ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

Bicyclic Chalcones as Mitotic Inhibitors for Overcoming Androgen Receptor-Independent and Multidrug-Resistant Prostate Cancer

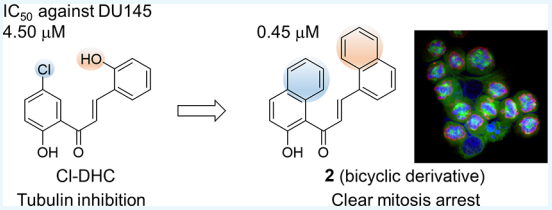
Yohei Saito, Atsushi Mizokami, Sayaka Maeda, Kyoko Takahashi, Kouji Izumi, Masuo Goto, and Kyoko Nakagawa-Goto*

Cite This: *ACS Omega* 2021, 6, 4842−4849

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: To improve the biological effects of the lead compound 5′-chloro-2,2′-dihydroxychalcone (Cl-DHC), bicyclic aromatic chalcones were designed, synthesized, and evaluated against androgen-independent prostate cancer (PCa) DU145 and PC-3 cell proliferation. Newly synthesized binaphthyl derivatives **2** and **3** suppressed the proliferation of these two cell lines and also taxane-resistant prostate cancer cell lines at a submicromolar level. The two compounds were 4−18 times more potent than the parent molecule Cl-DHC. A structure−activity relationship analysis revealed that the orientation of the 10π-electron ring-A naphthalene had a significant effect on the activity. Mode-of-action studies in KB-VIN cells demonstrated that **2** and **3** arrested cells in mitosis at prometaphase and metaphase followed by induction of sub-G1 accumulation. Thus, **2** and **3** have good potential as leads for continued development of treatments for cancers especially for not only androgen-independent PCa but also multidrug-resistant tumors.



INTRODUCTION

The incidence of prostate cancer (PCa) has increased recently in Asia, probably due to the prevalence of Westernized diets, whereas the survival rate from PCa has improved significantly due to early detection and effective treatments.[1] The hormonal therapy can be applied initially to control androgen receptor (AR) activity; however, this treatment is not effective permanently and the disease progresses to castration-resistant PCa (CRPC) after several years. CRPC resists hormonal therapy and induces serious problems, such as recurrence and metastasis. CRPC avoids hormonal therapy through mutations on the AR or the activation of androgen-independent pathways.[2] Taxane-derived antineoplastic agents are generally prescribed for CPRC; however, the progress of drug resistance always compromises successful treatment. Therefore, solutions are urgently needed for the problems of existing drugs.

Chalcone (1,3-diphenyl-2-propen-1-one) is a known biosynthetic precursor of other flavonoids, such as flavones, isoflavones, and flavanones, and is abundantly distributed in the plant kingdom. Its attractive biological profiles including antiproliferative activities[3,4] have intrigued researchers and encouraged the synthesis of various derivatives to improve the activity of interest.[5] We previously found that 5′-chloro-2,2′-dihydroxychalcone (Cl-DHC), inspired by the compound 2′-hydroxyflavanone,[6] inhibited androgen receptor (AR) activity and PCa cell proliferation by inducing tubulin depolymerization.[7]

In addition, naphthalene is an aromatic bicyclic compound with a 10π-electron system that is mostly present in natural products as a naphthoquinone.[8] Naphthalene is also known as a privileged skeleton with an attractive platform in medicinal chemistry.[9] Therefore, we incorporated the naphthalene structure into chalcones and synthesized various derivatives to improve their potential antitumor activities. Our goal was to create effective compounds against CRPC and to evaluate structure−activity relationships among the bicyclic chalcone derivatives.

We designed and synthesized 15 derivatives with bicyclic aromatic structures (Figure 1) and evaluated their antiproliferative activity against the DU145 and PC-3 androgen-independent PCa cell lines (CRPC cell lines). Then, selected compounds were further evaluated for growth inhibitory effect against various human tumor cell lines, including taxane-resistant PCa cell lines and a multidrug-resistant (MDR) subline. Furthermore, mechanism-of-action studies were performed using flow cytometric analysis and immunocytochemical staining. Our studies demonstrate the potential of bicyclic chalcone derivatives as drug candidates for the treatment of AR-independent PCa, including CRPC.

RESULTS AND DISCUSSION

Chemistry. Our primary focus in this investigation was to generate bicyclic aromatic chalcone derivatives with a 10(14)

Received: November 30, 2020
Accepted: December 29, 2020
Published: February 9, 2021

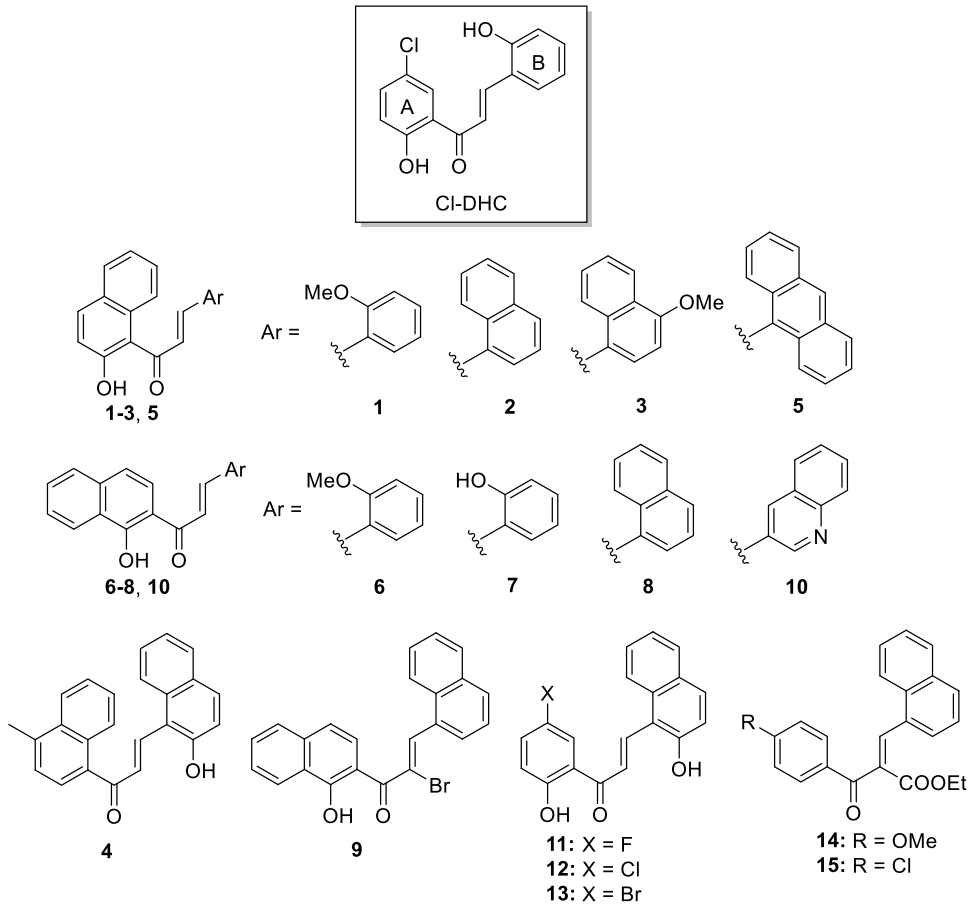
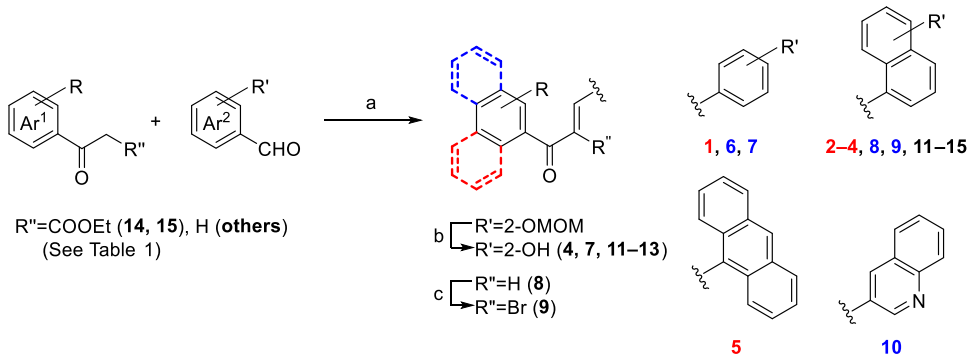


