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Flavonoid Dimers as Bivalent Modulators for P-Glycoprotein-Based Multidrug Resistance: Structure–Activity Relationships

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We recently described the modulatory activities of apigenin homodimers linked by ethylene glycol units in multidrug-resistant breast cancer and leukemic cells overexpressing ABCB1 (P-glycoprotein, P-gp). To further improve the potency of these dimers, a small library of flavonoid homodimers and heterodimers were synthesized, and their in vitro activity in reversing cellular resistance to paclitaxel, along with structure–activity relationships (SAR), were evaluated using a P-gp-expressing human breast cancer cell line. Among these synthesized homodimers, many showed more potent reversing activity than that of the parent compound and verapamil. Two compounds in particular showed promising reversing activity at sub-micromolar concentrations with no cytotoxic effects. Regarding SAR trends, flavonoid dimers with nonpolar and hydrophobic substituents (e.g., methyl and ethyl groups) generally showed more potent resistance-reversing activity than that of dimers with polar and hydrophilic substituents (e.g. hydroxy groups) at the C3, C6, and C7 positions, but not at C5. In terms of substituent steric bulk at C6, it was found that the flavonoid dimer with methyl groups was optimal, with bulkier substituents leading to lower reversing activity. Comparisons of flavonoid heterodimers with the corresponding homodimers revealed that the two binding sites on P-gp for flavonoid moieties are quite similar to each other. Besides paclitaxel, these new compounds also increased drug accumulation and enhanced the cytotoxicity of other cancer drugs such as doxorubicin, vincristine, and vinblastine by decreasing the IC_{50} values 4–45-fold.

Introduction

The problem of multidrug resistance (MDR) in cancer chemotherapy has drawn attention from both academia and industry. A major cause of MDR in cancer is the overexpression of the membrane drug efflux transporter ABCB1, also known as permeability glycoprotein (P-gp), which decreases the intracellular accumulation of drugs. P-gp belongs to the ATP binding cassette (ABC) transporter superfamily and is an ATP-dependent membrane-spanning multidrug transporter.[1,2] The P-gp gene encodes a 1280-residue protein that adopts a pseudo-dimeric conformation, with each unit consisting of approximately 610 amino acids joined by a linker region of about 60 amino acids.[3] Each unit has six transmembrane domains (TMD) and a hydrophilic nucleotide binding domain (NBD).[4] The NBDs, which are peripherally located at the cytoplasmic face of the membrane, bind ATP and couple ATP hydrolysis with the drug transport process. Although the three dimensional structure of P-gp has not yet been determined, the structure of its bacterial homologue Sav1886 was recently resolved.[5] Electron crystallography data for P-gp, determined at a resolution limit of ~2 nm, also support a pseudo-dimeric structure.[6] In its nucleotide-free state, the TMDs form a barrel 5–6 nm in diameter and ~5 nm deep with a central pore that is open to the extracellular surface. Upon nucleotide binding, the TMDs appear to reorganize to open the central pore in a manner that could allow access of the transport substrate from the lipid bilayer to the central pore of P-gp.[7–9]

Ever since the relationship between P-gp and MDR was demonstrated, many have tried to develop P-gp inhibitors with the ultimate goal of reversing MDR. The first P-gp inhibitor was verapamil (VP; $C_{27}H_{38}N_2O_4$) developed by Tsuruo et al.[10] Subsequently, a range of compounds including calcium channel blockers,[11,12] calmodulin inhibitors,[13,14] indole alkaloids,[15,16] cyclosporine,[17–20] quinolines,[21] and steroids[22–24] have also been demonstrated to have P-gp-inhibitory activity to varying extents. Most of these so-called first-generation P-gp modulators suffered from unacceptable toxicity. Searches for the congeners of these first-generation MDR modulators resulted in the less toxic and more potent agents such as dexverapamil,[25] dexniguldipine,[26] valspodar (PSC 833; $C_{63}H_{111}N_{11}O_{12}$),[24,27] and biricodar (VX-710; $C_{34}H_{41}N_3O_7$).[28–30] Although these second-generation MDR modulators showed some encouraging results, their use is limited by their unpre-

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dictable pharmacokinetic interactions with anticancer drugs.[31] The third-generation MDR modulators developed by structure–activity relationships and combinatorial chemistry approaches include zosuquidar LY335979, tariquidar XR9576, laniquidar R101933, acridonecarboxamide GF120918, and the substituted diarylimidazole ONT-090.[32–34]

Another P-gp modulator family is the naturally occurring flavonoids.[35] Flavonoids are polyphenolic compounds present in fruits, vegetables, nuts, stems, flowers, red wine, and tea.[36] Different classes of flavonoids have been demonstrated to have various beneficial properties for human health, such as antioxidant, free-radical scavenging, anti-inflammatory, antiviral, and anticancer properties.[37] Some flavonoids also have modulating activities toward P-gp.[38–44] There are a number of possible ways by which flavonoids assert their modulating effect on P-gp. Some flavonoids are good inhibitors of a variety of ATP binding proteins including protein kinases such as cyclic AMP-dependent protein kinase,[45,46] protein kinase C,[47] serine/threonine kinases,[48] tyrosine kinase,[49,50] topoisomerase II,[51] and myosin,[52] as well as various membrane ATPases such as mitochondrial H^+-ATPase,[53] Na^+/K^+-ATPase,[54] Ca^{2+}-ATPase,[55] and H^+/K^+-ATPase.[56] The mechanism by which the flavonoids interact with P-gp has also been studied. Chrysin, quercetin, kaempferol, and dehydrosilybin were reported to bind directly to the NBD2 cytosolic domain of mouse P-gp.[57] Increased hydrophobicity through the introduction of prenyl or other alkyl groups onto the A ring of the flavonoid structure often produced more efficient inhibitors; 8- or 6-prenylchrysin inhibits P-gp-mediated drug efflux in leukemic K562/R7 cells,[39] whereas 8-dimethylallylkaempferide is a better modulator than either cyclosporine A or VP in the inhibition of LtrMDR1.[58]

Flavonoid modulators also have limitations.[59] First, their activities tend to be moderate. Second, they have a broad spectrum of biological activities including anti-estrogen activity and the inhibition of other ATPases. We used an alternative approach to improve the potency and selectivity of flavonoids by taking advantage of the pseudo-dimeric nature of P-gp by using polyvalent interactions.[60,61] Polyvalent interactions in biological systems are characterized by the simultaneous binding of multiple ligands on one biological entity.[62] Successful bivalent[63] and multivalent[64,65] ligands to different receptor systems have been reported, with a level of potency 10^3–10^5-fold higher than that of the corresponding monovalent ligands. We[60,61] and others[66] have used synthetic dimers to design MDR modulators. Apigenin has been reported to be a modulator of MDR in colon HCT-15 cancer cells.[40,45,57] We have synthesized a series of apigenin-based flavonoid homodimers and demonstrated that these dimers can modulate drug chemosensitivity and retention in breast and leukemic MDR cells, with a linker of four ethylene glycol units being optimal (Figure 1; compound **92**, $n=4$). At a concentration of 5 μM, these dimers can increase drug accumulation in drug-resistant cells, thereby enhancing the in vitro cytotoxicity of paclitaxel ($C_{47}H_{51}NO_{14}$), doxorubicin (DOX), daunomycin, vincristine, and vinblastine in drug-resistant breast cancer and leukemia cells, resulting in a 5–50-fold decrease in IC_{50} values.[60]

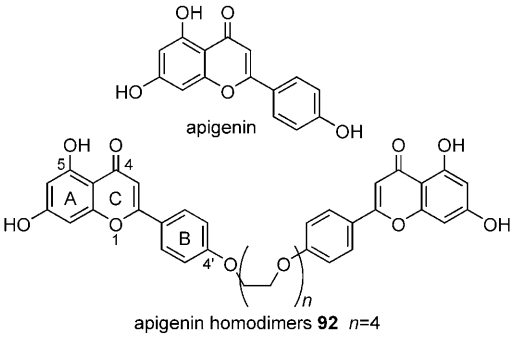


Figure 1. The structures of apigenin and apigenin homodimer **92**.

Herein we report our attempts to optimize the lead compound **92** by synthesizing a small library of flavonoid homodimers and heterodimers modified at the C3 and C5–C8 positions of ring A, together with an evaluation of their paclitaxel resistance reversing activity, cytotoxicity, and Clog *P* values. For a selected analogue **61**, we also modified the tetra(ethylene glycol) linkage from the C4′ position of ring B to C2′ or C3′. These novel ligands were then used to probe the size, shape, flexibility, and lipophilicity of the binding pocket.

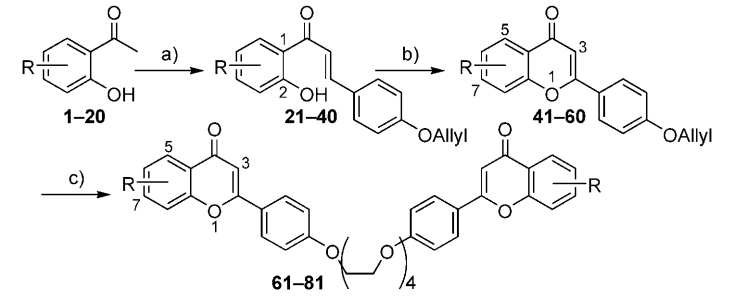
Results and Discussion

1. Chemistry

1A. Synthesis of flavonoid homodimers

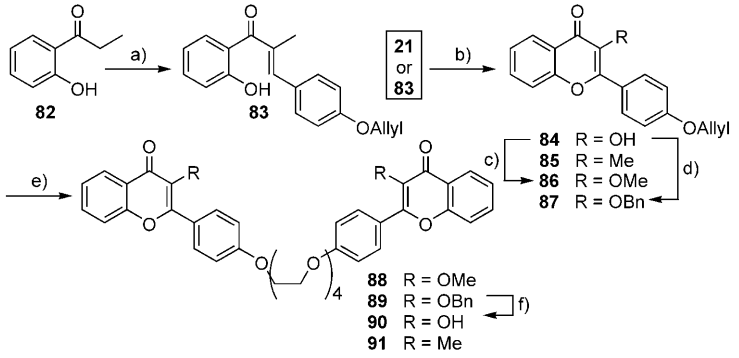
The flavonoid homodimers were prepared by the synthetic method we reported previously.[60] The 2-hydroxyacetophenones with various substitutions and *p*-allyloxybenzaldehyde required as starting materials were commercially available. 2-Hydroxyacetophenones **14**–**16** and **18** were synthesized by treatment of the corresponding precursors with benzyl bromide under basic conditions. As shown in Scheme 1, base-catalyzed aldol condensation of 2-hydroxyacetophenones **1**–**20** with *p*-allyloxybenzaldehyde afforded chalcones **21**–**40** in high yield. These chalcones were then cyclized with catalytic quantities of iodine in dimethyl sulfoxide (DMSO) at high temperature to furnish the desired flavones **41**–**60** in moderate yield. The allyl protecting group of these flavones was successfully cleaved with a catalytic amount of $[Pd(PPh_3)_4]$ using potassium carbonate in methanol at reflux to furnish the 4′-hydroxyflavones, which were pure enough for the next step. The intermolecular nucleophilic substitution of tetra(ethylene glycol) dimesylate by 4′-hydroxyflavones under basic conditions gave flavonoid dimers **61**–**80** in moderate yield. Their dimeric nature was evident from high-resolution mass spectrometric data. Palladium-catalyzed deprotection of the benzyl group of flavonoid dimer **76** gave compound **81** in high yield.

