Brief Articles

Antitumor Agents. 266. Design, Synthesis, and Biological Evaluation of Novel 2-(Furan-2-yl)naphthalen-1-ol Derivatives as Potent and Selective Antibreast Cancer Agents

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In a continuing study, we explored how the individual rings in neo-tanshinlactone (**1**) influence its potent and selective in vitro antibreast cancer activity. Accordingly, we discovered a novel class of antibreast cancer agents, 2-(furan-2-yl)naphthalen-1-ol derivatives, based on an active C-ring opened model compound **5**. Further optimization led to **18** and **21**, which showed decreased cytotoxic potency but better selectivity than neo-tanshinlactone analogue **2**. Interestingly, **20** showed broad cytotoxicity against human cancer cell lines.

Introduction

Breast cancer is the most common malignancy and the second leading cause of cancer death in women today.[1,2] According to the American Cancer Society, breast cancer accounts for more than one-quarter of cancers diagnosed in U.S. women. Estrogens play crucial roles in breast cancer development and growth, and estrogen-stimulated growth in tumor cells (and in normal cells) requires estrogen receptors (ERs[a]).[3] About two-thirds of human breast tumors express higher levels of ERs than normal breast tissues.[4] Much effort has been devoted to block estrogen formation and action.[2] The most widely used therapy for antagonizing ER function is the antiestrogen tamoxifen (TAM), which binds to the ER and blocks downstream signaling (Figure 1).

However, current breast cancer therapies like TAM achieve meaningful clinical results in only 30−40% of patients because drug resistance usually develops after 1 or 2 years of treatment.[2] This resistance occurs via several mechanisms, including induction of estrogen-independent pathways for breast cancer cell growth, overexpression of human epidermal growth factor receptor 2 (HER2), and functional crosstalk between ER and HER2.[5−7] A common clinical strategy to overcome drug resistance is to combine an antiestrogen with another cytotoxic drug, such as anastrozole, an aromatase inhibitor.[8,9] Even so, patients still relapse and cancer reoccurs; therefore, new drug chemotypes with new mechanisms of action are still needed.

Neo-tanshinlactone (**1**) (Figure 1), a component of the Chinese traditional medicine Tanshen, showed significant and selective cytotoxic activity as compared to TAM.[10] Compound **2** (Figure 1), a congener of **1**, is about twice as active as **1** against SK-BR-3 cell line.[11] **1** is a tetracyclic natural product and may be more structurally complex than is necessary for optimal pharmacologic effects. A complex lead compound may have a simpler pharmacophoric moiety buried within its structure, and if this pharmacophore can be clearly defined and "dissected out", the resulting biologically active, simpler molecule may have improved synthetic tractability and be more useful as a scaffold for further analogue design. To study the individual contribution of the A-, C-, and D-rings of **1** to the selective activity against breast cancer cells, we first prepared four novel ring-opened model compounds (**4**−**7**) (Figure 2).

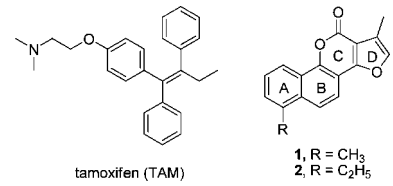

Figure 1. Structures of tamoxifen, neo-tanshinlactone (**1**), and a first generation optimized analogue (**2**).

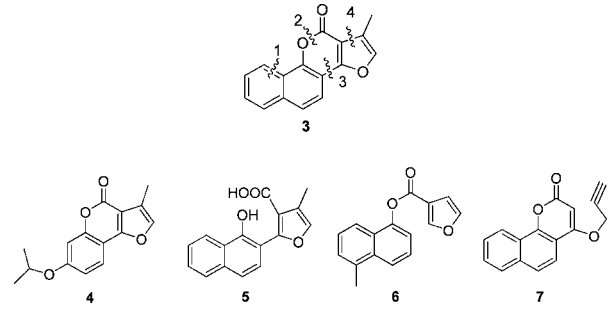

Figure 2. Design of ring-opened model compounds **4**−**7**.

