Dehydrozingerone, Chalcone, and Isoeugenol Analogues as in Vitro Anticancer Agents[#]

Jin Tatsuzaki,[†] Kenneth F. Bastow,[‡] Kyoko Nakagawa-Goto,[†] Seiko Nakamura,[†] Hideji Itokawa,[†] and Kuo-Hsiung Lee*[,†]

Natural Products Research Laboratories, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599-7360, and Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599-7360

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Twenty-eight compounds related to dehydrozingerone (**1**), isoeugenol (**3**), and 2-hydroxychalcone (**4**) were synthesized and evaluated in vitro against human tumor cell replication. Except for isoeugenol analogues **27**−**35**, most compounds exhibited moderate or strong cytotoxic activity against KB, KB-VCR (a multidrug-resistant derivative), and A549 cell lines. In particular, chalcone **15** showed significant cytotoxic activity against the A549 cell line with an IC_{50} value of 0.6 μg/mL. Furthermore, dehydrozingerone analogue **11** and chalcones **16** and **17** showed significant and similar cytotoxic activity against both KB (IC_{50} values of 2.0, 1.0, and 2.0 μg/mL, respectively) and KB-VCR (IC_{50} values of 1.9, 1.0, and 2.0 μg/mL, respectively) cells, suggesting that they are not substrates for the P-glycoprotein drug efflux pump.

Dehydrozingerone (**1**), isolated from ginger (*Zingiber officinale*),[1,2] is a well-known phenolic natural product with anti-inflammatory, antioxidant, and antitumor promoting activities.[3] It is the structural half analogue, as well as biosynthetic intermediate,[4] of curcumin (**2**), which possesses various remarkable bioactivities such as cytotoxic effects on cancer cell lines[5−8] and induction of apoptotic cell death in human promyelocytic leukemia HL-60 and human oral squamous carcinoma HSC-4 cells.[9] Dehydrozingerone (**1**), isoeugenol (**3**), and 2-hydroxychalcone (**4**) (Figure 1) have similar structures (acetyl, methyl, and benzoyl, respectively, attached to a styrene skeleton). Both **3** and **4** are also prominent bioactive compounds.[10,11] Thus, we expected that **1**-analogues should show a wide range of pharmacological activities. In spite of the interesting and simple structure of **1**, we found only a few literature reports on analogue syntheses and structure−activity relationships (SAR),[12,13] although we recently reported the cytotoxic effects of curcumin analogues.[7,14,15]

It is known that the presence of a prenyl or geranyl group on flavonoids, including chalcones, can lead to a remarkable increase in bioactivity.[16,17] As dehydrozingerone (**1**) is structurally related to chalcones, the introduction of a prenyl or geranyl group on any position of **1** might also increase activity. In fact, most prenylflavonoids and geranylflavonoids as well as related compounds are known to have potent cytotoxic effects.[18−21] Furthermore, with respect to cancer research, a prenyl moiety has been demonstrated to be essential for chemopreventive activity in many compound types.[22−24] Therefore, we herein report the syntheses and cytotoxic activities of dehydrozingerone analogues, including investigation of prenyl substitution.

Results and Discussion

As shown in Scheme 1, dehydrozingerone (**6**−**13**) and chalcone (**14**−**17**) analogues with various substitution patterns on the benzylidene ring were easily obtained from substituted benzaldehydes (**5**) reacted with the appropriate ketone (acetone for **6**−**13**, acetophenone for **14**−**17**) using an aldol condensation.[12] Alkylation/allylation of the phenol of **1** or **3** was achieved by a standard procedure[25] using an alkyl/allyl halide to give the corresponding phenoxy analogues **18**−**26** and **27**−**35**, respectively, as shown in Scheme 2.

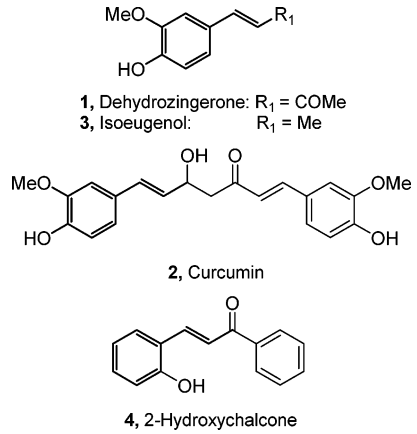

Figure 1. Structures of dehydrozingerone (**1**), curcumin (**2**), isoeugenol (**3**), and 2-hydroxychalcone (**4**).

Derivatives **6**−**35** were evaluated as inhibitors of human tumor cell replication using three human tumor cell lines: nasopharyngeal carcinoma KB, multidrug-resistant expressing P-glycoprotein KB-VCR, and lung carcinoma A549.[26,27] Curcumin (**2**) and doxorubicin were used as positive controls. The results are shown in Table 1.