Figure 1. Structures of synthesized chalcones.

Scheme 1. Synthesis of Chalcones[a,b]



[a]Reagents and conditions: (a) (except for **14** and **15**) 40% KOH, EtOH, room temp.; (a) (for **14** and **15**) piperidine, AcOH, MS 4 Å, reflux; (b) 1% H_2SO_4, AcOH, room temp.; (c) DMP, Et_4NBr, CH_2Cl_2, room temp. [b]Overall yield from the related acetophenone.

π-electron system replacing either the 6π-electron ring-A, ring-B, or both ring-A and ring-B of the chalcone core (ring-A = 1-phenyl and ring-B = 3-phenyl of the basic 1,3-diphenyl-2-propen-1-one structure). 1-Acetylnaphthalene and 2-acetylnaphthalene were selected as 10π-electron bicyclic ring-A systems in the chalcone skeleton of the new derivatives. The 10π-electrons in the resulting naphthyl chalcones are oriented in different directions relative to the rest of the molecule, which might affect the biological activity.

Bicyclic chalcone derivatives **1**−**13** were obtained via a Claisen−Schmidt condensation of a substituted aryl methyl ketone and an appropriate aromatic aldehyde in the presence of aqueous KOH followed, as needed, by removal of the methoxymethyl (MOM) ether protecting groups under acidic conditions (Scheme 1). Chalcone **9** was prepared by bromination at the α-position of the α,β-unsaturated ketone (enone) of **8** with Dess−Martin periodinane (DMP) and tetraethylammonium bromide.[10] Besides bromine, an ethyl carboxylate was also added at this position. These two substituents could exert electron-withdrawing effects on the enone between the two aromatic ring systems, which might act as a Michael acceptor for various nucleophilic biomolecules. Derivatives **14** and **15** were synthesized through a Knoevenagel condensation of a substituted ethyl benzoylacetate and 1-

https://dx.doi.org/10.1021/acsomega.0c05822
ACS Omega 2021, 6, 4842−4849

naphthaldehyde in the presence of piperidine and acetic acid. Most of reactions proceeded smoothly and the target compounds were obtained in relatively good yields. Exceptionally, the difficulty of purification gave the low yield of compound **10**. Figure 1 contains the structures of the synthetic target compounds. Compounds **1**,[11] **2**,[12] **5**,[13] **6**,[14] **7**,[15] and **8**[16] were reported previously.

Biological Evaluation. *Antiproliferative Activity of Compounds against AR-Independent Cells.* All synthesized derivatives were first evaluated for antiproliferative activity against two AR-independent cell lines, DU145 and PC-3 (Table 1).

Table 1. Antiproliferative Activity against Androgen-Independent Prostate Cancer Cell Lines, DU145 and PC-3

	cell lines/IC_{50} (μM)[a]			cell lines/IC_{50} (μM)[a]	
compounds	DU145	PC-3	compounds	DU145	PC-3
1	>5	>5	**9**	1.93	>5
2	0.45	0.53	**10**	>5	>5
3	0.71	0.64	**11**	4.38	>5
4	1.71	1.56	**12**	4.05	3.88
5	>5	>5	**13**	4.05	>5
6	3.22	3.84	**14**	1.69	3.13
7	>5	>5	**15**	>5	>5
8	>5	>5			

[a]The concentration of compound that caused 50% reduction of cell growth relative to untreated cells determined by cell counting.

Chalcones **1**−**5** and **6**−**10** were produced from 1-acetylnaphthalene and 2-acetylnaphthalene, respectively; the 10π-electron ring-A systems are oriented differently as seen in Figure 1. In contrast, chalcones **11**−**15** contain a 6π-electron benzene rather than a naphthalene as the ring-A unit. Among all compounds tested, bi-naphthyl chalcones **2** and **3** with naphthalenes at both ends of the enone showed the most potent antiproliferative activity against DU145 and PC-3 cell lines (IC_{50} 0.45−0.53 and 0.64−0.71 μM, respectively) (Table 1). These two compounds were 4−18 times more potent compared to the parent molecule 5′-chloro-2,2′-dihydroxychalcone (Cl-DHC) (IC_{50} 4.50 and 1.52 μM, respectively).[7] Structurally, compounds **2** and **8** differ in the carbon connecting the naphthalene to the enone carbonyl and the corresponding hydroxy position on the naphthalene. Biologically, compound **8** was clearly less potent than **2**; thus, the orientation of the 10π-electron system affected the antiproliferative activity. The 1-(2-hydroxynaphthalen-1-yl) unit found in **2** was more favorable than the 1-(1-hydroxynaphthalen-2-yl) unit found in **8**.

From the comparisons of **2** with the inactive **1** and **5** (IC_{50} > 5 μM), a naphthalene ring-B unit was more effective than methoxybenzene (**1**) or anthracene (**5**). Compounds **2** and **3**, which contain an unsubstituted or 4-methoxy-substituted naphthalen-1-yl ring-B unit, respectively, but the same 2-hydroxynaphthalen-1-yl ring-A unit, showed similar potencies. Chalcone **4** without an OH group on the ring-A naphthalene showed good antiproliferative activities (IC_{50} 1.56−1.71 μM) but was less potent than **2** and **3**. Therefore, further structural development of related derivatives is merited.

Among the chalcones **6**−**10** derived from 2-acetyl-1-hydroxynaphthalene, compound **6** with a 2-methoxyphenyl ring-B exhibited IC_{50} values of 3.2 and 3.8 μM against DU145 and PC-3 cells, respectively, while compound **7** with a 2-hydroxyphenyl ring-B was inactive (IC_{50} > 5 μM). Compound **8** with a naphthalen-1-yl ring-B was also inactive against both cell lines. However, compound **9** with an α-Br on the enone displayed significant antiproliferative activity against DU145 (IC_{50} 1.93 μM) but was inactive against PC-3. A halogen at the α-position might be important for antiproliferative activity against DU145. Finally, chalcone **10** with a quinoline ring-B was inactive against both cell lines, suggesting that the N atom has no effect on activity.