The preliminary structure−activity relationship (SAR) study results showed that only **5**, which has an opened C-ring (cleavage of bond 2), showed in vitro antibreast cancer activity, although it was somewhat less potent than parent **3** against MCF-7 cell replication. Further structural modification of **5** generated a series of 2-(furan-2-yl)naphthalen-1-ol derivatives (**18**−**28**), which retained potent in vitro antibreast cancer activity

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[a] Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PCH, pharmacophore; SAR, structure−activity relationship; TAM, tamoxifen; PM3, parameterized model number 3; MOE, molecular operating environment; CSD, Cambridge Structural Database; DIEA, diisopropylethylamine; DMAP, 4-(dimethylamino)pyridine; SAR, structure−activity relationship.

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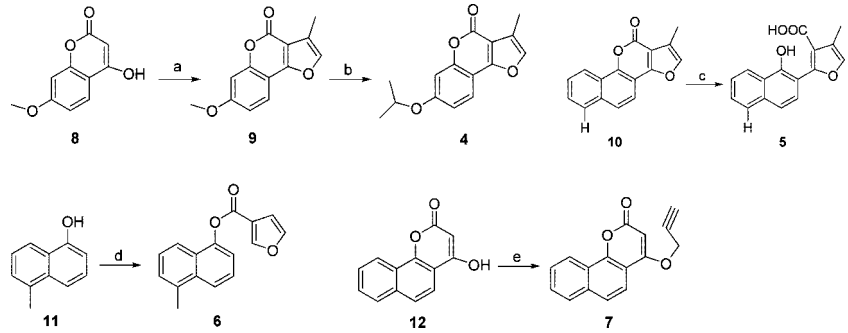
Scheme 1[a]



[a] Reagents and conditions: (a) HOAc, $AcNH_4$, chloroacetone, toluene, EtOH, 95 °C, 65%; (b) (i) BBr_3, DCM, 50°C; (ii) 2-iodopropane, $CsCO_3$, DMF, 50°C, 30%; (c) 5% NaOH(aq), reflux, 93%; (d) furan-3-carbonyl chloride, DIEA, DMAP, DMF, 46%; (e) 3-bromoprop-1-yne, K_2CO_3, acetone, 40%.

Table 1. In Vitro Anticancer Activity of **2**−**7** against Breast Cancer Cell Lines[a]

compd	MCF-7 (ER+)	SK-BR-3 (HER2+)
2	0.2	0.1
3	4.0	1.0
4	12.0	10.8
5	6.0	7.0
6	>20	>20
7	20.0	16.0

[a] Mean ED_{50} (μg/mL). Standard error of independent determinations was less than 5%.

and high selectivity against different breast cancer cell lines, especially **18**. Interestingly, **20**, a closely related structural derivative of **18**, showed broad in vitro cytotoxicity against all human cancer cell lines tested. Preliminary pharmacophore studies and dihedral energy analyses demonstrated that **18** could adopt a conformation close to the tetracyclic structure of **1** and **2** via intramolecular hydrogen bonding. In comparison, the conformation of **20** was more flexible, which could account for its broader spectrum of activity.

Results and Discussion

As a first step in the current work, we investigated the individual contributions of A-, C-, and D-rings of the neotanshinlactone molecule to the biological activity. Systematic structural simplification of **3** by removal of the A-, C-, and D-rings afforded model compounds **4**−**7** (Figure 2). Scheme 1 shows the syntheses of these target compounds. Intermediate **9** was obtained via a tandem alkylation/intramolecular aldol reaction with commercially available **8**.[12] **4** was obtained by treatment of **9** with boron tribromide at 50 °C, followed by treatment with 2-iodopropane to remove the methyl group and incorporate an isopropyl group. **5** was synthesized through hydrolysis of the lactone ring of **10**. **11** underwent esterification with furan-3-carbonyl chloride to provide **6**. **7** was synthesized from **12** with 3-bromoprop-1-yne.[13]

Compounds **4**−**7** were tested for in vitro anticancer activity against two human breast cancer cell lines, MCF-7 (ER+) and SK-BR-3 (HER2+) (Table 1). Compound **4**, without an A-ring moiety, was much less potent than its tetracyclic analogue **3**. The activity of **5**, a C-ring opened compound, was comparable to that of **3** against MCF-7 replication (less than 2-fold difference). However, **6**, another C-ring opened compound but with cleavage of bond 3 rather than bond 2, was inactive against the tested breast cancer cell lines. Compound **7**, a D-ring opened compound, showed marginal activity against the two breast cancer cell lines. The results demonstrated that the A-ring and D-ring are important in maintaining the biological activity of this compound type.

