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Synthesis and antiproliferative activities of *N*-(naphthalen-2-yl)acetamide and *N*-(substituted phenyl)acetamide bearing quinolin-2(1*H*)-one and 3,4-dihydroquinolin-2(1*H*)-one derivatives

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ABSTRACT

Certain *N*-(naphthalen-2-yl)acetamide and *N*-(substituted phenyl)acetamide bearing quinolin-2(1*H*)-one and 3,4-dihydroquinolin-2(1*H*)-one derivatives have been synthesized and evaluated *in vitro* for their antiproliferative activities against a panel of human cancer cell lines including nasopharyngeal (NPC-TW01), lung carcinoma (H661), hepatoma (Hep3B), renal carcinoma (A498), and gastric cancer (MKN45). Among them, *N*-(naphthalen-2-yl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yloxy)acetamide (**18**) was the most active against NPC-TW01 with an IC_{50} value of 0.6 μM. Studies on NPC-TW01 cell cycle distribution revealed that compound **18** inhibited proliferation of NPC-TW01 by the alteration of cell division, accumulation of cells in *S* phase in a time- and concentration-dependent manners. In addition, compound **18** demonstrated very specific cytotoxicity against human nasopharyngeal carcinoma (NPC-TW01) cell lines with no detectable cytotoxicity against peripheral blood mononuclear cells (PBMCs) at a concentration of up to 50 μM.

1. Introduction

We are especially interested in the identification of new compounds which selectively active against nasopharyngeal carcinoma which is commonly seen in southern regions of China. It occurs in about 25 cases per 100,000 people in this region, 25 times higher than the rest of the world. It is also quite common in Taiwan [1,2].

Since the discovery of carteolol as an β-adrenergic blocking agent, a large number of quinolin-2(1*H*)-one (carbostyril) and 3,4-dihydroquinolin-2(1*H*)-one derivatives have been synthesized and evaluated for their biological activities [3–13]. We have also synthesized certain quinolin-2(1*H*)-one derivatives for evaluation of their antiproliferative and cardiovascular activities [14–19]. Among them, *N*-(biphenyl-4-yl)-2-(2-oxo-1,2-dihydroquinolin-7-yloxy)acetamide (**1**) was the most active against the growth of nasopharyngeal carcinoma (NPC-TW01) with an IC_{50} value of less than 10 μM [18]. On the other hand, flavonoids and isoflavonoids are polyphenolic compounds which have been found in plants and dietary components such as fruits, soy beans, vegetables, and red wine. Their extensive biological activities have attracted substantial attention [20–23]. Therefore, certain amide-containing flavone and isoflavone derivatives were synthesized in our lab for antiproliferative evaluation. Among them, *N*-(naphthalen-2-yl)-2-(4-oxo-3-phenyl-4*H*-chromen-7-yloxy)acetamide (**2**) was especially active against the growth of NPC-TW01 with an IC_{50} value of 1.37 μM [19]. In order to explore potential anticancer agents, the present report describes the preparation of certain *N*-(naphthalen-2-yl)acetamide containing quinolin-2(1*H*)-one derivatives (target compound A) (Fig. 1) whose structures can be considered as the hybrid of compounds **1** and **2**. Their 3,4-dihydro counterparts (target compound B) and certain *N*-(substituted phenyl)acetamide derivatives have also been synthesized for antiproliferative evaluation.

2. Chemistry

Preparation of *N*-(naphthalen-2-yl)acetamide containing quinolin-2(1*H*)-one and 3,4-dihydroquinolin-2(1*H*)-one derivatives is

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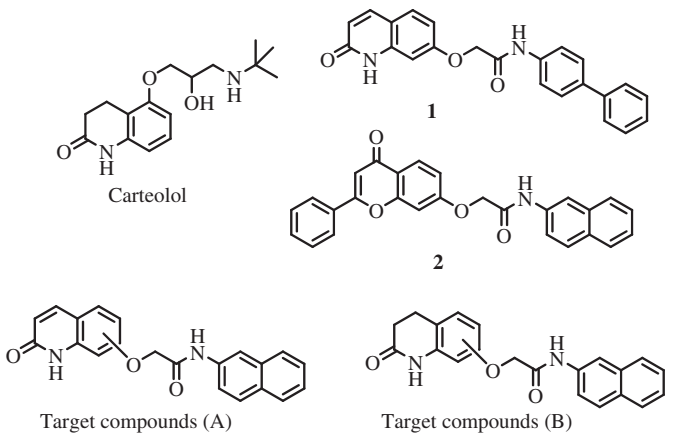
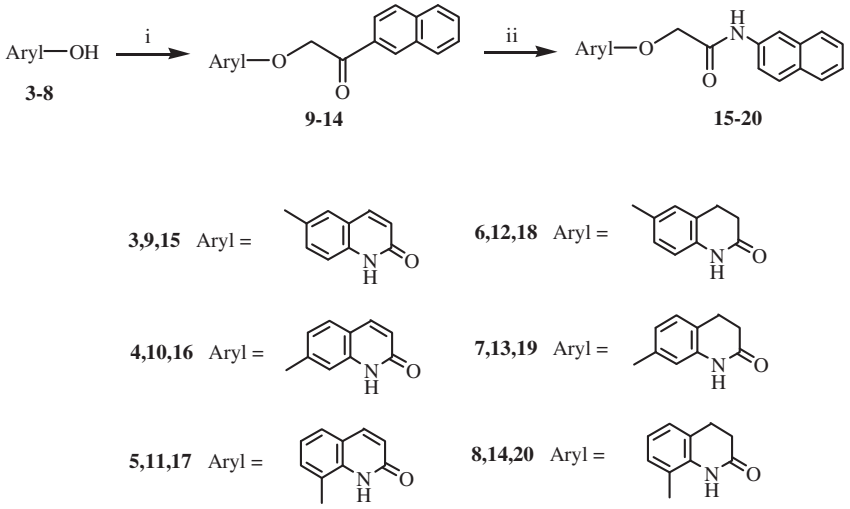
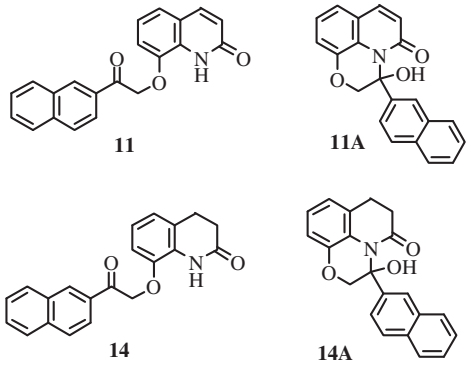


Fig. 1. Chemical structures of the target compounds.

