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Original article

Synthesis and *in vitro* anticancer activity of 6,7-methylenedioxy (or 5-hydroxy-6-methoxy)-2-(substituted selenophenyl)quinolin-4-one analogs

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ABSTRACT

6,7-Methylenedioxy (or 5-hydroxy-6-methoxy)-2-(substituted selenophenyl)quinolin-4-ones and their isosteric compounds were synthesized and evaluated for anticancer activity. Structure–activity relationships (SAR) of these compounds were established. Among all tested compounds, 6,7-methylenedioxy-2-(5-methylselenophen-2-yl)quinolin-4-one (**4d**) was found to be the most promising anticancer agent. In screening against NCI's 60 human tumor cell line panel, **4d** exhibited highly selective and potent inhibitory activity against MDA-MB-435 melanoma. Furthermore, the results of COMPARE analysis suggested that **4d** is an antimitotic agent with a different mechanism of action from the conventional antimitotic agents, such as colchicine, vinca alkaloids and paclitaxel. Therefore, **4d** was identified as a new lead compound that merits further optimization.

1. Introduction

Starting 1993, we have synthesized several 6,7-substituted 2-phenylquinolin-4-ones (2PQs) [1] (Chart 1) and identified them as novel antimitotic agents. As a consequence, a series of 2′,3′,4′,5′,5,6,7-substituted 2PQs were synthesized and evaluated for anticancer activity [2–6]. The resulted structure–activity relationships (SAR) indicated that the anticancer activity of 2PQs could be significantly improved either when the functional groups with lone pair electron (e.g. OR, NRR′, F, Cl) were incorporated in their R_6 or R_3' sites, or when methylenedioxy (–O–CH_2–O–) group was incorporated in their R_6–R_7 location (Chart 1). Besides, we have also synthesized and evaluated 2PQ analogs including 2-arylquinolin-4-ones (2AQs) [7], 2-heteroarylquinolin-4-ones (2HAQs) [7]. 2-arylnaphthyridin-4-ones (2ANs) [8–10] and 2-arylquinazolin-4-ones (2AQZs) [11,12] and identified a lot of potent anticancer agents among these 2PQ analogs (Chart 1).

The result of animal studies with more than 20 compounds of 2PQ analogs (ip administration) indicated that 2-(2-fluorophenyl)-6,7-methylenedioxyquinolin-4-one (**2AQ-1**) and 2-(3-fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-one (**2AQ-2**) possess superior antitumor activity. However, low water solubility and bioavailability have limited their further development. Thus, both **2AQ-1** and **2AQ-2** were phosphorylated to provide orally available drug candidates, **2AQ-1-P** and **2AQ-2-P** (Chart 2), that are currently under preclinical studies [13,14]. As reported in our previous studies, we proposed that the extraordinarily high antitumor activity of **2AQ-1-P** and **2AQ-2-P** might be associated with the presence of a 6,7-methylenedioxy or 5-hydroxy-6-methoxy moiety on the A-ring of these **2AQ** derivatives.

In the current work, we have synthesized 6,7-metylenedioxy-2-(5-substituted selenophen-2-yl)quinolin-4-ones (IA), 6,7-methylenedioxy-2-(selenophen-3-yl)-quinolin-4-ones (IB), 5-hydroxy-6-methoxy-2-(5-substituted selenophen-2-yl)-quinolin-4-ones (IIA), 5-hydroxy-6-methoxy-2-(5-substituted selenophen-3-yl)-quinolin-4-ones (IIB) and their 2-thienyl and 2-furyl isosteres (IIIA-B) as target compounds (Chart 3) with the aim to identified novel 2-selenophenylquinolin-4-one-type lead compounds for further development.

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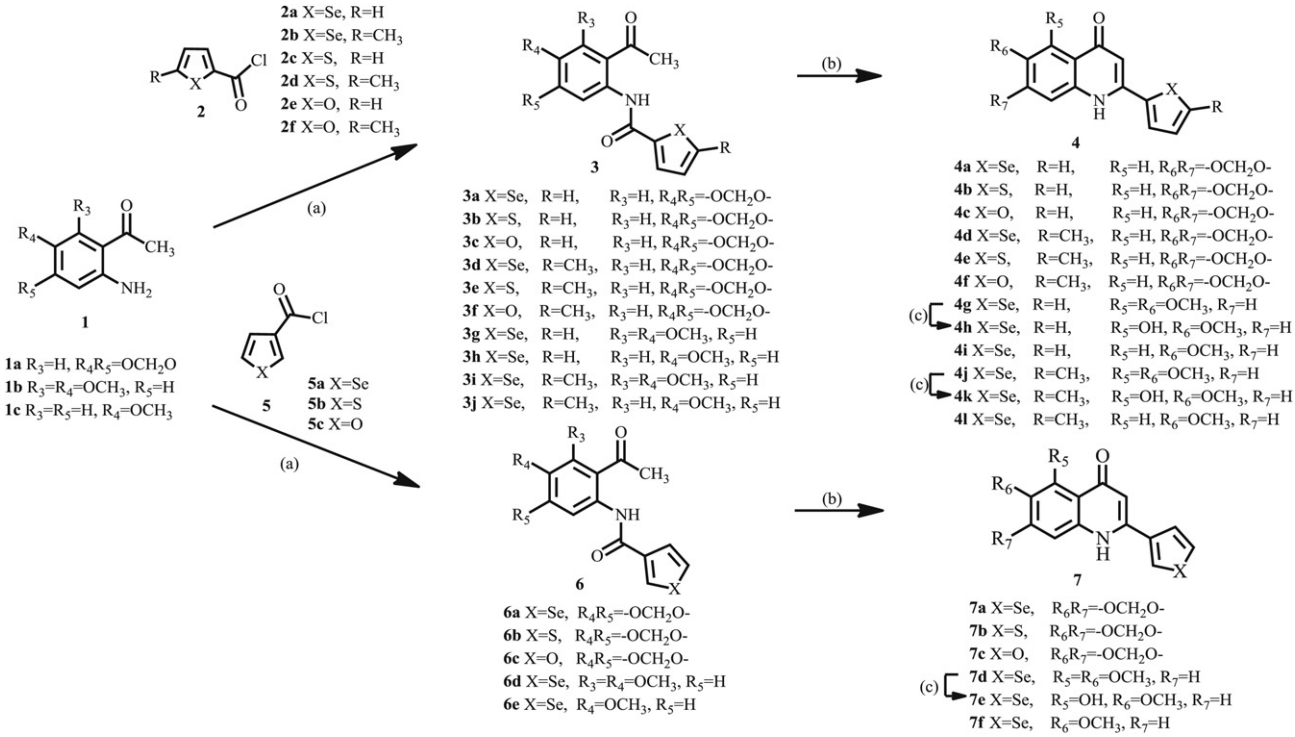
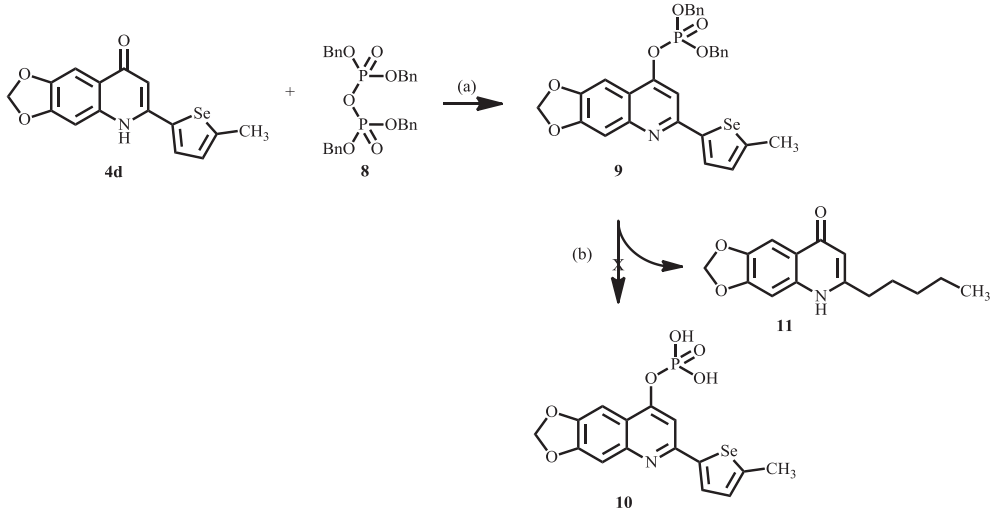


Scheme 1. Reagents and conditions:(a)Et_3N/toluene; (b)NaOH/dioxane; (c)BCl_3/DCM.

2. Chemistry

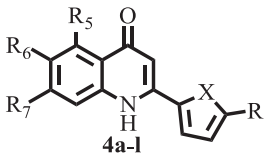
A number of synthetic methods for 2PQs were available on the literature [15]. Among them, the Camps quinolinol synthesis approach [16,17] was widely adopted. Consequently, a number of modification [16,17] to Camps approach for preparation of its key intermediate-(*O*-ketoaryl) amides, as well as modification to their subsequent cyclization condition [18–20], leading to the formation of 2-phenylquinolin-4-ones, have been reported. For instance, *t*-BuOK/BuOH [2–4,13,14], *t*-BuONa [19], NaOH/BuOH [20] and NaOH/dioxane [7,18] were reported separately as alternative media for cyclization. In the current study, the starting selenophenecarboxylic chlorides (**2**, **5**) were not available commercially and were prepared in house. Following a modified method of L. Buchwald [7,18], and our previously reported condition [7], our key intermediates (**3**, **6**) were cyclized at 110 °C, in NaOH/dioxane.