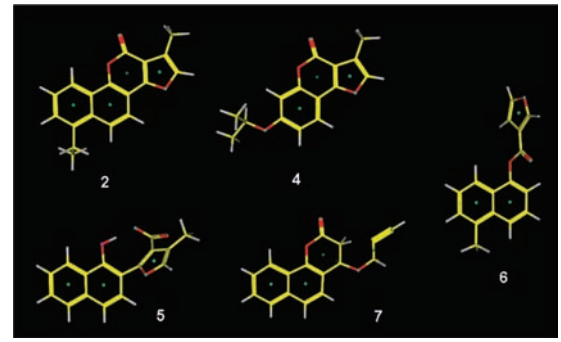


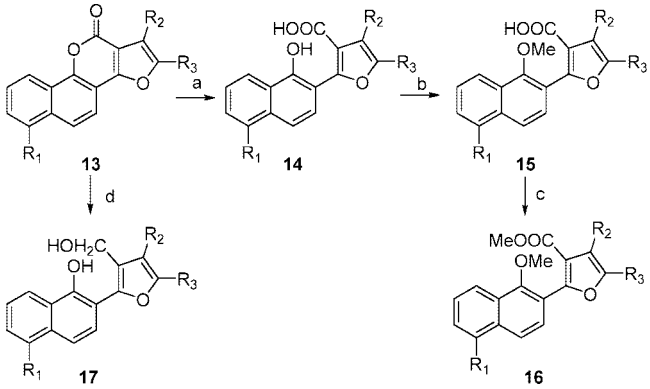
Figure 3. Pharmacophore analysis of **4**−**7** with reference to **2** using the PCH annotation scheme: purple, H-bond donor; blue, H-bond acceptor; light-green, Aaromatic ring center; deep-green, Hhydrophobic region. The structures of the global energy minima are shown by stick models.

The SAR results of **5** and **6** could be explained by the postulate that intramolecular hydrogen bonding between −COOH and OH groups in **5** maintains the compound's conformation in a more ringlike structure.

Accordingly, conformational analysis was conducted to study the molecular geometries of **4**−**7** and the potential SAR relevance of solution structures. As shown in Figure 3, **4**−**7** possess most of the pharmacophore (PCH) features present in the reference **2**, including aromatic center, hydrophobic region, and hydrogen bond donor and acceptor. However, several key features are also missing in **4**−**7** in comparison to **2**, i.e., two aromatic centers in **4** and **7** and a closed ring in **5** and **6**. Interestingly, **5** can form one additional intramolecular hydrogen bond between −COOH and −OH groups in the lowest energy conformer. This hydrogen bond could '"lock" the structure into a conformation that is close to the tetracyclic scaffold. Thus, intramolecular hydrogen bonding in **5** may help the compound retain biological potency. However, **5** was much less active compared with **2**, which may be due to their differences in susceptibility to efflux transporters or cellular uptake or different binding affinity with the targets. Additional studies will be performed to address these possibilities.

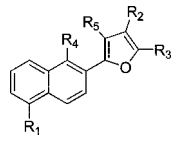
Compound **5** was selected for further structure optimization in order to establish SAR correlations and to identify more active derivatives with the desired biological properties. Substituents on the **5**-scaffold will affect the molecule's overall three-dimensional structure and thus the compound's interaction with its target, which will translate into increased or decreased antibreast cancer activity. We designed, synthesized, and tested 11 new analogues (Scheme 2, Table 2). Hydrolysis of **13** afforded **14**.[14] The hydroxy group of **14** was methylated by using

Scheme 2[a]



[a] Reagents and conditions: (a) 5% NaOH (aq), reflux; (b) 18-crown-6, MeI, CH_3CN, 90 °C; (c) $SOCl_2$, MeOH, room temp; (d) $LiAlH_4$, THF.