Most analogues, except isoeugenol analogues **27**−**35**, showed moderate or strong cytotoxic activity against all three cell lines. Comparison of the corresponding dehydrozingerone (**1**, **6**−**8**) and chalcone (**14**−**17**) analogues showed that the latter compounds were more potent in each case. Because the chalcones have a phenyl rather than methyl in the unsaturated ketone, these data suggest that this phenyl group is important for optimal activity. Chalcone **15** showed significant activity against the A549 cell line with an IC_{50} value of 0.6 μg/mL. Furthermore, the dehydrozingerone analogue **11** and chalcones **16** and **17** showed significant cytotoxic activity against both KB (IC_{50} values of 2.0, 1.0, and 2.0 μg/mL, respectively) and KB-VCR (IC_{50} values of 1.9, 1.0, and 2.0 μg/mL, respectively) cells. The similar potencies against the parental and drug-resistant cell lines suggested that these compounds were not substrates for the P-glycoprotein drug efflux pump.

The substitution pattern on the benzylidene ring had some influence on potency. In particular, among the dehydrozingerone analogues, compounds with an *ortho*-hydroxy group were more active than compounds with *meta*- or *para*-hydroxy substituents [compare **6** (2′-OH, 3′-OMe), **8** (2′-OH, 4′-OMe), and **11** (2′-OH, 3′-OEt) with **1** (3′-OMe, 4′-OH), **7** (3′-OH, 4′-OMe), and **10** (3′-OEt, 4′-OH)]. Compound **12** (2′-OH, 3′-F) also exhibited significant activity, showing that fluorine could be substituted for an alkoxy

[#] Antitumor Agents 249. For part 248, see: Wei, L.; Brossi, A.; Morris-Natschke, S. L.; Bastow, K. F.; Lee, K. H. Chemistry and Antitumor Activity of Tylophorine-related Alkaloids. *Stud. Nat. Prod. Chem.*, in press.

* Corresponding author. Tel: 919-962-0066. Fax: 919-966-3893. E-mail: khlee@unc.edu.

[†] Natural Products Research Laboratories.

[‡] Division of Medicinal Chemistry and Natural Products.

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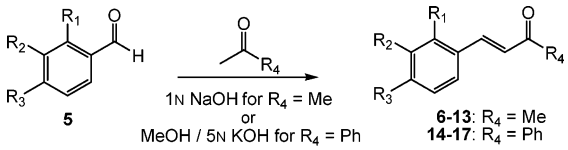
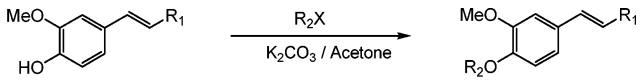
Scheme 1. Syntheses of Dehydrozingerone (**6**−**13**) and Chalcone (**14**−**17**) Analogues



	R_1	R_2	R_3	R_4
1	H	OMe	OH	Me
6	OH	OMe	H	Me
7	H	OH	OMe	Me
8	OH	H	OMe	Me
9	H	H	H	Me
10	H	OEt	OH	Me
11	OH	OEt	H	Me
12	OH	F	H	Me
13	H	F	OMe	Me
14	H	OMe	OH	Ph
15	OH	OMe	H	Ph
16	H	OH	OMe	Ph
17	OH	H	OMe	Ph

Scheme 2. C-4′-Alkylated Dehydrozingerone (**18**−**26**) and Isoeugenol (**27**−**35**) Analogues



1, Dehydrozingerone: R_1 = COMe
3, Isoeugenol: R_1 = Me

18-26: R_1 = COMe
27-35: R_1 = Me

Dehydrozingerone R_1 = COMe	Isoeugenol R_1 = Me	R_2
18	**27**	
19	**28**	
20	**29**	
21	**30**	
22	**31**	
23	**32**	Me
24	**33**	
25	**34**	
26	**35**	

group. In addition, substitution of 3′-fluoro for 3′-hydroxy (compare **13** with **7**) was beneficial.

The dehydrozingerone derivatives **18**−**26** showed cytotoxic activity, while the corresponding isoeugenol derivatives **27**−**35** were inactive. This result supported the supposition that the ketone on C-3 (numbering for dehydrozingerone) is important for anticancer properties.[28] Phenoxydehydrozingerone analogues **18** (C-4′-prenyloxy) and **21** (C-4′-geranyloxy) showed higher activity than dehydrozingerone itself and were as or more active than the other alkylated compounds **19**, **20**, and **22**−**26**. With a longer farnesyl group, analogue **22** showed decreased potency relative to **18** and **21**. This result supported those of prior investigations showing that

Table 1. Activities of Analogues against Human Tumor Cell Replication

	cell line/IC_{50} (μg/mL)[a]		
compound	KB[b]	KB-VCR[b]	A549[b]
Dehydrozingerone Analogues			
1	>10	>10	>10
6	3.8	2.0	2.5
7	10.0	8.2	>10
8	3.8	4.0	3.5
9	5.3	5.6	2.8
10	7.7	7.8	8.5
11	2.0	1.9	2.3
12	2.1	3.0	3.0
13	4.3	5.0	5.5
Chalcone Analogues			
14	3.5	1.9	2.3
15	2.4	1.3	0.6
16	1.0	1.0	3.5
17	2.0	2.0	3.8
C-4-Alkylated Dehydrozingerone Analogues			
18	5.7	3.5	3.8
19	6.8	5.0	5.8
20	4.8	3.4	6.8
21	2.2	3.3	3.4
22	6.5	7.4	7.4
23	8.6	7.8	8.0
24	5.5	8.0	>10
25	6.5	4.2	5.8
26	3.6	3.2	7.2
C-4-Alkylated Isoeugenol Analogues			
27−**35**[c]	>10	>10	ND[d]
Controls			
curcumin (**2**)	5.5	3.1	5.2
doxorubicin	0.1	2.7	0.1