For the synthesis of C3-substituted compounds as shown in Scheme 2, 2-hydroxypropiophenone **82** was condensed with *p*-allyloxybenzaldehyde to give chalcone **83**, which was then cyclized to give **85**. De-allylation followed by reaction with tetra(ethylene glycol) dimesylate gave **91**. Alternatively, 3-hydroxyflavone **84** was prepared from the cyclization of chalcone **21**



Compd	R=	Compd	R=	Compd	R=	Compd	R=
1, **21**	H	**11**, **31**	5-MeO	**41**, **61**	H	**51**, **71**	6-MeO
2, **22**	4-F	**12**, **32**	6-MeO	**42**, **62**	7-F	**52**, **72**	5-MeO
3, **23**	5-F	**13**, **33**	4,5-diMeO	**43**, **63**	6-F	**53**, **73**	6,7-diMeO
4, **24**	5-Cl	**14**, **34**	4-BnO	**44**, **64**	6-Cl	**54**, **74**	7-BnO
5, **25**	5-Br	**15**, **35**	5-BnO	**45**, **65**	6-Br	**55**, **75**	6-BnO
6, **26**	3,5-diCl	**16**, **36**	6-BnO	**46**, **66**	6,8-diCl	**56**, **76**	5-BnO
7, **27**	3,5-diBr	**17**, **37**	4,6-diMeO	**47**, **67**	6,8-diBr	**57**, **77**	5,7-diMeO
8, **28**	4-Me	**18**, **38**	4,6-diBnO	**48**, **68**	7-Me	**58**, **78**	5,7-diBnO
9, **29**	5-Me	**19**, **39**	5-Et	**49**, **69**	6-Me	**59**, **79**	6-Et
10, **30**	4-MeO	**20**, **40**	3-NO_2,5-Me	**50**, **70**	7-MeO	**60**, **80**	6-Me,8-NO_2
						81	5-OH

Scheme 1. Synthesis of flavonoid homodimers **61**–**81**: a) 3 M KOH in EtOH, *p*-allyloxybenzaldehyde, RT, 16 h; b) I_2 (cat), DMSO, 130 °C, 2–4 h; c) 1. $[Pd(PPh_3)_4]$ (cat), K_2CO_3, MeOH, reflux, 4 h, 2. tetra(ethylene glycol) dimesylate, K_2CO_3, DMF, reflux, 3 h; d) H_2, Pd/C (10%), $CHCl_3$, RT, 14 h.



Scheme 2. Synthesis of 3-substituted flavonoid homodimers **88**–**91**: a) 3 M KOH in EtOH, *p*-allyloxybenzaldehyde, RT, 16 h; b) for **84**: **21**, 3 M KOH in EtOH, 37% H_2O_2, RT, 0.5 h, for **85**: **83**, I_2 (cat), DMSO, 130 °C, 3 h; c) Me_2SO_4, K_2CO_3, acetone, reflux, 2 h; d) BnBr, K_2CO_3, DMF, reflux, 1 h; e) 1. $[Pd(PPh_3)_4]$ (cat), K_2CO_3, MeOH, reflux, 4 h, 2. tetra(ethylene glycol) dimesylate, K_2CO_3, DMF, reflux, 3 h; f) H_2, Pd/C (10%), $CHCl_3$, RT, 14 h.

with alkaline hydrogen peroxide in high yield. This hydroxyflavone was then transformed into 3-methoxy derivative **86** and 3-benzyloxy derivative **87** with dimethyl sulfate and benzyl bromide, respectively. Cleavage of the allyl protecting group followed by dimerization using tetra(ethylene glycol) dimesylate in basic medium respectively afforded flavonoid dimers **88** and **89**. Palladium-catalyzed deprotection of the benzyl group of flavonoid dimer **89** gave **90** in high yield.

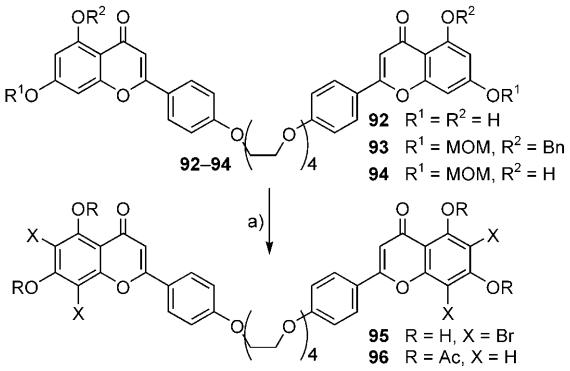
As shown in Scheme 3, bromination or acetylation of flavonoid dimer **92** under mild conditions gave compounds **95** and **96**, respectively. Compounds **93** and **94** were prepared as previously reported.[60]

Two 6-aryl-substituted flavonoid dimers **101** and **102** were synthesized via microwave-assisted copper- and palladium-catalyzed reactions as outlined in Scheme 4. Starting from 6-bromoflavone **45**, copper(I) iodide- and lysine-catalyzed cross-coupling with excess imidazole gave flavone **97**. Deprotection of the allyl group followed by dimerization with tetra(ethylene glycol) dimesylate furnished flavonoid dimer **101**. Palladium-catalyzed Suzuki cross-coupling of flavone **98**, which was prepared from 6-bromoflavone **45** after deprotection of the allyl group, with phenylboronic acid gave flavone **100**. Dimerization of this compound with tetra(ethylene glycol) dimesylate furnished flavonoid dimer **102**.

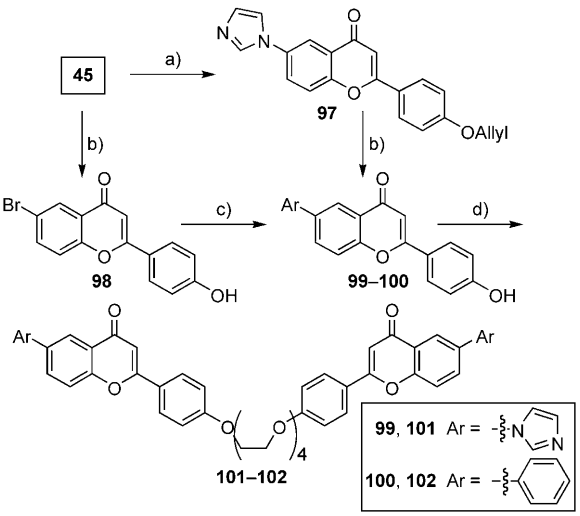
To evaluate the effect of the position of the poly(ethylene glycol) linkage at the B ring, we used compound **61** as a model and synthesized flavonoid dimers with the linkers positioned at C2′ and C3′. As shown in Scheme 5, treatment of commercially available monohydroxyflavones with tetra(ethylene glycol) dimesylate under basic conditions afforded the corresponding flavonoid dimers **103** and **104** with linkers respectively positioned at C2′ and C3′.

1B. Synthesis of flavonoid heterodimers

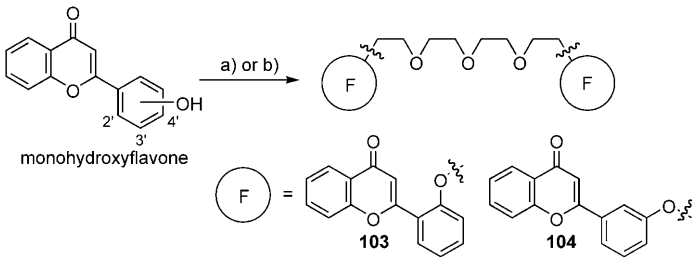
Five flavonoid heterodimers **110**–**114** were synthesized as shown in Scheme 6. During the synthesis of flavonoid dimer **61**, flavone monomer **105**, bearing a tetra(ethylene glycol) chain, was isolated as a minor product. This compound was then mesylated to furnish flavone **106**, which reacted with various 4-hydroxyflavones **107**–**109** in basic medium to give flavonoid dimers **110**, **113**, and **114**, respectively. 4′-Hydroxyflavone **107** was prepared as previously reported.[59] 4′-Hydroxyflavone **108** and **109** were synthesized from the corresponding allyl-group-protected flavones **48** and **54** by using catalytic amounts of $[Pd(PPh_3)_4]$ under basic conditions. Deprotection of the benzyl group of dimer **110** followed by acidic cleavage of the methoxymethyl (MOM) group afforded flavonoid dimers **111** and **112**, respectively, in high yield.



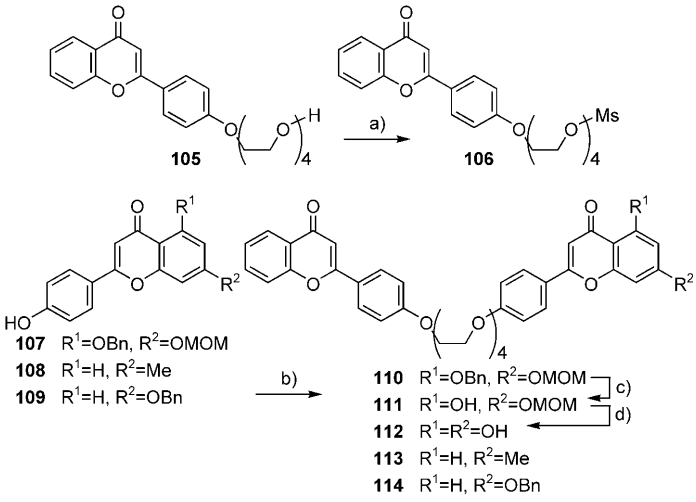
Scheme 3. Synthesis of flavonoid homodimers **95** and **96**: a) for **95**: **92**, Br_2, CH_2Cl_2, RT, 48 h, for **96**: **92**, Ac_2O, pyridine, RT, 24 h.



Scheme 4. Microwave-assisted synthesis of 6-aryl-substituted flavonoid homodimers **101** and **102**: a) imidazole, CuI, L-lysine, K_3PO_4, MW, 10 h; b) [Pd-(PPh_3)$_4$] (cat), K_2CO_3, MeOH, reflux, 2 h; c) for **100**: $PhB(OH)_2$, [$Pd(PPh_3)_4$] (cat), Cs_2CO_3, H_2O, MW, 6 h; d) tetra(ethylene glycol) dimesylate, K_2CO_3, DMF, reflux, 3 h.



Scheme 5. Synthesis of flavonoid homodimers with different linker positions **103**–**104**: a) for **103**: 2′-hydroxyflavone, $MsO(CH_2CH_2O)_4Ms$, K_2CO_3, DMF, reflux, 3 h; b) for **104**: 3′-hydroxyflavone, $MsO(CH_2CH_2O)_4Ms$, K_2CO_3, DMF, reflux, 3 h.



Scheme 6. Synthesis of flavonoid heterodimers **110**–**114**: a) MsCl, NEt_3, CH_2Cl_2, 0 °C for 0.5 h then RT for 2 h; b) **107**–**109**: K_2CO_3, DMF, reflux, 3 h; c) H_2, Pd/C (10%), $CHCl_3$, RT, 14 h; d) 6 M HCl, THF, 1 h.