The synthetic procedure for target compounds **4a**–**l** and **7a**–**f** is illustrated in Scheme 1. The starting substituted 2-aminoacetophenones (**1a**–**c**) were first reacted with a variety of acid chlorides (**2a**–**f** and **5a**–**c**) to give corresponding amides (**3a**–**j** and **6a**–**e**). Then, the intermediates (**3a**–**j** and **6a**–**e**) were cyclized in dioxane, in the presence of NaOH, to afford the corresponding 2-heteroarylquinolin-4-ones (**4a**–**g**, **4i**,**j**, **4l**, **7a**–**d** and **7f**). Structural determination of the target compounds (**4a**–**g**, **4i**–**j**, **4l**) was described in detail using 2-(5-methylselenophen-2-yl)-6,7-methylenedioxyquinolin-4-one (**4d**) as a sample. From its high-resolution

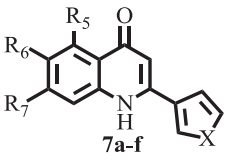


Scheme 2. Reagents and conditions:(a)NaOH/THF; (b)H_2,Pd/C, MeOH.

Table 1
Cytotoxicity of compounds **4a**–**l** and **7a**–**f**.



4a-l



7a-f

Compd NO.	X	R	R_5	R_6	R_7	IC_{50} (μM)[a]			
						HL-60	Hep 3B	H460	Detroit 551
4a	Se	H	H	$-OCH_2O-$		0.5	0.8	1.0	50
4b	S	H	H	$-OCH_2O-$		1.0	0.7	1.0	>5
4c	O	H	H	$-OCH_2O-$		6.8	>15	>15	>15
4d	Se	CH_3	H	$-OCH_2O-$		0.3	0.2	0.4	>25
4e	S	CH_3	H	$-OCH_2O-$		0.3	0.7	0.4	>5
4f	O	CH_3	H	$-OCH_2O-$		4.3	10	9.8	>10
4g	Se	H	OCH_3	OCH_3	H	7.7	>100	91.5	>100
4h	Se	H	OH	OCH_3	H	1.1	0.7	0.4	100
4i	Se	H	H	OCH_3	H	0.6	3.2	2.4	>10
4j	Se	CH_3	OCH_3	OCH_3	H	3.1	>50	>50	>50
4k	Se	CH_3	OH	OCH_3	H	0.4	0.8	0.9	>50
4l	Se	CH_3	H	OCH_3	H	0.4	3.0	2.0	>10
7a	Se	–	H	$-OCH_2O-$		0.9	0.8	1.4	>10
7b	S	–	H	$-OCH_2O-$		0.9	2.2	4.3	>25
7c	O	–	H	$-OCH_2O-$		3.4	9.6	15.8	>25
7d	Se	–	OCH_3	OCH_3	H	1.7	100	100	>100
7e	Se	–	OH	OCH_3	H	0.4	0.3	0.8	>100
7f	Se	–	H	OCH_3	H	0.7	3.7	2.3	>10

Human tumor cells were treated with different concentrations of samples for 48 h.
[a] Data are presented as IC_{50} (μM, the concentration of 50% proliferation-inhibitory effect).

mass spectrum (HRMS), the molecular formula was determined as $C_{15}H_{11}NO_3Se$ which agree with our expectation for compound **4d**. Furthermore, from its ^1H NMR spectrum and the aid of H–H COSY analysis the signals at δ 2.58 (s) and δ 6.16 (s) were assigned to the CH_3 and $-O-CH_2-O-$ group, respectively. The signal at δ 6.61 (br) was assigned to the H-3, and δ 7.06 (br) was assigned to the 4-proton on the selenophene ring. Next, the signals at δ 7.16 (s) and δ 7.36 (s) were assigned to H-8 and H-5, respectively. Finally, the signal at δ 7.66 (d, $J = 3.6$ Hz) was assigned to the 3-proton on the selenophene ring, and the signal at δ 11.35 (br) was assigned to NH. The structural information of compound **4d** obtain from its ^1H NMR spectrum matches with our expectation. The obtained 5,6-dimethoxy derivatives (**4g**, **4j** and **7d**) were demethylated with BCl_3 to afford the corresponding 5-hydroxy-6-methoxy derivatives (**4h**, **4k** and **7e**). Preliminary screening of the above target compounds revealed that compound **4d** exhibited the best *in vitro* anticancer activity. Therefore, in an attempt to synthesize an orally available phosphate derivative, compound **4d** was subjected to the reaction sequence shown in Scheme 2. Compound **4d** was first reacted with tetrabenzyl pyrophosphate (**8**) in THF in the presence of NaH to yield dibenzyl 2-(5-methylselenophen-2-yl)-6,7-methylenedioxyquinolin-4-yl phosphate (**9**). However, when compound **9** was subsequently debenzylated over Pd/C, following the synthetic procedure for **2AQ-1-P** [13], an unexpected major product (**11**), rather than the expected compound **10**, was obtained. The molecular formula of compound **11** was determined to be $C_{15}H_{17}NO_3$, based on HRMS data. The aromatic proton signals of the quinolone ring and methylene proton signals of the 6,7-methylenedioxy group were found in the ^1H NMR spectrum of the product. However, proton signals for the 5-methylselenophene ring in compound **10** were absent. Instead, a set of aliphatic proton signals corresponding to the *n*-pentyl group of **11** were observed. From the above data, we speculated that the unexpected product **11** resulted from cleavage of the expected selenophene ring of compound **10**. Alternative methods for the synthesis of the target phosphate **10** will be explored in the future.

Table 2
COMPARE analysis of **4d**.

r[a]	Compounds	Mechanism of action
0.648	Didemnin B	Apoptotic inducer
0.498	S-Trityl-L-cysteine	Antimitotic agent
0.377	Vinblastine	Antimitotic agent
0.353	Vincristine	Antimitotic agent
<0.372	Colchicine	Antimitotic agent
<0.386	Paclitaxel	Antimitotic agent
0.395	2AQ-1	Antimitotic agent
0.335	2AQ-2	Antimitotic agent

[a] r: Correlation coefficient.

3. Results and discussion

3.1. Growth inhibitory activity of compounds 4a–l and 7a–f against human cancer cell lines

The newly synthesized target compounds (**4a**–**l** and **7a**–**f**) were assayed for growth inhibitory activity against Detroit 551 normal human cells and three human cancer cell lines, HL-60 leukemia, Hep 3B hepatoma and H460 non-small-cell-lung cancer cell lines. The results are summarized in Table 1. Compound **4a** exhibited significant activity against HL-60, Hep 3B and H460 cancer cell lines, while showing 50–100-fold lower cytotoxicity toward Detroit 551 normal human cells. Isosteric replacement of the 2-selenophenyl group of compound **4a** with a 2-thienyl group (**4b**) led to slightly reduced inhibitory activity, but replacement with a 2-furyl group (**4c**) produced dramatically reduced inhibitory activity against cancer cells. On the other hand, compound **4d**, which contains a methyl group at the 5-position of the selenophene ring, exhibited enhanced inhibitory activity against HL-60, Hep 3B and H460 cancer cell lines, with IC_{50} values of 0.3, 0.2 and 0.4 μM, respectively. Thus, it showed greater than twice the inhibitory activity of **4a** against cancer cell lines, while still showing low cytotoxicity against Detroit 551 normal cells. As shown in Table 1, comparison of selenophenyl

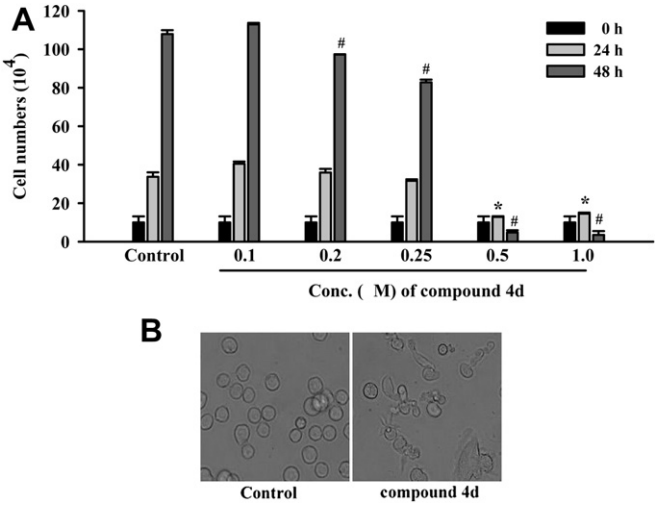
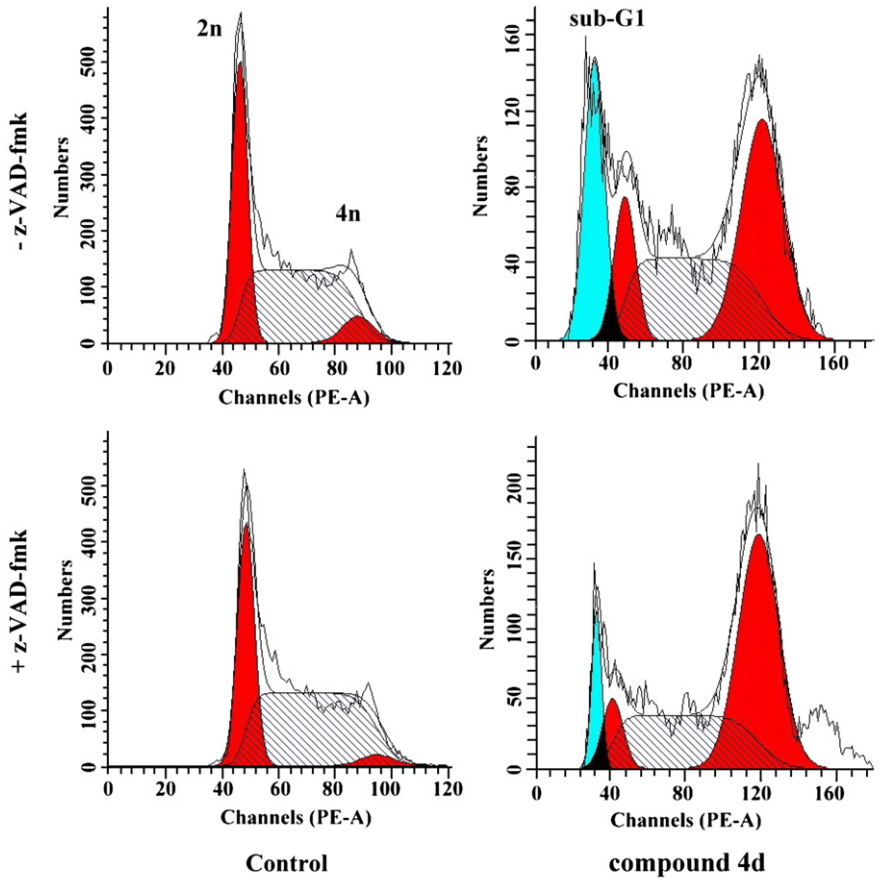