[a] Cytotoxicity as IC_{50} values for each cell line, the concentration of compound that caused 50% reduction in absorbance at 562 nm relative to untreated cells using the sulforhodamine B assay. The average value is from two independent determinations, and variation (SEM) was no greater than 10%. [b] Human epidermoid carcinoma of the nasopharynx (KB), multidrug-resistant expression P-glycoprotein (KB-VCR), and human lung carcinoma (A549). [c] **30** and **33** were not tested. [d] ND = not determined.

prenylated and/or geranylated flavonoids were more active than farnesylated compounds.[17,19] Derivative **26**, which has a saturated isoamyl rather than unsaturated prenyl group, showed equal and significant activity against KB and KB-VCR cells with IC_{50} values of 3.6 and 3.2 μg/mL, respectively. However, the prenylated analogue (**18**) was about twice as potent against the drug-resistant cell line (3.8 μg/mL, KB versus 2.0 μg/mL, KB-VCR).

In conclusion, chalcone **15** showed the highest in vitro potencies with IC_{50} values ranging from 0.6 to 2.4 μg/mL. The ketone at the C-3 and phenyl at the C-4 positions are necessary for optimal cytotoxic activity. Compounds with hydroxyl at the *ortho* position of the benzylidene moiety generally showed increased activity. Among alkylated **1**-analogues, alkylation of the phenolic OH with prenyl or geranyl resulted in the highest potency.

Experimental Section

General Experimental Procedures. Melting points were measured with a Fisher Johns melting point apparatus without correction. The proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on a Varian Gemini 2000 (300 MHz) NMR spectrometer with TMS as the internal standard. All chemical shifts are reported in ppm. Mass spectra were obtained on a TRIO 1000 mass spectrometer. Analytical thin layer chromatography (TLC) was performed on Merck precoated aluminum silica gel sheets (Kieselgel 60 F 254). Column chromatography was performed on a CombiFlash Companion system using RediSep normal-phase silica columns (ISCO, Inc., Lincoln, NE). Silica gel (200−400 mesh) from Natland (Durham, NC) was used for column chromatography. All other chemicals were obtained from Aldrich, Inc. unless otherwise noted.

General Procedure for Aldol Reaction.[12] The appropriately substituted benzaldehyde **5** was dissolved in acetone, and 1 N sodium hydroxide was added to the solution with continuous stirring. Stirring was continued overnight. Excess acetone was removed under reduced pressure. Upon acidification with 1 N HCl, the reaction mixture was extracted with $CHCl_3$ or CH_2Cl_2, and then the solution was dried over anhydrous Na_2SO_4. Solvent was removed, and the yellow solid obtained was recrystallized from EtOAc to give **6**−**13**. Similarly, for the preparation of **14**−**17**, benzaldehyde **5** was dissolved in MeOH with acetophenone, and 5 N potassium hydride was added to the solution with continuous stirring. Stirring was continued overnight. MeOH was removed under reduced pressure. After acidification with 1 N HCl, the crude mixture was extracted with CH_2Cl_2, and the solution was dried over anhydrous Na_2SO_4. Solvent was removed, and the solid obtained was purified with CombiFlash chromatography (EtOAc−hexane) to provide **14**−**17**.

(*E*)-1-(2-Hydroxy-3-methoxyphenyl)but-1-en-3-one (6). Starting with *o*-vanillin (5 g, 0.03 mol), acetone (40 mL), and 1 N NaOH (50 mL); yield 2.0 g (30%); powder, mp 79−80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, 1H, J = 16.5 Hz, 1-H), 7.12 (dd, 1H, J = 6.6, 2.7 Hz, 5′-H), 6.90−6.84 (m, 2H, 4′- and 6′-H), 6.81 (d, 1H, J = 16.5, 2-H), 6.16 (s, 1H, OH), 3.92 (s, 3H, OCH_3), 2.40 (s, 3H, 4-H); MS *m*/*z* 277 $[M + Na]^+$.

(*E*)-1-(3-Hydroxy-4-methoxyphenyl)but-1-en-3-one (7). Starting with 3-hydroxy-4-methoxybenzaldehyde (1 g, 6.6 mmol), acetone (8 mL), and 1 N NaOH (10 mL); yield 1.2 g (94%); powder, mp 96−97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, 1H, J = 16.2 Hz, 1-H), 7.15 (d, 1H, J = 1.5 Hz, 2′-H), 7.06 (dd, 1H, J = 8.3, 2.1 Hz, 5′-H), 6.86 (d, 1H, J = 8.3 Hz, 6′-H), 6.59 (d, 1H, J = 16.2 Hz, 2-H), 5.70 (s, 1H, OH), 3.93 (s, 3H, OCH_3), 3.36 (s, 3H, 4-H); MS *m*/*z* 193 $[M + H]^+$.