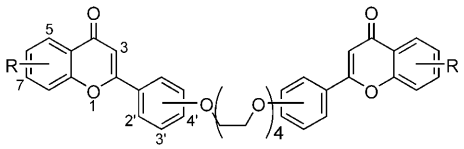
2. Biological assays

The synthesized flavonoid homodimers and heterodimers were evaluated for their activity in reversing cellular resistance to paclitaxel by using P-gp-expressing human breast cancer cell lines (resistant cell line: MDA435/LCC6MDR). Their resistance-reversing activities were assessed by the IC_{50} values of paclitaxel determined after exposure to a series of paclitaxel concentrations in the presence of various flavonoid dimer (modulator) concentrations. Also determined was the relative fold (RF), which was obtained by dividing the IC_{50} value of paclitaxel without modulator by the IC_{50} value of paclitaxel with modulator. A higher RF value means higher P-gp-modulating activity. The IC_{50} value of paclitaxel for resistant MDA435/LCC6MDR cells without modulator added is approximately 131.1 nM (Table 1, Entry 1), whereas for sensitive MDA435/LCC6 cells, IC_{50} = 2.9 nM. This reflects an approximate 45-fold greater resistance to paclitaxel for the MDR cells. None of the modulators used in this study has any observable cytotoxicity toward either MDA435/LCC6 or MDA435/LCC6MDR cells at the concentrations tested (5, 2, or 1 μM; data not shown). VP, when tested at 5, 2, and 1 μM, can decrease the IC_{50} of paclitaxel to 8.1, 19.2, and 40.2 nM, respectively (Table 1, Entry 36) and acts as a positive control. The lead compound **92**, when used at 5, 2, and 1 μM, can lower the IC_{50} of paclitaxel to 24.9, 42.6, and 124.6 nM, respectively (Table 1, Entry 2); at 1 μM compound **92** loses its paclitaxel resistance-reversing activity. The paclitaxel resistance-reversing activities of other synthesized flavonoid homodimers are summarized in Table 1. Generally speaking, the newly synthesized flavonoid dimers showed more potent reversing activity than compound **92**, except compounds **64**, **70**, **71**, **78**, **90**, and **95** (Table 1, Entries 21, 31, 26, 5, 14, and 3). Because lipophilicity has been cited as an important factor for P-gp inhibitory activity,[39,58] we calculated the log*P* values (Clog*P*) of all the tested flavonoid dimers in silico using the Osiris Property Explorer, and the results are included in Tables 1 and 2 as well. We found that all flavonoid dimers exhibited relatively high Clog*P* values (>5), which suggests that these flavonoid dimers are relatively lipophilic. Polar alkyloxy and hydroxy groups seem unfavorable for modulating P-gp, as reflected from the poor resistance-reversing activity of compounds **70**, **71**, **78**, and **90**. On the other hand, no significant correlation was observed between the Clog*P* and IC_{50} values of paclitaxel in the presence of modulator at 1 μM. Thus, compound **78**, with a relatively high Clog*P* value of 11.33, has poor resistance-reversing activity. Other factors must play a role, possibly including steric factors in the case of compound **78**, with its four bulky benzyloxy groups.

2A. Effects of structural modification of compound 92 on paclitaxel resistance-reversing activity

Because increased hydrophobicity of flavonoids has often been found to produce more efficient inhibitors,[38,57] it is of interest to compare the activity of compound **92** with its derivatives in which the four hydroxy groups are protected as methoxy (**73** and **77**), benzyloxy (compound **78**), and acetate groups (com-

Table 1. Paclitaxel cytotoxicity using flavonoid homodimers at various concentrations and Clog *P* values of flavonoid dimers.



Entry	Compd	R	Linker Position	IC_{50} [nM]			Clog *P*[b]	RF[c]
				FD at 5 μM[a]	FD at 2 μM[a]	FD at 1 μM[a]		
1[d]	/	/	/	131.1 ± 2.8[f]	131.1 ± 2.8	131.1 ± 2.8	/	1.0
2	**92**	5,7-diOH	4′	24.9	42.6	124.6 ± 16.7	5.08	1.1
3	**95**	5,7-diOH, 6,8-diBr	4′	98.0 ± 2.9	–	–	7.87	(1.3)[g]
4	**77**	5,7-diMeO	4′	–	–	37.9	5.86	3.5
5	**78**	5,7-diBnO	4′	–	–	131 ± 19.1	11.33	1.0
6	**96**	5,7-diAcO	4′	–	–	69.2	6.00	1.9
7	**93**	5-BnO, 7-MOMO	4′	–	–	31.6 ± 4.3	8.23	4.1
8	**94**	5-OH, 7-MOMO	4′	–	–	24.2 ± 4.9	5.10	5.4
9	**73**	6,7-diMeO	4′	16.0 ± 2.3	–	–	5.86	(8.2)[g]
10	**66**	6,8-diCl	4′	3.4 ± 1.1[f]	2.8	14.5 ± 7.4[f]	8.73	9.0
11	**67**	6,8-diBr	4′	–	–	113.1 ± 23.5	9.09	1.2
12	**61**	H	4′	2.7 ± 0.2[f]	3.3 ± 0.6[f]	8.9 ± 2.6[f]	6.28	14.7
13	**91**	3-Me	4′	–	–	16.3	7.06	8.0
14	**90**	3-OH	4′	52.4 ± 7.5	–	–	5.09	(2.5)[g]
15	**88**	3-MeO	4′	–	7.7	17.0 ± 1.7[f]	6.00	7.7
16	**89**	3-BnO	4′	–	–	29.6 ± 7.3[f]	8.74	4.4
17	**81**	5-OH	4′	–	15	14.3 ± 5.9[f]	5.68	9.2
18	**72**	5-MeO	4′	7.4 ± 2.6[f]	12.2	21.8 ± 1.8[f]	6.07	6.0
19	**76**	5-BnO	4′	–	7.8	7.6 ± 1.4[f]	8.81	17.2
20	**63**	6-F	4′	12.2 ± 4.1[f]	–	–	6.4	(10.7)[g]
21	**64**	6-Cl	4′	33.3 ± 3.0	–	–	7.50	(3.9)[g]
22	**65**	6-Br	4′	21.5 ± 1.9	–	–	7.67	(6.1)[g]
23	**69**	6-Me	4′	3.7 ± 0.6[f]	2.2	4.9 ± 2.1[f]	6.91	26.7
24	**79**	6-Et	4′	–	–	5.4 ± 1.3[f]	7.62	24.3
25	**102**	6-Ph	4′	–	–	30.9	9.64	4.2
26	**71**	6-MeO	4′	37.6 ± 1.4	–	–	6.07	(3.5)[g]
27	**75**	6-BnO	4′	–	–	77.4	8.81	1.7
28	**101**	6-imidazol-1-yl	4′	–	–	85.7	4.96	1.5
29	**80**	6-Me, 8-NO_2	4′	–	–	20.6 ± 1.0[f]	–	6.4
30	**68**	7-Me	4′	2.4 ± 0.5[f]	3.2	6.6 ± 3.7[f]	6.91	19.8
31	**70**	7-MeO	4′	32.0 ± 2.0[f]	–	–	6.07	(4.1)[g]
32	**62**	7-F	4′	3.1 ± 0.2[f]	3.7	10.6 ± 4.9[f]	6.40	12.4
33	**74**	7-BnO	4′	–	–	71.7 ± 4.7	8.81	1.8
34	**103**	H	2′	–	–	19.2 ± 3.2	6.28	6.8
35	**104**	H	3′	–	–	17.3 ± 5.4	6.28	7.6
36[e]	VP	/	/	8.1 ± 1.6[f]	19.2	40.2 ± 9.8[f]	–	3.3

[a] IC_{50} values were determined after exposure to a series of paclitaxel concentrations with different flavonoid dimers (FD) at 5, 2, or 1 μM; –: not determined. [b] Clog *P* values were calculated in silico using Osiris Property Explorer. [c] RF represents the fold change in drug sensitivity: relative fold (RF) = (IC_{50} without modulator)/(IC_{50} with modulator); RF was measured using a modulator concentration of 1 μM, except those with footnote[g]. [d] Paclitaxel alone and no modulator added; /: not applicable. [e] VP was added as positive control; /: not applicable. [f] Experiments were repeated multiple times, with n = 2–17. [g] RF was measured using a modulator concentration of 5 μM.

pound **96**). Among them, the methoxy analogues **77** and **73** showed greater paclitaxel resistance-reversing activities than compound **92**, with respective RF values of 3.5 and 8.2 (Table 1, Entries 4 and 9). However, compound **78** (Entry 5) showed no resistance-reversing activity at 1 μM. Acetate **96** was of intermediate activity (Entry 6). Compounds **93** and **94**, the synthetic precursors of compound **92**, also showed encouraging reversing activities, with respective RF values of 4.1 and 5.4 (Table 1, Entries 7 and 8). These results suggest that simple derivatization of the hydroxy function, while leading to somewhat more active compounds, does not provide a consistent pattern for further improvement.

One way to enhance lipophilicity is to modify the structure of **92** with both 5- and 7-OH groups replaced by hydrogen. This resulted in compound **61**, which showed a dramatic improvement in efficacy (Table 1, Entry 12). Compound **61**, when assayed at 5, 2, and 1 μM, can decrease the IC_{50} value of paclitaxel to 2.7 ± 0.2, 3.3 ± 0.6, and 8.9 ± 2.6 nM, respectively. For comparison, the IC_{50} value of paclitaxel for drug-sensitive MDA435/LCC6 cells is 2.9 nM. The EC_{50} value (concentration of modulator that decreases IC_{50} by 50%) of paclitaxel for compound **61** is 360 nM. This can be compared with the reported EC_{50} value of 60 nM for the highly effective modulator XR9576.[67]

These encouraging results prompted us to synthesize more analogues of compound **61**. The tetrachloro-substituted analogue, compound **66**, while showing improved efficacy relative to **92** (IC_{50} of paclitaxel: 3.4, 2.8, and 14.5 nM; Table 1, Entry 10), was, in fact, not superior to **61**. The tetrabromo analogue, compound **67**, showed even poorer resistance-reversing activity (Table 1, Entry 11).

To further understand the substituent effect at each position, analogues of **61** with substituents at C3, C5, C6, or C7 were evaluated. Among those with substituents at the C3 position (Table 1, Entries 13–16), compound **90**, with the polar and hydrophilic hydroxy group, showed the lowest reversing activity (Table 1, Entry 14); compound **91**, on the other hand, with the nonpolar and hydrophobic methyl group, showed the highest reversing activity (Table 1, Entry 13) with an RF value of 8.0. Increasing the substituent steric bulk from methoxy (compound **88**) to benzyloxy (compound **89**) decreased the reversing activity. These results are consistent with our observations with the methoxy compound **77** and the benzyloxy compound **78** mentioned above.

For C5-substituted flavonoid dimers (Table 1, Entries 17–19), we had a somewhat limited structural variation, all with oxygen substituents. Compound **76**, with a sterically hindered benzyloxy group, showed a higher resistance-reversing activity with an RF value of 17.2 (Table 1, Entry 19) than compounds **72** (Entry 18) or **81** (Entry 17), with methoxy or hydroxy groups, respectively. This result is different from what was observed before at C3. More interestingly, compound **76** is more active than either compound **61** without a benzyloxy group or compound **78** with benzyloxy groups at both C5 and C7. The series of **81**, **72**, and **76**, with oxygen substituents at C5, are all more active than the series **92**, **77**, and **78**, with the same oxygen substituents at C5 and C7. This suggests that oxygen substitution at C5 is favorable for activity, whereas oxygen substitution at C7 is unfavorable (see below).