Fig. 1. Compound **4d** induced growth inhibition in HL-60 leukemia cells. (A) HL-60 cells were treated with the indicated concentrations of **4d** for 24 h and 48 h. After treatment, the cell growth rate was examined using trypan blue exclusion assay to count the cell numbers. Data are presented as mean ± SD from four independent experiments. $^*P < 0.001$ was compared with the control at 24 h. $^\#P < 0.001$ was compared with the control at 48 h. (B) Morphologic observation. HL-60 cells were exposed to **4d** (1 μM) significantly induced apoptosis in 24 h (200×).



	Cell cycle phase (%)			
	Sub-G1	G0/G1 (2n)	S	G2/M (4n)
Control	0.2 ± 0.2	36.7 ± 0.5	56.5 ± 0.6	6.8 ± 0.4
4d	21.0 ± 0.4*	14.3 ± 0.2*	41.6 ± 0.3*	44.3 ± 0.3*
z-VAD-fmk	0.3 ± 0.1	33.9 ± 0.4*	58.2 ± 0.2*	5.3 ± 0.4*
z-VAD-fmk + 4d	10.2 ± 0.2*#	8.3 ± 0.3*#	36.2 ± 0.3*#	55.5 ± 0.5*#

Fig. 2. Compound **4d** affected the cell cycle distribution in HL-60 cells. HL-60 cells were pre-treated without or with pan-caspase inhibitors (z-VAD-fmk) for 3 h, and then co-treated with **4d** (1 μM) for 24 h. After treatment, the cells were collected and the DNA content was analyzed by FACS®. All data shown are representative of three independent experiments with similar results. $^{*}P < 0.001$ was compared with the control. $^{\#}P < 0.001$ was compared with **4d** (or z-VAD-fmk) alone.

4a and **4d** with corresponding thienyl (**4b** and **4e**) and furyl (**4c** and **4f**) compounds led to the same rank order of potency: selenophenyl derivative ≥ thienyl derivative >furyl derivative.

Another target compound, 5-hydroxy-6-methoxy-2-(5-methyl-selenophen-2-yl)quinolin-4-one (**4k**), also demonstrated significant inhibitory activity against HL-60, Hep 3B and H460 cancer cell lines, although with slightly lower potency than **4d**. Replacing the 5-hydroxy group of **4k** with a 5-methoxy group (**4j**) or eliminating the 5-hydroxy group (**4l**) resulted in reduced activity against Hep 3B and H460. Interestingly, **4j** showed selective cytotoxicity against HL-60, although it was less potent than **4k** or **4l** against this cell line. The methyl group on the 2-selenophenyl ring could be removed without much effect on the anticancer activity (**4k** versus **4h**), and similar general activity trends were found with **4g**–**i** as with **4j**–**l**.

Alternatively, the replacement of the 2-(selenophen-2-yl) group of **4a** with a 2-(selenophen-3-yl) group yielded the essentially equipotent **7a**. The results among the isosteric compounds **7a**, **7b** and **7c** were consistent with those observed with **4a**–**c** and **4d**–**f**.

Finally, 5-hydroxy-6-methoxy-2-(selenophen-3-yl)quinolin-4-one (**7e**) was also found to exhibit significant cancer cell growth inhibitory activity. As with **4g**–**i** and **4j**–**l**, replacing the 5-hydroxy group of **7e** with a 5-methoxy group (**7d**) or eliminating the 5-hydroxy group (**7f**) resulted in reduced activity against Hep 3B and H460 cell lines.

The above findings can be summarized with the following three SAR conclusions.

1. The *in vitro* anticancer activity of 6,7-methylenedioxy-2-(substituted selenophenyl) quinolin-4-ones (**4a**, **4d** and **7a**) and their isosteres (**4b**, **4c**, **4e**, **4f** and **7b**, **7c**) can be ranked in the following order of decreasing activity: selenophenyl derivatives ≥ thienyl derivatives >furyl derivatives.

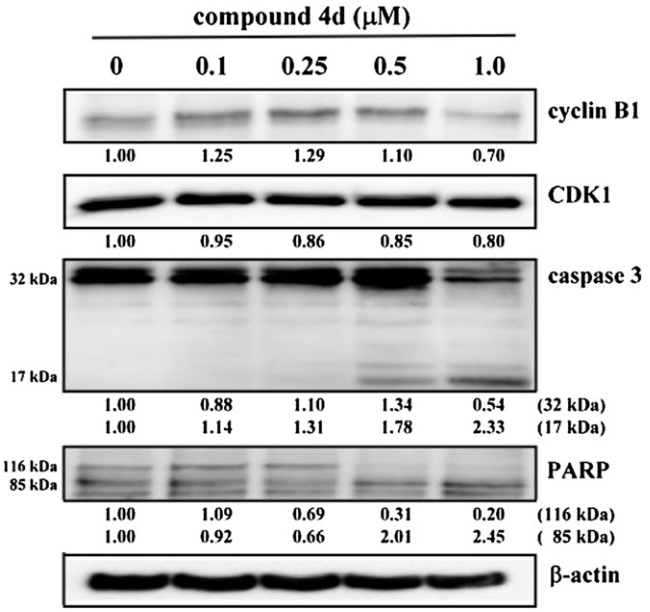


Fig. 3. Regulation of mitotic phase- and apoptosis-associated proteins expression by compound **4d**. HL-60 cells were treated with the indicated concentrations of **4d** for 24 h. After treatment, the cells were harvested and subjected to Western blot. The relative amounts of cyclin B1, CDK1, caspase-3, and PARP protein were quantified and normalized to the corresponding β-actin protein amount. The quantitative data are shown under each protein, respectively.

2. The *in vitro* anticancer activity of 5,6-substituted-2-(substituted selenophenyl) quinolin-4-ones (**4g**–**l** and **7d**–**f**) can be ranked in the following order of decreasing activity: 5-hydroxy-6-methoxy derivatives >6-methoxy derivatives >5,6-dimethoxy derivatives.
3. A 6-methoxy group is an important factor for cell line selectivity against HL-60 versus Hep 3B and H460 cancer cells.

3.2. Growth inhibitory activity of compound *4d* against human cancer cell line panel

The target compound **4d**, which demonstrated the highest anticancer potency, and had greater structural novelty, was submitted to NCI for evaluation of inhibitory activity against the NCI-60 human tumor cell lines panel. The resulting mean graph (supplementary information) indicated that **4d** exhibited significant inhibitory activity against a variety of human tumor cell lines. Compound **4d** had a mean graph midpoint(MID) value of log GI_{50} was −6.32, and its greatest activity was found against MDA-MB-435 melanoma, with a corresponding log GI_{50} value of −7.28, which is about 100-fold greater than the MID. With such highly selective and potent activity, compound **4d** could serve as a lead for further anticancer drug development.

The NCI anticancer drug screen fingerprint of **4d** was then analyzed by a pattern recognition computer program (COMPARE), which contains a database covering fingerprints from over 175 known anticancer agents with various mechanisms of action. The results of the COMPARE analysis at GI_{50} level in Table 2 suggested that the mechanism of action of compound **4d** matched best with that of the apoptotic inducer didemnin B and to a lesser extent with that of the antimitotic agent *S*-trityl-L-cysteine. However, based on the COMPARE analysis results, the mechanism of action of **4d** did not appear to have any similarity with that of other antimitotic agents, such as colchicine, vinca alkaloids and paclitaxel, or with 2-phenylquinolin-4-one derivatives **2AQ-1** and **2AQ-2** (Chart 2).

3.3. Mechanism of action of compound *4d*

In order to investigate the mechanism of action of **4d**, several studies were performed against HL-60 cell growth.

During the initial experiment, we used the trypan blue exclusion assay to examine the growth inhibitory effect of **4d**. As shown in Fig. 1A, **4d** inhibited cell growth in a concentration- and time-dependent manner. When the concentration of **4d** was higher than 0.5 μM, the treated cells always displayed the typical morphological features of apoptotic cells, with cell shrinkage and formation of apoptotic bodies (Fig. 1B).

Next, to assess whether the cell growth inhibition induced by **4d** was mediated via alterations in cell cycle regulation, we evaluated the effect of **4d** on the cell cycle distribution. As shown in Fig. 2, the DNA cell cycle analysis revealed typical G2/M arrest and apoptosis (a sub-G1 peak appeared) in response to the treatment with **4d**.