Table 2. Structures and Cytotoxicity Data of Analogues **18**−**28**[a]



compd	R_1	R_2	R_3	R_4	R_5	MCF-7 (ER+)	SK-BR-3 (HER2+)
TAM						5.0	5.0
5	H	Me	H	OH	COOH	6.0	7.0
18	Et	Me	H	OH	COOH	3.3	1.0
19	Et	Me	H	OMe	COOH	4.3	8.5
20	Et	Me	H	OMe	COOMe	2.5	1.2
21	OMe	Me	H	OH	COOH	>20	3.5
22	H	Me	H	OMe	COOH	18.0	16.7
23	H	Me	H	OMe	COOMe	8.5	6.5
24	Et	Et	H	OH	COOH	5.1	5.4
25	Et	Me	Me	OH	COOH	8.5	10.4
26	OEt	Me	H	OH	COOH	7.5	6.0
27	Et	Me	H	OH	CH_2OH	12.0	12.8
28	H	Me	H	OH	CH_2OH	7.0	9.5

[a] Mean ED_{50} (μg/mL). Standard error of independent determinations was less than 5%.

18-crown-6 as phase transfer agent, as reported by Glover et al.[15] The resulting analogue **15** was converted to the methyl ester **16** with thionyl chloride and methanol at room temperature.[16] Compound **17** was obtained by reduction of **13** with lithium aluminum hydride.

To test for a potential relationship between the intramolecular hydrogen bond (COOH and OH groups) and the selective in vitro antibreast cancer activity, a specific target subset (**18**−**20**, Table 2) was designed. **18**, with OH at position R_4 and COOH at position R_5, can form an intramolecular hydrogen bond. However, in **19**, one hydrogen donor has been effectively removed by methylation of the OH in **18**, and in **20**, both hydrogen bond donors are blocked with methyl groups. **21**−**28** were designed to further study SAR of various substituents on the molecule. The newly synthesized analogues **18**−**28** were tested initially for in vitro anticancer activity against two human breast cancer cell lines, MCF-7 (ER+) and SK-BR-3 cells (HER2+) (Table 2). **18** and **20** showed similar activity to TAM against MCF-7 (ED_{50} of 3.3 and 2.5 μg/mL, respectively), while **18** showed 5-fold better activity than TAM against SK-BR-3 (ED_{50} = 1.0 μg/mL) and **20** showed about 4-fold better activity than TAM against SK-BR-3 (ED_{50} = 1.2 μg/mL). **19** displayed similar activity to TAM against both cell lines. From the ED_{50} of **5**, **18**, and **21**, the SAR study suggested that the R_1 substituent influenced the in vitro anticancer activity and hydrophobic groups were favored at this position. At the R_2 position, methyl was preferable to ethyl (**18** vs **24**), and at the R_3 position, hydrogen was favored over methyl (**18** vs **25**).

To examine human tumor-tissue-type selectivity, active compounds **18**, **20**, and **21** (ED_{50} > 4.0 μg/mL was considered not active) were selected for testing against a limited but diverse set of human cancer cell lines, using **2** as a positive control and "gold standard" (Table 3). Compounds **18** and **21** were active only against certain breast cancer cell lines and not active against other tumor tissue cells tested, such as A549 lung cancer or DU145 prostate cancer cell lines. Thus, these two compounds had high tissue selectivity. More interestingly, **18** and **21** also showed very high potency (ED_{50} of 0.3 and 0.6 μg/mL, respectively) and selectivity toward the ZR-7-51 (ER+, HER2+) cell line. Compound **18** was 3 times less potent against SK-BR-3 (HER2+) (ED_{50} = 0.9 μg/mL) and 10 times less potent against MCF-7 (ER+) (ED_{50} = 3.3 μg/mL). **21** was 6 times less potent against SK-BR-3 (HER2+) (ED_{50} = 3.5 μg/mL) and 33 times less potent against MCF-7 (ER+) (ED_{50} > 20 μg/mL). Meanwhile, **2** showed similar potency against ZR-7-51 and SK-BR-3 and was only 2 times more potent against ZR-7-51 than MCF-7. In summary, **18** and **21** were more potent against ZR-75-1 than cell lines overexpressing ER or HER2 (MCF-7 or SK-BR-3) and much more potent than cell lines not overexpressing ER or HER2 (remaining cell lines in the panel). Unexpectedly, **20** showed activity against all cancer cell lines tested.

