Synthesis and Antiproliferative Evaluation of Amide-Containing Anthraquinone, Xanthone, and Carbazole

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Certain amide-containing anthraquinone, xanthone, and carbazole derivatives have been synthesized and evaluated *in vitro* for their antiproliferative activities against a panel of human cancer cell lines including nasopharyngeal carcinoma (NPC-TW01), lung carcinoma (NCI-H661), and leukemia (Jurkat). Among them, 2-(9,10-dioxo-9,10-dihydroanthracen-2-yloxy)-*N*-(naphthalen-2-yl)acetamide (13) was the most active against NPC-TW01 with an IC_{50} value of 2.62 μM while its xanthone and dibenzofuran counterparts, 14 and 15, were inactive with an IC_{50} value of 16.10 and 11.09 μM, respectively. Studies on NPC-TW01 cell cycle distribution revealed that compound 13 inhibited proliferation of NPC-TW01 by the alteration of cell division and the accumulation of cells in G_0/G_1 phase.

Key words anthraquinone; xanthone; carbazole; antiproliferative activity; nasopharyngeal carcinoma (NPC)

Nasopharyngeal carcinoma (NPC) is an uncommon type of head-and-neck cancer in Western countries, but is relatively endemic in southern regions of China.[1–3] It occurs in about 25 cases per 100000 people in this region, 25 times higher than the rest of the world. It is also quite common in Taiwan.[4,5] Despite an initial response to chemotherapy, the majority of patients with advanced NPC succumb to this disease.[6,7] Therefore, it is in an urgently need to search for new treatment and/or effective chemotherapeutical agents. For the past few years, we were especially interest in the identification of new compounds which selectively active against nasopharyngeal carcinoma. Certain quinolin-2(1*H*)-one, xanthone, carbazole, and flavonoid derivatives were synthesized for evaluation of their antiproliferarive and cardiovascular activities.[8–15] Among them, *N*-(biphenyl-4-yl)-2-(2-oxo-1,2-dihydroquinolin-7-yloxy)acetamide (**1**)[14] and *N*-(naphthalen-2-yl)-2-(4-oxo-2-phenyl-4*H*-chromen-7-yloxy)acetamide (**2**)[15] were found to be selectively active against the growth of NPC (NPC-TW01) with an IC_{50} value of <10 and 1.37 μM, respectively. More recently, we have prepared 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 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 (**3**) was the most active and selective against NPC-TW01 with an IC_{50} value of 0.6 μM.[16] In continuation of our studies to explore active and selective anti-NPC agents and establish structure–activity relationships, the present report describes the preparation of certain amide-containing anthraquinone, xanthone, and carbazole derivatives (target compounds) whose structures are similar to the lead compounds **1**–**3** (Fig. 1). Their 4-substituted *N*-phenyl counterparts have also been synthesized for antiproliferative evaluation.

Results and Discussion

Chemistry The preparation of amide-containing anthraquinone, xanthone, and carbazole derivatives is illustrated

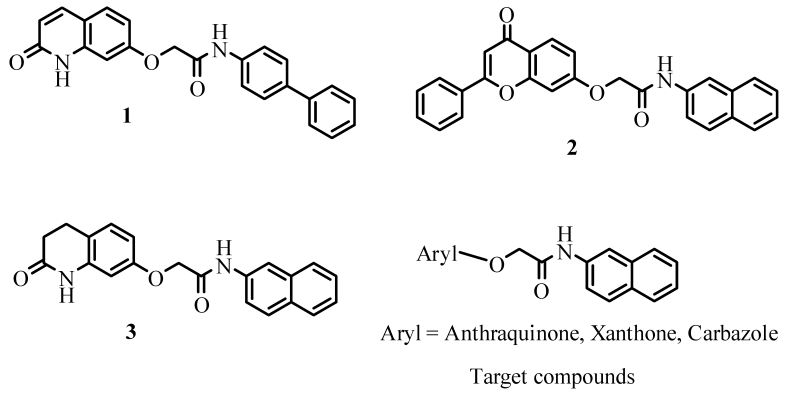

Fig. 1. Structures of Compounds **1**–**3** and Target Compounds

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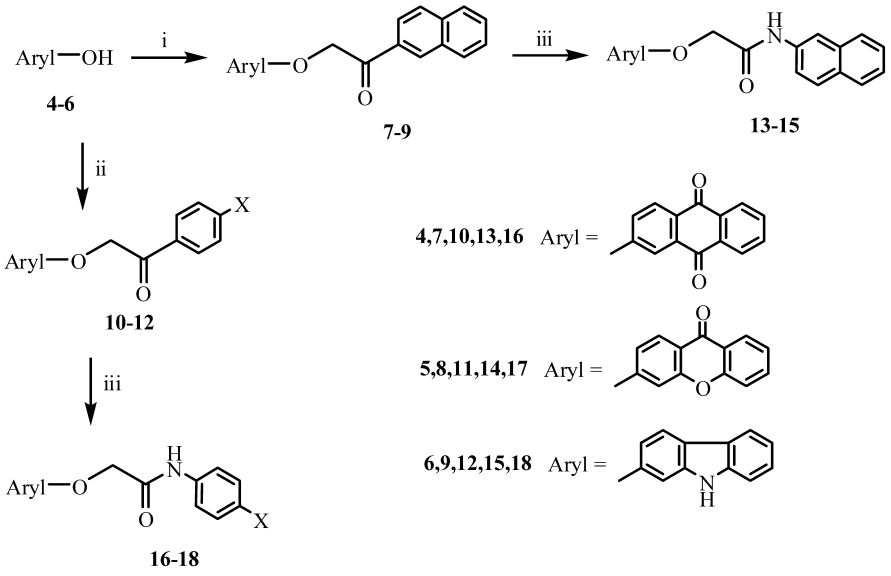

a: X = H; **b**: X = F; **c**: X = MeO; **d**: X = Ph

Reagents and conditions: (i) 2-(bromoacetyl)naphthalene / K_2CO_3 / DMF / rt; (ii) X-Ph-$COCH_2Br$ / K_2CO_3 / DMF / rt; (iii) NaN_3 / H_2SO_4 / rt.