Cyclin B and CDK1 are intricately involved in the cell cycle progression through the G2/M phase transition [21]. As shown in Fig. 3, **4d** induced a transient increase followed by a decrease in the cyclin B1 protein expression, whereas the CDK1 protein expression level decreased in a concentration-dependent manner.

Apoptosis is associated with the activation of caspases, an expanding family of cysteine proteases that play important roles in the execution phase of apoptosis triggered by various stimuli [22]. Among this family, caspase-3 is a widely expressed protease and mediates several apoptotic pathways. The activated caspase-3 abrogates the effects of several substrates that protect cellular integrity such as PARP, gelsolin, actin, lamins, fodrin, focal adhesion kinase (FAK) and DNA fragment factor (DFF). Thus, caspase-3 and its major substrate PARP were examined in a study to determine whether **4d** induced apoptosis through caspase-activation. As shown in Fig. 3, we found that caspase-3 was highly expressed in HL-60 cells. When the HL-60 cells were exposed to **4d**, the active form (17 kDa) of caspase-3 and the cleavage fragment (85 kDa) of PARP were clearly detected. Moreover, we treated HL-60 cells with **4d** in the presence of the pan-caspase inhibitor z-VAD-fmk to examine whether the apoptosis triggered by **4d** is directly mediated via caspase-activation. As shown in Fig. 2, z-VAD-fmk partly blocked the cell death of HL-60 cells induced by **4d** (the percentage of the sub-G1 peak decreased). The above preliminary investigation of the mechanism of action of **4d** suggested that the anticancer effect of **4d** against HL-60 cells is mediated via mitotic arrest and caspase-dependent apoptosis.

4. Conclusion

Novel 2-selenophenyl quinolin-4-ones and their isosteric compounds were designed, synthesized, and evaluated for *in vitro* anticancer activity. Preliminary SAR correlations of the new analogs of 2-arylquinolin-4-ones (2AQs) were established. The most promising target compound **4d** demonstrated highly selective and potent inhibition against MDA-MB-435 melanoma. Meanwhile, the result of a COMPARE analysis suggested that **4d** might act like an antimitotic agent. However, its action mechanism not only differs from that of conventional antimitotic agents, such as colchicine, vinca alkaloids and paclitaxel, but also from **2AQ-1** and **2AQ-2**, which have the same quinolone scaffold as **4d**. Therefore, we believe that **4d** is a promising lead compound that deserves further optimization.

5. Experimental section

5.1. Materials and physical measurements

All solvents and reagents were obtained commercially and used without further purification. The progress of all reactions was

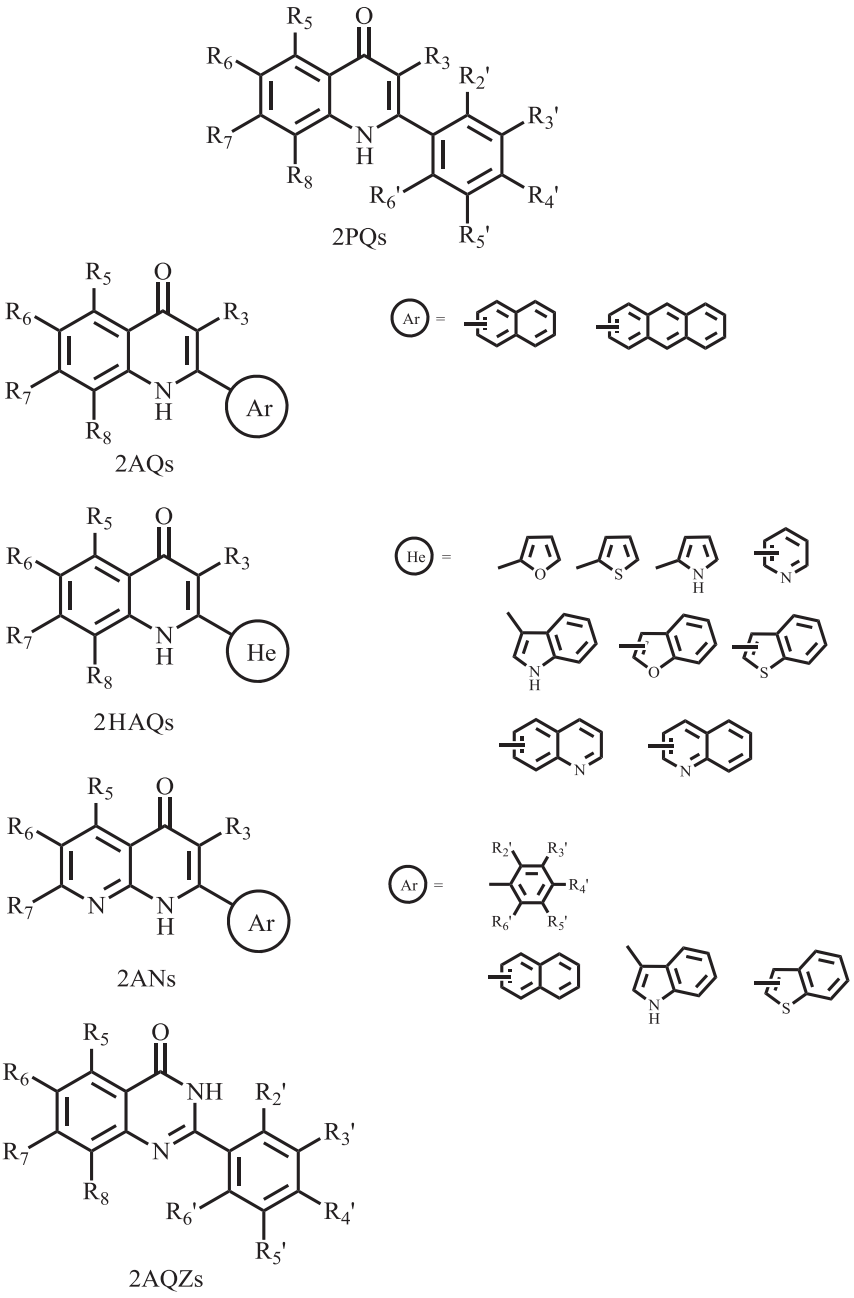


Chart 1. Structure of 2PQs derivatives.

monitored by TLC on 2 × 6 cm pre-coated silica gel 60 F_{254} plates of thickness 0.25 mm (Merck). The chromatograms were visualized under UV 254–366 nm. The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.040–0.063 mm). Melting points (mp) were determined with a Yanaco MP-500D melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu IR-Prestige-21 spectrophotometers as KBr pellets. ^{1}H NMR spectra were recorded on a Bruker Avance DPX-400 FT-NMR spectrometer at room temperature, and chemical shifts are reported in ppm (δ). The following abbreviations are used: s, singlet; d, doublet; t, triplet; dd, double doublet; and m, multiplet. ^{13}C NMR spectra were recorded on a Bruker Avance DPX-200 FT-NMR spectrometer at room temperature, and chemical shifts are reported in ppm (δ). Low-resolution mass spectra and high-resolution mass spectra were performed by Finnigan/Thermo Qust MAT95XL at National Chung Hsing University, Taichung, Taiwan.

5.2. Chemistry

5.2.1. General procedure for the synthesis of acid chlorides (*2a–f*, *5a–c*)

Heterocyclic carbolic acids [23–25] (1 equiv) were suspended in dry toluene (150 mL) at room temperature. Thionyl chloride (5 equiv) was added dropwise. The reaction mixtures were stirred for 5 min at room temperature and then DMF (3–5 drops) was added. The mixtures were stirred for 16 h and then evaporated to dryness. The residues were used directly in the next step.

5.2.2. General procedure for the synthesis of carboxamides (*3a–j* and *6a–e*) [7]

Into separate solutions of acid chlorides (**2a–f**, **5a–c**) in 150 mL dry toluene at room temperature were added 2,3,4-substituted-6-amino acetophenones (**1a–c**) [14,26,27] (1.1 equiv). The reaction

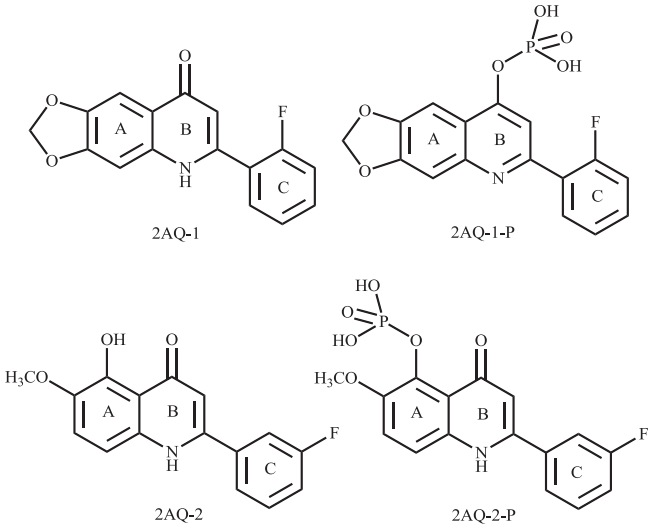


Chart 2. Structure of 2AQs derivatives.

mixtures were stirred and then triethylamine (3 mL) was added dropwise. The mixtures were stirred at room temperature for 48 h and then evaporated. The residues were isolated by chromatography, and then recrystallization gave the pure carboxamides.

*5.2.2.1. N-(6-Acetylbenzo[d][1,3]dioxol-5-yl)selenophene-2-carboxamide (**3a**).* Yield: 57.7%; yellow solid; mp: 205–206 °C; IR (KBr) ν (cm^{-1}): 3429 (N–H), 1654 (C=O, acetyl), 1639 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.63 (s, 3H), 6.17 (s, 2H), 7.52 (t, J = 4.70 Hz, 1H), 7.66 (s, 1H), 7.98 (d, J = 3.52 Hz, 1H), 8.22 (s, 1H), 8.57 (d, J = 5.48 Hz, 1H), 12.88 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 28.64, 101.36, 102.16, 109.75, 115.17, 130.57, 130.66, 137.32, 139.58, 142.59, 147.04, 153.10, 161.94, 200.95; MS (EI, 70 eV) m/z: 337.0 (M^+).