(*E*)-1-(2-Hydroxy-4-methoxyphenyl)but-1-en-3-one (8). Starting with 2-hydroxy-4-methoxybenzaldehyde (1 g, 6.6 mmol), acetone (8 mL), and 1 N NaOH (10 mL); yield 497 mg (39%); powder, mp 129−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H, J = 16.3 Hz, 1-H), 7.34 (d, 1H, J = 8.5 Hz, 6′-H), 7.01 (d, 1H, J = 16.3 Hz, 2-H) 6.50 (dd, 1H, J = 8.5, 2.1 Hz, 5′-H), 6.48 (d, 1H, J = 2.1 Hz, 3′-H), 6.16 (s, 1H, OH) 3.82 (s, 3H, OCH_3), 2.41 (s, 3H, 4-H); MS *m*/*z* 215 $[M + Na]^+$.

(*E*)-1-Phenylbut-1-en-3-one (9). Starting with benzaldehyde (500 mL, 4.9 mmol), acetone (4 mL), and 1 N NaOH (5 mL); yield 241 mg (34%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.53 (m, 2H, 2 × Ar-H), 7.52 (d, 1H, J = 16.2 Hz, 1-H), 7.42−7.40 (m, 3H, 3 × Ar-H), 6.73 (d, 1H, J = 16.2 Hz, 2-H), 2.39 (s, 3H, 4-H); MS *m*/*z* 169 $[M + Na]^+$.

(*E*)-1-(3-Ethoxy-4-hydroxyphenyl)but-1-en-3-one (10). Starting with 3-ethoxy-4-hydroxybenzaldehyde (1 g, 6.0 mmol), acetone (8 mL), and 1 N NaOH (10 mL); yield 1.1 g (42%); needles, mp 104−105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, 1H, J = 16.0 Hz, 1-H), 7.08 (br d, 1H, J = 8.4 Hz, 6′-H), 7.05 (br s, 1H, 2′-H), 6.93 (d, 1H, J = 8.4 Hz, 5′-H), 6.57 (d, 1H, J = 16.0 Hz, 2-H), 5.85 (s, 1H, OH), 4.16 (q, 2H, J = 7.0 Hz, 1′-H), 2.36 (s, 3H, 4-H), 1.48 (t, 3H, J = 7.0 Hz, 2′-H); MS *m*/*z* 229 $[M + Na]^+$.

(*E*)-1-(3-Ethoxy-2-hydroxyphenyl)but-1-en-3-one (11). Starting with 3-ethoxysalicylaldehyde (1 g, 6.0 mmol), acetone (8 mL), and 1 N NaOH (10 mL); yield 1.0 g (84%); powder, mp 77−78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, 1H, J = 16.5 Hz, 1-H), 7.11 (dd, 1H, J = 4.8, 2.1 Hz, 5′-H), 6.88−6.81 (m, 2H, 4′- and 6′-H) 6.21 (s, 1H, OH), 6.81 (d, 1H, J = 16.5 Hz, 2-H), 4.14 (q, 2H, J = 6.9 Hz, 1′-H), 2.40 (s, 3H, 1-H), 1.47 (t, 3H, J = 6.9 Hz, 2′-H); MS *m*/*z* 207 $[M + H]^+$.

(*E*)-1-(3-Fluoro-2-hydroxyphenyl)but-1-en-3-one (12). Starting with 3-fluorosalicylaldehyde (200 mg, 1.4 mmol), acetone (1.6 mL), and 1 N NaOH (2 mL); yield 239 mg (93%); prisms, mp 167−168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, 1H, J = 16.5 Hz, 1-H), 7.29 (br d, 1H, J = 8.1 Hz, 6′-H), 7.12 (br t, 1H, J = 8.1 Hz, 5′-H), 6.91−6.82 (m, 2H, 4′- and 2-H), 5.96 (br s, 1H, OH), 2.41 (s, 3H, 4-H); MS *m*/*z* 203 $[M + Na]^+$.

(*E*)-1-(3-Fluoro-4-methoxyphenyl)but-1-en-3-one (13). Starting with 3-fluoro-4-methoxybenzaldehyde (500 mg, 3.24 mmol), acetone (4 mL), and 1 N NaOH (5 mL); yield 139 mg (22%); needles, mp 96−97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, 1H, J = 16.2 Hz, 1-H), 7.34−7.25 (m, 2H, 2 × Ar-H), 6.97 (t, 1H, J = 8.7 Hz, 5′-H), 6.59 (d, 1H, J = 16.2 Hz, 2-H), 5.85 (s, 1H, OH), 3.93 (s, 3H, OCH_3), 2.37 (s, 3H, 4-H); MS *m*/*z* 217 $[M + Na]^+$.