illustrated in the Scheme 1. Alkylation of 6-hydroxyquinolin-2(1*H*)-one (**3**) with 2-bromo-1-(naphthalen-2-yl)ethanone under basic conditions gave 6-(2-naphthalen-2-yl-2-oxoethoxy)quinolin-2(1*H*)-one (**9**) which was then treated with H_2SO_4 and NaN_3 to afford *N*-(naphthalen-2-yl)-2-(2-oxo-1,2-dihydroquinolin-6-yloxy)acetamide (**15**) in a good overall yield. The same synthetic procedures were applied for the synthesis of 7-substituted counterpart **16** from its ketone precursor **10** which in turn was prepared *via* alkylation of 7-hydroxyquinolin-2(1*H*)-one (**4**). Alkylation of 8-hydroxyquinolin-2(1*H*)-one (**5**) with 2-bromo-1-(naphthalen-2-yl)ethanone under basic conditions gave a mixture of 8-(2-naphthalen-2-yl-2-ox-ethoxy)quinolin-2(1*H*)-one (**11**) and 2,3-dihydro-3-hydroxy-3-naphthalen-2-yl-5*H*-pyrido[1,2,3-*de*][1,4]benzoxazin-5-one (**11A**) in a ratio of 2.89:1 (42% yield) based on the ^{1}H NMR spectra [δ 5.88 (s, 2H, OCH_2 for **11**), 4.22, 4.35 (dd, $J = 11.6$ Hz, *AB* type, 2H—C(2) for **11A**)] [17]. Compounds **11** and **11A** are interconvertible: when the mixture was subjected to a Schmidt rearrangement, *N*-(naphthalen-2-yl)-2-(2-oxo-1,2-dihydroquinolin-8-yloxy)acetamide (**17**) was obtained in 48% yield. Accordingly, compounds **18** and **19** were prepared from their respective ketones **12** and **13** which in turn were prepared *via* alkylation of 6-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**6**) and 7-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**7**) respectively. Alkylation of 8-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**8**) with 2-bromo-1-(naphthalen-2-yl)ethanone under basic conditions gave a mixture of 8-(2-naphthalen-2-yl-2-oxoethoxy)-3,4-dihydroquinolin-2(1*H*)-one (**14**) and 3-hydroxy-3-naphthalen-2-yl-2,3,5,6-tetrahydro-1-oxa-3a-azaphenalen-4-one (**14A**) in a ratio of 1.1:1 (91% yield) based on the ^{1}H NMR spectra [δ 5.73 (s, 2H, OCH_2 for **14**), 3.89, 4.03 (dd, $J = 11.2$ Hz, *AB* type, 2H—C(2) for **14A**)] [17]. Compounds **14** and **14A** are interconvertible: when the mixture was subjected to a Schmidt rearrangement, *N*-(naphthalen-2-yl)-2-(2-oxo-1,2,3,4-



Reagent conditions: (i) 2-(bromoacetyl)naphthalene / K_2CO_3 / DMF / rt; (ii) NaN_3 / H_2SO_4 / rt.



Scheme 1.

tetrahydroquinolin-6-yloxy)acetamide (**18**) was obtained in 60% yield.

Synthesis of *N*-(substituted phenyl)acetamide derivatives is outlined in Scheme 2. Treatment of the known ketone precursors **24a**–**24d** [14,17] with H_2SO_4 and NaN_3 afforded the respective desired acetamide derivatives **30a**–**30d**. Accordingly, compounds **31a**–**31d** and **32a**–**32d** were prepared from their respective ketone precursors **25a**–**25d** and **26a**–**26d** [14,17]. Preparation of compounds **27**–**29** has been previously described [18].

3. Pharmacological results and discussion

The antiproliferative activity of all compounds is evaluated *in vitro* against a panel of human cancer cell lines including nasopharyngeal (NPC-TW01), lung carcinoma (H661), hepatoma (Hep3B), renal carcinoma (A498), and gastric cancer (MKN45). For the *N*-(naphthalen-2-yl)acetamide derivatives, quinolin-2(1*H*)-one derivatives **15**–**17** were less active than their respective 3,4-dihydroquinolin-2(1*H*)-one counterparts **18**–**20** against all the cancer cell lines tested as shown in Table 1. Compounds **15**–**17** were inactive (IC_{50} > 50 μM) against the growth of Hep3B and MKN45 while their 3,4-dihydroquinolin-2(1*H*)-one counterparts **18**–**20** exhibited marginal activities with GI_{50} values ranged from 6.2 to 34.1 μM. The inhibitory activity against the growth of NPC-TW01 decreased in an order of *N*-(naphthalen-2-yl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yloxy)acetamide (**18**) (IC_{50} = 0.6 μM) > 7-substituted isomer **19** (IC_{50} = 8.9 μM) > 8-substituted isomer **20** (IC_{50} = 18.3 μM) > 3,4-dehydroquinolin-2(1*H*)-one counterparts **15**–**17** (IC_{50} > 26 μM). Compound **18** has also exhibited a strong inhibitory activity against the growth of Hep3B with an IC_{50} value of 6.2 μM.

The antiproliferative activities of *N*-(substituted phenyl)acetamide derivatives are summarized in Table 2. Quinolin-2(1*H*)-one derivatives **27a**–**27d**, **28a**–**28d**, and **29a**–**29d** were inactive against all the cancer cell lines tested. Most of 3,4-dihydroquinolin-2(1*H*)-one derivatives **30a**–**30d**, **31a**–**31d**, and **32a**–**32d** were weakly active against cancer cell lines tested while compounds **30d** and **31d** demonstrated strong inhibitory activities against the growth of NPC-TW01 with an IC_{50} value of 2.5 and 2.9 μM respectively. Compounds **30d** and **31d** have also exhibited strong inhibitory activities against the growth of Hep3B with an IC_{50} value of 2.8 and 8.1 μM respectively. These results indicated that the bulky *N*-(biphenyl)acetamide derivative was more active antiproliferative agent than its *N*-(phenyl)acetamide, *N*-(bromophenyl)acetamide, or *N*-(methoxyphenyl)acetamide counterpart.

Table 1
In vitro antiproliferative activity of *N*-(naphthalen-2-yl)acetamide derivatives (μM)[a].

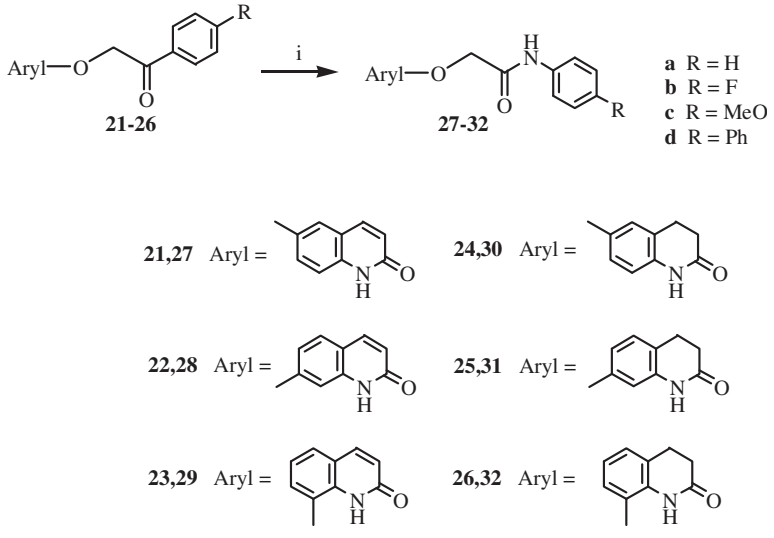
Compd	NPC-TW01[b]	H661	Hep3B	A498	MKN45
15	33.1 ± 1.7	43.6 ± 8.2	>50	31.1 ± 0.4	>50
16	40.9 ± 8.9	37.1 ± 1.1	>50	26.1 ± 7.8	>50
17	26.0 ± 6.8	30.8 ± 4.6	>50	39.6 ± 5.5	>50
18	0.6 ± 0.1	11.9 ± 0.7	6.2 ± 1.2	13.3 ± 3.1	34.1 ± 4.9
19	8.9 ± 0.6	11.2 ± 1.9	19.2 ± 4.7	8.6 ± 2.4	26.9 ± 3.1
20	18.3 ± 3.2	15.7 ± 4.0	14.8 ± 3.1	5.7 ± 2.7	15.0 ± 3.2

[a] Results are the average of three or more independent experiments.
[b] NPC-TW01: Nasopharyngeal carcinoma; H-661: Lung carcinoma; Hep3B: Hepatoma; A498: Renal carcinoma; MKN45: Gastric cancer.