Compounds **11**−**15** have a substituted benzene ring-A and a naphthalene ring-B. Chalcone **12** and Cl-DHC have the same A-ring unit but different B-ring units, 2-hydroxynaphthalen-1-yl in **12** and 2-hydroxyphenyl in Cl-DHC. With IC_{50} values of 4.05 and 3.88 μM, compound **12** was equipotent to Cl-DHC against DU145 and somewhat less potent against PC-3. When the chlorine atom on the phenyl ring of **12** was changed to fluorine (**11**) and bromine (**13**), the IC_{50} value against PC-3 did not change appreciably (4.38 and 4.05 μM, respectively). This finding indicated that the identity of the halogen did not affect the activity, despite the differences in atom size, electronegativity, and other properties. Interestingly, when the two compounds with an electron-withdrawing group (COOEt) at the α-position of the enone were compared, chalcone **14** inhibited cell growth with IC_{50} values of 1.69 (DU145) and 3.13 (PC-3) μM, while chalcone **15** was inactive (IC_{50} > 5 μM). Since **14** with an OMe group at the 4-position of ring-A was more potent than **15** with a Cl atom in the same position, in this case, an electron-donating group was more beneficial than an electron-withdrawing group.

Antiproliferative Activity of Compounds against Drug-Resistant Sublines. The development of drug resistance is a significant problem in CRPC treatment. To investigate the effect of the new chalcone derivatives against drug-resistant CRPC, chalcones **2** and **3**, which showed submicromolar antiproliferative activity against AR-independent DU145 and PC-3 cells, were used. The IC_{50} values were determined against taxane-resistant sublines established from DU145 (DU145/TxR) and PC-3 (PC-3/TxR) as well as cabazitaxel-resistant DU145/TxR (DU145/TxR/CxR) and PC-3/TxR (PC-3/TxR/CxR) sublines (Table 2).[17] Chalcones **2** and **3** exhibited potent antiproliferative activity against all tested resistant PCa cell lines with IC_{50} values of 0.42−0.58 and 0.82−1.21 μM,

Table 2. Antiproliferative Activity against Docetaxel- and Cabazitaxel-Resistant Prostate Cancer Cell Lines DU145/TxR, DU145/TxR/CxR, PC-3/TxR, and PC-3/TxR/CxR

	cell lines/IC_{50} (μM)[a]			
compounds	DU145/TxR	DU145/TxR/CxR	PC-3/TxR	PC-3/TxR/CxR
2	0.42	0.58	0.45	0.48
3	1.21	1.05	0.90	0.82

[a]The concentration of compound that caused 50% reduction of cell growth relative to untreated cells determined by cell counting.

https://dx.doi.org/10.1021/acsomega.0c05822
ACS Omega 2021, 6, 4842−4849

respectively. Compound **2** was 1.7- to 2.9-fold more potent than **3**. Consequently, both derivatives displayed significant effects against AR-independent PCa cell lines, whether chemosensitive or chemoresistant.

To further explore their anticancer spectra, chalcones **2** and **3** were assayed against five human tumor cell lines, non-small cell lung (A549), triple-negative breast (MDA-MB-231), estrogen-responsible breast (MCF-7), cervical cancer cell line HeLa derivative (KB), and a P-glycoprotein (P-gp) over-expressing multidrug-resistant KB subline (KB-VIN). Except for **2** against KB-VIN, the compounds were less active against these five human tumor cell lines compared with the tested prostate cancer cell lines (Table 3). These results suggest that chalcones **2** and **3** have selective antiproliferative activity against the tested AR-independent PCa cell lines and may target growth regulatory proteins expressed specifically in these cell types.

Table 3. Antiproliferative Activity of Compounds 2 and 3 against Other Tumor Cell Lines

	cell line[a] (IC_{50} μM)[b]				
compounds	A549	MDA-MB-231	MCF-7	KB	KB-VIN
2	3.95	5.05	5.13	3.51	0.77
3	5.83	7.59	8.47	7.33	5.07
paclitaxel (nM)	4.90	6.78	10.94	5.24	1843.5

[a]A549 (lung carcinoma), MDA-MB-231 (triple-negative breast cancer), MCF-7 (estrogen receptor-positive and HER2-negative breast cancer), KB (cervical cancer cell line HeLa derivative), KB-VIN (P-gp-overexpressing MDR subline of KB). [b]Antiproliferative activity expressed as IC_{50} values for each cell line, the concentration of compound that caused 50% reduction relative to untreated cells determined by the SRB assay.

Flow Cytometric Analysis and Immunocytochemical Staining of Compounds 2 and 3. Mechanism-of-action studies are also important in drug development. Flow cytometric analysis was conducted to examine the effects of chalcones **2** and **3** on cell cycle progression. KB-VIN cells treated with the compounds at 3-fold IC_{50} concentration showed G2/M accumulation at 24 h and sub-G1 accumulation, which is a typical pattern of apoptosis, at 48 h (Figure 2A).

The effects of chalcones **2** and **3** on cell morphology as well as microtubule and mitotic spindle formation were investigated using immunocytochemical staining. After the treatment of KB-VIN cells with compound at 3-fold IC_{50} concentration, cells were stained with antibodies to α-tubulin for microtubules, serine 10-phosphorylated histone H3 (p-H3) for mitotic chromosome condensation, and 4′,6-diamidino-2-phenylindole (DAPI) for DNA (Figure 2B). Compounds **2** and **3** clearly arrested the cells at prometaphase with condensed chromosomes and multipolar spindles or at metaphase with chromosome alignment at the metaphase plate and bipolar spindles. These morphologies were clearly distinguishable from those of cells treated with CA-4, a tubulin polymerization inhibitor. Unfortunately, the microtubules in interphase cells could not be observed because almost all cells were arrested at mitosis or apoptosis with nuclear fragmentation was induced. Thus, we assume that, compared with CA-4, compounds **2** and **3** induce mitotic arrest in a different mechanism, such as inhibition of cyclin B degradation.