(*E*)-1-(2-Hydroxy-3-methoxyphenyl)-3-phenylpropenone (15). Starting with *o*-vanillin (128 mg, 0.85 mmol), acetophenone (100 μL, 0.85 mmol), MeOH (1 mL), and 5 N NaOH (1 mL); yield 80 mg (37%); powder, mp 115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05−8.02 (m, 2H, 2 × Ar-H), 8.04 (d, 1H, J = 15.9 Hz, 1-H), 7.75 (d, 1H, J = 15.9 Hz, 2-H), 7.61−7.47 (m, 3H, 3 × Ar-H), 7.20 (dd, 1H, J = 3.3, 2.7 Hz, Ar-H), 6.92−6.86 (m, 2H, 2 × Ar-H), 6.27 (s, 1H, OH), 3.94 (s, 3H, OCH_3); MS *m*/*z* 277 $[M + Na]^+$.

(*E*)-1-(3-Hydroxy-4-methoxyphenyl)-3-phenylpropenone (16). Starting with 3-hydroxy-4-methoxybenzaldehyde (128 mg, 0.85 mmol), acetophenone (100 μL, 0.85 mmol), MeOH (1 mL), and 5 N NaOH (1 mL); yield 194 mg (90%); powder, 97−98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04−8.00 (m, 2H, 2 × Ar-H), 7.74 (d, 1H, J = 15.7 Hz, 1-H), 7.61−7.47 (m, 3H, 3 × Ar-H), 7.41 (d, 1H, J = 15.7 Hz, 2-H), 7.29 (d, 1H, J = 2.0 Hz, Ar-H), 7.15 (dd, 1H, J = 8.2, 2.0 Hz, Ar-H), 6.88 (d, 1H, J = 8.2 Hz, Ar-H), 5.69 (br s, 1H, OH), 3.95 (s, 3H, OCH_3); MS *m*/*z* 255 $[M + H]^+$.

(*E*)-1-(2-Hydroxy-4-methoxyphenyl)-3-phenylpropenone (17). Starting with 2-hydroxy-4-methoxybenzaldehyde (128 mg, 0.85 mmol), acetophenone (100 μL, 0.85 mmol), MeOH (1 mL), and 5 N NaOH (1 mL); yield 65 mg (30%); amorphous; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, 1H, J = 15.9 Hz, 1-H), 8.04−8.01 (m, 2H, 2 × Ar-H), 7.61 (d, 1H, J = 15.9 Hz, 2-H), 7.61−7.47 (m, 4H, 4Ar-H), 6.53 (dd, 1H, J = 8.7, 2.4 Hz, Ar-H), 6.49 (d, 1H, Ar-H), 3.82 (s, 3H, OCH_3); MS *m*/*z* 277 $[M + Na]^+$.

General Procedure for Alkylation.[25] The mixture of dehydrozingerone (**2**) or isoeugenol (**3**), an appropriate alkyl halide, and K_2CO_3 in acetone was heated to reflux overnight. The reaction mixture was evaporated under vacuum. The crude mixture was extracted with CH_2Cl_2, and the organic phase was washed with brine, dried over $NaSO_4$, and concentrated to obtain the product as a solid. The crude solid was purified with CombiFlash chromatography (EtOAc−hexane gradient) to obtain the target materials (**18**−**35**).[25]

(*E*)-1-[3-Methoxy-4-(3-methylbut-2-enyloxy)phenyl]but-1-en-3-one (18). Starting with **1** (50 mg, 0.26 mmol), 4-bromo-2-methyl-2-butene (48 μL, 0.39 mmol), and K_2CO_3 (252 mg, 1.82 mmol); yield 57 mg (87%); powder, mp 89−90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, 1H, J = 16.2 Hz, 1-H), 7.10 (dd, 1H, J = 8.2, 2.1 Hz, 6′-H), 7.07 (d, 1H, J = 2.1 Hz, 2′-H) 6.88 (d, 1H, J = 8.2 Hz, 5′-H), 6.60 (d, 1H, J = 16.2 Hz, 2-H), 5.51 (tt, 1H, J = 6.6, 1.2 Hz, 2′-H), 4.63 (d, 1H, J = 6.6 Hz, 1″-H), 3.90 (s, 3H, OCH_3), 2.37 (s, 3H, 4-H), 1.78 (br s, 3H, CH_3), 1.75 (br s, 3H, CH_3); MS *m*/*z* 261 $[M + H]^+$.

(*E*)-1-(4-Allyloxy-3-methoxyphenyl)but-1-en-3-one (19). Starting with **1** (100 mg, 0.52 mmol), allyl bromide (68.1 mL, 0.78 mmol), and K_2CO_3 (503 mg, 3.64 mmol); yield 115 mg (94%); needles, mp 71−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, 1H, J = 16.3 Hz, 1-H), 7.12−7.06 (m, 2H, 2′- and 6′-H), 6.88 (d, 1H, J = 7.8 Hz, 5′-H), 6.60 (d, 1H, J = 16.3 Hz, 2-H), 6.08 (ddt, 2H, J = 17.4, 10.5, 5.1 Hz, 2″-H), 5.42 (br d, 1H, J = 17.4 Hz, 3″-H), 5.32 (br d, 1H, J = 10.5 Hz, 3″-H), 3.91 (s, 3H, OCH_3), 2.37 (s, 3H, 4-H); MS *m*/*z* 233 $[M + H]^+$.