*5.2.2.2. N-(6-Acetylbenzo[d][1,3]dioxol-5-yl)thiophene-2-carboxamide (**3b**).* Yield: 89.9%; yellow solid; mp: 217 °C begin to vaporize; IR (KBr) ν (cm^{-1}): 1664 (C=O, acetyl), 1637 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.63 (s, 3H), 6.18 (s, 2H), 7.28 (dd, J = 4.11 Hz, 1H), 7.66 (s, 1H), 7.78 (d, J = 3.52 Hz, 1H), 7.94 (d, J = 4.70 Hz, 1H), 8.21 (s, 1H), 12.89 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 28.62, 101.42, 102.16, 109.73, 115.15, 127.94, 128.77, 131.27,139.53, 140.33, 142.60, 153.10, 160.74, 200.95; MS (EI, 70 eV) m/z: 289.3(M^+).

*5.2.2.3. N-(6-Acetylbenzo[d][1,3]dioxol-5-yl)furan-2-carboxamide (**3c**).* Yield: 81.1%; yellow solid; mp: 208–209 °C; IR (KBr) ν (cm^{-1}): 1660 (C=O, acetyl), 1645 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.62 (s, 3H), 6.17 (s, 2H), 6.75 (br. s, 1H), 7.28 (d, J = 3.52 Hz, 1H), 7.66 (s, 1H), 8.01 (s, 1H), 8.30 (s, 1H), 12.92 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 28.57, 101.63, 102.16, 109.73, 112.27, 115.32, 115.56, 138.90, 142.69, 144.98, 148.21, 152.88, 157.03, 200.63; MS (EI, 70 eV) m/z: 273.3 (M^+).

*5.2.2.4. N-(6-Acetylbenzo[d][1,3]dioxol-5-yl)-5-methylselenophene-2-carboxamide (**3d**).* Yield: 83.6%; yellow solid; mp: 207–208 °C;

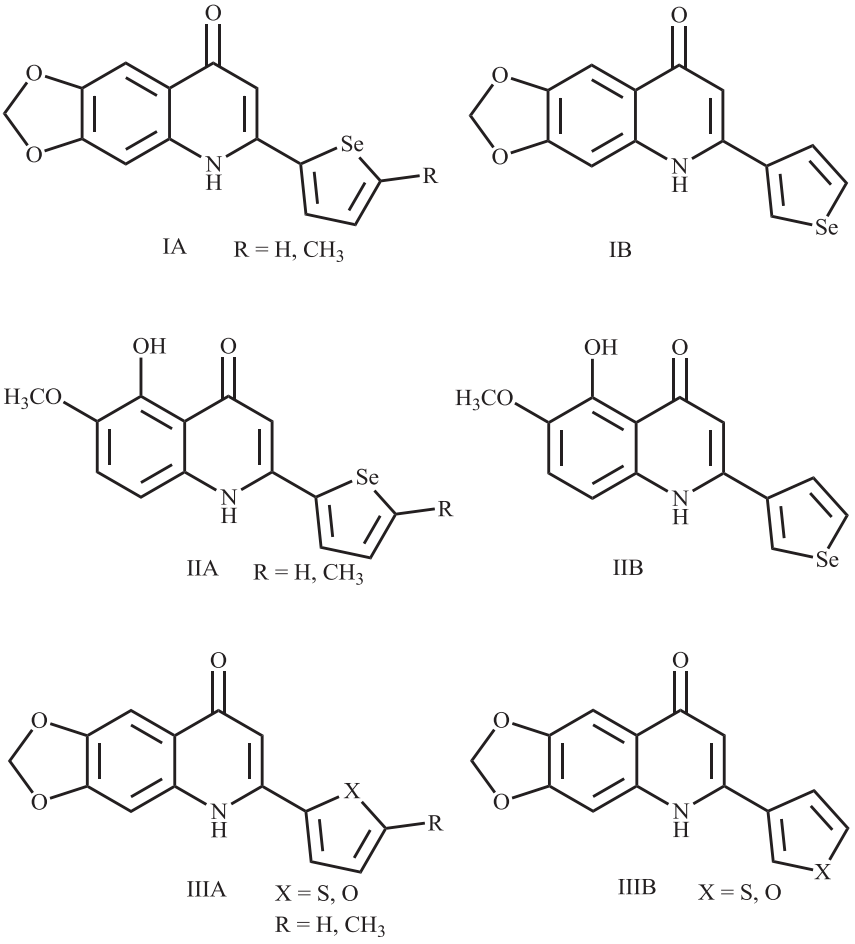


Chart 3. Structure of target compounds.

IR (KBr) ν (cm^{-1}): 1658 (C=O, acetyl), 1637 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.59 (s, 3H), 2.62 (s, 3H), 6.17 (s, 2H), 7.15 (d, J = 4.00 Hz, 1H), 7.65 (s, 1H), 7.77 (d, J = 3.52 Hz, 1H), 8.21 (s, 1H), 12.82 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 18.65, 28.61, 101.25, 102.12, 109.69, 115.02, 129.04, 131.12, 139.78, 142.43, 144.10, 153.08, 154.31, 161.99, 200.86; MS (EI, 70 eV) m/z: 337.0 (M^+).

*5.2.2.5. N-(6-Acetylbenzo[d][1,3]dioxol-5-yl)-5-methylthiophene-2-carboxamide (**3e**).* Yield: 85.6%; yellow solid; mp: 210–211 °C; IR (KBr) ν (cm^{-1}): 1664 (C=O, acetyl), 1639 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.53 (s., 3H), 2.63 (s, 3H), 6.17 (s, 2H), 6.99 (d, J = 3.52 Hz, 1H), 7.60 (d, J = 3.91 Hz, 1H), 7.65 (s, 1H), 8.22 (s, 1H), 12.83 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 15.78, 28.58, 101.32, 102.11, 109.67, 115.01, 126.46, 129.36, 137.44, 139.74, 142.43, 146.77, 153.06, 160.77, 200.86; MS (EI, 70 eV) m/z: 303.4 (M^+).

*5.2.2.6. N-(6-Acetylbenzo[d][1,3]dioxol-5-yl)-5-methylfuran-2-carboxamide (**3f**).* Yield: 49.8%; white solid; mp: 154–156 °C; IR (KBr) ν (cm^{-1}): 3468(N–H), 1672 (C=O, acetyl), 1637 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.41 (s, 3H), 2.62 (s, 3H), 6.16 (s, 2H), 6.38 (d, J = 3.13 Hz, 1H), 7.16 (d, J = 3.52 Hz, 1H), 7.65 (s, 1H), 8.30 (s, 1H),12.84 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 13.98, 28.54, 101.61, 102.09, 108.76, 109.67, 115.46, 116.60, 139.14, 142.51, 146.55, 152.82, 155.76, 157.19, 200.43; MS (EI, 70 eV) m/z: 287.4 (M^+).

*5.2.2.7. N-(2-Acetyl-3,4-dimethoxyphenyl)selenophene-2-carboxamide (**3g**).* Yield: 61.2%; brown needle crystal; mp: 109–110 °C; IR (KBr) ν (cm^{-1}): 3439 (N–H), 3307 (OCH_3), 1685 (C=O, acetyl), 1643 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.46 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 7.08–7.19 (m, 2H), 7.44 (dd, J = 5.28, 4.11 Hz, 1H), 8.06 (d, J = 3.52 Hz, 1H), 8.46 (d, J = 5.09 Hz, 1H), 10.13 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 33.21, 56.28, 61.54, 117.08, 117.36, 122.21, 130.04, 130.45, 131.04, 136.99, 146.85, 148.74, 149.62, 161.30, 204.68; MS (EI, 70 eV) m/z: 353.1 (M^+).

*5.2.2.8. N-(2-Acetyl-4-methoxyphenyl)selenophene-2-carboxamide (**3h**).* Yield: 78.4%; yellow solid; mp: 143–144 °C; IR (KBr) ν (cm^{-1}): 3466 (N–H), 1653 (C=O, acetyl), 1637 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.64 (s, 3H), 3.82 (s, 3H), 7.25 (dd, J = 9.00, 2.74 Hz, 1H), 7.43–7.53 (m, 2H), 7.97 (d, J = 3.52 Hz, 1H), 8.25 (d, J = 9.00 Hz, 1H), 8.51 (d, J = 5.48 Hz, 1H), 11.71 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm): 29.30, 56.03, 116.41, 120.24, 123.18, 126.72, 131.10, 131.22, 132.37, 139.11, 146.76, 155.27, 161.26, 203.23; MS (EI, 70 eV) m/z:323.0 (M^+).

*5.2.2.9. N-(2-Acetyl-3,4-dimethoxyphenyl)-5-methylselenophene-2-carboxamide (**3i**).* Yield: 43.8%; yellow needle crystal; mp: 116–117 °C; IR (KBr) ν (cm^{-1}): 3350 (N–H), 1666 (C=O, acetyl), 1649 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.43 (s, 3H), 2.54 (s, 3H), 3.78 (s, 3H), 3.84 (s, 3H), 7.02–7.17 (m, 3H), 7.83 (d, J = 3.91 Hz, 1H), 9.99 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 18.63, 33.19, 56.29, 61.53, 117.10, 117.32, 122.17, 128.88, 130.47, 131.20, 143.90, 148.59, 149.56, 153.89, 161.37, 204.65; MS (EI, 70 eV) m/z: 367.1 (M^+).