Our results indicated that compound **18** was the most active against the growth of NPC-TW01 with an IC_{50} value of 0.6 μM. Thus, compound **18** was subjected for further study of its antiproliferative mechanisms. Significant *S*-phase accumulation, accompanying with the decrease of G_0/G_1 population, was observed after 18 h co-cultured with compound **18** (Fig. 2). Above results suggested that the inhibitory activity of compound **18** against NPC-TW01 might through the interference of cell division and the cause accumulation of cells in *S* phase in both time-and dose-dependent manner (Fig. 3). Most importantly, no detectable cytotoxicity against the normal peripheral blood mononuclear cells (PBMCs) was observed at a concentration of 50 μM, except slightly cytotoxicity against HUVEC cells at the same concentration (Fig. 4).

4. Conclusion

We have synthesized certain *N*-(naphthalen-2-yl)acetamide and *N*-(substituted phenyl)acetamide bearing quinolin-2(1*H*)-one and 3,4-dihydroquinolin-2(1*H*)-one derivatives for antiproliferative evaluations against NPC-TW01, H661, Hep3B, A498, and MKN45. For the *N*-(naphthalen-2-yl)acetamide derivatives, quinolin-2(1*H*)-one derivatives **15**–**17** were less active than their



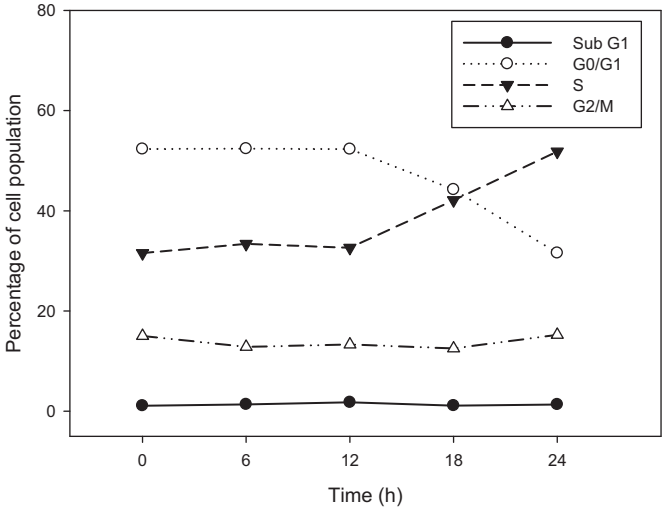
Reagent conditions: (i) NaN_3 / H_2SO_4 / rt.

Scheme 2.

Table 2
In vitro antiproliferative activity of *N*-(substituted phenyl)acetamide derivatives (μM).

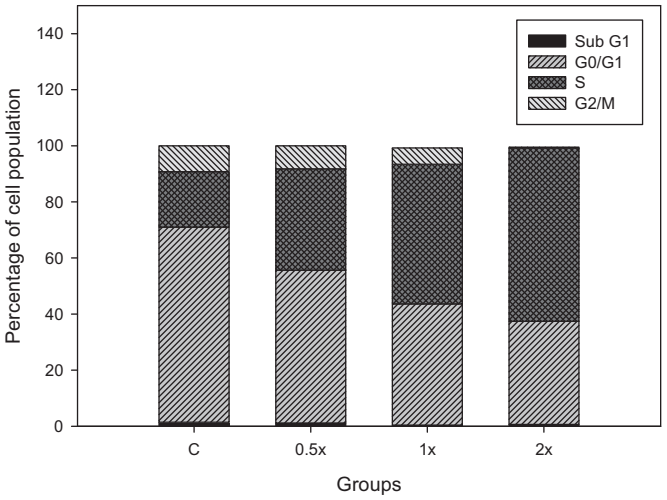
Compd	NPC-TW01	H661	Hep3B	A498	MKN45
27a	45.5 ± 5.9	34.9 ± 13.9	>50	34.6 ± 4.0	49.8 ± 0.2
27b	>50	43.8 ± 6.7	>50	>50	>50
27c	42.8 ± 4.3	>50	>50	26.8 ± 8.0	>50
27d	>50	>50	>50	44.4 ± 8.6	>50
28a	>50	>50	>50	>50	>50
28b	>50	>50	>50	18.8 ± 2.0	>50
28c	45.3 ± 5.7	33.3 ± 2.8	>50	30.6 ± 5.7	47.5 ± 5.2
28d	44.9 ± 9.5	34.7 ± 9.4	>50	24.6 ± 8.6	>50
29a	37.1 ± 6.4	>50	>50	32.6 ± 9.6	>50
29b	45.0 ± 6.4	49.3 ± 8.6	>50	41.9 ± 6.6	47.5 ± 3.6
29c	46.3 ± 0.2	44.51 ± 5.3	>50	33.1 ± 6.8	30.2 ± 6.1
29d	>50	30.2 ± 2.4	>50	>50	>50
30a	25.6 ± 2.4	22.6 ± 0.4	30.7 ± 5.2	10.4 ± 2.1	38.1 ± 3.9
30b	22.0 ± 3.7	28.4 ± 1.5	29.8 ± 4.7	13.3 ± 3.7	34.6 ± 4.7
30c	21.1 ± 1.2	22.4 ± 2.8	31.0 ± 4.3	11.1 ± 2.4	38.9 ± 5.3
30d	2.5 ± 0.4	19.4 ± 3.6	2.8 ± 1.1	15.7 ± 2.9	34.8 ± 6.1
31a	16.0 ± 1.3	21.8 ± 2.9	27.2 ± 2.4	12.0 ± 3.3	32.4 ± 2.9
31b	15.8 ± 0.4	15.3 ± 1.9	27.0 ± 4.9	11.3 ± 3.1	38.6 ± 5.7
31c	13.1 ± 1.9	16.4 ± 2.3	31.1 ± 3.9	19.3 ± 2.7	36.3 ± 5.1
31d	2.9 ± 0.4	15.4 ± 3.4	8.1 ± 1.1	12.0 ± 2.4	32.4 ± 1.4
32a	17.8 ± 1.6	17.0 ± 2.3	29.8 ± 4.5	13.6 ± 4.2	33.6 ± 7.1
32b	17.1 ± 2.0	13.6 ± 1.7	31.0 ± 4.5	20.8 ± 3.4	38.5 ± 5.5
32c	25.0 ± 3.4	20.2 ± 3.0	28.0 ± 3.6	11.8 ± 2.5	28.3 ± 3.8
32d	14.2 ± 3.3	17.1 ± 1.5	27.5 ± 6.8	8.6 ± 2.8	30.5 ± 5.7

respective 3,4-dihydroquinolin-2(1*H*)-one counterparts **18**–**20** against all the cancer cell lines tested. The inhibitory activity against the growth of NPC-TW01 decreased in an order of *N*-(naphthalen-2-yl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yloxy) acetamide (**18**) (IC_{50} = 0.6 μM) > 7-substituted isomer **19** (IC_{50} = 8.9 μM) > 8-substituted isomer **20** (IC_{50} = 18.3 μM) > 3,4-dehydroquinolin-2(1*H*)-one counterparts **15**–**17** (IC_{50} > 26 μM). Flow cytometric analysis indicated that **18** inhibit the growth of NPC-TW01 cells by inducing cell cycle arrest in *S* phase. Compound