To further explore the physicochemical basis for the different selectivity profiles between **18** and **20**, the dihedral energy analyses were performed over 360° (Figure 4). Compared with **2**, **18** retains three aromatic centers and possesses one additional intramolecular hydrogen bond. This hydrogen bond helps to "lock" the conformation close to that of **2**, which may explain why the activity pattern of **18** is similar to that of **2** but with increased selectivity. The narrow shape of the potential energy well for the dihedral angle between the naphthalene and furan rings implies that it is difficult to vary the angle from the minimum of −135° (Figure 4). Thus, the compound's structure is fairly rigid, leading to a small possibility for **18** to bind to a diverse set of targets. Compound **20** also retains three aromatic centers and hydrogen bond acceptors in common with the tetracyclic **2**. However, the intramolecular hydrogen bond found in **18** cannot be formed in **20**. The dihedral angle between the naphthalene ring and the furan ring is more flexible as seen in Figure 4.[17] In comparison to **18**, the potential energy surface around the minimum is much flatter and there are fewer energy barriers. As a result, the increased structural flexibility in **20**

Table 3. Cytotoxicity of Compounds against Tumor Cell Lines[a]

compd	MCF-7 (ER+)	SK-BR-3 (HER2+)	ZR-75-1 (ER+, HER2+)	MDA MB-231 (ER−)	A549	DU145	KB	KB-VIN
2	0.2	0.1	0.1	>10	10.6	15.9	13.1	13.2
18	3.3	1.0	0.3	>10	10.6	8.7	9.1	7.0
20	2.5	1.2	1.3	2.3	1.5	2.2	1.7	1.3
21	>20	3.5	0.6	>10	10.1	8.2	9.7	8.9

[a] Mean ED_{50} (μg/mL). Standard error of independent determinations was less than 5%.

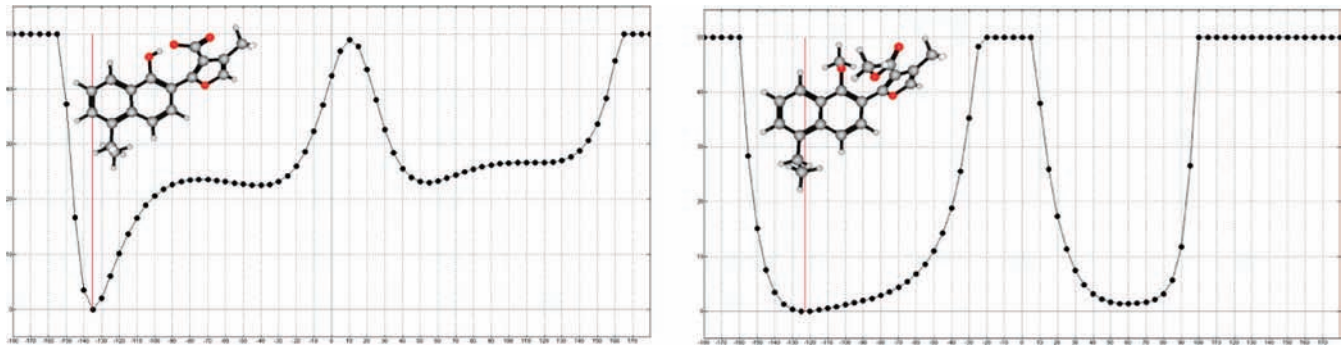


Figure 4. Dihedral energy analyses of **18** (top) and **20** (bottom) between the naphthalene ring and the furan ring. The structure of the global energy minimum is shown by a ball and stick model.

could permit multitarget interactions and account for its observed broader activity spectrum.