As shown in Table 1 (Entries 20–29), 10 flavonoid homodimers were synthesized to study SAR trends at the C6 position. Among the halogen-substituted flavonoid dimers **63**, **64**, and **65**, there is no clear trend (Table 1, Entries 20–22). The most active compound is the fluoro-substituted compound **63**, with an RF value of 10.9 at 5 μM, but which is much less active than the unsubstituted parent compound **61**. Compounds **71** and **75**, with oxygen substitution at C6, showed lower activity (Table 1, Entries 26 and 27) than compound **61**. On the other hand, alkyl substitution at C6, as in the case of compounds **69** and **79** (Table 1, Entries 23 and 24), led to compounds of much greater potency. The methyl-substituted compound **69** has an RF value of 26.7 and is about eightfold more effective than VP. A change from methyl to ethyl groups (compound **79**) has little effect on the activity (Entry 24). Bulkier substituents such as phenyl or imidazolyl (Entries 25 and 28) led to a substantial decrease in resistance-reversing activity. Introduction of a nitro group at the C8 position of compound **69** is not desirable either (Table 1, Entry 29).

Among the C7-substituted flavonoid dimers (Table 1, Entries 30–33), compounds **70** and **74**, with alkoxy groups, showed lower resistance-reversing activity (Table 1, Entries 31 and 33) which is consistent with the previous pattern observed. Compound **68** with a hydrophobic methyl group and compound **62** with fluorine showed high resistance-reversing activity (Table 1, Entries 30 and 32). These results suggest that the binding pocket near C6 may prefer a hydrophobic substituent at this site.

2B. Effect of linker attachment at different positions of the B ring of compound 61 on paclitaxel resistance-reversing activity

As flavonoid dimer **61** shows promising paclitaxel resistance-reversing activity, we targeted this compound as a model and synthesized flavonoid dimers varying the linker position at C2′ and C3′. As listed in Table 1 (Entries 34 and 35), flavonoid dimers with a poly(ethylene glycol) linker attached at C2′ and C3′ show lower reversing activity than that of the parent compound **61**. These results suggest that although the poly(ethylene glycol) linkers in compounds **61**, **103**, and **104** are of equal length and of presumably equal flexibility, the flavonoid moieties must be oriented in a certain manner that is best achieved with the linker attached at C4′ rather than at the C2′ or C3′ positions.

2C. Flavonoid homodimers versus heterodimers in P-gp-modulating activities

To shed further light on the binding pockets in P-gp for the two flavonoid moieties, we compared the modulating activities of flavonoid homodimers with those of heterodimers. To determine whether the two binding sites of flavonoids are similar, we studied the efficacy of five groups (1–5) of compounds; each group consists of the flavonoid heterodimers (**A**–**B**) and their homodimeric parent compounds (**A**–**A** and **B**–**B**), where **A** and **B** represent the monomeric flavonoids (Table 2). For groups 1–5, the unsubstituted parent (**A**–**A**) is more effective in modulating P-gp than the other (**B**–**B**), with the **B** moiety having the polar substituents except group 5. We reason that if the two binding sites on P-gp are similar, the heterodimer (**A**–**B**) will have an intermediate modulating activity between the two homodimers (**A**–**A** and **B**–**B**). Indeed, all compounds in groups 1–4 follow the general rules: RF values for **A**–**B** are approximately intermediate between those of **A**–**A** and **B**–**B** (Table 2). The results suggest that the two binding sites on P-gp are quite similar to each other.

The exception to this general observation is when the two parent flavonoid homodimers are similar to each other in structure and activity. This is the case for group 5, in which the difference between **A** and **B** is the replacement of hydrogen by a methyl group at position 7. The heterodimer (**A**–**B**) has an RF value of 6.1, which is lower than the individual parent flavonoid homodimers (RF values of 14.7 and 19.8). This suggests that the two binding sites, while similar, are not necessarily identical and may lead to poorer binding of the heterodimer than its parents.

Table 2. Paclitaxel cytotoxicity for comparing the P-gp-modulating activities of flavonoid homodimers and heterodimers and Clog *P* values of flavonoid dimers.

Group	Compd	General Structure[a]	IC_{50} [nM]		Clog *P*[c]	RF[d]
			FD at 2 μM[b]	FD at 1 μM[b]		
1	**61**	**A**–**A**	3.3 ± 0.6	–	6.28	39.7
1	**112**	**A**–**B**	17.8	–	5.68	7.4
1	**92**	**B**–**B**	42.6	–	5.08	3.1
2	**61**	**A**–**A**	–	8.9 ± 2.9	6.28	14.7
2	**114**	**A**–**B**	–	19.8 ± 2.9	7.54	6.6
2	**74**	**B**–**B**	–	71.7 ± 4.7	8.81	1.8
3	**61**	**A**–**A**	–	8.9 ± 2.9	6.28	14.7
3	**111**	**A**–**B**	–	12.9 ± 1.3	5.69	10.2
3	**94**	**B**–**B**	–	24.2 ± 4.9	5.10	5.4
4	**61**	**A**–**A**	–	8.9 ± 2.9	6.28	14.7
4	**110**	**A**–**B**	–	16.2 ± 2.1	7.25	8.1
4	**93**	**B**–**B**	–	31.6 ± 4.3	8.23	4.1
5	**61**	**A**–**A**	–	8.9 ± 2.9	6.28	14.7
5	**113**	**A**–**B**	–	21.5 ± 3.4	6.59	6.1
5	**68**	**B**–**B**	–	6.6 ± 3.7	6.91	19.8

[a] Flavonoid heterodimers are indicated with general structure **A**–**B**, for which **A** and **B** represent the parent monomeric flavonoid moieties; their parent flavonoid homodimers are indicated with general structures **A**–**A** or **B**–**B**. [b] IC_{50} values were determined after exposure to a series of paclitaxel concentrations with different flavonoid dimers (FD) at 2 or 1 μM; –: not determined. [c] Clog *P* values were calculated in silico using Osiris Property Explorer. [d] RF was measured using a modulator concentration of 2 μM for group 1 or 1 μM for groups 2–5.

2D. Flavonoid dimers can modulate P-gp-mediated MDR of other substrates

We were interested to determine if the more potent flavonoid dimers can also modulate resistance to other P-gp substrates, namely doxorubicin (DOX), vincristine, and vinblastine in MDA435/LCC6MDR cells. Using verapamil (VP) as the positive control, 1 μM VP has RF values of 3.1, 3.8, and 2.4 for DOX, vincristine, and vinblastine respectively (Table 3). Compound **92** has lower RF values of 1.0, 1.7, and 1.6 for the three drugs (Table 3). For comparison, compound **61** has higher potency, with RF values of 4.4, 16.8, and 7.7, and compound **69** has the highest RF values of 9.8, 44.8, and 14.1 for the three drugs, respectively (Table 3). The EC_{50} value of compound **69** for vincristine was determined to be 110 nM. This efficacy shows a significant improvement over that of compound **92** (EC_{50} = 1300 nM for vincristine) and is close to other highly efficient modulators such as XR9576 (EC_{50} = 22–38 nM for vincristine), as reported.[67]

Table 3. Relative fold (RF) for VP and flavonoid homodimers **92**, **61**, and **69** modulating P-gp-mediated resistance to DOX, vincristine, and vinblastine in MDA435/LCC6MDR cells.[a]

Compd	RF with DOX[a]	RF with Vincristine[a]	RF with Vinblastine
VP	3.1	3.8	2.4
92	1.0	1.7	1.6
61	4.4	16.8	7.7
69	9.8	44.8	14.1

[a] RF values were obtained by dividing IC_{50} of drug without modulator by IC_{50} of drug with 1 μM modulator.

These results suggest that compound **69** can modulate the activity of P-gp toward multiple substrates and is comparable with other highly efficient modulators in its efficacy.

2E. Flavonoid homodimers modulate P-gp by inhibiting its drug transport activity

To confirm that these flavonoid dimers function by inhibiting the drug transport activity of P-gp, we investigated the effect of flavonoid dimers on DOX accumulation in MDA435/LCC6MDR cells by both spectrofluorimetry and flow cytometry. Without any modulator, MDA435/LCC6MDR cells accumulate much less DOX than MDA435/LCC6 cells. Compound **61** can increase DOX accumulation in MDA435/LCC6MDR cells in a dose-dependent manner, but it has no effect on MDA435/LCC6 cells. Other weaker modulators such as compound **92** and VP can also increase DOX accumulation in MDA435/LCC6MDR cells, but with lower efficacy (Figure 2A). Compound **69** can also increase DOX accumulation in MDA435/LCC6MDR cells in a dose-dependent manner (Figure 2B). These data suggest that compounds **61** and **69** can decrease the activity of P-gp, resulting in an increased accumulation of intracellular drug, thus leading to increased drug sensitivity. The exact mechanism by which flavonoid dimers modulate P-gp is still unknown. We previously observed that apigenin dimers can stimulate the ATPase activity of P-gp,[60] suggesting that the apigenin dimer does not bind to the NBD.

Conclusions

In summary, a small library of flavonoid homodimers and heterodimers was synthesized, and their in vitro paclitaxel resistance-reversing activity was evaluated by using a P-gp-expressing human breast cancer cell line. SAR studies revealed the more potent flavonoid dimers **61** and **69**. These flavonoid dimers also increased the accumulation of anticancer drugs and enhanced the cytotoxicity of other drugs such as DOX, vincristine, and vinblastine. Within the flavonoid scaffold, it appears that an oxygen substituent at C5, a methyl group at C6, and methyl or fluoro groups at C7 are favorable in enhancing the resistance-reversing activity. This will be helpful in guiding further efforts in the search for more potent compounds.

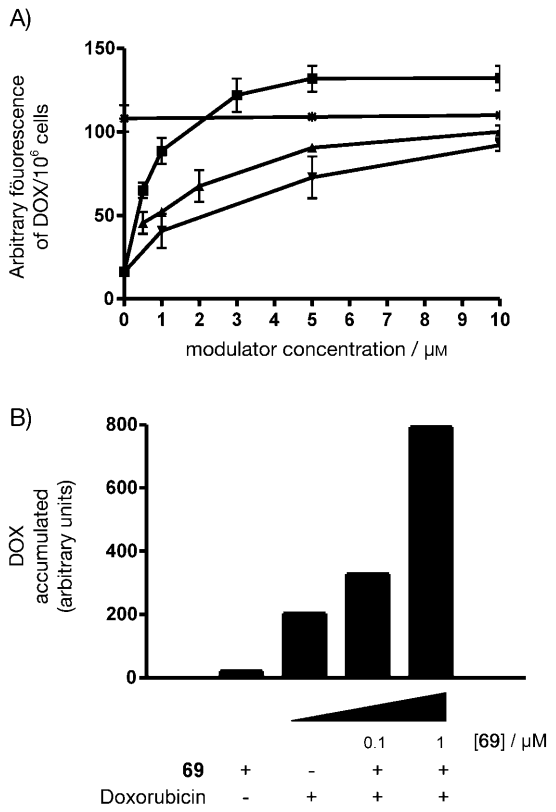


Figure 2. Effect of flavonoid dimers on DOX accumulation. Intracellular level of DOX was measured using either A) spectrofluorimetry [MDA435/LCC6MDR + **61**: ■, MDA435/LCC6MDR + VP: ▲, MDA435/LCC6MDR + **92**: ▼, MDA435/LCC6 + **61**: *; in each case, $n = 3$] or B) flow cytometry.

