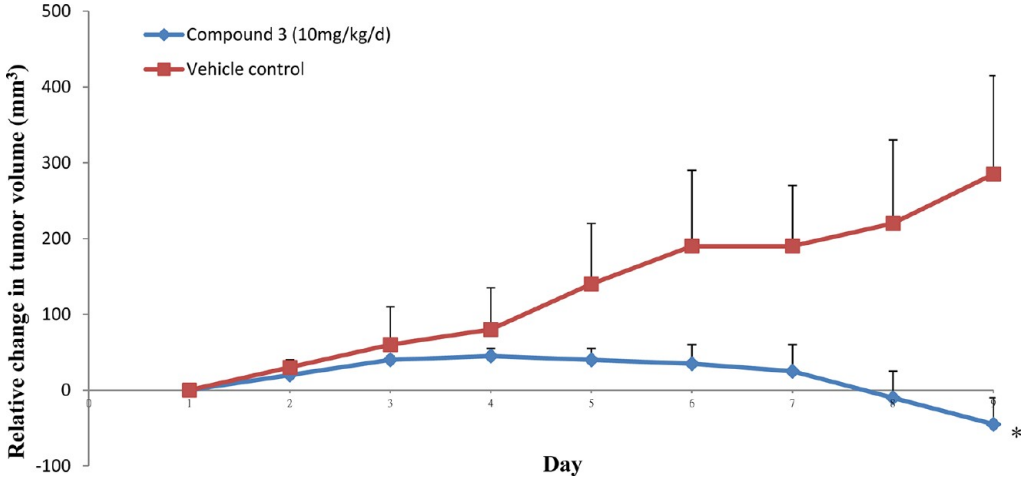

Figure 5. Relative changes of tumor volume (mm^3) of athymic nude mice with subcutaneous human hepatocellular carcinoma Hep3B xenografts treated with compound **3**. Both control and treated groups consisted of five mice. Results are shown as means + SDs of tumor volume. *P = 0.0155 (Student's t test).

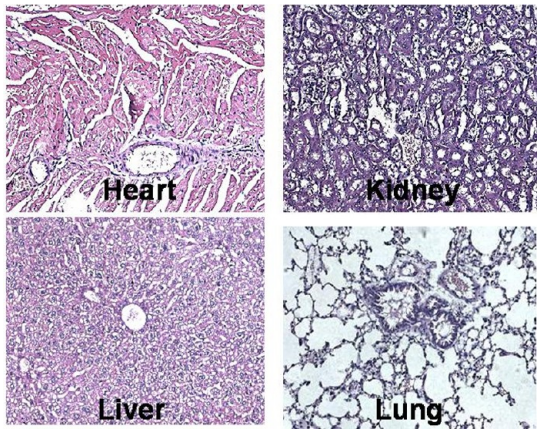

Figure 6. Representative examples of histological appearance of vital organs collected from an athymic nude mouse treated with compound **3** for 8 days showing no sign of tissue damage at the histological level. Original magnification: 200×.

(C−C motif) ligand 5] gene showed the highest level of down-regulation by 53.42% reduction of detection signal, and the CLGN (calmegin) gene showed the highest level of up-regulation by 65.42% increase of detection signal as compared with the vehicle control. It has been reported that CCL5 is involved in the pathway of chemokine recognition, and its suppression led to the inhibition of invasive capacity of cancer stem cells.[29] CLGN has been reported to act as a chaperone, which is involved in the histone-related pathway of cell division control.[30] Further molecular analyses based on the up- or down-regulated genes will be reported in a later separated paper.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic method and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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