Conclusions

In summary, current data have led to new developments and insights about neo-tanshinlactone-based selective antibreast cancer active compounds. We demonstrated that aromatic rings A and D were important for the activity. Importantly, we discovered that ring C could be opened through hydrolysis of the ester bond while keeping the desired biological activity. A new class of active C ring opened compounds, 2-(furan-2-yl)naphthalen-1-ol derivatives, was subsequently developed. Compounds **18** and **21** exhibited much higher selectivity against certain breast cancer cell lines than neo-tanshinlactone analogue **2**. In addition, **20** had potent activity against all cell lines tested, suggesting a different mechanism of action from its structural derivatives. Conformational searches and dihedral energy analyses of **18** and **20** suggested that intramolecular hydrogen bonding was important to form a rigid conformation and improved the in vitro anticancer selectivity of **18**. Refinement of the preliminary pharmacophore and conclusion about active conformation will require target identification and analysis of compound interaction. Mechanistic work is underway toward this goal, and results will be reported as they are available. Overall, our current results establish a new scaffold as a promising structure for the development of investigational antibreast cancer agents. Novel target compounds incorporating the important structural features identified herein are being synthesized for testing and will be reported in due course.

Experimental Section

Materials and Methods. Melting points were measured with a Fisher Johns melting apparatus without correction. The ^{1}H and ^{13}C NMR spectra were measured on a 300 MHz Varian Gemini 2000 spectrometer using TMS as internal standard. The solvent used was $CDCl_3$ unless indicated. Mass spectra were measured on a Shimadzu LC-MS2010 instrument. Thin-layer chromatography (TLC) and preparative TLC were performed on precoated silica gel GF plates purchased from Merck, Inc. Biotage Flash+ or Isco Companion systems were used for flash chromatography. Silica gel (200−400 mesh) from Aldrich, Inc., was used for column chromatography. All other chemicals were obtained from Aldrich, Inc., and Fisher, Inc. All final compounds are >95% pure on the basis of two HPLC conditions.

7-Methoxy-3-methyl-4*H*-furo[3,2-*c*]chromen-4-one (9). To a solution of **8** (199 mg, 1.04 mmol) in toluene (9 mL) was added a mixture of HOAc (0.30 mL, 5.20 mmol) and NH_4OAc (400 mg, 5.20 mmol) in EtOH (3 mL) and chloroacetone (0.42 mL, 5.20 mmol). The mixture was refluxed for 24 h. After cooling, the mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography to give **9** as white solid: 65% yield; mp 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 2.34 (d, J = 1.2 Hz, 3H, CH_3), 3.88 (s, 3H, OCH_3), 6.88−6.93 (m, 2H, aromatic), 7.33 (d, J = 1.5 Hz, 1H, OC*H*), 7.71−7.74 (m, 1H, aromatic).

7-Isopropoxy-3-methyl-4*H*-furo[3,2-*c*]chromen-4-one (4). To a solution of **9** (46 mg, 0.2 mmol) in DCM (3 mL) was added BBr_3 (0.6 mL, 0.6 mmol) dropwise at 0 °C. The mixture was refluxed for 3 h. Water was added to quench the reaction. The solution was extracted with $CHCl_3$ and concentrated for the next step. The above concentrated solid was dissolved in DMF (1 mL) and acetone (3 mL). $CsCO_3$ (195 mg, 0.6 mmol) and 2-iodopropane (0.06 mL, 0.6 mmol) were added to the above solution. The mixture was stirred at room temperature for 12 h. After removal of solvent, the residue was purified by column chromatography to give **4** as a white solid: 30% yield; mp 85−87 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.38 (d, J = 6.0 Hz, 6H, CH(CH_3)$_2$), 2.34 (s, 3H, CH_3), 4.61 (h, J = 6.0 Hz, 1H, C*H*), 6.86−6.90 (m, 2H, aromatic), 7.33 (s, 1H, OC*H*), 7.71 (d, J = 8.4 Hz, 1H, aromatic); HRMS for ([M + H]$^+$) calcd 259.0965, found 259.0961.