Experimental Section

Chemistry

All NMR spectra were recorded on a Bruker DPX400 spectrometer at 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C. All NMR measurements were carried out at room temperature, and the chemical shifts are reported as parts per million (ppm) relative to the resonance of $CDCl_3$ (7.26 ppm for ^{1}H NMR, and 77.0 ppm for the central line of the triplet in ^{13}C NMR). Low- and high-resolution mass spectra were obtained on a Micromass Q-TOF-2 instrument in electrospray ionization (ESI) mode or on a Finnigan MAT95 ST instrument in electron ionization (EI) mode. Melting points were measured with an Electrothermal IA9100 digital melting point apparatus and are uncorrected. All reagents and solvents were reagent grade and were used without further purification unless otherwise stated. Plates used for thin-layer chromatography (TLC) were E. Merck silica gel 60 F_{254} (0.25 mm thickness) and were visualized under UV ($\lambda = 254$ nm) light. Chromatographic purification was carried out with MN silica gel 60 (230–400 mesh). Substituted 4′-hydroxyflavone **107** and flavonoid dimers **92**–**94** were prepared as previously reported.[60] Clog *P* values were calculated by using the online Osiris Property Explorer available at http://www.organic-chemistry.org (accessed February 18, 2009).

General procedure I for the synthesis of chalcones 21–40: Excess KOH (3 M solution in 96% EtOH, 3–4 equiv) was added to a mixture of 4-allyloxybenzaldehyde (1.0 equiv) and corresponding 2′-hydroxyacetophenone (1.0 equiv). The mixture was stirred at room temperature for 16 h. When TLC indicated complete consumption of starting material, the reaction mixture was acidified to pH 5 with 1 M HCl at ice-bath temperature. The yellow precipitate formed was collected by suction filtration. The yellow solid was washed with *n*-hexane and subjected to crystallization from MeOH to afford the desired chalcones. If no precipitate was formed after the addition of 1 M HCl, then the mixture was continuously extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a crude mixture, which was subjected to flash column chromatography using 15% EtOAc in hexane as eluent to furnish the desired chalcones.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxyphenyl)propenone (21)**: This compound was obtained from 4-allyloxybenzaldehyde (16.2 g, 0.1 mol), acetophenone **1** (13.6 g, 0.1 mol), and KOH (100 mL) as a yellow solid (24.0 g, 86%) according to general procedure I: mp: 85–86 °C; ^{1}H NMR ($CDCl_3$): $\delta = 4.59$ (d, $J = 5.2$ Hz, 2H), 5.32 (dd, $J = 1.6$, 10.2 Hz, 1H), 5.44 (dd, $J = 1.6$, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.95 (d, $J = 8.8$ Hz, 2H), 6.96 (d, $J = 8.0$ Hz, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 7.48 (d, $J = 8.2$ Hz, 1H), 7.53 (A of AB, $J = 15.2$ Hz, 1H), 7.61 (d, $J = 8.8$ Hz, 2H), 7.89 (B of AB, $J = 15.6$ Hz, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 12.95 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 68.9$, 115.2, 117.6, 118.1, 118.5, 118.7, 120.1, 127.4, 129.5, 130.5, 132.6, 136.1, 145.3, 161.0, 163.5, 193.6 ppm; LRMS (ESI) *m/z* 281 [M^++H, 96], 303 [M^++Na, 100]; HRMS (ESI) calcd for $C_{18}H_{17}O_3$ [M^++H] 281.1178, found 281.1194.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-4-fluorophenyl)propenone (22)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **2** (1.54 g, 10 mmol), and KOH (15 mL) as a yellow solid (2.35 g, 79%) according to general procedure I: mp: 84–85 °C; ^{1}H NMR ($CDCl_3$): $\delta = 4.58$ (d, $J = 5.2$ Hz, 2H), 5.32 (dd, $J = 1.6$, 10.2 Hz, 1H), 5.45 (dd, $J = 1.6$, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.65 (d, $J = 8.4$ Hz, 1H), 6.68 (d, $J = 8.4$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 2H), 7.43 (A of AB, $J = 15.2$ Hz, 1H), 7.60 (d, $J = 8.0$ Hz, 2H), 7.88 (B of AB, $J = 15.2$ Hz, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 13.35 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 68.9$, 105.0 (d, $J = 23.2$ Hz, C5), 106.9 (d, $J = 22.7$ Hz, C3), 115.2, 117.2 (d, $J = 20.0$ Hz, C6), 118.1, 127.3, 130.5, 131.8 (d, $J = 11.8$ Hz, C2), 132.5, 145.5, 161.1, 166.0, 166.0, 167.3 (d, $J = 237$ Hz, C4), 192.4 ppm; LRMS (ESI) *m/z* 299 [M^++H, 13]; HRMS (ESI) calcd for $C_{18}H_{16}O_3F$ [M^++H] 299.1083, found 299.1085.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-5-fluorophenyl)propenone (23)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62, 10 mmol), acetophenone **3** (1.54 g, 10 mmol), and KOH (15 mL) as a yellow solid (2.32 g, 78%) according to general procedure I: mp: 104–105 °C; ^{1}H NMR ($CDCl_3$): $\delta = 4.60$ (d, $J = 5.2$ Hz, 2H), 5.32 (dd, $J = 1.6$, 10.2 Hz, 1H), 5.45 (dd, $J = 1.6$, 17.4 Hz, 1H), 6.02–6.08 (m, 1H), 6.97 (d, $J = 8.8$ Hz, 2H), 6.99 (d, $J = 2.4$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.41 (A of AB, $J = 15.2$ Hz, 1H), 7.57 (d, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 8.8$ Hz, 2H), 7.91 (B of AB, $J = 15.2$ Hz, 1H), 12.65 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 68.9$, 114.5 (d, $J = 23.1$ Hz, C6), 115.3, 117.0, 118.1, 119.7 (d, $J = 6.2$ Hz, C1), 119.7 (d, $J = 7.4$ Hz, C3), 123.6 (d, $J = 23.5$ Hz, C4), 127.2, 130.7, 132.5, 146.2, 154.8 (d, $J = 236.3$ Hz, C5), 159.6, 161.2, 192.7 ppm; LRMS (ESI) *m/z* 299 [M^++H, 6]; HRMS (ESI) calcd for $C_{18}H_{16}O_3F$ [M^++H] 299.1083, found 299.1085.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-5-chlorophenyl)propenone (24)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **4** (1.70 g, 10 mmol), and KOH (15 mL) as a yellow solid (2.51 g, 80%) according to general procedure I: mp: 125–126 °C; ^{1}H NMR ($CDCl_3$): $\delta = 4.59$ (d, $J = 5.2$ Hz, 2H), 5.32 (dd, $J = 1.2$, 10.2 Hz, 1H), 5.45 (dd, $J = 1.2$, 17.4 Hz,