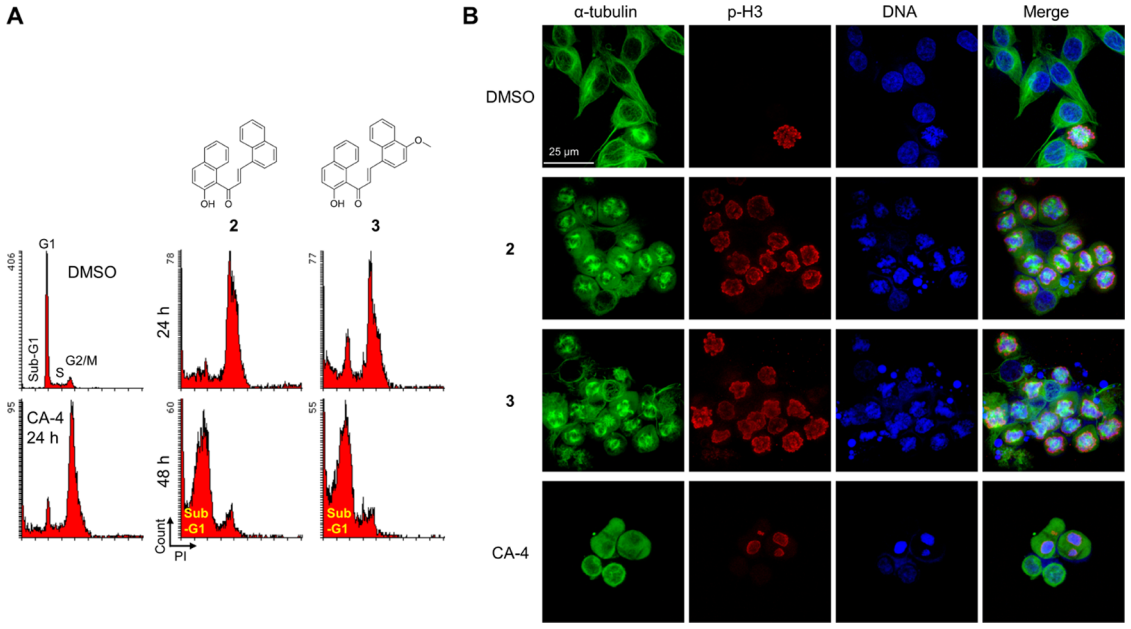


Figure 2. Effects of **2** and **3** on cell cycle progression and immunochemical staining. (A) Multidrug-resistant KB-VIN cells were treated with **2** and **3** for 24 or 48 h. DMSO was used as a vehicle control (CTRL). Compounds **2** and **3** were used at 2.1 μM (3× IC_{50}) and 15 μM (3× IC_{50}), respectively. Combretastatin A-4 (CA-4) was used at 0.1 μM (3× IC_{50}). Tubulin polymerization inhibitor CA-4 was used as a control for mitotic inhibitor (G2/M). Cell cycle distributions of treated cells were analyzed by flow cytometry (LSRFortessa operated by FACS Diva software, BD Bioscience) after staining with propidium iodide (PI) in the presence of RNase. (B) KB-VIN cells were seeded in an eight-well chamber slide (2.4×10^4 cells/well) 24 h prior to treatment with **2** and **3** for 24 h at 2.1 μM (3× IC_{50}) and 15 μM (3× IC_{50}), respectively. DMSO or 0.2 μM CA-4 was used for negative control or tubulin polymerization inhibitor, respectively. Fixed cells were labeled with antibodies to α-tubulin (green) and serine 10-phosphorylated histone H3 (p-H3, red) as a chromosome condensation marker; DAPI was used for DNA (blue). Confocal images of whole cell were superimposed and merged. Scale bar = 25 μm.

https://dx.doi.org/10.1021/acsomega.0c05822
ACS Omega 2021, 6, 4842−4849

CONCLUSIONS

Among 15 synthesized chalcones, we found two bi-naphthyl chalcones **2** and **3** that inhibited DU145 and PC-3 cell growth at submicromolar concentrations. However, chalcone **8** with a different orientation of the ring-A naphthalene was less potent; thus, the activity was dependent on an appropriate direction of the π-electron system. Importantly, chalcones **2** and **3** also exerted antiproliferative effects at submicromolar concentrations against taxane-resistant PCa. Because AR-independent PCa cell lines were more sensitive to **2** and **3** than other cancer cell lines except for **2** against KB-VIN, they may efficiently target growth regulatory proteins expressed in PCa cells. Mechanism-of-action studies revealed that **2** and **3** clearly arrested mitosis at prometaphase and metaphase followed by induction of apoptosis. Thus, bi-naphthyl chalcones **2** and **3** have good potential as new leads for drug development focused on the treatment of AR-independent PCa as well as taxane-resistant CRPC.

EXPERIMENTAL SECTION

Chemistry. All chemicals and solvents were purchased. The reactions were monitored using Merck Millipore precoated silica gel glass plates (TLC Silica gel 60 F254). Column chromatography was carried out with Kanto Chemical silica gel 60 N (spherical, neutral), or preparative TLC was performed with Merck Millipore precoated SiO_2 glass plates (PLC silica gel 60 F254, 1 mm) for the purification. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECS 400 or JNM-ECA 600 using $CDCl_3$ as a solvent and referenced to TMS or residual solvent peak. Chemical shifts δ are described in ppm. Mass spectrometric analyses were performed using JEOL JMS-T100TD or JMS-700 Mstation. Purity of all compounds was determined as >95% by ^{1}H NMR or HPLC.

General Procedures for Chalcones. To a solution of 2-methoxybenzaldehyde (15 mg, 0.11 mmol) and 1-acetyl-2-hydroxynaphthalene (20 mg, 0.11 mmol) in EtOH (0.1 mL) was added 40% KOH aq. (0.1 mL), and the mixture was stirred at room temperature. After completion of the reaction, ice-water was added to the mixture, which was neutralized with 1 N HCl. The mixture was extracted with EtOAc, and the resultant organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 and eluted with hexane−EtOAc (15:1) to give (*E*)-1-(2-hydroxynaphthalen-1-yl)-3-(2-methoxyphenyl)prop-2-en-1-one (**1**) (15 mg, 0.050 mmol) in 46% yield as a yellow solid. Chalcones **2**, **3**, **5**, **6**, **8**, and **10** were produced by the same procedure.

*(E)-1-(2-Hydroxynaphthalen-1-yl)-3-(2-methoxyphenyl)-prop-2-en-1-one (**1**).*[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.73 (s, 1H, OH), 8.24 (d, *J* = 16.0 Hz, 1H, CH═C*H*Ar), 8.16 (d, *J* =8.4 Hz, 1H, H-Ar), 7.91 (d, *J* = 8.4 Hz, 1H, H-Ar), 7.81 (d, *J* = 8.0 Hz, 1H, H-Ar), 7.67 (d, *J* = 16.0 Hz, 1H, C*H*═CHAr), 7.58 (m, 1H, H-Ar), 7.53 (m, 1H, H-Ar), 7.42−7.40 (m, 2H, H-Ar), 7.19 (d, *J* = 8.8 Hz, 1H, H-Ar), 7.01−6.96 (m, 2H, H-Ar), 3.92 (s, 3H, OCH_3).

*(E)-1-(2-Hydroxynaphthalen-1-yl)-3-(naphthalen-1-yl)-prop-2-en-1-one (**2**).*[12] ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.66 (s, 1H, OH), 8.79 (d, *J* = 15.2 Hz, 1H, CH═C*H*Ar), 8.34 (d, *J* = 8.8 Hz, 1H, H-Ar), 8.12 (d, *J* = 8.4 Hz, 1H, H-Ar), 7.95−7.91 (m, 3H, H-Ar), 7.86−7.82 (m, 2H, H-Ar), 7.66−7.49 (m, 5H, C*H*═CHAr, H-Ar), 7.41 (dd, *J* = 7.6, 7.6 Hz, 1H, H-Ar), 7.22 (d, *J* = 8.8 Hz, 1H, H-Ar).