Cell cycle \ Time (h)	0	6	12	18	24
Sub G_1	1.1	1.4	1.8	1.1	1.3
G_0/G_1	52.3	52.4	52.3	44.2	31.6
S	31.6	33.4	32.6	42.1	51.8
G_2/M	15.0	12.8	13.3	12.5	15.2

Fig. 2. Cell-cycle analysis indicated compound **18** caused cell arrest in S-phase in a time-dependent manner.



Cell cycle \ Flop (IC_{50})	Control	0.5x	1x	2x
Sub G_1	1.4	1.2	0.4	0.7
G_0/G_1	69.6	54.5	43.2	36.7
S	19.7	36.2	49.8	61.7
G_2/M	9.3	8.2	5.8	0.4

Fig. 3. The dose-effects of compound **18** on the cell-cycle distribution in NPC-TW01.

18 demonstrated very specific cytotoxicity against NPC-TW01 cell lines with no detectable cytotoxicity against peripheral blood mononuclear cells (PBMCs) at a concentration of up to 50 μM. Further structural optimization and mechanism studies on **18** are on-going.

5. Experimental protocols

5.1. General

Melting points were determined on an Electrothermal IA9100 melting point apparatus and are uncorrected. Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Varian-Unity-400 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane (TMS) as an internal standard.

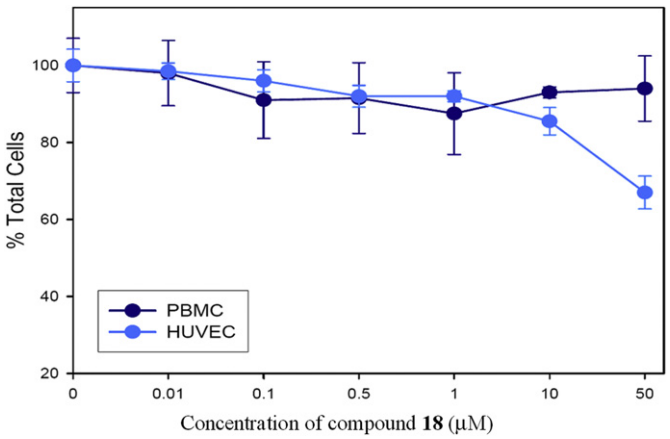


Fig. 4. Compound **18** was non-cytotoxic against peripheral blood mononuclear cells (PBMCs) but was weakly toxic to HUVEC at a high concentration.

Thin-layer chromatography was performed on silica gel 60 F-254 plates purchased from E. Merck and Co. The elemental analyses were performed in the Instrument Center of National Science Council at National Cheng-Kung University using Heraeus CHN–O Rapid EA, and all values are within ±0.4% of the theoretical compositions.

5.1.1. 6-(2-Naphthalen-2-yl-2-oxoethoxy)quinolin-2(1H)-one (**9**)

6-Hydroxyquinolin-2(1*H*)-one (**3**, 1.61 g, 10 mmol), K_2CO_3 (1.38 g, 10 mmol), and dry DMF (50 mL) were stirred at room temperature (r.t.) for 30 min. To this solution was added 2-(bromoacetyl)naphthalene (2.49 g, 10 mmol) in DMF (10 mL) in one portion. The resulting mixture was stirred continuously at r.t. for 24 h (TLC monitoring) and then poured into ice-water (100 mL). The white solid thus obtained was collected and crystallized from Et_2O to give **9** (3.06 g, 93%). M.p.: 220–221 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.74 (s, 2H, OCH_2), 6.48 (d, J = 9.6 Hz, 1H–C(3)), 7.27–7.30 (m, 3H, Ar–H), 7.64–7.72 (m, 2H, Ar–H), 7.81 (d, J = 9.6 Hz, 1H–C(4)), 8.00–8.08 (m, 3H, Ar–H), 8.14 (d, J = 8.4 Hz, 1H, Ar–H), 8.77 (s, 1H, Ar–H), 11.67 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 70.61 (CH_2O), 111.61, 116.41, 119.65, 119.94, 122.43, 123.36, 127.20, 127.84, 128.52, 128.97, 129.62, 129.89, 131.72, 132.15, 133.61, 135.35, 139.79, 152.89, 161.61 (C(2)), 194.43 (C=O). Anal. calcd. for $C_{21}H_{15}NO_3 \cdot 0.1H_2O$: C 76.16, H 4.64, N 4.23; found: C 75.93, H 4.24, N, 4.25.

5.1.2. 7-(2-Naphthalen-2-yl-2-oxoethoxy)quinolin-2(1H)-one (**10**)

From 7-hydroxyquinolin-2(1*H*)-one (**4**) as described for **9**: 43% yield. M.p.: 216–217 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.81 (s, 2H, OCH_2), 6.30 (d, J = 9.6 Hz, 1H–C(3)), 6.81 (d, J = 2.4 Hz, 1H-(8)), 6.91 (dd, J = 8.8, 2.4 Hz, 1H-(6)), 5.58 (d, J = 8.8 Hz, 1H, Ar–H), 7.65–7.74 (m, 2H, Ar–H), 7.81 (d, J = 9.2 Hz, 1H, Ar–H), 8.00–8.05 (m, 2H, Ar–H), 8.09 (d, J = 8.8 Hz, Ar–H), 8.15 (dd, J = 7.6, 0.8 Hz, 1H, Ar–H), 8.78 (d, J = 0.8 Hz, 1H, Ar–H), 11.51 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 70.36 (CH_2O), 99.36, 110.63, 113.71, 118.81, 123.29, 127.23, 127.84, 128.58, 129.04, 129.30, 129.62, 129.94, 131.56, 132.13, 135.39, 140.01, 140.49, 159.77, 162.21 (C(2)), 194.13 (C=O). Anal. calcd. for $C_{21}H_{15}NO_3$: C 76.58, H 4.59, N 4.25; found: C 76.45, H 4.63, N 4.21.