5-Methylnaphthalen-1-yl Furan-3-carboxylate (6). 5-Methylnaphthalen-1-ol (158 mg, 1.00 mmol) was dissolved in THF (5 mL), then DMAP (5 mg) and ethyldiisopropylamine (0.18 mL, 1.02 mmol) were added, and the mixture was cooled to 0 °C for 10 min. Freshly prepared 2-bromo-4-methylbenzoyl chloride in dry THF (10 mL) was added to the mixture, and the resulting mixture was stirred at 25 °C for 2 h and quenched by the addition of water (15 mL). The organic layer was washed with HCl and $NaHCO_3$ and then dried (Na_2SO_4) and concentrated in vacuo. The residue was purified with flash chromatography to give **6**: 46% yield; mp 53−55 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 2.72 (s, 3H, CH_3), 6.97 (dd, J = 0.6, 5.2 Hz, 1H, aromatic), 7.33−7.42 (m, 3H, aromatic), 7.51−7.56 (m, 2H, aromatic), 7.79 (d, J = 8.1 Hz, 1H, aromatic), 7.93 (d, J = 8.4 Hz,1H, aromatic), 8.32−8.33 (m, 1H, aromatic); HRMS for ([M + H]$^+$) calcd 253.0859, found 253.0869.

4-(Prop-2-ynyloxy)-2*H*-benzo[*h*]chromen-2-one (7). To a mixture of **12** (212 mg, 1.00 mmol mmol), K_2CO_3 (300 mg, 2.17 mmol) in acetone (8 mL) was added 3-bromoprop-1-yne (0.17 mL, 1.50 mmol). The mixture was refluxed 12 h. After cooling, the mixture was filtered, concentrated, diluted with H_2O, and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography to give **7** as a light-yellow solid: 40% yield; mp 205−207 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 2.70 (t, J = 2.4 Hz, 1H, CC*H*), 4.92 (d, J = 2.4 Hz, 2H, OCH_2), 5.93 (s, 1H, COC*H*), 7.62−7.71 (m, 3H, aromatic), 7.80−7.90 (m, 2H, aromatic), 8.54−8.58 (m, 1H, aromatic); HRMS for ([M + H]$^+$) calcd 251.0703, found 251.0697.

General Procedure for Synthesis of 5, 18, 21, 24−26. Lactone **13** (0.1 mmol) was refluxed in ethanolic aqueous potassium

hydroxide (5%, 5 mL) for 3.5 h. Then the mixture was cooled and quenched by pouring into ice, acidified with 6 N HCl, and extracted with $CHCl_3$ (3 × 5 mL). Removal of solvent, drying (Na_2SO_4), and chromatographic purification gave the hydrolyzed product as a solid.

2-(1-Hydroxynaphthalen-2-yl)-4-methylfuran-3-carboxylic Acid (5). 93% yield; mp 194−196 °C; ^{1}H NMR (300 MHz, CD_3COCD_3, ppm) δ 2.27 (d, J = 1.2 Hz, 3H, CH_3), 7.51−7.55 (m, 5H, aromatic and OCH), 7.86−7.89 (m, 1H, aromatic), 8.40−8.44 (m, 1H, aromatic); ^{13}C NMR (300 MHz, CD_3COCD_3, ppm) δ 10.40, 114.23, 116.83, 120.49, 122.77, 124.28, 126.32, 127.57, 128.16, 128.27, 128.28, 136.14, 141.59, 152.66, 157.87, 169.28; HRMS for ([M − H]$^+$) calcd 267.0657, found 267.0663.

Compounds **18**, **21**, and **24**−**26** were prepared in an analogous manner to **5**.

