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Design and synthesis of 2-(3-alkylaminophenyl)-6-(pyrrolidin-1-yl)quinolin-4-ones as potent antitumor agents

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ABSTRACT

2-(3-Alkylaminophenyl)-6-(pyrrolidin-1-yl)quinolin-4-ones **1**–**3** were synthesized and screened for anti-proliferative activity against three human cancer cell lines, as well as the normal cell line Detroit 551. All of the synthesized target compounds **1**–**3** demonstrated potent cytotoxic activity against the cancer cell lines, but weak inhibitory activity toward the normal cell line. 2-(3-Methyl aminophenyl)-6-(pyrrolidin-1-yl)quinolin-4-one (**1**), one of the potent compounds in vitro, was also tested in an in vivo Hep3B xenograft nude mice model, and its significant anticancer activity was reconfirmed. Therefore, compound **1** merits further investigation as an antitumor clinical trial candidate and potential anticancer agent.

In our continuing effort to develop novel anticancer agents during the last decade, we have synthesized various derivatives of 2-phenylquinolin-4-ones (PQs),[1–4] tetrahydro-2-phenylquinolin-4-ones (THPQs)[5] and 2-phenylquinazolin-4-ones (QZs),[6,7], as summarized in Chart 1. These compounds were evaluated for in vitro anticancer activity, and structure–activity relationship (SAR) correlations were established. Based on this work, we have identified a subset of compounds with potential for further development. From the SAR, we found that the incorporation of a 6-pyrrolidinyl group on certain PQ, THPQ and QZ compounds, for example, 2-(3-methoxyphenyl)-6-(pyrrolidin-1-yl)quinolin-4-one (PQ1),[3] 2-(3-methoxyphenyl)-6-(pyrrolidin-1-yl)tetrahydroquinolin-4-one (THPQ1)[5] and 2-(3-methoxyphenyl)-6-(pyrrolidin-1-yl)qunazolin-4-one (OZ1)[7] (shown in Chart 1), resulted in enhanced anti-proliferative potency compared with than their corresponding analogs, namely, PQ2–5, THPQ2 and QZ2–6. Among these 6-pyrrolidinyl derivatives, the most potent compound, PQ1, was evaluated against the USNCI-60 human cell line panel, where it exhibited GI_{50} values in the nanomolar or sub-nanomolar level with an average $\log GI_{50}$ value of −8.72.

Based on the above findings, we believe that the 6-pyrrolidinyl group plays a critical role in potentiating the anticancer activity of PQ, THPQ and QZ compounds. Undoubtedly, further investigation of the anticancer activity of these pyrrolidinyl derivatives is warranted. More recently, the mechanism of action of compound **1** toward HL-60 leukemia cell line has been proposed in our separate report.[8] In this Letter, we focused on its anticancer activity against hepatocellular carcinoma cell lines (HCC) instead. Hence, a series of new derivatives of compound **1** were synthesized, and evaluated for in vitro and in vivo anticancer activity in order to identify new anticancer drug candidates with potential for further development.

The target compounds **1**–**3** were synthesized according to our previously reported method for PQs (Scheme 1). Initially, compound **4** underwent a condensation reaction with **5** to afford the amide intermediate **6**, which was subjected to catalytic hydrogenation to give the amide intermediate **7**, which was N-alkylated separately with methyl iodide or ethyl iodide to yield the corresponding mono-alkylamino derivatives **8**, **10** or di-alkylamino derivatives **9**. Compounds **8**–**10** were further cyclized in 1,4-dioxane, in the presence of NaOH, to give the corresponding target compounds **1**–**3**.

The above synthesized target compounds **1**–**3** were evaluated for anti-proliferative activity against HL-60, Hep3B and H460 cancer lines, as well as the Detroit 551 normal human cell line. From the results in Table 1, all of the tested target compounds **1**–**3** exhibited significant anti-proliferative activity against HL-60, Hep3B and H460 cells, but weak inhibitory activity toward the normal cell line Detroit 551.