(*E*)-1-(4-But-2-enyloxy-3-methoxyphenyl)but-1-en-3-one (20). Starting with **1** (100 mg, 0.52 mmol), crotyl bromide (95 μL, 0.78 mmol), and K_2CO_3 (503 mg, 3.64 mmol); yield 119 mg (93%); powder, mp 68−69 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, 1H, J = 16.2 Hz, 1-H), 7.12−7.06 (d, 2H, 2′- and 6′-H), 6.88 (d, 1H, J = 8.4 Hz, 5′-H), 6.60 (d, 1H, J = 16.2 Hz, 2-H), 5.94−5.72 (m, 2H, 2″- and 3″-H), 4.56 (d, 1H, J = 6.0 Hz, 1″-H), 3.91 (s, 3H, OCH_3), 2.37 (s, 3H, 4-H), 1.75 (d, 3H, J = 5.1 Hz, 4″-H); MS *m*/*z* 247 $[M + H]^+$.

(*E*)-1-[4-(3,7-Dimethylocta-2,6-dienyloxy)-3-methoxyphenyl]but-1-en-3-one (21). Starting with **1** (100 mg, 0.52 mmol), crotyl bromide (149 μL, 0.78 mmol), and K_2CO_3 (503 mg, 3.64 mmol); yield 160 mg (93%); powder, mp 56−57 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, 1H, J = 16.2 Hz, 1-H), 7.10 (dd, 1H, J = 8.2, 1.9 Hz, 6′-H), 7.07 (d, 1H, J = 1.9 Hz, 2′-H), 6.87 (d, 1H, J = 8.2 Hz, 5′-H), 6.60 (d, 1H, J = 16.2 Hz, 2-H), 5.51 (br t, 1H, J = 6.6 Hz, 2″-H), 5.07 (br t, 1H, J = 6.6 Hz, 6″-H), 4.67 (d, 2H, J = 6.6 Hz, 1″-H), 3.91 (s, 3H, OCH_3), 2.37 (s, 3H, 4-H), 2.16−2.05 (m, 4H, 4″- and 5″-H), 0.74 (br s, 3H, CH_3), 1.66 (br s, 3H, CH_3), 1.60 (br s, 3H, CH_3); MS *m*/*z* 351 $[M + H]^+$.

(*E*)-1-[3-Methoxy-4-(3,7,11-trimethyldodeca-2,6,10-trienyloxy)-phenyl]but-1-en-3-one (22). Starting with **1** (100 mg, 0.52 mmol), farnesyl bromide (222.8 μL, 0.78 mmol), and K_2CO_3 (503 mg, 3.64 mmol); yield 182 mg (88%); powder, mp 66−67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, 1H, J = 16.2 Hz, 1-H), 7.10 (dd, 2H, J = 7.8,

2.0 Hz, 6′-H), 7.07 (d, 1H, J = 2.0 Hz, 2′-H), 6.87 (d, 1H, J = 7.8 Hz, 5′-H), 6.60 (d, 1H, J = 16.2 Hz, 2-H), 5.51 (br t, 1H, J = 6.0 Hz, 2″-H), 5.12−5.04 (m, 2H, 6″- and 10″-H), 4.67 (d, 2H, J = 6.3 Hz, 1″-H), 3.91 (s, 3H, OCH_3), 2.37 (s, 3H, 4-H), 2.18−1.92 (m, 8H, 4″-, 5″-, 8″-, and 9″-H), 0.75 (br s, 3H, 3″- or 7″-CH_3), 1.68 (br s, 3H, 3″- or 7″-CH_3), 1.59 (br s, 6H, *gem*-diMe); MS *m*/*z* 397 $[M + H]^+$.

(*E*)-1-(3,4-Dimethoxyphenyl)but-1-en-3-one (23). Starting with **1** (100 mg, 0.52 mmol), bromomethane (50 μL, 0.78 mmol), and K_2CO_3 (503 mg, 3.64 mmol); yield 72 mg (78%); needles, mp 87−88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, 1H, J = 16.2 Hz, 1-H), 7.13 (br d, 1H, 6′-H), 7.08 (br s, 1H, 2′-H) 6.88 (d, 1H, J = 8.2 Hz, 5′-H), 6.61 (d, 1H, J = 16.2 Hz, 2-H), 4.08 (t, 2H, J = 6.6 Hz, 1″-H), 3.92 (s, 3H, OCH_3 × 2), 2.37 (s, 3H, 4-H); MS *m*/*z* 179 $[M + H]^+$.