Chart 1. Reagents and Conditions: (i) 2-((Bromoacetyl)naphthalene/K_2CO_3/DMF/rt; (ii) X-Ph-$COCH_2Br$/K_2CO_3/DMF/rt; (iii) NaN_3/H_2SO_4/rt

Table 1. Antiproliferative Activities of Amide-Containing Anthraquinone, Xanthone, and Carbazole Derivatives

Compds	Substituents		IC_{50} (μM)[a, b]		
	Aryl	R	NPC-TW01	NCI-H661	Jurkat
13	Anthraquinone-2-yl	Naph	2.62±0.39	30.56±5.5	37.18±2.97
16a	Anthraquinone-2-yl	Ph	8.62±0.49	20.33±1.20	33.79±2.70
16b	Anthraquinone-2-yl	4-F-Ph	8.09±0.32	6.88±0.89	25.58±2.04
16c	Anthraquinone-2-yl	4-MeO-Ph	5.14±0.26	7.60±0.23	37.29±3.73
16d	Anthraquinone-2-yl	4-Ph-Ph	20.32±1.01	24.91±3.74	22.11±2.21
14	Xanthone-3-yl	Naph	16.10±1.29	20.31±1.20	36.41±1.82
17a	Xanthone-3-yl	Ph	17.94±1.76	15.21±1.12	34.79±2.43
17b	Xanthone-3-yl	4-F-Ph	21.78±2.18	20.08±1.40	37.33±2.61
17c	Xanthone-3-yl	4-MeO-Ph	43.16±1.90	30.73±1.54	36.55±4.75
17d	Xanthone-3-yl	4-Ph-Ph	7.94±0.24	22.04±1.76	34.97±2.45
15	Carbazole-2-yl	Naph	11.09±0.55	11.04±1.66	25.91±0.78
18a	Carbazole-2-yl	Ph	42.77±0.23	16.54±0.83	30.71±0.31
18b	Carbazole-2-yl	4-F-Ph	11.87±0.47	28.05±3.65	24.46±3.18
18c	Carbazole-2-yl	4-MeO-Ph	13.68±0.41	22.31±2.23	22.66±1.82
18d	Carbazole-2-yl	4-Ph-Ph	16.68±1.00	16.10±1.77	18.54±0.56

a) Cells were treated with various concentrations of anthraquinone, xanthone, and carbazole derivatives for 72 h. Cell survival was determined by MTT assay. Drug molar concentration causing 50% cell growth inhibition (IC_{50}) was calculated. Each value represents the mean±S.D. of three independent experiments. *b*) NCI-H661: Human lung carcinoma; NPC-TW01: Human nasopharyngeal carcinoma; Jurkat: leukemia.

in Chart 1. Alkylation of 2-hydroxyanthraquinone (**4**) with 2-(bromoacetyl)naphthalene under basic conditions gave 2-(2-(naphthalen-2-yl)-2-oxoethoxy)anthracene-9,10-dione (**7**) which was then treated with H_2SO_4 and NaN_3 to afford 2-(9,10-dioxo-9,10-dihydroanthracen-2-yloxy)-*N*-(naphthalen-2-yl)acetamide (**13**) in a good overall yield. The same synthetic procedures were applied for the synthesis of xanthone counterpart **14** from its ketone precursor **8** which in turn was prepared *via* alkylation of 2-hydroxyxanthone (**5**). Accordingly, carbazole counterpart **15** was prepared from its ketone precursor **9** which in turn was prepared *via* alkylation of 2-hydroxycarbazole (**6**). Compounds **16a–d**, **17a–d**, and **18a–d** were also prepared by the same reaction sequences from their respective ketones **10a–d**, **11a–d**,[12] and **12a–d**[13] which in turn were prepared *via* alkylation of 2-hydroxyanthraquinone (**4**), 2-hydroxyxanthone (**5**), and 2-hydroxycarbazole (**6**) respectively. Structures of newly synthesized compounds were confirmed by NMR spectra and elementary analysis.

Cytotoxicity All compounds were evaluated *in vitro* against a 3-cell line panel consisting of NPC-TW01 (human nasopharyngeal carcinoma), NCI-H661 (human lung carcinoma), and Jurkat (leukemia). Results from Table 1 indicated 2-(9,10-dioxo-9,10-dihydroanthracen-2-yloxy)-*N*-(naphthalen-2-yl)acetamide (**13**) was the most active against NPC-TW01 with an IC_{50} value of 2.62 μM while its xanthone and carbazole counterparts, **14** and **15**, were inactive with an IC_{50} value of

Table 2. Compound **13** Arrested NPC-TW01 Cells at G_0/G_1 Phase

Cell distribution (%)	Control	24 h	48 h	72 h
G_0/G_1	40.1±5.2	41.6±3.8	52.2±5.9	77.0±9.3
S	25.7±5.4	26.1±5.1	29.5±4.9	8.0±2.0
G_2M	34.2±4.6	32.4±4.6	28.3±3.6	15.0±3.5
$SubG_1$	1.5±0.5	2.6±1.1	2.4±0.8	3.0±1.2