*5.2.2.10. N-(2-Acetyl-4-methoxyphenyl)-5-methylselenophene-2-carboxamide (**3j**).* Yield: 84.8%; yellow solid; mp: 160–161 °C; IR (KBr) ν (cm^{-1}): 3458 (N–H), 1660 (C=O, acetyl), 1635 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.58 (s, 3H), 2.66 (s, 3H), 3.84 (s, 3H), 7.14 (d, J = 3.13 Hz, 1H), 7.27 (dd, J = 9.00, 2.74 Hz, 1H), 7.50 (d, J = 2.74 Hz, 1H), 7.79 (d, J = 3.91 Hz, 1H), 8.29 (d, J = 9.00 Hz, 1H), 11.70 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm): 18.70, 29.30, 56.03, 116.47, 120.36, 122.39, 126.25, 129.87, 131.21, 132.67, 143.99, 154.30, 155.09, 161.13, 203.30; MS (EI, 70 eV) m/z: 337.0 (M^+).

*5.2.2.11. N-(6-Acetylbenzo[d][1,3]dioxol-5-yl)selenophene-3-carboxamide (**6a**).* Yield: 63.0%; white solid; mp: 192–193 °C; IR (KBr) ν (cm^{-1}): 1664 (C=O, acetyl), 1635 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.63 (s, 3H), 6.17 (s, 2H), 7.66 (s, 1H), 7.81 (d, J = 5.09 Hz, 1H), 8.30 (s, 1H), 8.33 (dd, J = 5.28, 2.15 Hz, 1H), 8.96 (s, 1H), 12.74 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 28.65, 101.44, 102.13, 109.74, 115.22, 128.99, 131.39, 135.72, 139.77, 140.77, 142.51, 153.09, 162.11, 200.89; MS (EI, 70 eV) m/z: 337.3 (M^+).

*5.2.2.12. N-(6-Acetylbenzo[d][1,3]dioxol-5-yl)thiophene-3-carboxamide (**6b**).* Yield: 80.8%; white solid; mp: 202–203 °C; IR (KBr) ν (cm^{-1}): 1668 (C=O, acetyl), 1637 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.63 (s, 3H), 6.17 (s, 2H), 7.55 (d, J = 4.69 Hz, 1H), 7.66 (s, 1H), 7.75 (dd, J = 5.09, 2.74 Hz, 1H), 8.27 (d, J = 1.96 Hz, 1H), 8.29 (s, 1H), 12.74 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm): 29.33, 100.70, 102.90, 111.18, 116.20, 126.30, 128.69, 130.73, 138.07, 138.49, 142.96, 152.68, 161.15, 202.13; MS (EI, 70 eV) m/z: 289.0 (M^+).

*5.2.2.13. N-(6-Acetylbenzo[d][1,3]dioxol-5-yl)furan-3-carboxamide (**6c**).* Yield: 13.2%; yellow solid; mp: 171–172 °C; IR (KBr) ν (cm^{-1}): 3462 (N–H), 1670 (C=O, acetyl), 1639 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.61 (s, 3H), 6.16 (s, 2H), 6.86 (s, 1H), 7.64 (s, 1H), 7.87 (s, 1H), 8.22 (s, 1H), 8.35 (s, 1H), 12.52 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm): 29.28, 100.74, 102.89, 108.53, 111.09, 116.16, 123.67, 138.26, 142.98, 145.56, 146.59, 152.62, 160.86, 202.03; MS (EI, 70 eV) m/z: 273.1 (M^+).

*5.2.2.14. N-(2-Acetyl-3,4-dimethoxyphenyl)selenophene-3-carboxamide (**6d**).* Yield: 75.0%; brown cubi crystal; mp: 141–143 °C; IR (KBr) ν (cm^{-1}): 3325 (OCH_3), 1685 (C=O, acetyl), 1656 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.47 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 7.07–7.20 (m, 2H), 7.77 (d, J = 5.48 Hz, 1H), 8.22 (dd, J = 5.48, 2.35 Hz, 1H), 8.92 (s, 1H), 9.96 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 33.18, 56.29, 61.54, 117.03, 117.50, 122.44, 128.81, 131.11, 131.47, 135.06, 140.60, 148.70, 149.53, 161.58, 204.67; MS (EI, 70 eV) m/z: 353.1 (M^+).

*5.2.2.15. N-(2-Acetyl-4-methoxyphenyl)selenophene-3-carboxamide (**6e**).* Yield: 52.1%; yellow solid; mp: 96–97 °C; IR (KBr) ν (cm^{-1}): 3439 (N–H), 1672 (C=O, acetyl), 1645 (C=O, amide); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.67 (s, 3H), 3.84 (s, 3H), 7.28 (dd, J = 9.00, 2.74 Hz, 1H), 7.51 (d, J = 2.74 Hz, 1H), 7.81 (dd, J = 5.48, 1.17 Hz, 1H), 8.31 (dd, J = 5.48, 2.35 Hz, 1H), 8.35 (d, J = 9.00 Hz, 1H), 8.95 (s, 1H), 11.63 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 28.62, 55.73, 116.93, 120.40, 122.15, 122.81, 128.94, 131.36, 134.92, 135.27, 140.91, 154.27, 161.83, 202.90; MS (EI, 70 eV) m/z: 323.3 (M^+).

5.2.3. General procedure for the synthesis of quinolin-4-ones (**4a**–**g**, **4i**–**j**, **4l**, **7a**–**d** and **7f**) [7]

Compound **3a**–**j** or **6a**–**e** (1 equiv) was added into 100 mL 1,4-dioxane at room temperature, and then NaOH powder (5 equiv) was added. The reaction mixtures were stirred for 16 h under reflux. The mixtures were evaporated, added into 10% NH_4Cl aq solution (100 mL), and stirred for 30 min. The residues were washed with water to neutral pH, and then, recrystallization gave the pure compound.

*5.2.3.1. 6,7-Methylenedioxy-2-(selenophen-2-yl)quinolin-4-one (**4a**).* Yield: 58.6%; yellow solid; mp: >350 °C; IR (KBr) ν (cm^{-1}): 3396 (N–H), 1637 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.17 (s, 2H), 7.19 (s, 2H), 7.36 (s, 1H), 7.44 (br. s, 1H), 7.84 (br. s, 1H), 8.23 (br. s,

1H), 11.45 (br. s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6 + HCl) δ (ppm): 97.53, 98.80, 103.16, 103.92, 115.51, 131.76, 134.52, 138.46, 138.54, 140.53, 147.43, 148.55, 154.32, 167.00; MS (EI, 70 eV) m/z: 319.0 (M^+); HRMS (EI) m/z: calc. for $C_{14}H_9NO_3Se$: 318.9748; found: 318.9740.

*5.2.3.2. 6,7-Methylenedioxy-2-(thiophen-2-yl)quinolin-4-one (**4b**).* Yield: 88.0%; white solid; mp: >300 °C; IR (KBr) ν (cm^{-1}): 3446 (N–H), 1639 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.16 (s, 2H), 6.66 (br. s, 1H), 7.20 (s, 1H), 7.23 (br. s, 1H), 7.37 (s, 1H), 7.74 (br. s, 2H), 11.47 (br. s, 1H); MS (EI, 70 eV) m/z: 271.3 (M^+); HRMS (EI) m/z: calc. for $C_{14}H_9NO_3S$: 271.0303; found: 271.0301.

*5.2.3.3. 2-(Furan-2-yl)-6,7-methylenedioxyquinolin-4-one (**4c**).* Yield: 80.2%; white solid; mp: >300 °C; IR (KBr) ν (cm^{-1}): 3398 (N–H), 1645 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.15 (s, 2H), 6.42 (br. s, 1H), 6.75 (br. s, 1H), 7.23 (s, 1H), 7.33 (br. s, 1H), 7.37 (s, 1H), 7.97 (br. s, 1H), 11.55 (br. s, 1H); MS (EI, 70 eV) m/z: 255.3 (M^+); HRMS (EI) m/z: calc. for $C_{14}H_9NO_4$: 255.0532; found: 255.0535.

*5.2.3.4. 2-(5-Methylselenophen-2-yl)-6,7-methylenedioxyquinolin-4-one (**4d**).* Yield: 84.5%; white solid; mp: 310 °C begin to vaporize; IR (KBr) ν (cm^{-1}): 3334(N–H), 1645 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.57 (s, 3H), 6.15 (s, 2H), 6.60 (br. s, 1H), 7.07 (br. s, 1H), 7.16 (s, 1H), 7.35 (s, 1H), 7.67 (br. s, 1H), 11.37 (br. s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6 + HCl) δ (ppm): 18.56, 97.88, 98.95, 102.97, 103.99, 115.60, 130.85, 135.14, 136.24, 138.86, 147.44, 148.49, 154.20, 155.94, 167.30; MS (EI, 70 eV) m/z: 333.0 (M^+); HRMS (EI) m/z: calc. for $C_{15}H_{11}NO_3Se$: 332.9904; found: 332.9912.

*5.2.3.5. 2-(5-Methylthiophen-2-yl)-6,7-methylenedioxyquinolin-4-one (**4e**).* Yield: 74.7%; yellow solid; mp: 292 °C begin to vaporize; IR (KBr) ν (cm^{-1}): 3427(N–H), 1637 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.15 (s, 2H), 6.44 (br. s, 1H), 6.93 (br. s, 1H), 7.17 (s, 1H), 7.35 (s, 1H), 7.56 (br. s, 1H), 11.40 (br. s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6 + HCl) δ (ppm): 15.70, 97.82, 99.03, 101.74, 103.98, 115.62, 128.73, 130.93, 132.78, 138.91, 145.65, 148.00, 148.54, 154.29, 167.37; MS (EI, 70 eV) m/z: 285.3 (M^+); HRMS (EI) m/z: calc. for $C_{15}H_{11}NO_3S$: 285.0460; found: 285.0464.