*(E)-1-(2-Hydroxynaphthalen-1-yl)-3-(4-methoxynaphthalen-1-yl)prop-2-en-1-one (**3**).* ^{1}H NMR (600 MHz, $CDCl_3$): δ 12.65 (s, 1H, OH), 8.76 (d, *J* = 15.2 Hz, 1H, CH═C*H*Ar), 8.35 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.32 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.14 (d, *J* = 9.0 Hz, 1H, H-Ar), 7.93 (d, *J* = 9.0 Hz, 1H, H-Ar), 7.86 (d, *J* = 7.8 Hz, 1H, H-Ar), 7.82 (d, *J* = 7.8 Hz, 1H, H-Ar), 7.65 (m, 1H, H-Ar), 7.58−7.51 (m, 3H, C*H*═CHAr, H-Ar), 7.40 (m, 1H, H-Ar), 7.21 (d, *J* = 9.0 Hz, 1H, H-Ar), 6.87 (d, *J* = 7.8 Hz, 1H, H-Ar), 4.06 (s, 3H, OMe); ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.5, 162.7, 158.2, 140.1, 136.7, 133.1, 131.7, 129.4, 128.8, 127.9, 126.9, 126.8, 125.9, 125.8, 125.5, 124.5, 124.0, 123.3, 122.9, 119.6, 116.2, 104.0, 55.9; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{19}O_3$ 355.1334, found 355.1331.

*(E)-3-(Anthracen-9-yl)-1-(2-hydroxynaphthalen-1-yl)-prop-2-en-1-one (**5**).* ^{1}H NMR (600 MHz, $CDCl_3$): δ 12.82 (s, 1H, OH), 8.96 (d, *J* = 15.6 Hz, 1H, CH═C*H*Ar), 8.51 (s, 1H, H-Ar), 8.35 (d, *J* = 8.4 Hz, 2H, H-Ar), 8.07−8.05 (m, 3H, H-Ar), 7.95 (d, *J* = 9.0 Hz, 1H, H-Ar), 7.78 (d, *J* = 7.8 Hz, 1H, H-Ar), 7.56−7.50 (m, 5H, H-Ar, C*H*═CHAr), 7.41 (m, 1H, H-Ar), 7.33 (m, 1H, H-Ar), 7.25 (d, *J* = 9.0 Hz, 1H, H-Ar); ^{13}C NMR (150 MHz, $CDCl_3$): δ 194.0, 163.5, 140.7, 137.3, 135.7, 131.49, 131.46, 129.94, 129.90, 129.4, 129.1, 129.0, 128.7, 128.1, 126.7, 125.6, 125.4, 125.3, 124.2, 119.6; HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{19}O_2$ 375.1385, found 375.1387.

*(E)-1-(1-Hydroxynaphthalen-2-yl)-3-(2-methoxyphenyl)-prop-2-en-1-one (**6**).*[14] ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.97 (s, 1H, OH), 8.50 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.30 (d, *J* = 15.6 Hz, 1H, CH═C*H*Ar), 8.16 (d, *J* =8.4 Hz, 1H, H-Ar), 7.91 (d, *J* = 8.4 Hz, 1H, H-Ar), 7.88 (d, *J* = 16.0 Hz, 1H, C*H*═CHAr), 7.86 (d, *J* = 9.2 Hz, 1H, H-Ar), 7.78 (d, *J* = 8.8 Hz, 1H, H-Ar), 7.69 (m, 1H, H-Ar), 7.64 (m, 1H, H-Ar), 7.54 (m, 1H, H-Ar), 7.42 (m, 1H, H-Ar), 7.31 (d, *J* = 8.8 Hz, 1H, H-Ar), 7.03 (t, *J* = 7.2 Hz, 1H, H-Ar), 6.98 (d, *J* = 8.0 Hz, 1H, H-Ar), 3.97 (s, 3H, OCH_3).

*(E)-1-(1-Hydroxynaphthalen-2-yl)-3-(naphthalen-1-yl)-prop-2-en-1-one (**8**).*[16] ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.86 (d, *J* = 15.2 Hz, 1H, CH═C*H*Ar), 8.53 (d, *J* = 8.4 Hz, 1H, H-Ar), 8.33 (d, *J* = 8.8 Hz, 1H, H-Ar), 7.98−7.96 (m, 2H, H-Ar), 7.92 (d, *J* = 8.8 Hz, 1H, H-Ar), 7.90 (d, *J* = 8.8 Hz, 1H, H-Ar), 7.86 (d, *J* = 15.2 Hz, 1H, C*H*=CHAr), 7.80 (d, *J* = 8.0 Hz, 1H, H-Ar), 7.68−7.62 (m, 2H, H-Ar), 7.60−7.55 (m, 3H, H-Ar), 7.33 (d, *J* = 8.0 Hz, 1H, H-Ar).

*(E)-1-(1-Hydroxynaphthalen-2-yl)-3-(quinolin-3-yl)prop-2-en-1-one (**10**).* ^{1}H NMR (400 MHz, DMSO-d_6): δ 15.02 (s, 1H, OH), 9.54 (d, *J* = 1.6 Hz, 1H, CH=NAr), 8.97 (s, 1H, H-Ar), 8.51 (d, *J* = 16.0 Hz, 1H, CH═C*H*Ar), 8.41 (d, *J* = 9.2 Hz, 1H, H-Ar), 8.40 (d, *J* = 8.0 Hz, 1H, H-Ar), 8.17 (d, *J* = 16.0 Hz, 1H, C*H*=CHAr), 8.10 (d, *J* = 8.8 Hz, 1H, H-Ar), 8.06 (d, *J* = 7.2 Hz, 1H, H-Ar), 7.98 (d, *J* = 8.0 Hz, 1H, H-Ar), 7.86 (m, 1H, H-Ar), 7.77 (m, 1H, H-Ar), 7.71 (m, 1H, H-Ar), 7.64 (m, 1H, H-Ar), 7.53 (d, *J* = 8.0 Hz, 1H, H-Ar); ^{13}C NMR of this compound was not able to record due to the low solubility to any organic solvent. HRMS (FAB) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{16}NO_2$ 326.1181, found 326.1195.

General Procedure for 2-Hydroxychalcones. (*E*)-3-[2-(Methoxymethoxy)naphthalen-1-yl]-1-(4-methylnaphthalen-1-yl)prop-2-en-1-one (165 mg, 0.43 mmol) was dissolved in AcOH (1.0 mL) containing 1% H_2SO_4 (v/v) and stirred at room temperature. After completion of the reaction, the mixture was extracted three times with EtOAc. The combined organic phase was washed with water, saturated $NaHCO_3$ aq.

https://dx.doi.org/10.1021/acsomega.0c05822
ACS Omega 2021, 6, 4842−4849

and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 and eluted with hexane−EtOAc (4:1) to give (*E*)-3-(2-hydroxynaphthalen-1-yl)-1-(4-methylnaphthalen-1-yl)prop-2-en-1-one (**4**) (125 mg, 0.37 mmol) in 85% yield as a yellow solid. 2-Hydroxy derivatives **7**, **11**, **12**, and **13** were obtained by the same procedure.