16.10 and 11.09 μM respectively. Replacement of *N*-naphthlen-2-yl moiety with phenyl group resulted in a decrease of antiproliferative activity in which 2-(9,10-dioxo-9,10-dihydroanthracen-2-yloxy)-*N*-phenylacetamide (**16a**) exhibited an IC_{50} value of 8.62 μM against NPC-TW01. Further substitution of *N*-phenyl group did not significantly enhance antitproliferative activity in which 4-fluoro derivative **16b** and 4-methoxy derivative **16c** exhibited an IC_{50} value of 8.09 and 5.14 μM respectively while 4-phenyl derivative **16d** was inactive with an IC_{50} value of 20.32 μM. These newly synthesized compounds are either weakly active or inactive against the growth of NCI-H460 and Jurkat cancer cells.

Compound **13** was found to be the most active against the growth of NPC-TW01 with an IC_{50} value of 2.62 μM and therefore, was subjected for further study on NPC-TW01 cell cycle distribution. Results from Table 2 revealed that compound **13** inhibited proliferation of NPC-TW01 by the alteration of cell division and the accumulation of cells in G_0/G_1 phase. Compound **13** was approximately four-folds less active than its dihydroquinolinone isomer **3** against the growth of NPC-TW01. However, the antiproliferative mechanism was different in which compound **13** induced cell-cycle arrest in G_0/G_1 phase while compound **3** induced cell-cycle arrest in S phase.

Conclusion

We have synthesized certain amide-containing anthraquinone, xanthone, and carbazole derivatives for antiproliferative evaluations against NPC-TW01, NCI-H661, and Jurkat cancer cells. Among them, 2-(9,10-dioxo-9,10-dihydroanthracen-2-yloxy)-*N*-(naphthalen-2-yl)acetamide (**13**) demonstrated the most active and selective cytotoxicity against NPC-TW01 cell lines with no significant cytotoxicity against NCI-H661 and Jurkat at a concentration of up to 30 μM. Flow cytometric analysis indicated that **13** inhibit the growth of NPC-TW01 cells by inducing cell cycle arrest in G_0/G_1 phase. Further structural optimization and mechanism studies on **13** are on-going.

Experimental

Synthesis. General TLC: precoated (0.2 mm) silica gel *60 F_{254}* plates from *EM Laboratories, Inc.*; detection by UV light (254 nm). mp: *Electrothermal IA9100* digital melting-point apparatus; uncorrected. ^{1}H-NMR spectra: *Varian-Unity-400* spectrometer at 400 or *Varian-Gemini-200* spectrometer at 200, chemical shifts δ in ppm with $SiMe_4$ as an internal standard (=0 ppm), coupling constants *J* in Hz. Elemental analyses were carried out on a *Heraeus CHN-O-Rapid* elemental analyzer, and results were within ±0.4% of calc. values.

Production of 7–9 and 10a–d. General Procedure 2-Hydroxyanthraquinone (**4**)/2-hydroxyxanthone (**5**)/2-hydroxycarbazole (**6**) (10 mmol), K_2CO_3 (10 mmol), and dry *N*,*N*-dimethylformamide (DMF) (50 mL) were stirred at room temperature (r.t.) for 30 min. To this soln. was added 2-(bromoacetyl)naphthalene/different substituents 2-bromoacetophenone (10 mmol) in dry DMF (10 mL) in one portion. The resulting mixture was stirred at r.t. for 24 h (TLC monitoring) and then poured into ice-water (100 mL). The yellow solid thus obtained was collected and purified by column chromatography on silica gel using CH_2Cl_2/MeOH 20 : 1. The proper fractions were combined and evaporated to furnish a residual solid which was crystallized from Et_2O and CH_2Cl_2.

2-(2-(Naphthalen-2-yl)-2-oxoethoxy)anthracene-9,10-dione (**7**): Yield 89%. mp 194–195°C. ^{1}H-NMR (DMSO-d_6) δ: 6.05 (s, 2H, OCH_2), 7.57 (dd, *J*=8.8, 2.8 Hz, 1H-C(3)), 7.66–7.67 (m, 1H, Ar-H), 7.68 (d, *J*=2.8 Hz, 1H-C(1)), 7.70–7.75 (m, 1H, Ar-H), 7.88–7.95 (m, 2H, Ar-H), 8.03–8.11 (m, 3H, Ar-H), 8.16–8.21 (m, 3H, Ar-H), 8.19 (d, *J*=8.8 Hz, 1H-C(4)), 8.83 (s, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6) δ: 70.69 (CH_2O), 111.17, 121.32, 123.23, 126.66, 126.71, 127.20, 127.81, 128.55, 129.03, 129.50, 129.61, 130.07, 131.37, 132.08, 133.06, 133.08, 134.19, 134.63, 135.03, 135.40, 162.88, 181.30, 182.38, 193.61 (C=O). *Anal.* Calcd for $C_{26}H_{16}O_4$: C 79.58, H 4.11. Found: C 79.35, H 4.20.