*5.2.3.6. 2-(5-Methylfuran-2-yl)-6,7-methylenedioxyquinolin-4-one (**4f**).* Yield: 97.4%; yellow solid; mp: >300 °C; IR (KBr) ν (cm^{-1}): 3327(N–H), 1643 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.42 (s, 3H), 6.14 (s, 2H), 6.32 (br. s, 1H), 6.37 (br. s, 1H), 7.22 (s, 2H), 7.36 (s, 1H), 11.42 (br. s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm): 13.98, 97.54, 101.78, 102.34, 102.78, 107.12, 109.50, 112.77, 137.38, 139.02, 145.46, 145.58, 151.52, 155.15, 175.75; MS (EI, 70 eV) m/z: 269.3 (M^+); HRMS (EI) m/z: calc. for $C_{15}H_{11}NO_4$: 269.0688; found: 269.0695.

*5.2.3.7. 5,6-Dimethoxy-2-(selenophen-2-yl)quinolin-4-one (**4g**).* Yield: 86.5%; yellow needle crystal; mp: 76–78 °C; IR (KBr) ν (cm^{-1}): 3404 (N–H), 1625 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.86 (br. s, 3H), 3.91 (s, 3H), 6.94 (br. s, 1H), 7.40–7.48 (m, 1H), 7.53–7.66 (m, 2H) 7.95 (d, J = 3.91 Hz, 1H), 8.31 (d, J = 5.09 Hz, 1H), 10.94 (br. s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6 + HCl) δ (ppm): 57.20, 62.01, 104.30, 115.24, 116.73, 122.43, 131.91, 135.35, 135.54, 138.27,141.53, 143.99, 148.32, 151.01, 169.31; MS (EI, 70 eV) m/z: 335.1 (M^+); HRMS (EI) m/z: calc. for $C_{15}H_{13}NO_3Se$: 335.0061; found: 335.0059.

*5.2.3.8. 6-Methoxy-2-(selenophen-2-yl)quinolin-4-one (**4i**).* Yield: 93.8%; white solid; mp: 298–299 °C; IR (KBr) ν (cm^{-1}): 3466 (N–H), 1618 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.86 (s, 3H), 6.42 (br. s, 1H), 7.32 (dd, J = 9.00, 2.74 Hz, 1H), 7.46 (br. s, 2H), 7.73 (d, J = 9.00 Hz, 1H), 7.95 (br. s, 1H), 8.36 (br. s, 1H), 11.55 (br. s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6 + HCl) δ (ppm): 56.34, 101.74, 104.03, 120.91, 122.29, 126.52, 131.92, 135.35 (2C), 138.91, 141.12, 148.10, 158.31, 167.84; MS (EI, 70 eV) m/z: 305.0 (M^+); HRMS (EI) m/z: calc. for $C_{14}H_{11}NO_2Se$: 304.9955; found: 304.9959.

*5.2.3.9. 5,6-Dimethoxy-2-(5-methylselenophen-2-yl)quinolin-4-one (**4j**).* Yield: 90.1%; yellow cubic crystal; mp: 83–85 °C; IR (KBr) ν (cm^{-1}): 3373 (N–H), 1625 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.57 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 6.63 (br. s, 1H), 7.07 (br. s, 1H), 7.56 (s, 2H), 7.74 (d, J = 3.52 Hz, 1H), 10.85 (br. s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6 + HCl) δ (ppm): 18.58, 57.15, 61.96, 103.76, 115.06, 116.58, 122.20, 130.94, 135.27, 135.49, 135.83, 143.99, 148.06, 150.89, 157.23, 169.04; MS (EI, 70 eV) m/z: 349.1 (M^+); HRMS (EI) m/z: calc. for $C_{16}H_{15}NO_3Se$: 349.0217; found: 349.0214.

*5.2.3.10. 6-Methoxy-2-(5-methylselenophen-2-yl)quinolin-4-one (**4l**).* Yield: 92.7%: yellow solid; mp: 270 °C begin to vaporize; IR (KBr) ν (cm^{-1}): 3417 (N–H), 1631 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.59 (s, 3H), 3.86 (s, 3H), 6.21 (br. s, 1H), 7.10 (br. s, 1H), 7.31 (dd, J = 9.19, 2.93 Hz, 1H), 7.45 (br. s, 1H), 7.71 (d, J = 9.00 Hz, 1H), 7.74–7.82 (m, 1H), 11.47 (br. s, 1 H); ^{13}C NMR (50 MHz, DMSO-d_6 + HCl) δ (ppm): 18.56, 56.23, 101.61, 103.29, 120.52, 121.93, 126.22, 130.88, 134.97, 135.49, 135.87, 147.81, 156.85, 158.07, 167.33; MS (EI, 70 eV) m/z: 319.1 (M^+); HRMS (EI) m/z: calc. for $C_{15}H_{13}NO_2Se$: 319.0112; found: 319.0100.

*5.2.3.11. 6,7-Methylenedioxy-2-(selenophen-3-yl)quinolin-4-one (**7a**).* Yield: 59.9%, brown solid; mp: >300 °C; IR (KBr) ν (cm^{-1}): 3398 (N–H), 1635 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.15 (s, 2H), 6.34 (s, 1H), 7.19 (s, 1H), 7.38 (s, 1H), 7.87 (d, J = 5.48 Hz, 1H), 8.37 (d, J = 3.52 Hz, 1H), 8.84 (br. s, 1H), 11.38 (br. s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6 + HCl) δ (ppm): 97.85, 98.90, 102.89, 103.96, 115.74, 128.91, 134.94, 135.07, 138.22, 138.85, 147.86, 148.67, 154.27, 167.59; MS (EI, 70 eV) m/z: 319.3 (M^+); HRMS (EI) m/z: calc. for $C_{14}H_9NO_3Se$: 318.9748; found: 318.9743.

*5.2.3.12. 6,7-Methylenedioxy-2-(thiophen-3-yl)quinolin-4-one (**7b**).* Yield: 98.3%; white solid; mp: >350 °C; IR (KBr) ν (cm^{-1}): 1637 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.15 (s, 2H), 6.44 (br. s, 1H), 7.19 (s, 1H), 7.38 (s, 1H), 7.67 (d, J = 4.70 Hz, 1H), 7.75 (br. s, 1H), 8.22 (br. s, 1H), 11.41 (br. s, 1 H); ^{13}C NMR (50 MHz, DMSO-d_6 + HCl) δ (ppm): 98.04, 99.01, 102.90, 104.02, 115.99, 127.14, 129.25, 130.97, 133.02, 139.12, 146.90, 148.75, 154.27, 167.86; MS (EI, 70 eV) m/z: 271.1 (M^+); HRMS (EI) m/z: calc. for $C_{14}H_9NO_3S$: 271.0303; found: 271.0310.

*5.2.3.13. 2-(Furan-3-yl)-6,7-methylenedioxyquinolin-4-one (**7c**).* Yield: 91.3%; white solid; mp: 329–330 °C; IR (KBr) ν (cm^{-1}): 1647 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.15 (s, 2H), 6.35 (br. s, 1H), 7.10 (br. s, 1H), 7.12 (br. s, 1H), 7.38 (s, 1H), 7.87 (br. s, 1H), 8.42 (br. s, 1H), 11.29 (br. s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm): 97.26, 101.80, 102.36, 105.77, 109.07, 120.88, 121.34, 137.58, 141.62, 142.73, 145.32, 145.47, 151.52, 176.12; MS (EI, 70 eV) m/z: 255.1 (M^+); HRMS (EI) m/z: calc. for $C_{14}H_9NO_4$: 255.0532; found: 255.0540.

*5.2.3.14. 5,6-Dimethoxy-2-(selenophen-3-yl)quinolin-4-one (**7d**).* Yield: 75.8%; brown cubic crystal; mp: 173 °C begin to vaporize; IR (KBr) ν (cm^{-1}): 3408 (N–H), 1631 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.76 (s, 3H), 3.85 (s, 3H), 6.31 (br. s, 1H), 7.40–7.61 (m, 2H), 7.90 (d, J = 5.09 Hz, 1H), 8.34 (dd, J = 5.28, 2.15 Hz, 1H), 8.87 (s, 1H), 11.13 (br. s, 1 H); ^{13}C NMR (50 MHz, DMSO-d_6 + HCl) δ (ppm): 57.24, 62.02, 103.91, 115.39, 116.88, 122.39, 129.01, 134.70, 135.19, 135.55, 139.45, 144.06, 148.50, 151.03, 169.73; MS (EI, 70 eV) m/z: 335.1 (M^+); HRMS (EI) m/z: calc. for $C_{15}H_{13}NO_3Se$: 335.0061; found: 335.0051.

*5.2.3.15. 6-Methoxy-2-(selenophen-3-yl)quinolin-4-one (**7f**).* Yield: 56.4%; brown solid; mp: 302 °C begin to vaporize; IR (KBr) ν (cm^{-1}): 3444 (N–H), 1614 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.85 (s, 3H), 6.43 (br. s, 1H), 7.31 (dd, J = 9.00, 2.74 Hz, 1H), 7.49 (d, J = 2.74 Hz, 1H), 7.72 (d, J = 9.00 Hz, 1H), 7.92 (d, J = 5.48 Hz, 1H), 8.37 (dd, J = 5.28, 1.76 Hz, 1H), 8.89 (s, 1H), 11.51 (br. s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6 + HCl) δ (ppm): 56.40, 101.83, 103.74, 121.09, 122.53, 126.33, 129.20, 135.16, 135.29, 135.58, 139.07, 148.42, 158.44, 168.28; MS (EI, 70 eV) m/z: 305.3 (M^+); HRMS (EI) m/z: calc. for $C_{14}H_{11}NO_2Se$: 304.9955; found: 304.9954.