1H), 6.02–6.09 (m, 1H), 6.96 (d, J=8.4 Hz, 1H), 6.97 (d, J=8.4 Hz, 2H), 7.41 (d, J=2.4 Hz, 1H), 7.42 (A of AB, J=15.2 Hz, 1H), 7.62 (d, J=8.8 Hz, 2H), 7.84 (d, J=2.4 Hz, 1H), 7.90 (B of AB, J=15.2 Hz, 1H), 12.85 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=68.9, 115.3, 116.9, 118.2, 120.1, 120.7, 123.4, 127.1, 128.6, 130.7, 132.5, 135.8, 146.3, 161.3, 162.0, 192.6 ppm; LRMS (ESI) m/z 315 [M^++H, 35]; HRMS (ESI) calcd for $C_{18}H_{16}O_3Cl$ [M^++H] 315.0788, found 315.0800.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-5-bromophenyl)propenone (25)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **5** (2.15 g, 10 mmol), and KOH (20 mL) as a yellow solid (2.91 g, 81%) according to general procedure I: mp: 136–137 °C; ^{1}H NMR ($CDCl_3$): δ=4.59 (d, J=5.2 Hz, 2H), 5.32 (dd, J=1.2, 10.2 Hz, 1H), 5.45 (dd, J=1.2, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.92 (d, J=9.2 Hz, 1H), 6.96 (d, J=8.8 Hz, 2H), 7.42 (A of AB, J=15.2 Hz, 1H), 7.54 (dd, J=2.4, 8.4 Hz, 1H), 7.63 (d, J=8.8 Hz, 2H), 7.90 (B of AB, J=15.6 Hz, 1H), 7.98 (d, J=2.4 Hz, 1H), 12.87 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=68.9, 110.3, 115.3, 116.8, 118.2, 120.5, 121.3, 127.1, 130.8, 131.7, 132.5, 138.6, 146.4, 161.3, 162.4, 192.5 ppm; LRMS (ESI) m/z 382 [M^++Na, 24]; HRMS (ESI) calcd for $C_{18}H_{16}O_3Br$ [M^++H] 359.0283, found 359.0274.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-3,5-dichlorophenyl)propenone (26)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **6** (2.05 g, 10 mmol), and KOH (15 mL) as a yellow solid (3.11 g, 89%) according to general procedure I: mp: 115–116 °C; ^{1}H NMR ($CDCl_3$): δ=4.61 (d, J=5.2 Hz, 2H), 5.32 (dd, J=1.2, 10.2 Hz, 1H), 5.45 (dd, J=1.2, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.97 (d, J=8.8 Hz, 2H), 7.40 (A of AB, J=15.2 Hz, 1H), 7.56 (d, J=2.4 Hz, 1H), 7.63 (d, J=8.8 Hz, 2H), 7.78 (d, J=2.4 Hz, 1H), 7.94 (B of AB, J=15.6 Hz, 1H), 13.53 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=68.9, 115.3, 116.3, 118.2, 121.1, 123.1, 124.0, 126.9, 127.2, 131.0, 132.4, 135.4, 147.4, 157.9, 161.5, 192.3 ppm; LRMS (ESI) m/z 350 [M^++H, 30]; HRMS (ESI) calcd for $C_{18}H_{15}O_3Cl_2$ [M^++H] 349.0398, found 349.0412.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-3,5-dibromophenyl)propenone (27)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **7** (2.93 g, 10 mmol), and KOH (20 mL) as a yellow solid (3.80 g, 87%) according to general procedure I: mp: 143–144 °C; ^{1}H NMR ($CDCl_3$): δ=4.61 (d, J=5.2 Hz, 2H), 5.32 (dd, J=1.6, 10.2 Hz, 1H), 5.45 (dd, J=1.6, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.97 (d, J=8.8 Hz, 2H), 7.39 (A of AB, J=15.2 Hz, 1H), 7.63 (d, J=8.8 Hz, 2H), 7.85 (d, J=2.4 Hz, 1H), 7.94 (B of AB, J=15.2 Hz, 1H), 7.96 (s, 1H), 13.53 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=68.9, 110.1, 113.3, 115.3, 116.2, 118.2, 121.6, 126.9, 130.9, 131.0, 132.4, 140.9, 147.5, 159.2, 161.6, 192.1 ppm; LRMS (ESI) m/z 439 [M^++H, 23]; HRMS (ESI) calcd for $C_{18}H_{15}O_3Br_2$ [M^++H] 436.9388, found 436.9410.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-4-methylphenyl)propenone (28)**: This compound was obtained from 4-allyloxybenzaldehyde (16.2 g, 0.1 mol), acetophenone **8** (15.0 g, 0.1 mol), and KOH (100 mL) as a yellow solid (25.9 g, 88%) according to general procedure I: mp: 90–91 °C; ^{1}H NMR ($CDCl_3$): δ=2.37 (s, 3H), 4.59 (d, J=5.2 Hz, 2H), 5.32 (dd, J=1.6, 10.2 Hz, 1H), 5.45 (dd, J=1.6, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.74 (d, J=8.0 Hz, 1H), 6.83 (s, 1H), 6.96 (d, J=8.4 Hz, 2H), 7.51 (A of AB, J=15.6 Hz, 1H), 7.61 (d, J=8.8 Hz, 2H), 7.79 (d, J=8.4 Hz, 1H), 7.87 (B of AB, J=15.2 Hz, 1H), 13.00 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=21.9, 68.9, 115.2, 117.8, 117.9, 118.1, 118.6, 120.0, 127.5, 129.4, 130.4, 132.6, 144.7, 147.8, 160.9, 163.7, 193.0 ppm; LRMS (ESI) m/z 295 [M^++H, 100], 317 [M^++Na, 25]; HRMS (ESI) calcd for $C_{19}H_{19}O_3$ [M^++H] 295.1334, found 295.1328.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-5-methylphenyl)propenone (29)**: This compound was obtained from 4-allyloxybenzaldehyde (16.2 g, 0.1 mol), acetophenone **9** (15.0 g, 0.1 mol), and KOH (100 mL) as a yellow solid (23.8 g, 81%) according to general procedure I: mp: 79–80 °C; ^{1}H NMR ($CDCl_3$): δ=2.34 (s, 3H), 4.58 (d, J=5.2 Hz, 2H), 5.32 (dd, J=1.6, 10.2 Hz, 1H), 5.45 (dd, J=1.6, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.92 (d, J=8.4 Hz, 1H), 6.95 (d, J=8.4 Hz, 2H), 7.29 (d, J=8.4 Hz, 1H), 7.52 (A of AB, J=15.2 Hz, 1H), 7.61 (d, J=8.4 Hz, 2H), 7.67 (s, 1H), 7.87 (B of AB, J=15.2 Hz, 1H), 12.78 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=20.6, 68.9, 115.2, 117.7, 118.1, 118.3, 119.7, 127.5, 127.8, 129.2, 130.5, 132.6, 137.3, 145.0, 160.9, 161.4, 193.5 ppm; LRMS (ESI) m/z 295 [M^++H, 88], 317 [M^++Na, 30]; HRMS (ESI) calcd for $C_{19}H_{19}O_3$ [M^++H] 295.1334, found 295.1339.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-4-methoxyphenyl)propenone (30)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **10** (1.66 g, 10 mmol), and KOH (15 mL) as a yellow solid (2.26 g, 73%) according to general procedure I: mp: 98–99 °C; ^{1}H NMR ($CDCl_3$): δ=3.84 (s, 3H), 4.58 (d, J=5.2 Hz, 2H), 5.32 (dd, J=1.6, 10.2 Hz, 1H), 5.45 (dd, J=1.6, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.47 (d, J=8.0 Hz, 1H), 6.48 (d, J=2.4 Hz, 1H), 6.95 (d, J=8.8 Hz, 2H), 7.44 (A of AB, J=15.2 Hz, 1H), 7.59 (d, J=8.4 Hz, 2H), 7.80 (s, 1H), 7.84 (B of AB, J=15.6 Hz, 1H), 13.56 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=55.5, 68.8, 101.0, 107.6, 114.1, 115.1, 117.8, 118.0, 127.6, 130.3, 131.1, 132.6, 144.2, 160.8, 166.0, 166.6, 191.8 ppm; LRMS (ESI) m/z 311 [M^++H, 19]; HRMS (ESI) calcd for $C_{19}H_{19}O_4$ [M^++H] 311.1283, found 311.1294.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-5-methoxyphenyl)propenone (31)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **11** (1.66 g, 10 mmol), and KOH (15 mL) as a brick-red solid (2.02 g, 65%) according to general procedure I: mp: 71–72 °C; ^{1}H NMR ($CDCl_3$): δ=3.84 (s, 3H), 4.59 (d, J=5.2 Hz, 2H), 5.32 (dd, J=1.2, 10.4 Hz, 1H), 5.45 (dd, J=1.6, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.96 (d, J=8.8 Hz, 2H), 6.96 (d, J=9.2 Hz, 1H), 7.13 (dd, J=3.2, 9.2 Hz, 1H), 7.35 (d, J=3.2 Hz, 1H), 7.46 (A of AB, J=15.6 Hz, 1H), 7.61 (d, J=8.8 Hz, 2H), 7.89 (B of AB, J=15.6 Hz, 1H), 12.48 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=56.1, 68.9, 112.9, 115.2, 117.6, 118.1, 119.2, 119.7, 123.6, 127.4, 130.5, 132.6, 145.4, 151.6, 157.8, 161.0, 193.2 ppm; LRMS (ESI) m/z 311 [M^++H, 21]; HRMS (ESI) calcd for $C_{19}H_{19}O_4$ [M^++H] 311.1283, found 311.1297.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-6-methoxyphenyl)propenone (32)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **12** (1.66 g, 10 mmol), and KOH (15 mL) as a yellow solid (2.60 g, 84%) according to general procedure I: mp: 76–77 °C; ^{1}H NMR ($CDCl_3$): δ=3.95 (s, 3H), 4.59 (d, J=5.2 Hz, 2H), 5.32 (dd, J=1.2, 10.4 Hz, 1H), 5.45 (dd, J=1.6, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.43 (d, J=8.4 Hz, 1H), 6.61 (d, J=7.6 Hz, 1H), 6.94 (d, J=8.8 Hz, 2H), 7.34 (dd, J=8.0, 8.4 Hz, 1H), 7.57 (d, J=8.8 Hz, 2H), 7.77 (A of AB, J=15.2 Hz, 1H), 7.80 (B of AB, J=15.2 Hz, 1H), 13.24 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=55.9, 68.8, 101.5, 110.9, 112.0, 115.1, 118.0, 125.2, 128.2, 130.2, 132.7, 135.6, 143.0, 160.5, 160.9, 164.8, 194.3 ppm; LRMS (ESI) m/z 311 [M^++H, 100], 333 [M^++Na, 40]; HRMS (ESI) calcd for $C_{19}H_{19}O_4$ [M^++H] 311.1283, found 311.1290.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-4,5-dimethoxyphenyl)-propenone (33)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **13** (1.96 g, 10 mmol), and KOH (20 mL) as a yellow solid (2.89 g, 85%) according to general procedure I: mp: 143–144 °C; ^{1}H NMR ($CDCl_3$): δ=3.91 (s, 3H), 3.92 (s, 3H), 4.59 (d, J=5.2 Hz, 2H), 5.32 (dd, J=1.2, 10.4 Hz, 1H),

5.45 (dd, J=1.6, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.49 (s, 1H), 6.95 (d, J=8.8 Hz, 2H), 7.25 (s, 1H), 7.38 (A of AB, J=15.2 Hz, 1H), 7.60 (d, J=8.4 Hz, 2H), 7.86 (B of AB, J=15.2 Hz, 1H), 13.47 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=56.1, 56.9, 68.9, 100.8, 111.0, 112.0, 115.2, 117.8, 118.1, 127.6, 130.3, 132.6, 141.8, 144.3, 156.8, 160.8, 161.6, 191.5 ppm; LRMS (ESI) m/z 341 [M^++H, 100], 363 [M^++Na, 24]; HRMS (ESI) calcd for $C_{20}H_{21}O_5$ [M^++H] 341.1389, found 341.1387.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-4-benzyloxyphenyl)propenone (34)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **14** (2.42 g, 10 mmol), and KOH (20 mL) as a yellow solid (2.90 g, 75%) according to general procedure I: mp: 118–119 °C; ^{1}H NMR ($CDCl_3$): δ=4.60 (d, J=5.2 Hz, 2H), 5.11 (s, 2H), 5.32 (dd, J=1.2, 10.4 Hz, 1H), 5.45 (dd, J=1.6, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.54 (s, 1H), 6.56 (d, J=6.4 Hz, 1H), 6.95 (d, J=8.8 Hz, 2H), 7.38–7.44 (m, 5H), 7.47 (A of AB, J=15.2 Hz, 1H), 7.60 (d, J=8.8 Hz, 2H), 7.83 (d, J=6.4 Hz, 1H), 7.86 (B of AB, J=15.2 Hz, 1H), 13.53 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=68.9, 70.2, 102.1, 108.1, 114.3, 115.2, 117.8, 118.1, 127.5, 127.6, 128.3, 128.7, 130.3, 131.1, 132.6, 135.9, 144.3, 160.8, 165.1, 166.5, 191.8 ppm; LRMS (ESI) m/z 387 [M^++H, 14], 409 [M^++Na, 5]; HRMS (ESI) calcd for $C_{25}H_{23}O_4$ [M^++H] 387.1596, found 387.1575.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-5-benzyloxyphenyl)propenone (35)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **15** (2.42 g, 10 mmol), and KOH (20 mL) as a brick-red solid (2.35 g, 61%) according to general procedure I: mp: 113–114 °C; ^{1}H NMR ($CDCl_3$): δ=4.60 (d, J=5.2 Hz, 2H), 5.08 (s, 2H), 5.32 (dd, J=1.2, 10.4 Hz, 1H), 5.45 (dd, J=1.6, 17.4 Hz, 1H), 6.03–6.09 (m, 1H), 6.95 (d, J=8.4 Hz, 1H), 6.97 (d, J=8.8 Hz, 2H), 7.19 (dd, J=2.4, 8.4 Hz, 1H), 7.36 (A of AB, J=15.2 Hz, 1H), 7.35–7.47 (m, 6H), 7.59 (d, J=8.4 Hz, 2H), 7.87 (B of AB, J=15.2 Hz, 1H), 12.48 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=68.9, 71.3, 114.7, 115.2, 117.6, 118.1, 119.2, 119.8, 124.5, 127.4, 127.6, 128.1, 128.7, 130.5, 132.6, 136.9, 145.4, 150.7, 158.0, 161.0, 193.2 ppm; LRMS (ESI) m/z 387 [M^++H, 28], 409 [M^++Na, 8]; HRMS (ESI) calcd for $C_{25}H_{23}O_4$ [M^++H] 387.1596, found 387.1599.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-6-benzyloxyphenyl)propenone (36)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **16** (2.42 g, 10 mmol), and KOH (20 mL) as a yellow solid (3.09 g, 80%) according to general procedure I: mp: 127–128 °C; ^{1}H NMR ($CDCl_3$): δ=4.55 (d, J=5.2 Hz, 2H), 5.11 (s, 2H), 5.33 (dd, J=1.2, 10.8 Hz, 1H), 5.44 (dd, J=1.2, 17.2 Hz, 1H), 6.01–6.09 (m, 1H), 6.53 (d, J=8.4 Hz, 1H), 6.65 (d, J=8.4 Hz, 1H), 6.74 (d, J=8.4 Hz, 2H), 7.05 (d, J=8.8 Hz, 2H), 7.35–7.49 (m, 5H), 7.48 (dd, J=8.4, 8.6 Hz, 1H), 7.74 (A of AB, J=15.6 Hz, 1H), 7.78 (B of AB, J=15.6 Hz, 1H), 13.70 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=68.8, 71.3, 102.2, 111.3, 111.8, 114.9, 118.1, 125.3, 127.9, 128.0, 128.6, 128.7, 128.9, 130.3, 132.7, 135.7, 143.4, 160.2, 160.3, 165.5, 194.3 ppm; LRMS (ESI) m/z 409 [M^++Na, 35]; HRMS (ESI) calcd for $C_{25}H_{23}O_4$[M^++H] 387.1596, found 387.1575.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)propenone (37)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **17** (1.96 g, 10 mmol), and KOH (20 mL) as a yellow solid (2.92 g, 86%) according to general procedure I: mp: 99–100 °C; ^{1}H NMR ($CDCl_3$): δ=3.82 (s, 3H), 3.90 (s, 3H), 4.57 (d, J=5.2 Hz, 2H), 5.31 (dd, J=1.2, 10.8 Hz, 1H), 5.42 (dd, J=1.2, 17.2 Hz, 1H), 5.95 (d, J=2.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.09 (d, J=2.4 Hz, 1H), 6.93 (d, J=8.8 Hz, 2H), 7.54 (d, J=8.8 Hz, 2H), 8.01 (A of AB, J=15.6 Hz, 1H), 8.02 (B of AB, J=15.6 Hz, 1H), 14.42 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=55.5, 55.8, 68.8, 91.2, 93.8, 106.3, 115.1, 118.0, 125.1, 128.4, 130.0, 132.8, 142.4, 160.3, 162.4, 166.0, 168.3, 192.5 ppm; LRMS (ESI) m/z 341 [M^++H, 100], 363 [M^++Na, 25]; HRMS (ESI) calcd for $C_{20}H_{21}O_5$[M^++H] 341.1389, found 341.1393.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-4,6-dibenzyloxyphenyl)propenone (38)**: This compound was obtained from 4-allyloxybenzaldehyde (0.81 g, 5 mmol), acetophenone **18** (1.74 g, 5 mmol), and KOH (15 mL) as a yellow solid (1.87 g, 76%) according to general procedure I: mp: 140–141 °C; ^{1}H NMR ($CDCl_3$): δ=4.55 (d, J=5.2 Hz, 2H), 5.05 (s, 2H), 5.10 (s, 2H), 5.32 (dd, J=1.2, 10.4 Hz, 1H), 5.43 (dd, J=1.6, 17.4 Hz, 1H), 6.01–6.09 (m, 1H), 6.17 (d, J=2.4 Hz, 1H), 6.22 (d, J=2.0 Hz, 1H), 6.72 (d, J=8.4 Hz, 2H), 7.00 (d, J=8.8 Hz, 2H), 7.39–7.51 (m, 10H), 7.71 (A of AB, J=15.6 Hz, 1H), 7.78 (B of AB, J=15.6 Hz, 1H), 14.73 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=68.8, 70.3, 71.4, 92.5, 95.0, 106.3, 114.8, 118.0, 125.2, 127.7, 127.9, 128.2, 128.3, 128.5, 128.7, 128.9, 130.1, 132.8, 135.5, 135.9, 142.8, 160.1, 161.7, 165.1, 168.8, 192.6 ppm; LRMS (ESI) m/z 493 [M^++H, 26], 515 [M^++Na, 10]; HRMS (ESI) calcd for $C_{32}H_{29}O_5$ [M^++H] 493.2015, found 493.2031.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-5-ethylphenyl)propenone (39)**: This compound was obtained from 4-allyloxybenzaldehyde (16.2 g, 0.1 mol), acetophenone **19** (16.4 g, 0.1 mol), and KOH (100 mL) as a yellow solid (27.1 g, 88%) according to general procedure I: mp: 82–83 °C; ^{1}H NMR ($CDCl_3$): δ=1.26 (t, J=7.6 Hz, 3H), 2.66 (q, J=7.6 Hz, 2H), 4.59 (d, J=5.2 Hz, 2H), 5.32 (dd, J=1.2, 10.4 Hz, 1H), 5.43 (dd, J=1.6, 17.4 Hz, 1H), 6.03–6.09 (m, 1H), 6.95 (d, J=8.4 Hz, 1H), 6.96 (d, J=8.8 Hz, 2H), 7.33 (dd, J=2.0, 8.4 Hz, 1H), 7.54 (A of AB, J=15.6 Hz, 1H), 7.63 (d, J=8.8 Hz, 2H), 7.68 (d, J=1.6 Hz, 1H), 7.88 (B of AB, J=15.6 Hz, 1H), 12.80 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=15.9, 28.1, 68.9, 115.2, 117.8, 118.1, 118.4, 119.8, 127.5, 128.1, 130.5, 132.6, 134.3, 136.1, 145.0, 160.9, 161.6, 193.6 ppm; LRMS (ESI) m/z 309 [M^++H, 100], 331 [M^++Na, 25]; HRMS (ESI) calcd for $C_{20}H_{21}O_3$[M^++H] 309.1491, found 309.1500.