*(E)-3-(2-Hydroxynaphthalen-1-yl)-1-(4-methylnaphthalen-1-yl)prop-2-en-1-one (**4**).* ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.94 (brs, 1H, OH), 8.41 (dd, J = 7.2, 1.8 Hz, 1H, H-Ar), 8.28 (d, J = 15.6 Hz, 1H, CH═C*H*Ar), 8.41 (dd, J = 7.2, 1.8 Hz, 1H, H-Ar), 8.16 (dd, J = 7.2, 1.8 Hz, 1H, H-Ar), 8.04 (d, J = 9.0 Hz, 1H, H-Ar), 7.88 (d, J = 9.0 Hz, 1H, H-Ar), 7.85 (d, J = 7.8 Hz, 1H, H-Ar), 7.84 (d, J = 7.8 Hz, 1H, H-Ar), 7.79 (d, J = 15.6 Hz, 1H, C*H*═CHAr), 7.68−7.63 (m, 2H, H-Ar), 7.54−7.52 (m, 2H, H-Ar), 7.37 (dd, J = 7.2, 7.2 Hz, 1H, H-Ar), 7.28 (d, J = 9.0 Hz, 1H, H-Ar), 2.76 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6): δ 195.0, 156.7, 138.3, 137.9, 135.5, 132.8, 132.4, 132.5, 130.1, 130.0, 128.9, 128.1, 127.7, 127.2, 127.0, 126.4, 126.0, 125.6, 124.7, 123.3, 122.0, 118.4, 112.7, 19.5; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{24}H_{19}O_2$ 339.1385, found 339.1385.

*(E)-1-(1-Hydroxynaphthalen-2-yl)-3-(2-hydroxyphenyl)-prop-2-en-1-one (**7**).*[15] ^{1}H NMR (400 MHz, DMSO-d_6): δ 15.18 (brs, 1H, OH), 10.43 (brs, 1H, OH), 8.38 (d, J =8.8 Hz, 1H, H-Ar), 8.31 (d, J = 15.2 Hz, 1H, CH═C*H*Ar), 8.24 (d, J = 9.2 Hz, 1H, H-Ar), 8.12 (d, J = 15.2 Hz, 1H, C*H*=CHAr), 8.01 (dd, J = 8.0, 1.2 Hz, 1H, H-Ar), 7.95 (d, J = 8.0 Hz, 1H, H-Ar), 7.74 (ddd, J = 8.0, 7.2, 1.2 Hz, 1H, H-Ar), 7.62 (ddd, J = 8.0, 7.2, 1.2 Hz, 1H, H-Ar), 7.48 (d, J = 8.4 Hz, 1H, H-Ar), 7.33 (ddd, J = 8.0, 7.2, 1.2 Hz, 1H, H-Ar), 6.97 (d, J = 7.2 Hz, 1H, H-Ar), 6.92 (dd, J = 8.0, 8.0 Hz, 1H, H-Ar).

*(E)-1-(5-Fluoro-2-hydroxyphenyl)-3-(2-hydroxynaphthalen-1-yl)prop-2-en-1-one (**11**).* ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.9 (s, 1H), 7.90 (d, J = 15.6 Hz, 1H), 7.87 (d, J = 2.4 Hz, 1H), 7.43 (dd, J = 9.0, 3.0 Hz, 1H), 7.41 (d, J = 15.6 Hz, 1H), 7.28 (dd, J = 7.8, 1.8 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 6.989 (d, J = 8.4 Hz, 1H), 6.987 (d, J = 9.6 Hz, 1H), 6.00 (s, 1H), 4.01 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 192.6, 157.2, 156.8, 154.8 (d, J = 235.5 Hz), 137.9, 132.9, 132.7, 128.9, 128.1, 127.8, 125.4, 123.3, 122.5 (d, J = 5.7 Hz), 122.4 (d, J = 23.0 Hz) 122.3, 119.1 (d, J = 7.2 Hz), 118.3, 115.2 (d, J = 23.0 Hz), 112.0; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{19}H_{14}FO_3$ 309.0927, found 309.0921.

*(E)-1-(5-Chloro-2-hydroxyphenyl)-3-(1-hydroxynaphthalen-2-yl)prop-2-en-1-one (**12**).* ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.00 (brs, 1H, OH), 11.02 (brs, 1H, OH), 8.46 (d, J = 15.2 Hz, 1H, CH=C*H*Ar), 8.19 (d, J =8.4 Hz, 1H, H-Ar), 8.12 (d, J = 15.2 Hz, 1H, C*H*═CHAr), 7.91 (d, J = 9.2 Hz, 1H, H-Ar), 7.87 (d, J = 8.4 Hz, 1H, H-Ar), 7.84 (d, J = 2.4 Hz, 1H, H-Ar), 7.59−7.54 (m, 2H, H-Ar), 7.39 (t, J = 7.6 Hz, 1H, H-Ar), 7.28 (d, J = 9.2 Hz, 1H, H-Ar), 7.06 (d, J = 9.2 Hz, 1H, H-Ar); ^{13}C NMR (150 MHz, DMSO-d_6): δ 192.4, 158.9, 157.3, 137.8, 134.6, 132.9, 132.8, 129.1, 128.9, 128.1, 127.8, 125.7, 124.0, 123.4, 122.8, 122.3, 119.7, 118.4, 112.9; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{19}H_{14}ClO_3$ 325.0631, found 325.0644.

*(E)-1-(5-Bromo-2-hydroxyphenyl)-3-(2-hydroxynaphthalen-1-yl)prop-2-en-1-one (**13**).* ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.00 (brs, 1H, OH), 11.02 (brs, 1H, OH), 8.45 (d, J = 15.2 Hz, 1H, CH═C*H*Ar), 8.19 (d, J = 8.4 Hz, 1H, H-Ar), 8.11 (d, J = 15.2 Hz, 1H, C*H*=CHAr), 7.95 (d, J = 2.8 Hz, 1H, H-Ar), 7.91 (d, J = 9.2 Hz, 1H, H-Ar), 7.87 (d, J = 8.0 Hz, 1H, H-Ar), 7.66 (dd, J = 8.4, 2.4 Hz, 1H, H-Ar), 7.57 (dd, J = 7.2, 7.2 Hz, 1H, H-Ar), 7.37 (dd, J = 7.2, 7.2 Hz, 1H, H-Ar), 7.28 (d, J = 9.2 Hz, 1H, H-Ar), 7.01 (d, J = 9.2 Hz, 1H, H-Ar); ^{13}C NMR (150 MHz, CD_3OD): δ 195.4, 163.3, 159.0, 140.4, 139.5, 135.2, 134.2, 133.2, 130.1, 130.0, 128.8, 124.6, 124.1, 123.3, 123.2, 121.4, 119.2, 114.4, 111.4; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{19}H_{14}BrO_3$ 369.0126, found 369.0142.