(*E*)-1-(4-Ethoxy-3-methoxyphenyl)but-1-en-3-one (24). Starting with **1** (100 μL, 0.65 mmol), bromoethane (59 μL, 0.97 mmol), and K_2CO_3 (626 mg, 4.53 mmol); yield 70 mg (61%); needles, mp 108−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, 1H, J = 16.0 Hz, 1-H), 7.10 (br d, 1H, J = 8.1, 6′-H), 7.08 (br s, 1H, 2′-H), 6.87 (d, 1H, J = 8.1 Hz, 5′-H), 6.60 (d, 1H, J = 16.0 Hz, 2-H), 4.14 (q, 2H, J = 6.9 Hz, 1″-H), 3.91 (s, 3H, OCH_3), 2.37 (s, 3H, 4-H), 1.48 (t, 2H, 7.0 Hz, 2″-H); MS *m*/*z* 221 $[M + H]^+$.

(*E*)-1-(3-Methoxy-4-propoxyphenyl)but-1-en-3-one (25). Starting with **1** (100 mg, 0.52 mmol), 1-iodopropane (77 μL, 0.78 mmol), and K_2CO_3 (503 mg, 3.64 mmol); yield 57 mg (47%); needles, mp 101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, 1H, J = 16.2 Hz, 1-H), 7.10 (br d, 1H, 6′-H), 7.08 (br s, 1H, 2′-H) 6.87 (d, 1H, J = 8.0 Hz, 5′-H), 6.60 (d, 1H, J = 16.1 Hz, 2-H), 4.02 (t, 2H, J = 6.9 Hz, 1″-H), 3.90 (s, 3H, OCH_3), 2.37 (s, 3H, 4-H), 1.89 (qt, 2H, J = 7.3, 6.9 Hz, 2″-H), 1.05 (t, 3H, J = 7.3 Hz, 3″-H); MS *m*/*z* 207 $[M + H]^+$.

(*E*)-1-[3-Methoxy-4-(3-methylbutoxy)phenyl]but-1-en-3-one (26). Starting with **1** (100 mg, 0.52 mmol), 1-methyl-3-bromobutane (102.3 μL, 0.78 mmol), and K_2CO_3 (503 mg, 3.64 mmol); yield 32 mg (23%); needles, mp 77−78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, 1H, J = 16.1 Hz, 1-H), 7.10 (br d, 1H, J = 8.4 Hz, 6′-H), 7.07 (br s, 1H, 2′-H) 6.88 (d, 1H, J = 8.4 Hz, 5′-H), 6.60 (d, 1H, J = 16.1 Hz, 2-H), 4.08 (t, 2H, J = 6.6 Hz, 1″-H), 3.90 (s, 3H, OCH_3), 2.37 (s, 3H, 4-H), 1.92−1.70 (m, 1H, 3′-H), 1.77 (br t, 2H, J = 6.6 Hz, 2″-H), 0.98 (br s, 3H, CH_3), 0.96 (br s, 3H, CH_3); MS *m*/*z* 263 $[M + H]^+$.

2-Methoxy-1-(3-methylbut-2-enyloxy)-4-propenylbenzene (27). Starting with **3** (100 μL, 0.65 mmol), 4-bromo-2-methyl-2-butene (118 μL, 0.97 mmol), and K_2CO_3 (626 mg, 4.53 mmol); yield 45 mg (30%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89−6.78 (m, 3H, 3-, 5-, and 6-H), 6.33 (d, 1H, J = 15.6 Hz, 1″-H), 6.16−6.04 (m, 1H, 2″-H), 5.89−5.71 (m, 2H, 2′- and 3′-H), 4.50 (d, 2H, J = 5.4 Hz, 1′-H), 3.87 (s, 3H, OCH_3), 1.86 (d, 3H, J = 6.3 Hz, 3″-H), 1.76 (s, 3H, CH_3), 1.72 (s, 3H, CH_3); MS *m*/*z* 233 $[M + H]^+$, 255 $[M + Na]^+$.

1-Allyloxy-2-methoxy-4-propenylbenzene (28). Starting with **3** (100 μL, 0.65 mmol), allyl bromide (85 μL, 0.97 mmol), and K_2CO_3 (626 mg, 4.53 mmol); yield 78 mg (59%); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89−6.78 (m, 3H, 3-, 5-, and 6-H), 6.33 (d, 1H, J = 16.2 Hz, 1″-H) 6.16−6.02 (m, 1H, 2″-H), 5.42 (br d, 1H, J = 17.4 Hz, 3′-H), 5.27 (br d, 1H, J = 9.6 Hz, 3′-H), 4.60 (d, 2H, J = 5.7 Hz, 1′-H), 3.88 (s, 3H, OCH_3), 1.86 (d, 3H, J = 6.3 Hz, 3″-H); MS *m*/*z* 205 $[M + H]^+$.