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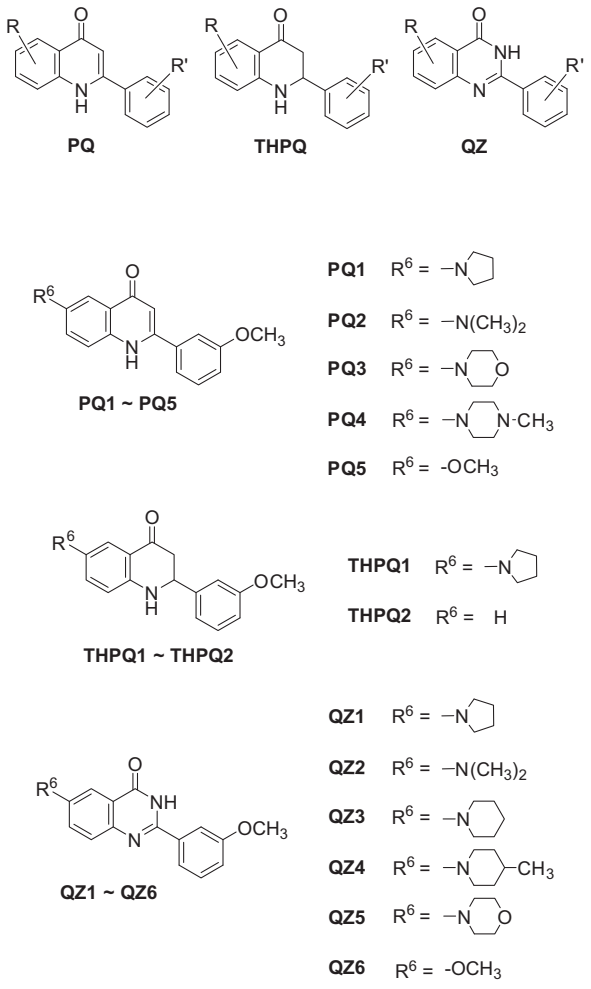
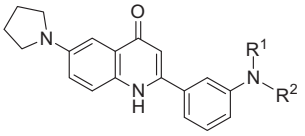


Chart 1. .

Table 1
IC_{50} (μM) values from in vitro cytotoxicity testing of **1**–**3**

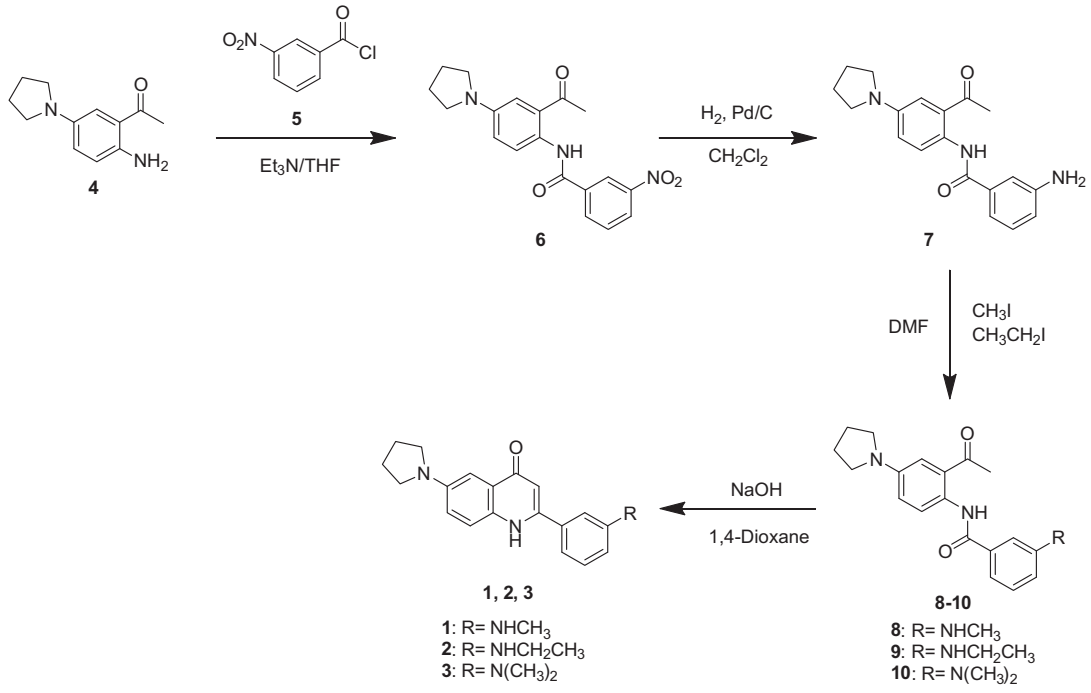


Compounds **1 - 3**

Compd	R^1	R^2	IC_{50}[a] (μM)			
			HL-60[b]	Hep3B[b]	H460[b]	Detroit 551[b]
1	H	CH_3	0.006	0.021	0.035	>10
2	H	CH_2CH_3	0.005	0.020	0.020	>10
3	CH_3	CH_3	0.005	0.015	0.013	>1

[a] Data are presented as IC_{50} (μM) for each cell line; the concentration of compound that caused a 50% proliferation–inhibitory effect after 2 days incubation.
[b] Cell lines include human promyelocytic leukemia (HL-60), human hepatoma (Hep3B), human lung cancer (H460), and embryonic skin fibroblast cell line (Detroit 551).

In fact, compounds **1**–**3**, with methylamino, ethylamino, and dimethylamino groups in the 3-position, demonstrated the equivalent potency against the Hep3B HCC cell line. 2-(3-Methylaminophenyl)-6-(pyrrolidin-1-yl)quinolin-4-one (**1**), one of the these potent compounds, was selected for evaluation of in vivo antitumor activity. Compound **1** was evaluated against a Hep3B xenograft nude mice model, and the results were summarized in Figures 1. As indicated in Figure 1A, at dosages of 5, 10 and 20 mg/kg/day (ip), compound **1** demonstrated dose- and time-dependent inhibition of Hep3B tumor growth. For instance, at the 20 mg/kg/day dosage, the inhibition rate for tumor growth was about 70% (calculated as $1\text{-}\Delta T/\Delta C$). Meanwhile, as shown in Figure 1C, no significant variation of mean body weight of Hep3B



Scheme 1. Synthesis of 2-(3-alkylaminophenyl)-6-(pyrrolidin-1-yl)quinolin-4-ones (**1**–**3**).