5.1.3. 8-(2-Naphthalen-2-yl-2-oxoethoxy)quinolin-2(1H)-one (**11**) and 2,3-dihydro-3-hydroxy-3-naphthalen-2-yl-5H-pyrido[1,2,3-de][1,4]benzoxazin-5-one (**11A**)

A mixture of **11** and **11A** (2.89:1) was obtained from 8-hydroxyquinolin-2(1*H*)-one (**5**) as described for **9**: 42% yield. M.p.: 194–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.88 (s, 2H, OCH_2 of **11**), 4.22, 4.35 (2d, J = 11.6 Hz, *AB* type, 2H–C(2) of **11A**); ^{13}C NMR (100 MHz, DMSO-d_6): δ 71.66 (C(1′) of **11**), 161.47 (C(2) of **11**), 194.71 (C=O of **11**), 73.95 (C(2) of **11A**), 84.50 (C(3) of **11A**), 160.70 (C(5) of **11A**). Anal. calcd. for $C_{21}H_{15}NO_3$: C 76.58, H 4.59, N 4.25; found: C 76.35, H 4.56, N 4.15.

5.1.4. 6-(2-Naphthalen-2-yl-2-oxoethoxy)-3,4-dihydroquinolin-2(1H)-one (**12**)

From 6-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**6**) as described for **9**: 91% yield. M.p.: 195–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39–2.43 (m, 2H–C(3)), 2.77–2.81 (m, 2H–C(4)), 5.64 (s, 2H, OCH_2), 6.48 (d, J = 2.4 Hz, 1H–C(5)), 6.57 (dd, J = 8.4, 2.4 Hz, 1H–C(7)), 7.05 (d, J = 8.4 Hz, 1H–C(8)), 7.64–7.73 (m, 2H, Ar–H), 7.99–8.01 (m, 1H, Ar–H), 8.03 (d, J = 8.0 Hz, 1H, Ar–H), 8.07 (d, J = 8.4 Hz, 1H, Ar–H), 8.14 (d, J = 8.0 Hz, 1H,Ar–H), 8.76 (s, 1H, Ar–H), 9.96 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.68 (C(4)), 31.38 (C(3)), 70.92 (CH_2O), 102.76, 108.18, 116.77, 123.98, 127.83, 128.47, 129.02, 129.16, 129.61, 130.26, 130.51, 132.36, 132.80, 135.99, 139.90, 157.90, 170.94 (C(2)), 195.24 (C=O). Anal. calcd. for $C_{21}H_{17}NO_3$: C 76.12, H 5.17, N 4.23; found: C 75.91, H 5.21, N 4.17.

5.1.5. 7-(2-Naphthalen-2-yl-2-oxoethoxy)-3,4-dihydroquinolin-2(1H)-one (**13**)

From 7-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**7**) as described for **9**: 95% yield. M.p.: 191–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39–2.42 (m, 2H–C(3)), 2.81–2.85 (m, 2H–C(4)), 5.63 (s, 2H, OCH_2), 6.76 (d, J = 8.4 Hz, 1H–C(5)), 6.81 (dd, J = 8.4, 2.4 Hz, 1H–C(6)), 6.89 (d, J = 2.4 Hz, 1H–C(8)), 7.64–7.73 (m, 2H, Ar–H), 7.99–8.08 (m, 3H, Ar–H), 8.14 (d, J = 7.6 Hz, 1H, Ar–H), 8.76 (s, 1H, Ar–H), 9.92 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.76 (C(4)), 31.01 (C(3)), 71.20 (CH_2O), 113.93, 114.88, 116.40, 124.01, 125.52, 127.80, 128.47, 129.13, 129.57, 130.26, 130.49, 132.42, 132.80, 135.97, 153.88, 170.46 (C(2)), 195.36 (C=O). Anal. calcd. for $C_{21}H_{17}NO_3$: C 76.12, H 5.17, N 4.23; found: C 75.83, H 5.18, N, 4.12.

5.1.6. 8-(2-Naphthalen-2-yl-2-oxoethoxy)-3,4-dihydroquinolin-2(1H)-one (**14**) and 3-hydroxy-3-naphthalen-2-yl-2,3,5,6-tetrahydro-1-oxa-3a-azaphenalen-4-one (**14A**)

A mixture of **14** and **14A** (1.1:1) was obtained from 8-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**8**) as described for **9**: 91% yield. M.p.: 199–200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.73 (s, 2H, OCH_2 of **14**), 3.89, 4.03 (2d, J = 11.2 Hz, *AB* type, 2H–C(2) of **14A**); ^{13}C NMR (100 MHz, DMSO-d_6): δ 71.77 (C(1′) of **14**) 169.51 (C(2) of **14**), 194.93 (C=O of **14**), 74.89 (C(2) of **14A**), 84.06 (C(3) of **14A**), 168.61 (C(5) of **14A**). Anal. calcd. for $C_{21}H_{17}NO_3$: C 76.12, H 5.17, N 4.23; found: C 76.00, H 5.20, N 4.13.

5.1.7. N-(Naphthalen-2-yl)-2-(2-oxo-1,2-dihydroquinolin-6-yloxy) acetamide (**15**)

A solution of **9** (0.33 g, 1 mmol) in H_2SO_4 (3 mL) was stirred at r.t. for 10 min. To this solution, was added sodium azide (0.13 g, 2 mmol) in one portion. The mixture was stirred continuously at r.t. for 1 h (TLC monitoring) and then poured into ice-water (100 mL). The white solid thus obtained was collected and purified by flash column chromatography (FC; silica gel; CH_2Cl_2/EtOAc 5:1) and crystallized from CH_2Cl_2 to give **15** (0.28 g, 81%). M.p.: 287–288 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.79 (s, 2H, OCH_2), 6.49 (d, J = 8.8 Hz, 1H–C(3)), 7.27–7.33 (m, 3H, Ar–H), 7.40–7.49 (m, 2H, Ar–H), 7.68 (dd, J = 8.8, 1.6 Hz, 1H–C(7)), 8.81–8.89 (m, 4H, Ar–H), 8.33 (s, 1H, Ar–H), 10.31 (s, 1H, NH), 11.70 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 67.74 (CH_2O), 110.88, 116.04, 116.42, 119.61, 120.01, 120.37, 122.49, 124.85, 126.49, 127.36, 127.49, 128.39, 130.00, 133.33, 133.85, 135.98, 139.79, 152.69, 161.58 (C=O), 166.79 (C(2)). Anal. calcd. for $C_{21}H_{16}N_2O_3 \cdot 0.2H_2O$: C 72.48, H 4.76, N 8.05; found: C 72.30, H 4.56, N 8.44.

5.1.8. N-(Naphthalen-2-yl)-2-(2-oxo-1,2-dihydroquinolin-7-yloxy) acetamide (**16**)

From 7-(2-naphthalen-2-yl-2-oxoethoxy)quinolin-2(1*H*)-one (**10**) as described for **15**: 62% yield. M.p.: 255–256 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.83 (s, 2H, OCH_2), 6.31–6.33 (m, 1H, Ar–H), 6.87 (d, J = 2.4 Hz, 1H-(8)), 6.91 (dd, J = 8.8, 2.4 Hz, 1H-(6)), 7.40–7.50 (m, 2H, Ar–H), 7.60–7.68 (m, 2H, Ar–H), 7.81–7.90 (m, 4H, Ar–H), 8.31 (d, J = 1.2 Hz, 1H, Ar–H), 10.40 (s, 1H, NH), 11.68 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 67.14 (CH_2O), 99.23, 110.85, 113.84, 115.97, 118.96, 120.28, 124.87, 126.55, 127.37, 127.52, 128.45, 129.36, 129.99, 133.33, 136.00, 140.04, 140.53, 159.66, 162.29 (C=O), 166.35 (C(2)). Anal. calcd. for $C_{21}H_{16}N_2O_3 \cdot 0.1H_2O$: C 72.86, H 4.73, N 8.09; found: C 72.79, H 4.74, N 8.15.