***trans*-3-(4-Allyloxyphenyl)-1-(2-hydroxy-3-nitro-5-methylphenyl)propenone (40)**: This compound was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **20** (1.95 g, 10 mmol), and KOH (20 mL) as a yellow solid (2.75 g, 81%) according to general procedure I: mp: 140–141 °C; ^{1}H NMR ($CDCl_3$): δ=2.40 (s, 3H), 4.59 (d, J=5.6 Hz, 2H), 5.32 (dd, J=1.6, 10.4 Hz, 1H), 5.43 (dd, J=1.6, 17.2 Hz, 1H), 6.02–6.09 (m, 1H), 6.96 (d, J=8.8 Hz, 2H), 7.43 (A of AB, J=15.6 Hz, 1H), 7.61 (d, J=8.8 Hz, 2H), 7.88 (B of AB, J=15.2 Hz, 1H), 7.92 (d, J=2.0 Hz, 1H), 7.99 (d, J=1.6 Hz, 1H), 13.40 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=20.3, 68.9, 115.3, 118.2, 124.2, 127.0, 128.0, 130.8, 131.0, 132.5, 136.1, 137.2, 146.8, 154.7, 161.4, 192.3 ppm; LRMS (ESI) m/z 340 [M^++H, 51], 362 [M^++Na, 100]; HRMS (ESI) calcd for $C_{19}H_{18}NO_5$ [M^++H] 340.1185, found 340.1191.

General procedure II for the iodine-catalyzed cyclization of chalcones to flavones 41–60: A catalytic amount of iodine crystal (3–4 mol%) was added to well-stirred solution of chalcone in DMSO (using the minimum amount of solvent that can dissolve chalcone completely) at 50 °C. The reaction mixture was then heated and stirred at 130–150 °C for 2–4 h. During heating, the reaction mixture slowly turned from pale brown to dark brown. When TLC indicated complete consumption of chalcone, the reaction mixture was poured into a separating funnel containing H_2O. The mixture was extracted with CH_2Cl_2. The combined organic layers were washed with a solution of $Na_2S_2O_3$ (0.1%), dried over $MgSO_4$, filtered, and evaporated to give a crude reaction mixture, which was passed through a short pad of silica gel to remove any remaining DMSO. The obtained brown filtrate was crystallized from 50% acetone in hexane to afford the desired flavones.

2-(4′-Allyloxyphenyl)-4*H*-chromen-4-one (41): This compound was obtained from chalcone **21** (14.0 g, 50 mmol) and I_2 (cat, 0.4 g) as an off-white solid (11.0 g, 79%) according to general procedure II: mp: 105–106 °C; ^{1}H NMR ($CDCl_3$): δ = 4.60 (d, J = 5.2 Hz, 2H), 5.32 (dd, J = 1.2, 10.2 Hz, 1H), 5.44 (dd, J = 1.6, 17.4 Hz, 1H), 6.00–6.09 (m, 1H), 6.72 (s, 1H), 7.02 (d, J = 9.2 Hz, 2H), 7.38 (dd, J = 7.2, 7.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.65 (ddd, J = 1.2, 8.4, 8.4 Hz, 1H), 7.85 (d, J = 8.8 Hz, 2H), 8.20 ppm (dd, J = 1.6, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 68.9, 106.1, 115.1, 117.9, 118.2, 123.9, 124.1, 125.0, 125.6, 127.9, 132.5, 133.5, 156.1, 161.4, 163.3, 178.3 ppm; LRMS (ESI) *m/z* 279 [M^++H, 100]; HRMS (ESI) calcd for $C_{18}H_{15}O_3$ [M^++H] 279.1021, found 279.1031.

7-Fluoro-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (42): This compound was obtained from chalcone **22** (1.10 g, 3.69 mmol) and I_2 (cat, 30 mg) as a white solid (0.62 g, 57%) according to general procedure II: mp: 135–137 °C; ^{1}H NMR ($CDCl_3$): δ = 4.62 (d, J = 5.6 Hz, 2H), 5.32 (dd, J = 1.2, 10.2 Hz, 1H), 5.44 (dd, J = 1.2, 17.4 Hz, 1H), 6.03–6.10 (m, 1H), 6.71 (s, 1H), 7.03 (d, J = 8.8 Hz, 2H), 7.12 (ddd, J = 2.4, 8.4, 8.6 Hz, 1H), 7.23 (dd, J = 2.4, 9.0 Hz, 1H), 7.84 (d, J = 8.8 Hz, 2H), 8.23 ppm (dd, J = 6.4, 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 68.9, 104.7 (d, J = 25.2 Hz, C6), 106.1, 113.9 (d, J = 22.7 Hz, C8), 115.2, 118.3, 120.7, 123.7, 127.9, 128.1 (d, J = 10.5 Hz, C5), 132.4, 157.2 (d, J = 13.1 Hz, C9), 161.5, 163.7, 165.6 (d, J = 252.9 Hz, C7), 177.4 ppm; LRMS (ESI) *m/z* 297 [M^++H, 75], 319 [M^++Na, 62]; HRMS (ESI) calcd for $C_{18}H_{14}O_3F$ [M^++H] 297.0927, found 297.0933.

6-Fluoro-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (43): This compound was obtained from chalcone **23** (0.82 g, 2.75 mmol) and I_2 (cat, 25 mg) as a white solid (0.47 g, 58%) according to general procedure II: mp: 142–143 °C; ^{1}H NMR ($CDCl_3$): δ = 4.62 (d, J = 5.6 Hz, 2H), 5.32 (dd, J = 1.2, 10.2 Hz, 1H), 5.44 (dd, J = 1.2, 17.4 Hz, 1H), 6.03–6.10 (m, 1H), 6.72 (s, 1H), 7.02 (dd, J = 2.8, 11.4 Hz, 2H), 7.39 (ddd, J = 2.8, 7.8, 8.6 Hz, 1H), 7.54 (dd, J = 4.0, 9.2 Hz, 1H), 7.84 (d, J = 8.8 Hz, 2H), 8.23 ppm (dd, J = 6.4, 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 68.9, 105.5, 110.6 (d, J = 23.5 Hz, C5), 115.2, 118.2, 119.9 (d, J = 8.1 Hz, C10), 121.7 (d, J = 25.2 Hz, C7), 123.8, 125.1 (d, J = 7.4 Hz, C8), 128.0, 132.4, 152.3, 159.5 (d, J = 245.1 Hz, C6), 161.5, 163.6, 177.5 ppm; LRMS (ESI) *m/z* 297 [M^++H, 100], 319 [M^++Na, 9]; HRMS (ESI) calcd for $C_{18}H_{14}O_3F$ [M^++H] 297.0927, found 297.0923.