3-(2-(Naphthalen-2-yl)-2-oxoethoxy)-9*H*-xanthen-9-one (**8**): Yield 80%. mp 171–172°C. ^{1}H-NMR (DMSO-d_6) δ: 5.99 (s, 2H, OCH_2), 7.19 (dd, *J*=8.8, 2.4 Hz, 1H-C(2)), 7.32 (d, *J*=2.4 Hz, 1H-C(4)), 7.46–7.61 (m, 2H, Ar-H), 7.66–7.75 (m, 2H, Ar-H), 7.82–7.87 (m, 1H, Ar-H), 8.05 (d, *J*=8.8 Hz, 1H-C(1)), 8.09–8.20 (m, 5H, Ar-H), 8.32 (s, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6) δ: 70.75 (CH_2O), 101.54, 113.99, 115.15, 117.80, 121.11, 123.18, 124.27, 125.83, 127.10, 127.55, 127.73, 128.40, 128.91, 129.50, 129.97, 131.34, 132.00, 135.01, 135.29, 155.54, 157.34, 163.67, 174.84, 193.31 (C=O). *Anal.* Calcd for $C_{25}H_{16}O_4$: C 78.94, H 4.24. Found: C 78.91, H 4.27.

2-(9*H*-Carbazol-2-yloxy)-1-(naphthalen-2-yl)ethanone (**9**): Yield 93%. mp 176–177°C. ^{1}H-NMR (DMSO-d_6) δ: 5.79 (s, 2H, OCH_2), 6.89 (dd, *J*=8.8, 2.0 Hz, 1H-C(3)); 7.02 (d, *J*=2.0 Hz, 1H-C(1)), 7.09–7.13 (m, 1H, Ar-H), 7.27–7.31 (m, 1H, Ar-H), 7.40–7.42 (m, 1H, Ar-H), 7.65–7.74 (m, 2H, Ar-H), 7.98–8.10 (m, 4H, Ar-H), 7.99 (d, *J*=8.8 Hz, 1H-C(4)), 8.16–8.18 (m, 1H, Ar-H), 8.84 (s, 1H, Ar-H), 11.08 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 70.50 (CH_2O), 95.59, 107.97, 110.51, 116.50, 118.46, 119.22, 120.79, 122.45, 123.25, 124.15, 127.04, 127.68, 128.40, 128.82, 129.50, 129.82, 131.69, 132.03, 135.21, 139.68, 140.78, 157.00, 194.78 (C=O). *Anal.* Calcd for $C_{24}H_{17}NO_2 \cdot 0.1\ H_2O$: C 81.61, H 4.92, N 3.97. Found: C 81.45, H 4.93, N 3.99.

2-(2-Oxo-2-phenylethoxy)anthracene-9,10-dione (**10a**): Yield 86%. mp 208–209°C. ^{1}H-NMR (DMSO-d_6) δ: 5.93 (s, 2H, OCH_2), 7.53 (dd, *J*=8.8, 2.8 Hz, 1H-C(3)), 7.60–7.62 (m, 2H, Ar-H), 7.63 (d, *J*=2.8 Hz, 1H-C(1)), 7.73–7.76 (m, 1H, Ar-H), 7.89–7.96 (m, 2H, Ar-H), 8.06–8.12 (m, 2H, Ar-H), 8.19 (d, *J*=8.8 Hz, 1H-C(4)), 8.20–8.22 (m, 2H, Ar-H). ^{13}C-NMR (DMSO-d_6) δ: 70.69 (CH_2O), 111.19, 121.36, 126.73, 126.79, 128.02, 128.99, 129.56, 133.13, 134.15, 134.29, 134.72, 135.06, 162.89, 181.40, 182.45, 193.83 (C=O). *Anal.* Calcd for $C_{22}H_{14}O_4$: C 77.18, H 4.12. Found: C 76.93, H4.22.

2-(2-(4-Fluorophenyl)-2-oxoethoxy)anthracene-9,10-dione (**10b**): Yield 82%. mp 221–222°C. ^{1}H-NMR (DMSO-d_6) δ: 5.91 (s, 2H, OCH_2), 7.43–7.48 (m, 2H, Ar-H), 7.52 (dd, *J*=8.8, 2.8 Hz, 1H-C(3)), 7.64 (d, *J*=2.8 Hz, 1H-C(1)), 7.89–7.96 (m, 2H, Ar-H), 8.13–8.17 (m, 3H, Ar-H), 8.18 (d, *J*=8.8 Hz, 1H-C(4)), 8.21–8.22 (m, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6) δ: 70.56 (CH_2O), 111.18, 115.90, 116.12, 121.29, 126.68, 126.73,

129.49, 130.87, 130.90, 131.05, 131.14, 133.09, 134.22, 134.66, 135.03, 162.81, 164.23, 166.74, 181.33, 182.39, 192.42 (C=O). *Anal.* Calcd for $C_{22}H_{13}FO_4$: C 73.33, H 3.64. Found: C 73.25, H 3.69.

2-(2-(4-Methoxyphenyl)-2-oxoethoxy)anthracene-9,10-dione (**10c**): Yield 89%. mp 186–187°C. ^{1}H-NMR (DMSO-d_6) δ: 3.89 (s, 3H, MeO), 5.85 (s, 2H, OCH_2), 7.12–7.15 (m, 2H, Ar-H), 7.50 (dd, J=8.8, 2.8 Hz, 1H-C(3)), 7.60 (d, J=2.8 Hz, 1H-C(1)), 7.88–7.95 (m, 2H, Ar-H), 8.03–8.06 (m, 2H, Ar-H), 8.15–8.22 (m, 2H, Ar-H), 8.18 (d, J=8.8 Hz, 1H-C(4)). ^{13}C-NMR (DMSO-d_6) δ: 55.66 (MeO), 70.33 (CH_2O), 111.09, 114.14, 121.29, 126.65, 126.71, 126.98, 129.46, 130.33, 133.07, 134.19, 134.63, 134.98, 162.94, 163.78, 181.30, 182.37, 191.99 (C=O). *Anal.* Calcd for $C_{23}H_{16}O_5$: C 74.19, H 4.33. Found: C 74.12, H 4.33.