5.1.9. N-(Naphthalen-2-yl)-2-(2-oxo-1,2-dihydroquinolin-8-yloxy) acetamide (**17**)

From a mixture of **11** and **11A** as described for **15**: 48% yield. M.p.: 281–282 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.89 (s, 2H, OCH_2), 6.58 (d, J = 9.6 Hz, 1H, Ar–H), 7.16 (t, J = 8.0 Hz, 1H, Ar–H), 7.29–7.35 (m, 2H, Ar–H), 7.44–7.53 (m, 2H, Ar–H), 7.73 (dd, J = 8.8,

2.0 Hz, 1H–C(3′)), 7.88–7.96 (m, 4H, Ar–H), 8.25 (d, J = 2.0 Hz, 1H–C(1′)), 10.54 (s, 1H, NH), 11.51 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 68.11 (CH_2O), 112.91, 118.09, 119.98, 120.85, 121.75, 121.88, 122.59, 125.18, 126.54, 127.46, 127.56, 128.33, 128.73, 130.35, 133.23, 135.37, 140.48, 143.84, 161.91 (C=O), 166.35 (C(2)). Anal. calcd. for $C_{21}H_{16}N_2O_3$: C 73.24, H 4.68, N 8.13; found: C 73.18, H 4.65, N, 8.10.

5.1.10. N-(Naphthalen-2-yl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yloxy)acetamide (**18**)

From 6-(2-naphthalen-2-yl-2-oxoethoxy)-3,4-dihydroquinolin-2(1*H*)-one (**12**) as described for **15**: 75% yield. M.p.: 236–237 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39–2.43 (m, 2H–C(3)), 2.83–2.87 (m, 2H–C(4)), 4.69 (s, 2H, OCH_2), 6.80 (d, J = 8.8 Hz, 1H–C(8)), 6.84 (dd, J = 8.8, 2.4 Hz, 1H–C(7)), 6.91 (d, J = 2.4 Hz, 1H–C(5)), 7.40–7.50 (m, 2H, Ar–H), 7.67–7.70 (m, 1H, Ar–H), 7.82–7.90 (m, 3H, Ar–H), 8.33 (m, 1H, Ar–H), 9.96 (s, 1H, NH), 10.24 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.77 (C(4)), 30.98 (C(3)), 68.33 (CH_2O), 113.95, 115.16, 116.43, 116.62, 120.99, 125.50, 125.58, 127.16, 128.03, 128.15, 129.05, 130.63, 133.08, 133.98, 136.65, 153.69, 167.70 (C=O), 170.51 (C(2)). Anal. calcd. for $C_{21}H_{18}N_2O_3$: C 72.82, H 5.24, N 8.09; found: C 72.67, H 5.24, N 8.05.

5.1.11. N-(Naphthalen-2-yl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yloxy)acetamide (**19**)

From 7-(2-naphthalen-2-yl-2-oxoethoxy)-3,4-dihydroquinolin-2(1*H*)-one (**13**) as described for **15**: 56% yield. M.p.: 247–248 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40–2.44 (m, 2H–C(3)), 2.78–2.81 (m, 2H–C(4)), 4.70 (s, 2H, OCH_2), 6.56 (d, J = 2.4 Hz, 1H–C(8)), 6.59 (dd, J = 8.0, 2.4 Hz, 1H–C(6)), 7.09 (d, J = 8.0 Hz, 1H–C(5)), 7.40–7.50 (m, 2H, Ar–H), 7.66–7.69 (m, 1H, Ar–H), 7.81–7.89 (m, 3H, Ar–H), 8.32 (d, J = 1.2 Hz, 1H, Ar–H), 10.08 (s, 1H, NH), 10.29 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.71 (C(4)), 31.37 (C(3)), 67.98 (CH_2O), 102.83, 108.32, 116.62, 117.08, 120.98, 125.48, 127.16, 128.01, 128.15, 129.03, 129.11, 130.63, 133.99, 136.70, 139.96, 157.83, 167.48 (C=O), 171.00 (C(2)). Anal. calcd. for $C_{21}H_{18}N_2O_3$: C 72.82, H 5.24, N 8.09; found: C 72.81, H 5.25, N 8.04.

5.1.12. N-(Naphthalen-2-yl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-8-yloxy)acetamide (**20**)

From a mixture of **14** and **14A** as described for **15**: 60% yield. M.p.: 199–200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.46–2.50 (m, 2H–C(3)), 2.89–2.93 (m, 2H–C(4)), 4.77 (s, 2H, OCH_2), 6.86–7.01 (m, 3H, Ar–H), 7.45–7.51 (m, 2H, Ar–H), 7.70 (dd, J = 8.8, 2.0 Hz, 1H, Ar–H), 7.87–7.94 (m, 3H, Ar–H), 8.25 (d, J = 2.0 Hz, 1H, Ar–H), 9.86 (s, 1H, NH), 10.34 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.69 (C(4)), 31.19 (C(3)), 68.72 (CH_2O), 112.11, 118.33, 121.61, 122.12, 122.95, 125.76, 125.87, 127.18, 127.86, 128.09, 128.19, 128.98, 130.93, 133.89, 136.12, 144.98, 167.33 (C=O), 170.80 (C(2)). Anal. calcd. for $C_{21}H_{18}N_2O_3$: C 72.82, H 5.24, N 8.09; found: C 72.45, H 5.18, N 7.99.

5.1.13. 2-(2-Oxo-1,2,3,4-tetrahydroquinolin-6-yloxy)-N-phenylacetamide (**30a**)

From 6-(2-oxo-2-phenylethoxy)-3,4-dihydroquinolin-2(1*H*)-one (**24a**) as described for **15**: 85% yield. M.p.: 222–223 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38–2.42 (m, 2H–C(3)), 2.82–2.86 (m, 2H–C(4)), 4.62 (s, OCH_2), 6.78 (d, J = 8.8 Hz, 1H–C(8)), 6.81 (dd, J = 8.8, 2.4 Hz, 1H–C(7)), 6.87 (d, J = 2.4 Hz, 1H–C(5)), 7.06–7.10 (m, 1H, Ar–H), 7.30–7.34 (m, 2H, Ar–H), 7.63–7.65 (m, 2H, Ar–H), 9.95 (s, 1H, NH), 10.02 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.78 (C(4)), 30.97 (C(3)), 68.29 (CH_2O), 113.92, 115.13, 116.41, 120.42, 124.38, 125.56, 129.41, 133.07, 139.04, 153.67, 167.39 (C=O), 170.49 (C(2)). Anal. calcd. for $C_{17}H_{16}N_2O_3$: C 68.91, H 5.44, N 9.45; found: C 68.84, H, 5.44, N 9.43.