General Procedure for Synthesis of Methyl Ethers. Compound **13** (0.1 mmol) was refluxed in ethanolic aqueous potassium hydroxide (5%, 5 mL) for 3.5 h. The solution was washed with $CHCl_3$ and evaporated to give the dipotassium salt, which was refluxed for 24 h with 18-crown-6 (4.35 mg, 0.0145 mmol) and methyl iodide (0.01 mL, 0.159 mmol) in acetonitrile (5 mL). The acetonitrile was removed in vacuo and after dilution with $CHCl_3$. The mixture was washed with water, dried, and concentrated to give an oil. The residue was purified with flash chromatography to give the methyl ether derivative.

2-(5-Ethyl-1-methoxynaphthalen-2-yl)-4-methylfuran-3-carboxylic Acid (19). 39% yield; mp 128−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.37 (t, J = 7.8 Hz, 3H, CH_2CH_3), 2.46 (d, J = 1.2 Hz, 3H, CH_3), 3.09 (q, J = 7.8 Hz, 2H, CH_2CH_3), 3.73 (s, 3H, OCH_3), 7.35−7.52 (m, 4H, aromatic and OCH), 7.82 (d, J = 9.3 Hz, 1H, aromatic), 8.08 (d, J = 9.9 Hz, 1H, aromatic); HRMS for ([M − H]$^+$) calcd 309.1127, found 309.1139.

Compound **22** was prepared in an analogous manner to **19**.

General Procedure for Synthesis of Methyl Esters. Thionyl chloride (0.05 mL, 0.45 mmol) was added dropwise at 0 °C to a solution of **15** (0.14 mmol) in MeOH (15 mL). The solution was then stirred at room temperature for 12 h. The solvent was evaporated, and the residue was dissolved in EtOAc and washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to give methyl ester derivative.

Methyl 2-(5-Ethyl-1-methoxynaphthalen-2-yl)-4-methylfuran-3-carboxylate (20). 82% yield; mp 121−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.39 (t, J = 7.8 Hz, 3H, CH_2CH_3), 2.52 (s, 3H, CH_3), 3.11 (q, J = 7.5 Hz, 1H, CH_2CH_3), 3.68 (s, 3H, OCH_3), 3.69 (s, 3H, COOCH_3), 7.34−7.49 (m, 3H, aromatic and OCH), 7.54 (d, J = 8.7 Hz, 1H, aromatic), 7.85 (d, J = 8.7 Hz, 1H, aromatic), 8.10 (d, J = 8.4 Hz, 1H, aromatic); ^{13}C NMR (300 MHz, CD_3COCD_3, ppm) δ 10.02, 15.95, 27.00, 51.77, 62.77, 117.86, 120.08, 120.42, 122.15, 123.08, 127.46, 127.58, 128.31, 129.72, 134.87, 141.41, 141.87, 155.77, 156.62, 165.47; HRMS for ([M + H]$^+$) calcd 325.1434, found 325.1430.

Compound **23** was prepared in an analogous manner to **20**.

General Procedure for Synthesis of 27 and 28. $LiAlH_4$ (60 mg, 16 mmol) was added at 0 °C to a solution of **13** (0.1 mmol) in THF (5 mL). The solution was then refluxed for 5 h. Then the mixture was cooled and quenched by pouring into ice, acidified with 2 N HCl, and extracted with diethyl ether/DCM = 2:1. The solvent was evaporated after drying. The residue was purified by flash chromatography to give the product.

5-Ethyl-2-(3-(hydroxymethyl)-4-methylfuran-2-yl)naphthalen-1-ol (27). 95% yield; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.38 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.14 (s, 3H, CH_3), 3.08 (q, J = 7.8 Hz, 2H, CH_2CH_3), 4.64 (s, 2H, CH_2OH), 7.35−7.44 (m, 3H, aromatic), 7.54 (d, J = 8.7 Hz, 1H, aromatic), 7.64 (d, J = 9.3 Hz, 1H, aromatic), 7.99 (br, 1H, OH), 8.25 (d, J = 8.1 Hz, 1H, aromatic); HRMS for ([M-H]$^+$) calcd 281.1183, found 281.1197.

Compound **28** was prepared in an analogous manner to **27**.

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Supporting Information Available: Cell growth inhibition assay, computational methods, HPLC analysis for final compounds, and physical and spectroscopic data for **18**, **21**−**26**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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