1-But-2-enyloxy-2-methoxy-4-propenylbenzene (29). Starting with **3** (100 μL, 0.65 mmol), crotyl bromide (118 μL, 0.97 mmol), and K_2CO_3 (626 mg, 4.53 mmol); yield 98 mg (69%); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89−6.78 (m, 3H, 3-, 5-, and 6-H), 6.33 (d, 1H, J = 15.3 Hz, 1″-H) 6.16−6.04 (m, 1H, 2″-H), 5.51 (m, 1H, 2′-H), 4.55 (d, 2H, J = 6.6 Hz, 1′-H), 3.87 (s, 3H, OCH_3), 1.86 (d, 3H, J = 6.3 Hz, 3″-H), 1.71 (d, 3H, J = 5.1 Hz, 4′-H); MS *m*/*z* 219 $[M + H]^+$.

2-Methoxy-4-propenyl-1-(3,7,11-trimethyldodeca-2,6,10-trienyloxy)benzene (30). Starting with **3** (100 μL, 0.65 mmol), farnesyl bromide (277 μL, 0.78 mmol), and K_2CO_3 (626 mg, 4.53 mmol); yield 215 mg (90%); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88−6.78 (m, 3H, 3-, 5-, and 6-H), 6.33 (d, 1H, J = 15.3 Hz, 1″-H) 6.16−6.04 (m, 1H, 2″-H), 5.51 (m, 1H, 2′-H), 5.10 (m, 2H, 6′- and 10′-H), 4.60 (d, 2H, J = 6.3 Hz, 1′-H), 3.87 (s, 3H, OCH_3), 2.15−1.90 (m, 8H, 4′-, 5′-, 8′-, 9′-H), 1.86 (d, 3H, J = 6.3 Hz, 3″-H), 1.77 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.59 (s, 6H, *gem*-diCH_3); MS *m*/*z* 369 $[M + H]^+$.

1,2-Dimethoxy-4-propenylbenzene (32). Starting with **3** (100 μL, 0.65 mmol), bromomethane (61 μL, 0.97 mmol), and K_2CO_3 (626 mg, 4.53 mmol); yield 101 mg (88%); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89−6.78 (m, 3H, 3-, 5-, and 6-H), 6.34 (d, 1H, J = 15.9 Hz, 1″-H), 6.16−6.04 (m, 1H, 2″-H), 3.89 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 1.87 (d, 3H, J = 6.3 Hz, 3″-H); MS *m*/*z* 179 $[M + H]^+$.

2-Methoxy-4-propenyl-1-propoxybenzene (34). Starting with **3** (100 μL, 0.65 mmol), 1-iodopropane (96 μL, 0.97 mmol), and K_2CO_3 (626 mg, 4.53 mmol); yield 129 mg (96%); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89−6.80 (m, 3H, 3-, 5-, and 6-H), 6.33 (d, 1H, J = 15.6 Hz, 1″-H) 6.15−6.04 (m, 1H, 2″-H), 3.96 (t, 3H, J = 6.7 Hz, 1′-H), 3.87 (s, 3H, OCH_3), 1.91−1.79 (m, 5H, 3″- and 2-H), 1.03 (t, 3H, J = 7.5 Hz, 3′-H); MS *m*/*z* 235 $[M + H]^+$.

2-Methoxy-1-(3-methyl-butoxy)-4-propenylbenzene (35). Starting with **3** (100 μL, 0.65 mmol), 1-methyl-3-bromobutane (127 μL, 0.97 mmol), and K_2CO_3 (626 mg, 4.53 mmol); yield 91 mg (59%); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89−6.78 (m, 3H, 3-, 5-, and 6-H), 6.33 (d, 1H, J = 15.9 Hz, 1″-H), 6.16−6.04 (m, 1H, 2″-H), 4.03 (t, 2H, J = 6.9 Hz, 1′-H), 3.87 (s, 3H, OCH_3), 1.86 (d, 3H, J = 6.6 Hz, 3″-H), 1.92−1.70 (m, 3H, 2′- and 3′-H), 0.97 (s, 3H, CH_3), 0.95 (s, 3H, CH_3); MS *m*/*z* 263 $[M + H]^+$.

Cytotoxic Activity Assay. The in vitro cytotoxicity assay was carried out according to procedures described in Rubinstein et al.[26] Drug stock solutions were prepared in DMSO, and the final solvent concentration was <1% DMSO (v/v), a concentration without effect on cell replication. The human tumor cell line panel consisted of epidermoid carcinoma of the nasopharynx (KB) and lung carcinoma (A-549). The drug-resistant cell line was KB-VCR, an MDR variant selected for growth in vincristine. It is cross-resistant to doxorubicin (Table 1). Detailed characterization of this cell line is described elsewhere.[27] Cells were cultured at 37 °C in RPMI-1640 with 100 μg/mL kanamycin and 10% (v/v) fetal bovine serum in a humidified atmosphere containing 5% CO_2. Initial seeding densities varied among the cell lines to ensure a final absorbance of 1−2.5 A_{562} units. Drug exposure was for 2 days, and the IC_{50} value, the drug concentration that reduced the absorbance by 50%, was interpolated from dose−response data. Each test was performed in duplicate, and absorbance readings varied no more than 5% between replicates.

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