*(Z)-2-Bromo-1-(1-hydroxynaphthalen-2-yl)-3-(naphthalen-1-yl)prop-2-en-1-one (**9**).* Tetraethylammonium bromide (47 mg, 0.22 mmol) and Dess−Martin periodinane (94 mg, 0.22 mmol) were dissolved in CH_2Cl_2. After stirring for 10 min at room temperature, compound **8** (61 mg, 0.18 mmol) was added to the mixture. After additional stirring for 30 min, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHSO_3$ and saturated aqueous $NaHCO_3$. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 and eluted with hexane−EtOAc (10:1) to give (*Z*)-2-bromo-1-(1-hydroxynaphthalen-2-yl)-3-(naphthalen-1-yl)prop-2-en-1-one (**9**) (4 mg, 0.01 mmol) in 6% yield as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.88 (s, 1H, OH), 8.89 (d, J = 15.2 Hz, 1H, CH═C*H*Ar), 8.57 (d, J = 8.0 Hz, 1H, H-Ar), 8.32 (d, J = 8.0 Hz, 1H, H-Ar), 8.19 (s, 1H, H-Ar), 8.18 (d, J = 8.0 Hz, 1H, H-Ar), 8.02−7.98 (m, 2H, H-Ar), 7.93 (d, J = 8.0 Hz, 1H, H-Ar), 7.79 (m, 1H, H-Ar), 7.77 (d, J = 15.2 Hz, 1H, C*H*═CHAr), 7.66−7.57 (m, 4H, H-Ar); ^{13}C NMR (150 MHz, $CDCl_3$): δ 192.3, 164.2, 143.0, 135.6, 133.9, 132.1, 132.0, 131.6, 129.0, 127.4, 127.3, 127.0, 126.9, 126.6, 125.73, 125.66, 125.1, 123.5, 122.5, 114.3, 111.4; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{23}H_{16}BrO_2$ 403.0334, found 403.0322.

General Procedure for α-Carbonylchalcones. To a solution of 1-naphthalaldehyde (84 mg, 0.54 mmol) in benzene (2.5 mL) were added ethyl *p*-anisoylacetate (109 mg, 0.49 mmol), piperidine (5 μL, 0.049 mmol), acetic acid (14 μL, 0.25 mmol), and molecular sieves 4A (18 mg), and the mixture was refluxed at 95 °C. After the reaction was complete, water was added to the reaction mixture at room temperature. The mixture was extracted with EtOAc, and the resultant organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 and eluted with hexane−EtOAc (5:1) to give ethyl (*Z*)-2-(4-methoxybenzoyl)-3-(naphthalen-1-yl)acrylate (**14**) (120 mg, 0.33 mmol) in 68% yield as a pale yellow oil.

*Ethyl (Z)-2-(4-Methoxybenzoyl)-3-(naphthalen-1-yl)-acrylate (**14**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H, H-Ar), 8.15 (d, J = 8.0 Hz, 1H, H-Ar), 7.85−7.80 (m, 3H, H-Ar), 7.74 (d, J = 8.4 Hz, 1H, H-Ar), 7.60 (ddd, J = 8.0, 7.2, 1.2 Hz, 1H, H-Ar), 7.52 (ddd, J = 8.0, 7.2, 1.2 Hz, 1H, H-Ar), 7.46 (d, J = 7.6 Hz, 1H, H-Ar), 7.24 (dd, J = 7.6 Hz, 1H, H-Ar), 6.75 (d, J = 9.2 Hz, 2H, H-Ar), 4.30 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 3.76 (s, 3H, OCH_3), 1.26 (t, J = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.6, 165.2, 164.0, 140.2, 133.9, 133.4, 131.58, 131.55, 130.49, 130.45, 129.6, 128.9, 127.8, 127.0, 126.4, 125.4, 124.0, 114.0, 61.8, 55.5, 14.3; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{23}H_{21}O_4$ 361.1440, found 361.1423.

*Ethyl (Z)-2-(4-Chlorobenzoyl)-3-(naphthalen-1-yl)acrylate (**15**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H, H-Ar), 8.11 (d, J = 8.4 Hz, 1H, H-Ar), 7.82 (d, J = 8.0 Hz, 1H, H-Ar), 7.79−7.75 (m, 3H, H-Ar), 7.61 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H, H-Ar), 7.54 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H, H-Ar), 7.38 (d, J = 6.8 Hz, 1H, H-Ar), 7.26−7.23 (m, 3H, H-Ar), 4.31 (q, J = 7.2

https://dx.doi.org/10.1021/acsomega.0c05822
ACS Omega 2021, 6, 4842−4849

Hz, 2H, OCH_2CH_3), 1.26 (t, J = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.8, 164.8, 141.2, 140.2, 134.7, 133.5, 133.4, 131.5, 130.8, 130.4, 130.3, 129.1, 129.0, 127.9, 127.2, 126.6, 125.3, 123.9, 61.9, 14.3; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{22}H_{18}ClO_3$ 365.0944, found 365.0946.

Cell Proliferation Assay Using PCa Cells. DU145 cells (5×10^4) or PC-3 cells (5×10^4) were seeded on 12-well plates (two-layer chambers) with DMEM containing 5% charcoal-stripped fetal calf serum (CCS) (HyClone Laboratories, Logan, UT). After 24 h in culture, the cells were treated with compounds for 4 days. Medium containing compound was replaced once, on day 2 of treatment. To determine cell proliferation, trypsinized cells were counted in triplicate using a hemocytometer. The data represent the mean ± SD of three replicates.

Antiproliferative Activity against Nonprostate Cancer Cell Lines. Antiproliferative activity of compounds was determined by the sulforhodamine B (SRB) method, as described previously.[18] Briefly, cell suspensions were freshly prepared and seeded in 96-well microtiter plates at densities of 4000−11 000 cells per well with compounds. After 72 h in culture with test compounds, the attached cells were fixed in 10% trichloroacetic acid followed by staining with 0.04% SRB. The protein-bound dye was solubilized by 10 mM Tris base, and the absorbance at 515 nm was measured using a microplate reader (ELx800, BioTek) operated by Gen5 software (BioTek). The mean IC_{50} is the average from at least three independent experiments of duplication for an assay and similar determinations.

Flow Cytometric Analysis. KB-VIN (7×10^4 cells/well) cells were seeded in a 12-well plate 24 h prior to treatment with compounds for 24 or 48 h. Compounds were used at a concentration 3-fold of their IC_{50} value ($3\times$ IC_{50}) against KB-VIN. Harvested and 70% EtOH-fixed cells were stained with propidium iodide (PI) containing RNase (BD Bioscience) subjected to flow cytometry (BD LSRFortessa, BD Biosciences). 200 nM CA-4 was used as tubulin polymerization inhibitor arresting cells in G2/M.

Immunostaining. KB-VIN cells (2.4×10^4 cells/well) were seeded in an eight-well chamber slide (Lab-Tech) for 24 h prior to treatment with compounds. The cells were treated for 24 h with **2**, **3**, or DMSO as a control for 24 h. Fixed (4% paraformaldehyde in PBS) and permeabilized (0.5% Triton X-100 in PBS) cells were labeled with mouse monoclonal antibody to α-tubulin (B5-1-2, Sigma), rabbit IgG to serine 10-phosphorylated histone H3 (p-H3) (#06570, EMD Millipore) followed by FITC-conjugated antibody to mouse IgG (Sigma) and Alexa Fluor 549-conjugated antibody to rabbit IgG (Life Technologies).[19] Nuclei were labeled with DAPI (Sigma). Fluorescence labeled cells were observed using a confocal microscope (Zeiss, LSM700) controlled by ZEN software (Zeiss). Confocal images of whole cells were superimposed and merged using ZEN (black edition) software. Final images were prepared using Adobe Photoshop CS6.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c05822.