2-(2-(Biphenyl-4-yl)-2-oxoethoxy)anthracene-9,10-dione (**10d**): Yield 92%. mp 195–196°C. ^{1}H-NMR (DMSO-d_6) δ: 5.96 (s, 2H, OCH_2), 7.45–7.48 (m, 1H, Ar-H), 7.52–7.54 (m, 2H, Ar-H), 7.55 (dd, J=8.8, 2.8 Hz, 1H-C(3)), 7.65 (d, J=2.8 Hz, 1H-C(1)), 7.79–7.81 (m, 2H, Ar-H), 7.89–7.96 (m, 4H, Ar-H), 8.15–8.20 (m, 3H, Ar-H), 8.20 (d, J=8.8 Hz, 1H-C(4)), 8.21–8.22 (m, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6) δ: 70.71 (CH_2O), 111.21, 121.36, 126.73, 126.78, 127.11, 128.63, 128.77, 129.20, 129.56, 132.91, 133.13, 134.28, 134.71, 135.07, 138.82, 145.43, 162.91, 181.39, 182.46, 193.37 (C=O). *Anal.* Calcd for $C_{28}H_{18}O_4$: C 80.37, H 4.34. Found: C 80.29, H 4.37.

Production of 13–15, 16a–d, 17a–d, and 18a–d. General Procedure A solution of **7**/**8**/**9**/**10a–d**/**11a–d**/**12a–d** (1 mmol) in H_2SO_4 (3 mL) was stirred at r.t. for 10 min. To this solution, was added sodium azide (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 on silica gel using CH_2Cl_2/MeOH 10 : 1. The proper fractions were combined and evaporated to furnish a residual solid which was crystallized from Et_2O and CH_2Cl_2.

2-(9,10-Dioxo-9,10-dihydroanthracen-2-yloxy)-*N*-(naphthalen-2-yl)acetamide (**13**): Yield 86%. mp 229–230°C. ^{1}H-NMR (DMSO-d_6) δ: 5.06 (s, 2H, OCH_2), 7.41–7.50 (m, 2H, Ar-H), 7.57 (dd, J=8.8, 2.4 Hz, 1H-C(3)), 7.67–7.69 (m, 1H, Ar-H), 7.74 (d, J=2.4 Hz, 1H-C(1)), 7.82–7.92 (m, 5H, Ar-H), 8.19–8.32 (m, 3H, Ar-H), 8.22 (d, J=8.8 Hz, 1H-C(4)), 10.48 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 67.18 (CH_2O), 111.23, 115.94, 120.15, 121.24, 124.84, 126.49, 126.66, 126.72, 126.85, 127.31, 127.44, 128.43, 129.52, 129.95, 133.03, 133.25, 134.21, 134.64, 134.97, 135.81, 162.58, 165.96 (C=O), 181.32, 181,35. *Anal.* Calcd for $C_{26}H_{17}NO_4$: C 76.65, H 4.21, N 3.44. Found: C 76.45, H 4.28, N 3.42.

N-(Naphthalen-2-yl)-2-(9-oxo-9*H*-xanthen-3-yloxy)-acetamide (**14**): Yield 89%. mp 234–235°C. ^{1}H-NMR (DMSO-d_6) δ: 5.02 (s, 2H, OCH_2), 7.21 (dd, J=8.8, 2.4 Hz, 1H-C(2)), 7.24 (d, J=2.4 Hz, 1H-C(4)), 7.42–7.50 (m, 3H, Ar-H), 7.63–7.69 (m, 2H, Ar-H), 7.83–7.88 (m, 3H, Ar-H), 7.91 (d, J=8.8 Hz, 1H-C(1)), 8.16–8.20 (m, 2H, Ar-H), 8.33–8.34 (m, 1H, Ar-H), 10.44 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 67.44 (CH_2O), 101.62, 114.06, 115.44, 115.93, 118.00, 120.19, 121.22, 124.44, 124.90, 125.95, 126.56, 127.39, 127.52, 127.76, 128.51, 130.01, 133.34, 135.19, 135.93, 155.67, 157.37, 163.58, 166.01 (C=O), 175.00. *Anal.* Calcd for $C_{25}H_{17}NO_4 \cdot 0.25\ H_2O$: C 75.09, H 4.41, N 3.50. Found: C 74.97, H 4.40, N 3.49.

2-(9*H*-Carbazol-2-yloxy)-*N*-(naphthalen-2-yl)acetamide (**15**): Yield 83%. mp 274–275°C. ^{1}H-NMR (DMSO-d_6) δ: 4.85 (s, 2H, OCH_2), 6.92 (dd, J=8.8, 2.0 Hz, 1H-C(3)), 7.07 (d, J=2.0 Hz, 1H-C(1)), 7.10–7.13 (m, 1H, Ar-H), 7.27–7.31 (m, 1H, Ar-H), 7.41–7.50 (m, 3H, Ar-H), 7.70–7.73 (m, 1H, Ar-H), 7.82–7.86 (m, 2H, Ar-H), 7.89 (d, J=8.8 Hz, 1H-C(4)), 7.80–8.03 (m, 2H, Ar-H), 8.33–8.36 (m, 1H, Ar-H), 10.36 (s, 1H, CONH), 11.18 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 67.79 (CH_2O), 95.75, 108.15, 110.63, 115.98, 116.83, 118.59, 119.37, 120.33, 120.93, 122.51, 124.33, 124.80, 126.47, 127.33, 127.46, 128.36, 129.96, 133.31, 136.01, 139.80, 140.85, 156.95, 167.09 (C=O). *Anal.* Calcd for $C_{23}H_{17}N_2O_2 \cdot 0.2\ H_2O$: C 77.90, H 5.02, N 7.57. Found: C 77.76, H 5.02, N 7.54.