5.1.14. N-(4-Fluorophenyl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yloxy)acetamide (**30b**)

From 6-[2-(4-fluorophenyl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one (**24b**) as described for **15**: 86% yield. M.p.: 212–213 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39–2.43 (m, 2H–C(3)), 2.82–2.86 (m, 2H–C(4)), 4.62 (s, OCH_2), 6.78 (d, J = 8.8 Hz, 1H–C(8)), 6.81 (dd, J = 8.8, 2.4 Hz, 1H–C(7)), 6.88 (d, J = 2.4 Hz, 1H–C(5)), 7.14–7.19 (m, 2H, Ar–H), 7.65–7.69 (m, 2H, Ar–H), 9.96 (s, 1H, NH), 10.09 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.76 (C(4)), 30.97 (C(3)), 68.27 (CH_2O), 113.95, 115.15, 115.86, 116.08, 116.41, 122.27, 122.35, 125.56, 133.11, 135.41, 153.62, 157.75, 160.13, 167.36 (C=O), 170.48 (C(2)). Anal. calcd. for $C_{17}H_{15}FN_2O_3 \cdot 0.25H_2O$: C 64.04, H 4.90, N 8.78; found: C 64.17, H 4.94, N 8.48.

5.1.15. N-(4-Methoxyphenyl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yloxy)acetamide (**30c**)

From 6-[2-(4-methoxyphenyl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one (**24c**) as described for **15**: 86% yield. M.p.: 186–187 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39–2.43 (m, 2H–C(3)), 2.82–2.86 (m, 2H–C(4)), 3.72 (s, 3H, OMe), 4.58 (s, 2H, OCH_2), 6.78 (d, J = 8.8 Hz, 1H–C(8)), 6.81 (dd, J = 8.8, 2.4 Hz, 1H–C(7)), 6.87 (d, J = 2.4 Hz, 1H–C(5)), 6.88–6.90 (m, 2H, Ar–H), 7.53–7.55 (m, 2H, Ar–H), 9.89 (s, 1H, NH), 9.96 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.76 (C(4)), 30.97 (C(3)), 55.84 (MeO), 68.30 (CH_2O), 113.94, 114.50, 115.15, 116.41, 122.09, 125.55, 132.09, 133.04, 153.67, 156.23, 166.92 (C=O), 170.52 (C(2)). Anal. calcd. for $C_{18}H_{18}N_2O_4$: C 66.25, H 5.56, N 8.58; found: C 66.15, H 5.58, N 8.59.

5.1.16. N-(Biphenyl-4-yl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yloxy)acetamide (**30d**)

From 6-(2-biphenyl-4-yl-2-oxoethoxy)-3,4-dihydroquinolin-2(1*H*)-one (**24d**) as described for **15**: 83% yield. M.p.: 246–247 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39–2.43 (m, 2H–C(3)), 2.83–2.87 (m, 2H–C(4)), 4.65 (s, 2H, OCH_2), 6.80 (d, J = 8.4 Hz, 1H–C(8)), 6.83 (dd, J = 8.4, 2.0 Hz, 1H–C(7)), 6.89 (d, J = 2.0 Hz, 1H–C(5)), 7.33–7.47 (m, 5H, Ar–H), 7.64–7.76 (m, 4H, Ar–H), 9.96 (s, 1H, NH), 10.14 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.77 (C(4)), 30.97 (C(3)), 68.34 (CH_2O), 113.95, 115.16, 116.43, 120.78, 125.58, 126.97, 127.60, 127.79, 129.60, 133.08, 136.05, 138.52, 140.30, 153.68, 167.48 (C=O), 170.52 (C(2)). Anal. calcd. for $C_{23}H_{20}N_2O_3 \cdot 0.5H_2O$: C 72.42, H 5.55, N 7.34; found: C 72.65, H 5.49, N 7.29.

5.1.17. 2-(2-Oxo-1,2,3,4-tetrahydroquinolin-7-yloxy)-N-phenylacetamide (**31a**)

From 7-(2-oxo-2-phenylethoxy)-3,4-dihydroquinolin-2(1*H*)-one (**25a**) as described for **15**: 84% yield. M.p.: 249–250 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39–2.43 (m, 2H–C(3)), 2.77–2.81 (m, 2H–C(4)), 4.62 (s, 2H, OCH_2), 6.53 (d, J = 2.4 Hz, 1H–C(8)), 6.55 (dd, J = 8.0, 2.4 Hz, 1H–C(6)), 7.09 (d, J = 8.0 Hz, 1H–C(5)), 7.06–7.10 (m, 1H, Ar–H), 7.30–7.34 (m, 2H, Ar–H), 7.62–7.64 (m, 2H, Ar–H), 10.06 (s, 1H, NH), 10.06 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.71 (C(4)), 31.36 (C(3)), 67.91 (CH_2O), 102.80, 108.27, 117.05, 120.39, 124.35, 129.09, 129.40, 139.09, 139.94, 157.80, 167.18 (C=O), 171.00 (C(2)). Anal. calcd. for $C_{17}H_{16}N_2O_3$: C 68.91, H 5.44, N 9.45; found: C 68.52, H 5.42, N 9.36.

5.1.18. N-(4-Fluorophenyl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yloxy)acetamide (**31b**)

From 7-[2-(4-fluorophenyl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one (**25b**) as described for **15**: 86% yield. M.p.: 264–265 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40–2.44 (m, 2H–C(3)), 2.77–2.81 (m, 2H–C(4)), 4.62 (s, 2H, OCH_2), 6.53 (d, J = 2.4 Hz, 1H–C(8)), 6.55 (dd, J = 8.0, 2.4 Hz, 1H–C(6)), 7.08 (d, J = 8.0 Hz, 1H–C(5)), 7.14–7.19 (m, 2H, Ar–H), 7.64–7.67 (m, 2H, Ar–H), 10.08

(s, 1H, NH), 10.15 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.68 (C(4)), 31.34 (C(3)), 67.84 (CH_2O), 102.79, 108.30, 115.87, 116.09, 117.10, 122.25, 122.33, 129.12, 135.40, 135.43, 139.91, 157.73, 160.13, 167.18 (C═O), 171.07 (C(2)). Anal. calcd. for $C_{17}H_{15}FN_2O_3$: C 64.96, H 4.81, N 8.91; found: C 64.94, H 4.96, N 9.18.

*5.1.19. N-(4-Methoxyphenyl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yloxy)acetamide (**31c**)*

From 7-[2-(4-methoxyphenyl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one (**25c**) as described for **15**: 83% yield. M.p.: 248–249 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40–2.44 (m, 2H–C(3)), 2.77–2.81 (m, 2H–C(4)), 3.72 (s, 3H, OMe), 4.58 (s, 2H, OCH_2), 6.52 (d, J = 2.4 Hz, 1H–C(8)), 6.55 (dd, J = 8.0, 2.4 Hz, 1H–C(6)), 6.88–6.91 (m, 2H, Ar–H), 7.08 (d, J = 8.0 Hz, 1H–C(5)), 7.52–7.56 (m, 2H, Ar–H), 9.93 (s, 1H, NH), 10.07 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.70 (C(4)), 31.35 (C(3)), 55.85 (MeO), 67.92 (CH_2O), 102.82, 108.29, 114.49, 117.05, 122.06, 129.09, 132.13, 139.92, 156.21, 157.79, 166.70 (C═O), 171.02 (C(2)). Anal. calcd. for $C_{18}H_{18}N_2O_4$: C 66.25, H 5.56, N 8.58; found: C 66.22, H 5.57, N 8.59.