^1H NMR and ^{13}C NMR spectra of the synthesized chalcones (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Kyoko Nakagawa-Goto − *School of Pharmaceutical Sciences, College of Medical, Pharmaceutical and Health Science, Kanazawa University, Kanazawa 920-1192, Japan; Chemical Biology and Medicinal Chemistry, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599, United States;* orcid.org/0000-0002-1642-6538; Phone: 81-76-264-6305; Email: kngoto@p.kanazawa-u.ac.jp

Authors

Yohei Saito − *School of Pharmaceutical Sciences, College of Medical, Pharmaceutical and Health Science, Kanazawa University, Kanazawa 920-1192, Japan*

Atsushi Mizokami − *Department of Integrative Cancer Therapy and Urology, School of Medical Sciences, Kanazawa University, Kanazawa 920-8641, Japan*

Sayaka Maeda − *School of Pharmaceutical Sciences, College of Medical, Pharmaceutical and Health Science, Kanazawa University, Kanazawa 920-1192, Japan*

Kyoko Takahashi − *School of Pharmaceutical Sciences, College of Medical, Pharmaceutical and Health Science, Kanazawa University, Kanazawa 920-1192, Japan*

Kouji Izumi − *Department of Integrative Cancer Therapy and Urology, School of Medical Sciences, Kanazawa University, Kanazawa 920-8641, Japan*

Masuo Goto − *Chemical Biology and Medicinal Chemistry, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599, United States;* orcid.org/0000-0002-9659-1460

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.0c05822

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors appreciate critical comments, suggestions, and editing on the manuscript by Dr. Susan L. Morris-Natschke (UNC-CH). They thank the Microscope Service Laboratory (UNC-CH) for their expertise in confocal microscopy. This work was supported by JSPS KAKENHI Grant Number 18H02583 awarded to K.N.G., 17H04325 awarded to A.M., and 18K14344 awarded to Y.S. This work was also supported in part by IBM junior faculty grant awarded to M.G.

■ REFERENCES

(1) Kushi, L. H.; Doyle, C.; McCullough, M.; Rock, C. L.; Demark-Wahnefried, W.; Bandera, E. V.; Gapstur, S.; Patel, A. V.; Andrews, K.; Gansler, T. The American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. *Ca-Cancer J. Clin.* **2012**, *62*, 30−67.

(2) Feldman, B. J.; Feldman, D. The development of androgen-independent prostate cancer. *Nat. Rev. Cancer* **2001**, *1*, 34−45.

(3) Ren, W.; Qiao, Z.; Wang, H.; Zhu, L.; Zhang, L. Flavonoids: Promising anticancer agents. *Med. Res. Rev.* **2003**, *23*, 519−534.

(4) Fu, Y.; Hsieh, T.-C.; Guo, J.; Kunicki, J.; Lee, M. Y. W. T.; Darzynkiewicz, Z.; Wu, J. M. Licochalcone-A, a novel flavonoid isolated from licorice root (*Glycyrrhiza glabra*), causes G2 and late-G1 arrests in androgen-independent PC-3 prostate cancer cells. *Biochem. Biophys. Res. Commun.* **2004**, *322*, 263−270.

(5) Zhuang, C.; Zhang, W.; Sheng, C.; Zhang, W.; Xing, C.; Miao, Z. Chalcone: A privileged structure in medicinal chemistry. *Chem. Rev.* **2017**, *117*, 7762−7810.
(6) Ofude, M.; Mizokami, A.; Kumaki, M.; Izumi, K.; Konaka, H.; Kadono, Y.; Kitagawa, Y.; Shin, M. Y.; Zhang, J.; Keller, E. T.; Namiki, M. Repression of cell proliferation and androgen receptor activity in prostate cancer cells by 2′-hydroxyflavanone. *Anticancer Res.* **2013**, *33*, 4453−4461.
(7) Saito, Y.; Mizokami, A.; Tsurimoto, H.; Izumi, K.; Goto, M.; Nakagawa-Goto, K. 5′-chloro-2,2′-dihydroxychalcone and related flavonoids as treatment for prostate cancer. *Eur. J. Med. Chem.* **2018**, *157*, 1143−1152.
(8) Widhalm, J. R.; Rhodes, D. Biosynthesis and molecular actions of specialized 1,4-naphthoquinone natural products produced by horticultural plants. *Hortic. Res.* **2016**, *3*, No. 16046.
(9) Makar, S.; Saha, T.; Singh, S. K. Naphthalene, a versatile platform in medicinal chemistry: Sky-high perspective. *Eur. J. Med. Chem.* **2019**, *161*, 252−276.
(10) Ramanarayanan, G. V.; Shukla, V. G.; Akamanchi, K. G. A novel and one step procedure for preparation of α-bromo-α,β-unsaturated carbonyl compounds. *Synlett* **2002**, *12*, 2059−2061.
(11) Cotterill, W. D.; Livingstone, R.; Walshaw, M. V. 1,3- and 3,3-Bis(methoxyphenyl)naphtho[2,1-b]pyrans. *J. Chem. Soc. C* **1970**, 1758−1764.
(12) Kaneda, K.; Arai, T. Mechanistic approach to the cyclization reaction of a 2′-hydroxychalcone analogue with light and solvent. *Org. Biomol. Chem.* **2003**, *1*, 2041−2043.
(13) Prasad, Y. R.; Kumar, P. R.; Deepti, C. A.; Ramana, M. V. Synthesis and antimicrobial activity of some novel chalcones of 2-hydroxy-1-acetonaphthone and 3-acetylcoumarin. *J. Chem.* **2006**, *3*, 236−241.
(14) Mahal, H. S.; Venkataraman, K. Synthetical experiments in the chromone group. XIV. Action of sodamide on 1-acyloxy-2-acetonaphthones. *J. Chem. Soc.* **1934**, 1767−1769.
(15) Schraufstatter, E.; Deutsch, S. Chalcones. I. The preparation of chalcones. *Chem. Ber.* **1948**, *81*, 489−499.
(16) Kaneda, K.; Sato, S.; Hamaguchi, H.; Arai, T. The photoinduced hydrogen atom transfer and trans−cis isomerization of the C═C double bond in 1-(1-hydroxy-2-naphthyl)-3-(1-naphthyl)-2-propen-1-one and related compounds studied using nanosecond time-resolved infrared spectroscopy. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1529−1535.
(17) Machioka, K.; Izumi, K.; Kadono, Y.; Iwamoto, H.; Naito, R.; Makino, T.; Kadomoto, S.; Natsugdorj, A.; Keller, E. T.; Zhang, J.; Mizokami, A. Establishment and characterization of two cabazitaxel-resistant prostate cancer cell lines. *Oncotarget* **2018**, *9*, 16185−16196.
(18) Nakagawa-Goto, K.; Taniguchi, Y.; Watanabe, Y.; Oda, A.; Ohkoshi, E.; Hamel, E.; Lee, K.-H.; Goto, M. Triethylated chromones with substituted naphthalenes as tubulin inhibitors. *Bioorg. Med. Chem.* **2016**, *24*, 6048−6057.
(19) Nakagawa-Goto, K.; Oda, A.; Hamel, E.; Ohkoshi, E.; Lee, K.-H.; Goto, M. Development of a novel class of tubulin inhibitor from desmosdumotin B with a hydroxylated bicyclic B-ring. *J. Med. Chem.* **2015**, *58*, 2378−2389.

https://dx.doi.org/10.1021/acsomega.0c05822
ACS Omega 2021, 6, 4842−4849