2-(9,10-Dioxo-9,10-dihydroanthracen-2-yloxy)-*N*-phenyl-acetamide (**16a**): Yield 92%. mp 204–205°C. ^{1}H-NMR (DMSO-d_6) δ: 4.98 (s, 2H, OCH_2), 7.09–7.12 (m, 1H, Ar-H), 7.33–7.37 (m, 2H, Ar-H), 7.54 (dd, J=8.8, 2.4 Hz, 1H-C(3)), 7.63–7.65 (m, 2H, Ar-H), 7.70 (d, J=2.4 Hz, 1H-C(1)), 7.89–7.95 (m, 2H, Ar-H), 8.18–8.22 (m, 2H, Ar-H), 8.21 (d, J=8.8 Hz, 1H-C(4)), 10.27 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 67.83 (CH_2O), 111.86, 120.42, 121.96, 124.56, 127.38, 127.45, 127.55, 129.50, 130.23, 133.73, 134.94, 135.37, 135.67, 138.90, 163.27, 166.40 (C=O), 182.05, 183.07. *Anal.* Calcd for $C_{22}H_{15}NO_4$: C 73.94, H 4.23, N 3.92. Found: C 73.91, H 4.25, N 3.92.

2-(9,10-Dioxo-9,10-dihydroanthracen-2-yloxy)-*N*-(4-fluorophenyl)acetamide (**16b**): Yield 98%. mp 215–216°C. ^{1}H-NMR (DMSO-d_6) δ: 4.97 (s, 2H, OCH_2), 7.16–7.21 (m, 2H, Ar-H), 7.54 (dd, J=8.8, 2.4 Hz, 1H-C(3)), 7.64–7.68 (m, 2H, Ar-H), 7.70 (d, J=2.4 Hz, 1H-C(1)), 7.91–7.94 (m, 2H, Ar-H), 8.19–8.22 (m, 2H, Ar-H), 8.21 (d, J=8.8 Hz, 1H-C(4)), 10.30 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 67.05 (CH_2O), 111.18, 115.18, 115.41, 121.13, 121.49, 121.57, 126.60, 126.66, 126.81, 129.46, 132.97, 134.15, 134.51, 134.53, 134.59, 134.90, 157.04, 159.43, 162.44, 165.58 (C=O), 181.26, 182.29. *Anal.* Calcd for $C_{22}H_{14}FNO_4$: C 70.40, H 3.76, N 3.73. Found: C 70.37, H 3.88, N 3.76.

2-(9,10-Dioxo-9,10-dihydroanthracen-2-yloxy)-*N*-(4-methoxyphenyl)acetamide (**16c**): Yield 82%. mp 204–205°C. ^{1}H-NMR (DMSO-d_6) δ: 3.73 (s, 3H, MeO), 4.95 (s, 2H, OCH_2), 6.90–6.92 (m, 2H, Ar-H), 7.53 (dd, J=8.8, 2.8 Hz, 1H-C(3)), 7.54–7.56 (m, 2H, Ar-H), 7.70 (d, J=2.8 Hz, 1H-C(1)), 7.91–7.94 (m, 2H, Ar-H), 8.18–8.21 (m, 2H, Ar-H), 8.20 (d, J=8.8 Hz, 1H-C(4)), 10.30 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 55.86 (MeO), 67.88 (CH_2O); 111.97, 114.58, 121.92, 122.06, 127.38, 127.45, 127.55, 130.22, 132.00, 133.76, 134.92, 135.35, 135.68, 156.30, 163.28, 165.90 (C=O), 182.03, 183.07. *Anal.* Calcd for $C_{23}H_{17}NO_5$: C 71.31, H 4.42, N 3.62. Found: C 71.14, H 4.42, N 3.62.

N-(Diphenyl-4-yl)-2-(9,10-dioxo-9,10-dihydroanthracen-2-yloxy)acetamide (**16d**). Yield 87%. mp 254–255°C. ^{1}H-NMR (DMSO-d_6) δ: 5.02 (s, 2H, OCH_2), 7.32–7.36 (m, 1H, Ar-H), 7.43–7.47 (m, 2H, Ar-H), 7.55 (dd, J=8.8, 2.8 Hz, 1H-C(3)), 7.65–7.67 (m, 4H, Ar-H), 7.72 (d, J=2.8 Hz, 1H-C(1)), 7.74–7.76 (m, 2H, Ar-H), 7.90–7.95 (m, 2H, Ar-H), 8.19–8.22 (m, 2H, Ar-H), 8.22 (d, J=8.8 Hz, 1H-C(4)), 10.35 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 67.91 (CH_2O), 111.91, 120.76, 121.98, 126.98, 127.39, 127.45, 127.59, 127.68, 127.82, 129.61, 130.25, 133.76, 134.94, 135.37, 135.70, 136.18, 138.41, 140.27, 163.29, 166.46 (C=O), 182.05, 183.08. *Anal.* Calcd. for $C_{28}H_{19}NO_4$: C 77.59, H 4.42, N 3.23. Found: C 77.39, H 4.48, N 3.27.