*5.2.4. General procedure for the synthesis of 5-hydroxyquinolin-4-ones (**4h**, **4k** and **7e**) [14]*

Compound **4g**, **4j**, or **7d** (1 equiv) was added into 100 mL dichloromethane(DCM) at 0 °C. Then BCl_3 (5 equiv) was added slowly dropwise. The solution was then warmed to room temperature and stirred 2 h. The residue was evaporated and purified by recrystallization.

*5.2.4.1. 5-Hydroxy-6-methoxy-2-(selenophen-2-yl)quinolin-4-one (**4h**).* Yield: 25.6%; yellow lamellar crystal; mp: 277–278 °C; IR (KBr) ν (cm^{-1}): 3454 (N–H), 1591 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.82 (s, 3H), 6.26 (s, 1H), 7.14 (d, J = 9.00 Hz, 1H), 7.42 (d, J = 9.00 Hz, 1H), 7.48–7.55 (m, 1H), 8.08 (d, J = 3.52 Hz, 1H), 8.50 (d, J = 5.09 Hz, 1H), 11.90 (br. s, 1H), 14.60 (br. s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm): 57.19, 104.23, 106.71, 113.20, 121.04, 131.19, 131.70, 135.32, 137.45, 141.39, 141.55, 146.96, 149.69, 182.42; MS (EI, 70 eV) m/z: 321.0 (M^+); HRMS (EI) m/z: calc. for $C_{14}H_{11}NO_3Se$: 320.9904; found: 320.9902.

*5.2.4.2. 5-Hydroxy-2-(5-methylselenophen-2-yl)-6-methoxyquinolin-4-one (**4k**).* Yield: 66.0%; yellow solid; mp: 267–269 °C; IR (KBr) ν (cm^{-1}): 3462 (N–H), 1602 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.61 (s, 3H), 3.81 (s, 3H), 6.15 (s, 1H), 7.12 (d, J = 9.00 Hz, 1H), 7.16 (d, J = 3.13 Hz, 1H), 7.41 (d, J = 9.00 Hz, 1H), 7.90 (d, J = 3.91 Hz, 1H), 11.80 (br. s, 1H), 14.58 (br. s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm): 18.42, 57.19, 103.75, 106.60, 113.10, 120.97, 129.94, 131.67, 135.28, 138.72, 141.50, 146.89, 149.71, 152.50, 182.31; MS (EI, 70 eV) m/z: 335.0 (M^+); HRMS (EI) m/z: calc. for $C_{15}H_{13}NO_3Se$: 335.0061; found: 335.0059.

*5.2.4.3. 5-Hydroxy-6-methoxy-2-(selenophen-3-yl)quinolin-4-one (**7e**).* Yield: 75.8%; brown cubic crystal; mp: 293–294 °C; IR (KBr) ν (cm^{-1}): 3460 (N–H), 1600 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.81 (s, 3H), 6.41 (s, 1H), 7.14 (d, J = 9.00 Hz, 1H), 7.41 (d, J = 9.00 Hz, 1H), 7.94 (d, J = 5.48 Hz, 1H), 8.39 (dd, J = 5.48, 1.96 Hz, 1H), 8.99 (s, 1H), 11.84 (br. s, 1H), 14.73 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm): 57.25, 103.84, 106.63, 113.25, 121.03, 129.12, 134.10, 134.38, 135.50, 137.22, 141.37, 147.37, 149.79, 182.78; MS (EI, 70 eV) m/z: 321.0 (M^+); HRMS (EI) m/z: calc. for $C_{14}H_{11}NO_3Se$: 320.9904; found: 320.9897.

*5.2.5. Synthesis of dibenzyl 2-(5-methylselenophen-2-yl)-6,7-methylenedioxyquinolin-4-yl phosphate (**9**) [13]*

Compound **4d** (50 mg, 0.15 mmol), sodium hydride (50 mg) and tetrabenzyl pyrophosphate (161.5 mg, 0.30 mmol) were mixed under N_2 at room temperature. Dry 10 mL of tetrahydrofuran (THF) was injected and stirring was continued for 20 min. The mixture was filtered and washed with EtOAc. The filtrate was evaporated and purified by column chromatographic (EtOAc:n-hexane = 1:2) to give compound **9**. Yield: 83.9%; yellow solid; mp: 150–151 °C; IR (KBr) ν (cm^{-1}): 1620 (C=C), 1585 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.56 (s, 3H), 5.29 (s, 2H), 5.31 (s, 2H), 6.23 (s, 2H), 7.03 (d, J = 2.74 Hz, 1H), 7.08 (s, 1H), 7.27 (s, 1H), 7.30–7.44 (m, 10H), 7.47 (d, J = 3.91 Hz, 1H), 7.54 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm): 18.61, 70.45, 70.56, 97.38, 102.85, 103.97, 105.23, 128.29, 128.57, 129.01, 129.13, 129.88, 135.83, 135.95, 147.99, 148.22, 148.47, 150.24, 152.06, 152.52, 153.50, 153.62; MS (ESI, MeOH) m/z: 594.1 ([M + H] $^+$).

*5.2.6. Synthesis of 6,7-methylenedioxy-2-(n-pentyl)quinolin-4-one (**11**)*

Compound **9** (50 mg) and Pd/C (50 mg) were added to 10 mL of MeOH and the mixture under H_2 at room temperature for 10 min. The mixture was filtered and washed with MeOH. The filtrate was evaporated and the residue purified by recrystallization to provide compound **11**. Yield: 64.3%; white solid; mp: 281 °C begin to vaporize; IR (KBr) ν (cm^{-1}): 1618 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.88 (t, J = 6.8 Hz, 3H), 1.26–1.36 (m, 4H), 1.63–1.67 (m, 2H), 2.55–2.68 (m, 2H), 5.83 (s, 1H), 6.12 (s, 2H), 6.96 (s, 1H), 7.74 (s, 1H), 11.35 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm): 14.32, 22.28, 28.48, 31.15, 33.48, 97.01, 101.78, 102.20, 107.36, 120.39, 137.48, 145.15, 151.25, 152.42, 176.13; MS (EI, 70 eV) m/z: 259.1 (M^+); HRMS (EI) m/z: calc. for $C_{15}H_{17}NO_3$: 259.1208; found: 259.1211.

5.3. Biological evaluation

5.3.1. Cell culture

The human leukemia HL-60 cells and non-small-cell-lung cancer H460 cells were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum (GIBCO/BRL), penicillin (100 U/mL)/streptomycin (100 g/ml)(GIBCO/BRL) and 1% L-glutamine (GIBCO/BRL) at 37 °C in a humidified atmosphere containing 5% CO_2. The human hepatoma Hep 3B and normal skin Detroit 551 cells were maintained in DMEM medium supplemented with 10% fetal bovine serum (GIBCO/BRL), penicillin (100 U/mL)/streptomycin (100 g/mL) (GIBCO/BRL) and 1% L-glutamine (GIBCO/BRL) at 37 °C in a humidified atmosphere containing 5% CO_2. Logarithmically growing cancer cells were used for all experiments.

5.3.2. Cytotoxicity evaluation

HL-60, Hep 3B, H460 and Detroit 551 cells were treated with vehicle or test compounds for 48 h. The cell growth rate was determined by MTT [3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyltetrazoliun bromide] reduction assay [28,29]. After 48 h treatment, the cell growth rate was measured by scanning with an ELISA reader with a 570 nm filter and the IC_{50} values of test compounds were calculated.

5.3.3. Cell cycle distribution analysis

Cell cycle analysis by FACS® was performed as described in the previous paper [30]. Hep 3B cells were pre-treated without or with pan-caspase inhibitor z-VAD-fmk for 3 h, and then co-treated with compound **4d** (1 μM) for another 24 h. After treatment, the cells were washed once with PBS and fixed with 70% ice-cold ethanol at −20 °C overnight. Then the cells were stained with a solution containing 1% Triton-X 100 (Sigma), 0.1 mg/ml RNase (Sigma) and 4 μg/mL propidium iodide (PI, Sigma) in the dark for 30 min. Cell cycle distribution were measured using a FACScan flow cytometer (Becton Dickinson, San Jose, CA, USA) and all histograms were analyzed by ModFit software.

5.3.4. Western blot analysis

HL-60 cells (2×10^5/mL) were treated with the indicated concentrations of **4d** for 24 h. After treatment, cells were washed once with PBS before total protein extraction buffer was added for the preparation of total cell lysate. The Western blotting was conducted according to the previous paper [29,30]. Approximately 15 μg of total cellular proteins were separated on 5–12% SDS-polyacrylamide gel, which was then electrotransferred onto

nitrocellulose membranes (Amersham Pharmacia Biotech, Piscataway, NJ, USA). The primary antibodies used in this study were ordered from Upstate Biotechnology Inc., Lake Placid, NY, USA, except for β-actin (Chemicon International, Inc., Temecula, CA, USA). Horseradish peroxidase-conjugated secondary antibodies (Jackson Immuno Research laboratories, Inc.) were used, and the detection of signal was performed with an enhanced chemiluminescence detection kit (PerkinElmer Life Sciences, Inc., Boston, MA, USA).

5.3.5. Statistical analysis

All data shown were representative of three independent experiments with similar results. Student's *t* tests were used to assess the statistical significance of the differences, with "*P*" values of less than 0.05 being considered statistically significant.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.10.017.

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