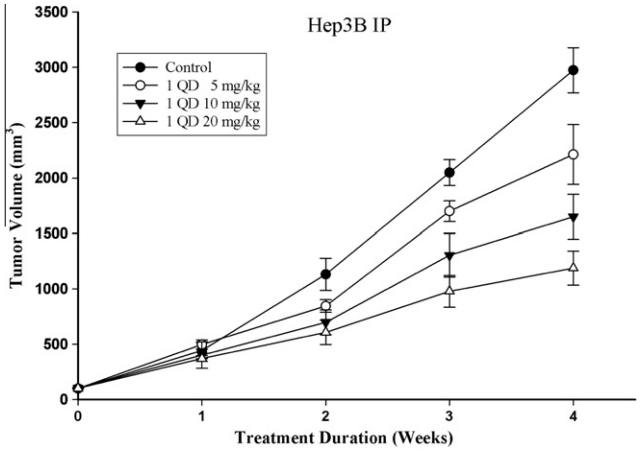


Figure 1A. Mean tumor volume–time profiles in Hep3B xenograft nude mice ($n = 11$) following ip dosing of **1** at 5, 10, and 20 mg/kg 5 days per week for 4 consecutive weeks. Dosing was started after the tumor had grown to 100 mm^3 (early stage).

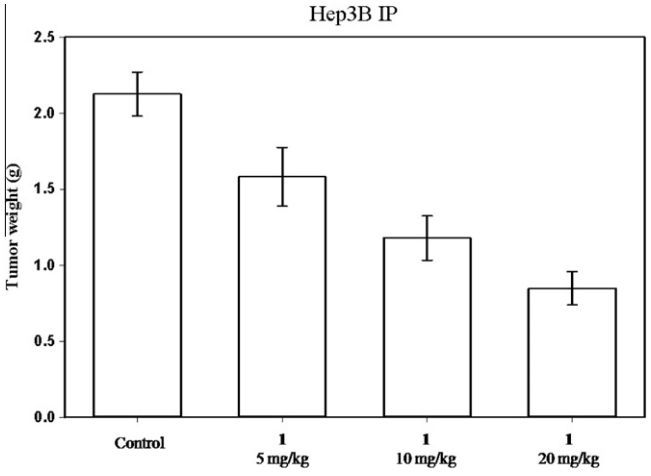


Figure 1B. Mean tumor weight–time profiles in Hep3B xenograft nude mice ($n = 11$) following ip dosing of **1** at 5, 10, and 20 mg/kg 5 days per week for 4 consecutive weeks. Dosing was started after the tumor had grown to 100 mm^3 (early stage).

xenograft nude mice was observed between the control and compound **1**-treated group over 4 weeks. In brief, our results suggested that **1** efficiently inhibited the growth of Hep3B tumor, at 10 and 20 mg/kg/day dosages, without causing significant toxicity.

Compound **1** exhibited potent anti-proliferative activity against several human cancer cell lines, and significant inhibitory activity against tumor growth of Hep3B in vivo. Therefore, we recommend **1** for further development as an anticancer drug candidate.

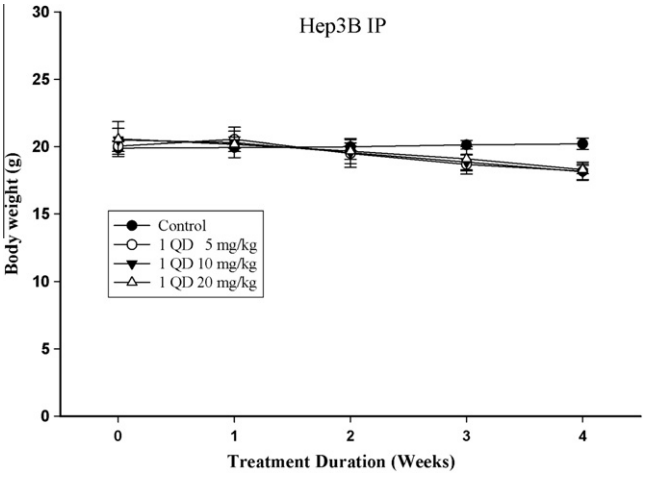


Figure 1C. Mean body weight–time profiles in Hep3B xenograft nude mice ($n = 11$) following ip dosing of **1** at 5, 10, and 20 mg/kg 5 days per week for 4 consecutive weeks. Dosing was started after the tumor had grown to 100 mm^3 (early stage).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.11.105.

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