*5.1.20. N-(Biphenyl-4-yl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yloxy)acetamide (**31d**)*

From 7-(2-biphenyl-4-yl-2-oxoethoxy)-3,4-dihydroquinolin-2(1*H*)-one (**25d**) as described for **15**: 86% yield. M.p.: 235–236 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40–2.44 (m, 2H–C(3)), 2.77–2.81 (m, 2H–C(4)), 4.65 (s, 2H, OCH_2), 6.54 (d, J = 2.4 Hz, 1H–C(8)), 6.57 (dd, J = 8.0, 2.4 Hz, 1H–C(6)), 7.09 (d, J = 8.0 Hz, 1H–C(5)), 7.33–7.35 (m, 1H, Ar–H), 7.43–7.47 (m, 2H, Ar–H), 7.63–7.66 (m, 4H, Ar–H), 7.73–7.76 (m, 2H, Ar–H), 10.07 (s, 1H, NH), 10.18 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.72 (C(4)), 31.37 (C(3)), 67.98 (CH_2O), 102.83, 108.31, 117.09, 120.75, 126.97, 127.59, 127.78, 129.11, 129.59, 136.02, 138.57, 139.97, 140.33 157.81, 167.26 (C═O), 171.00 (C(2)). Anal. calcd. for $C_{23}H_{20}N_2O_3$: C 74.18, H 5.41, N 7.52; found: C 74.17, H 5.43, N 7.46.

*5.1.21. 2-(2-Oxo-1,2,3,4-tetrahydroquinolin-8-yloxy)-N-phenylacetamide (**32a**)*

From 8-(2-oxo-2-phenylethoxy)-3,4-dihydroquinolin-2(1*H*)-one (**26a**) as described for **15**: 88% yield. M.p.: 180–181 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.45–2.49 (m, 2H–C(3)), 2.88–2.92 (m, 2H–C(4)), 4.70 (s, 2H, OCH_2), 6.85–6.97 (m, 3H, Ar–H), 7.12–7.16 (m, 1H, Ar–H), 7.35–7.39 (m, 2H, Ar–H), 7.60–7.62 (m, 2H, Ar–H), 9.81 (s, 1H, NH), 10.13 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.88 (C(4)), 30.38 (C(3)), 67.87 (CH_2O), 111.29, 120.79, 121.14, 122.14, 124.19, 125.06, 127.05, 128.59, 137.68, 144.17, 166.26 (C═O), 169.97 (C(2)). Anal. calcd. for $C_{17}H_{16}N_2O_3$: C 68.91, H 5.44, N 9.45; found: C 68.79, H 5.51, N 9.38.

*5.1.22. N-(4-Fluorophenyl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-8-yloxy)acetamide (**32b**)*

From 8-[2-(4-fluorophenyl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one (**26b**) as described for **15**: 80% yield. M.p.: 187–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.45–2.49 (m, 2H–C(3)), 2.88–2.92 (m, 2H–C(4)), 4.70 (s, 2H, OCH_2), 6.85–6.97 (m, 3H, Ar–H), 7.20–7.24 (m, 2H, Ar–H), 7.61–7.64 (m, 2H, Ar–H), 9.81 (s, 1H, NH), 10.18 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.88 (C(4)), 30.38 (C(3)), 67.80 (CH_2O), 111.25, 115.11, 115.33, 120.82, 122.17, 123.16, 123.25, 125.06, 126.99, 133.97, 133.99, 144.12, 157.43, 159.82, 166.27 (C═O), 170.03 (C(2)). Anal. calcd. for $C_{17}H_{15}FN_2O_3$: C 64.96, H 4.81, N 8.91; found: C 64.74, H 4.92, N 8.83.

*5.1.23. N-(4-Methoxyphenyl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-8-yloxy)acetamide (**32c**)*

From 8-[2-(4-methoxyphenyl)-2-oxoethoxy]-3,4-dihydroquinolin-2(1*H*)-one (**26c**) as described for **15**: 83% yield. M.p.: 189–190 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.45–2.49 (m, 2H–C(3)), 2.88–2.92 (m, 2H–C(4)), 3.75 (s, 3H, OMe), 4.66 (s, 2H, OCH_2), 6.87–6.95 (m, 5H, Ar–H), 7.48–7.50 (m, 2H, Ar–H), 9.86 (s, 1H, NH), 10.03 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.68 (C(4)), 31.18 (C(3)), 55.88 (MeO), 68.56 (CH_2O), 111.99, 114.49, 121.54, 122.93, 123.90, 125.83, 127.76, 131.31, 144.93, 156.76, 166.66 (C═O), 170.83 (C(2)). Anal. calcd. for $C_{18}H_{18}N_2O_4$: C 66.25, H 5.56, N 8.58; found: C 66.31, H 5.57, N 8.56.

*5.1.24. N-(Biphenyl-4-yl)-2-(2-oxo-1,2,3,4-tetrahydroquinolin-8-yloxy)acetamide (**32d**)*

From 8-(2-biphenyl-4-yl-2-oxoethoxy)-3,4-dihydroquinolin-2(1*H*)-one (**26d**) as described for **15**: 81% yield. M.p.: 197–198 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.46–2.50 (m, 2H–C(3)), 2.89–2.93 (m, 2H–C(4)), 4.73 (s, 2H, OCH_2), 6.86–6.99 (m, 3H, Ar–H), 7.33–7.37 (m, 1H, Ar–H), 7.44–7.48 (m, 2H, Ar–H), 7.66–7.75 (m, 6H, Ar–H), 9.81 (s, 1H, NH), 10.22 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.91 (C(4)), 30.41 (C(3)), 67.97 (CH_2O), 111.36, 120.86, 121.30, 122.20, 125.11, 126.27, 126.80, 127.11, 128.86, 135.81, 137.23, 139.50, 144.22, 166.42 (C═O), 170.02 (C(2)). Anal. calcd. for $C_{23}H_{20}N_2O_3$: C 74.18, H 5.41, N 7.52; found: C 74.13, H 5.43, N 7.53.

5.2. Antiproliferative activity

5.2.1. Cell lines

Human non-small cell lung carcinoma (NCI-H661), gastric cancer (MKN45), hepatoma (Hep3B), and renal carcinoma (A498) were purchased from American Type Culture Collection (ATCC; Rockville, MD). Nasopharyngeal carcinoma (NPC-TW01) was purchased from Bioresource Collection and Research Center (BCRC, Taiwan). All the tumor cell lines were maintained in either RPMI-1640 or Modified essential medium (MEM) supplied with 10% fetal bovine serum at 37 °C in a humidified atmosphere of 5% CO_2/95% air in the absence of antibiotics.

5.2.2. Growth inhibition assay

Logarithmic phase cells were seeded in a 96-well plate and incubated overnight prior to addition of the designated compounds. After incubation with different concentrations of the tested compounds for 72 h, cells were incubated with MEM containing 0.4 mg/mL MTT for 2 h. The conversion of MTT to formazan by metabolically viable cells was measured by the absorbance at 570 nm in a 96-well microtiter plate reader. The percentage conversion by mock-treated control cells was used to evaluate the effect of the chemicals on cell growth and to determine the concentration that inhibited 50% of growth (GI_{50}) [24].

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2012.11.016.

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