2-(9-Oxo-9*H*-xanthen-3-yloxy)-*N*-phenylacetamide (**17a**):

Yield 86%. mp 229–230°C. ^{1}H-NMR (DMSO-d_6) δ: 4.95 (s, 2H, OCH_2), 7.09–7.12 (m, 1H, Ar-H), 7.18 (dd, J=8.4, 2.4 Hz, 1H-C(2)), 7.19 (d, J=2.4 Hz, 1H-C(4)), 7.33–7.37 (m, 2H, Ar-H), 7.46–7.50 (m, 1H, Ar-H), 7.63–7.67 (m, 2H, Ar-H), 7.64 (d, J=8.4 Hz, 1H-C(1)), 7.83–7.87 (m, 1H, Ar-H), 8.14–8.19 (m, 2H, Ar-H), 10.24 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 67.41 (CH_2O), 101.57, 114.01, 115.42, 117.98, 119.71, 121.21, 123.85, 124.42, 125.93, 127.74, 128.83, 135.16, 138.31, 155.65, 157.34, 163.52, 165.70 (C=O), 174.98. *Anal.* Calcd for $C_{21}H_{15}NO_4$: C 73.03, H 4.38, N 4.06. Found: C 72.90, H 4.40, N 3.94.

N-(4-Fluorophenyl)-2-(9-oxo-9*H*-xanthen-3-yloxy)acetamide (**17b**): Yield 84%. mp 247–248°C. ^{1}H-NMR (DMSO-d_6) δ: 4.94 (s, 2H, OCH_2), 7.18 (dd, J=8.4, 2.8 Hz, 1H-C(2)), 7.20 (d, J=2.8 Hz, 1H-C(4)), 7.21–7.22 (m, 2H, Ar-H), 7.46–7.50 (m, 1H, Ar-H), 7.64 (d, J=8.4 Hz, 1H-C(1)), 7.66–7.69 (m, 2H, Ar-H), 7.83–7.88 (m, 1H, Ar-H), 8.14–8.19 (m, 2H, Ar-H), 10.29 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 67.38 (CH_2O), 101.61, 114.02, 115.32, 115.46, 115.54, 118.00, 121.22, 121.59, 121.67, 124.45, 125.95, 127.77, 134.66, 134.69, 135.19, 155.68, 157.18, 157.35, 159.56, 163.48, 165.70 (C=O), 175.01. *Anal.* Calcd for $C_{21}H_{14}FNO_4$: C 69.42, H 3.88, N 3.85. Found: C 69.22, H 3.93, N 3.80.

N-(4-Methoxyphenyl)-2-(9-oxo-9*H*-xanthen-3-yloxy)-acetamide (**17c**): Yield 81%. mp 194–195°C. ^{1}H-NMR (DMSO-d_6) δ: 3.71 (s, 3H, MeO), 4.88 (s, 2H, OCH_2), 6.88 (dd, J=8.8, 2.4 Hz, 1H-C(2)), 6.89–6.90 (m, 1H, Ar-H), 7.14 (d, J=2.4 Hz, 1H-C(4)), 7.15–7.17 (m, 1H, Ar-H), 7.44–7.54 (m, 3H, Ar-H), 7.62 (d, J=8.8 Hz, 1H-C(1)), 7.81–7.84 (m, 1H, Ar-H), 8.12–8.17 (m, 2H, Ar-H), 10.06 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 55.86 (MeO), 68.10 (CH_2O); 102.24, 114.59, 114.72, 116.07, 118.66, 121.89, 122.01, 125.10, 126.60, 128.40, 132.03, 135.84, 156.29, 156.33, 158.01, 164.19, 165.87 (C=O), 175.65. *Anal.* Calcd for $C_{22}H_{17}NO_5$: C 70.39, H 4.56, N 3.73. Found: C 70.06, H 4.59, N 3.72.

N-(Biphenyl-4-yl)-2-(9-oxo-9*H*-xanthen-3-yloxy)acetamide (**17d**): Yield 85%. mp 275–276°C. ^{1}H-NMR (DMSO-d_6) δ: 4.97 (s, 2H, OCH_2), 7.18 (dd, J=8.8, 2.4 Hz, 1H-C(2)), 7.21 (d, J=2.4 Hz, 1H-C(4)), 7.31–7.35 (m, 1H, Ar-H), 7.42–7.50 (m, 3H, Ar-H), 7.64–7.67 (m, 5H, Ar-H), 7.73–7.74 (m, 1H, Ar-H), 7.75 (d, J=8.8 Hz, 1H-C(1)), 7.83–7.87 (m, 1H, Ar-H), 8.15–8.19 (m, 2H, Ar-H), 10.34 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 67.44 (CH_2O), 101.60, 114.03, 115.45, 117.99, 120.05, 121.22, 124.44, 125.94, 126.31, 127.01, 127.15, 127.75, 128.93, 135.17, 135.49, 137.76, 139.60, 155.67, 157.35, 163.52, 165.76 (C=O), 174.99. *Anal.* Calcd for $C_{27}H_{19}NO_4$: C 76.95, H 4.54, N 3.32. Found: C 76.82, H 4.46, N 3.21.

2-(9*H*-Carbazol-2-yloxy)-*N*-phenylacetamide (**18a**): Yield 97%. mp 261–262°C. ^{1}H-NMR (DMSO-d_6) δ: 4.78 (s, 2H, OCH_2), 6.89 (dd, J=8.4, 2.0 Hz, 1H-C(3)), 7.03 (d, J=2.0 Hz, 1H-C(1)), 7.09–7.14 (m, 2H, Ar-H), 7.30–7.36 (m, 3H, Ar-H), 7.41–7.43 (m, 1H, Ar-H), 7.66–7.68 (m, 2H, Ar-H), 7.99–8.02 (m, 1H, Ar-H), 8.01 (d, J=8.4 Hz, 1H-C(4)), 10.14 (s, 1H, CONH), 11.16 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 68.39 (CH_2O), 96.40, 108.81, 111.33, 117.49, 119.31, 120.06, 120.46, 121.62, 123.19, 124.44, 125.04, 129.43, 139.06, 140.47, 141.51, 157.60, 167.51 (C=O). *Anal.* Calcd for $C_{20}H_{16}N_2O_2$: C 75.93, H 5.10, N 8.86. Found: C 75.61, H 5.15, N 8.89.

2-(9*H*-Carbazol-2-yloxy)-*N*-(4-fluorophenyl)acetamide (**18b**): Yield 89%. mp 259–260°C. ^{1}H-NMR (DMSO-d_6) δ: 4.78 (s, 2H, OCH_2), 6.90 (dd, J=8.8, 2.0 Hz, 1H-C(3)), 7.04 (d, J=2.0 Hz, 1H-C(1)), 7.10–7.20 (m, 3H, Ar-H), 7.28–7.32 (m, 1H, Ar-H), 7.41–7.43 (m, 1H, Ar-H), 7.68–7.72 (m, 2H, Ar-H), 7.99–8.01 (m, 1H, Ar-H), 8.01 (d, J=8.8 Hz, 1H-C(4)), 10.21 (s, 1H, CONH), 11.17 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 68.39 (CH_2O), 96.43, 108.81, 111.33, 115.88, 116.11, 117.52, 119.30, 120.06, 121.62, 122.32, 122.39, 123.19, 125.05, 135.43, 135.46, 140.48, 141.51, 157.57, 157.78, 160.17, 167.48 (C=O). *Anal.* Calcd for $C_{20}H_{15}FN_2O_2$: C 71.85, H 4.52, N 8.38. Found: C 71.54, H 4.65, N 8.37.

2-(9*H*-Carbazol-2-yloxy)-*N*-(4-methoxyphenyl)acetamide (**18c**): Yield 82%. mp 254–255°C. ^{1}H-NMR (DMSO-d_6) δ: 3.73 (s, 3H, MeO), 4.74 (s, 2H, OCH_2), 6.90 (dd, J=8.4, 2.4 Hz, 1H-C(3)), 6.91–6.92 (m, 2H, Ar-H), 7.04 (d, J=2.4 Hz, 1H-C(1)), 7.10–7.14 (m, 1H, Ar-H), 7.28–7.43 (m, 2H, Ar-H), 7.56–7.58 (m, 2H, Ar-H), 7.99–8.01 (m, 1H, Ar-H), 8.00 (d, J=8.4 Hz, 1H-C(4)), 10.00 (s, 1H, CONH), 11.16 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 55.86 (MeO), 68.38 (CH_2O); 96.40, 108.83, 111.32, 114.52, 117.47, 119.31, 120.06, 121.60, 122.14, 123.18, 125.04, 132.10, 140.47, 141.51, 156.26, 157.60, 167.03 (C=O). *Anal.* Calcd for $C_{21}H_{18}N_2O_3 \cdot 0.25\ H_2O$: C 71.88, H 5.32, N 7.98. Found: C 72.24, H 5.31, N 7.95.

2-(9*H*-Carbazol-2-yloxy)-*N*-(biphenyl-4-yl)acetamide (**18d**): Yield 94%. mp >300°C. ^{1}H-NMR (DMSO-d_6) δ: 4.81 (s, 2H, OCH_2), 6.91 (dd, J=8.4, 2.0 Hz, 1H-C(3)), 7.05 (d, J=2.0 Hz, 1H-C(1)), 7.10–7.13 (m, 1H, Ar-H), 7.27–7.35 (m, 2H, Ar-H), 7.41–7.46 (m, 3H, Ar-H), 7.62–7.67 (m, 4H, Ar-H), 7.78–7.80 (m, 2H, Ar-H), 7.99–8.01 (m, 1H, Ar-H), 8.01 (d, J=8.4 Hz, 1H-C(4)), 10.27 (s, 1H, CONH), 11.19 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 67.75 (CH_2O), 95.70, 108.17, 110.67, 116.82, 118.63, 119.42, 120.11, 120.98, 122.53, 124.38, 126.32, 126.96, 127.13, 128.94, 135.38, 137.93, 139.65, 139.82, 140.86, 156.95, 166.92 (C=O). *Anal.* Calcd for $C_{26}H_{20}N_2O_2 \cdot 0.5\ H_2O$: C 77.79, H 5.28, N 6.98. Found: C 77.76, H 5.17, N 6.88.

Antiproliferative Activity Cell Lines—Human non-small cell lung carcinoma (NCI-H661) and T-cell leukemia (Jurkat) were purchased from American Type Culture Collection (ATCC; Rockville, MD, U.S.A.). 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.

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 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (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 (IC_{50}).[17]

Cell-Cycle Analysis—Exponentially growing cells were incubated with various concentrations of the tested compounds for the indicated times. The cells were then fixed, incubated with RNase, and stained with 50 μg/mL of propidium iodide. DNA content was evaluated on a Becton Dickinson FACScan flow cytometer and the percentage of cells in various cell-cycle phases was determined by using the ModFit LT software

(Verity Software House, Inc.). For each analysis, 10000 events were recorded.

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