6-Chloro-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (44): This compound was obtained from chalcone **24** (0.90 g, 2.87 mmol) and I_2 (cat, 25 mg) as a pale-yellow solid (0.72 g, 81%) according to general procedure II: mp: 165–166 °C; ^{1}H NMR ($CDCl_3$): δ = 4.62 (d, J = 5.6 Hz, 2H), 5.33 (dd, J = 1.2, 10.2 Hz, 1H), 5.45 (dd, J = 1.2, 17.4 Hz, 1H), 6.03–6.09 (m, 1H), 6.73 (s, 1H), 7.02 (d, J = 9.2 Hz, 2H), 7.49 (d, J = 8.8 Hz, 1H), 7.61 (dd, J = 2.8, 9.0 Hz, 1H), 7.84 (d, J = 8.8 Hz, 2H), 8.17 ppm (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 68.9, 105.9, 115.2, 118.3, 119.6, 123.6, 124.8, 125.1, 128.0, 131.0, 132.4, 133.7, 154.4, 161.6, 163.7, 177.1 ppm; LRMS (ESI) *m/z* 313 [M^++H, 100]; HRMS (ESI) calcd for $C_{18}H_{14}O_3Cl$ [M^++H] 313.0631, found 313.0630.

6-Bromo-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (45): This compound was obtained from chalcone **25** (0.98 g, 2.73 mmol) and I_2 (cat, 24 mg) as a pale-yellow solid (0.70 g, 72%) according to general procedure II: mp: 173–174 °C; ^{1}H NMR ($CDCl_3$): δ = 4.62 (d, J = 5.2 Hz, 2H), 5.33 (dd, J = 1.2, 10.4 Hz, 1H), 5.44 (dd, J = 1.2, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.72 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 1H), 7.74 (dd, J = 2.4, 8.6 Hz, 1H), 7.84 (d, J = 8.8 Hz, 2H), 8.32 ppm (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 68.9, 106.0, 115.2, 118.3, 118.5, 119.9, 123.6, 125.2, 128.0, 128.3, 132.4, 136.5, 154.9, 161.6, 163.6, 176.9 ppm; LRMS (ESI) *m/z* 358 [M^++H, 100], 380 [M^++Na, 18]; HRMS (ESI) calcd for $C_{18}H_{14}O_3Br$ [M^++H] 357.0126, found 357.0127.

6,8-Dichloro-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (46): This compound was obtained from chalcone **26** (1.00 g, 2.87 mmol) and I_2 (cat, 25 mg) as a pale-yellow solid (0.79 g, 79%) according to general procedure II: mp: 168–169 °C; ^{1}H NMR ($CDCl_3$): δ = 4.63 (d, J = 5.2 Hz, 2H), 5.35 (dd, J = 1.2, 10.4 Hz, 1H), 5.47 (dd, J = 1.2, 17.4 Hz, 1H), 6.03–6.10 (m, 1H), 6.76 (s, 1H), 7.05 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 2.4 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 8.08 ppm (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 69.0, 105.7, 115.3, 118.3, 123.1, 123.8, 124.3, 125.7, 128.2, 130.7, 132.3, 133.5, 150.4, 161.8, 163.5, 176.4 ppm; LRMS (ESI) *m/z* 347 [M^++H, 100]; HRMS (ESI) calcd for $C_{18}H_{13}O_3Cl_2$ [M^++H] 347.0242, found 347.0237.

6,8-Dibromo-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (47): This compound was obtained from chalcone **27** (0.78 g, 1.78 mmol) and I_2 (cat, 15 mg) as a pale-yellow solid (0.54 g, 70%) according to general procedure II: mp: 177–178 °C; ^{1}H NMR ($CDCl_3$): δ = 4.62 (d, J = 5.2 Hz, 2H), 5.34 (dd, J = 1.2, 10.4 Hz, 1H), 5.45 (dd, J = 1.2, 17.2 Hz, 1H), 6.03–6.10 (m, 1H), 6.75 (s, 1H), 7.03 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 9.2 Hz, 2H), 7.99 (d, J = 2.0 Hz, 1H), 8.26 ppm (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 68.9, 105.6, 112.9, 115.3, 118.3, 118.3, 123.1, 125.9, 127.7, 128.2, 132.3, 139.1, 151.6, 161.9, 163.6, 176.3 ppm; LRMS (ESI) *m/z* 437 [M^++H, 74]; HRMS (ESI) calcd for $C_{18}H_{13}O_3Br_2$ [M^++H] 434.9231, found 434.9250.

7-Methyl-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (48): This compound was obtained from chalcone **28** (1.01 g, 3.44 mmol) and I_2 (cat, 30 mg) as a pale-yellow solid (0.92 g, 92%) according to general procedure II: mp: 58–59 °C; ^{1}H NMR ($CDCl_3$): δ = 2.29 (s, 3H), 4.41 (d, J = 5.6 Hz, 2H), 5.22 (dd, J = 1.2, 10.2 Hz, 1H), 5.32 (dd, J = 1.2, 17.4 Hz, 1H), 5.86–5.95 (m, 1H), 6.47 (s, 1H), 6.78 (d, J = 9.2 Hz, 2H), 6.98 (d, J = 8.0 Hz, 1H), 7.07 (s, 1H), 7.59 (d, J = 9.0 Hz, 2H), 8.01 ppm (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 21.6, 68.7, 105.6, 114.8, 117.5, 117.9, 121.3, 123.7, 125.0, 126.3, 127.6, 132.4, 144.7, 155.9, 161.1, 162.7, 177.9 ppm; LRMS (ESI) *m/z* 293 [M^++H, 100], 315 [M^++Na, 13]; HRMS (ESI) calcd for $C_{19}H_{17}O_3$[M^++H] 293.1178, found 293.1179.

6-Methyl-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (49): This compound was obtained from chalcone **29** (0.73 g, 2.48 mmol) and I_2 (cat, 20 mg) as a pale-yellow solid (0.63 g, 87%) according to general procedure II: mp: 104–105 °C; ^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3H), 4.58 (d, J = 5.6 Hz, 2H), 5.32 (dd, J = 1.2, 10.2 Hz, 1H), 5.43 (dd, J = 1.2, 17.4 Hz, 1H), 6.01–6.08 (m, 1H), 6.70 (s, 1H), 6.99 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 1H), 7.46 (dd, J = 2.0, 8.4 Hz, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.97 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 20.9, 68.9, 105.9, 115.1, 117.7, 118.1, 123.4, 124.1, 124.9, 127.9, 132.5, 134.8, 135.0, 154.4, 161.3, 163.2, 178.5 ppm; LRMS (ESI) *m/z* 293 [M^++H, 100], 315 [M^++Na, 15]; HRMS (ESI) calcd for $C_{19}H_{17}O_3$ [M^++H] 293.1178, found 293.1171.

7-Methoxy-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (50): This compound was obtained from chalcone **30** (1.00 g, 3.23 mmol) and I_2 (cat, 25 mg) as a white solid (0.70 g, 70%) according to general procedure II: mp: 115–116 °C; ^{1}H NMR ($CDCl_3$): δ = 3.87 (s, 3H), 4.56 (d, J = 5.6 Hz, 2H), 5.31 (dd, J = 1.2, 10.2 Hz, 1H), 5.42 (dd, J = 1.2, 17.4 Hz, 1H), 6.01–6.08 (m, 1H), 6.61 (s, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.91 (dd, J = 2.0, 9.0 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 8.06 ppm (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 55.7, 68.9, 100.3, 105.9, 114.1, 115.0, 117.7, 118.1, 124.1, 126.9, 127.7, 132.5, 157.8, 161.2, 162.9, 164.0, 177.7 ppm; LRMS (ESI) *m/z* 309 [M^++H, 100], 331 [M^++Na, 3]; HRMS (ESI) calcd for $C_{19}H_{17}O_4$ [M^++H] 309.1127, found 309.1132.

6-Methoxy-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (51): This compound was obtained from chalcone **31** (1.00 g, 3.23 mmol) and I_2 (cat, 25 mg) as a pale-yellow solid (0.65 g, 65%) according to general procedure II: mp: 111–112 °C; ^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3H), 4.61 (d, J = 5.6 Hz, 2H), 5.31 (dd, J = 1.2, 10.2 Hz, 1H), 5.43 (dd, J = 1.2, 17.4 Hz, 1H), 6.01–6.09 (m, 1H), 6.72 (s, 1H), 7.01 (d, J = 8.8 Hz, 2H), 7.26 (dd, J = 2.0, 8.6 Hz, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.57 (d, J = 3.2 Hz, 1H), 7.84 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 55.9, 68.9, 104.8, 105.4, 115.1, 118.2, 119.3, 123.5, 124.1, 124.4, 127.9, 132.5, 150.9, 156.9, 161.3, 163.2, 178.3 ppm; LRMS (ESI) m/z 309 [M^++H, 100], 331 [M^++Na, 5]; HRMS (ESI) calcd for $C_{19}H_{17}O_4$ [M^++H] 309.1127, found 309.1134.

5-Methoxy-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (52): This compound was obtained from chalcone **32** (1.00 g, 3.23 mmol) and I_2 (cat, 25 mg) as a white solid (0.60 g, 60%) according to general procedure II: mp: 136–137 °C; ^{1}H NMR ($CDCl_3$): δ = 3.97 (s, 3H), 4.61 (d, J = 5.6 Hz, 2H), 5.31 (dd, J = 1.2, 10.2 Hz, 1H), 5.43 (dd, J = 1.2, 17.4 Hz, 1H), 6.00–6.08 (m, 1H), 6.62 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.4 Hz, 1H), 7.53 (dd, J = 8.4, 8.4 Hz, 1H), 7.81 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 56.4, 68.9, 106.3, 107.7, 110.0, 114.5, 115.1, 118.1, 123.8, 127.7, 132.5, 133.5, 158.2, 159.7, 161.0, 161.1, 178.3 ppm; LRMS (ESI) m/z 309 [M^++H, 100], 331 [M^++Na, 12]; HRMS (ESI) calcd for $C_{19}H_{17}O_4$ [M^++H] 309.1127, found 309.1125.

6,7-Dimethoxy-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (53): This compound was obtained from chalcone **33** (1.40 g, 4.12 mmol) and I_2 (cat, 35 mg) as a pale-yellow solid (0.64 g, 46%) according to general procedure II: mp: 157–158 °C; ^{1}H NMR ($CDCl_3$): δ = 3.95 (s, 3H), 3.99 (s, 3H), 4.59 (d, J = 5.6 Hz, 2H), 5.31 (dd, J = 1.2, 10.2 Hz, 1H), 5.43 (dd, J = 1.2, 17.4 Hz, 1H), 6.00–6.08 (m, 1H), 6.67 (s, 1H), 6.94 (s, 1H), 6.99 (d, J = 8.8 Hz, 2H), 7.52 (s, 1H), 7.81 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 56.3, 56.4, 68.9, 99.7, 104.3, 105.6, 115.1, 117.2, 118.1, 124.3, 127.6, 132.5, 147.5, 152.1, 154.2, 161.1, 162.7, 177.6 ppm; LRMS (ESI) m/z 339 [M^++H, 71], 361 [M^++Na, 10]; HRMS (ESI) calcd for $C_{20}H_{19}O_5$ [M^++H] 339.1232, found 339.1230.

7-Benzyloxy-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (54): This compound was obtained from chalcone **34** (0.81 g, 2.10 mmol) and I_2 (cat, 20 mg) as a white solid (0.56 g, 69%) according to general procedure II: mp: 153–154 °C; ^{1}H NMR ($CDCl_3$): δ = 4.61 (d, J = 5.6 Hz, 2H), 5.18 (s, 2H), 5.33 (dd, J = 1.2, 10.2 Hz, 1H), 5.45 (dd, J = 1.2, 17.4 Hz, 1H), 6.02–6.11 (m, 1H), 6.67 (s, 1H), 7.01–7.06 (m, 4H), 7.35–7.47 (m, 5H), 7.84 (d, J = 8.8 Hz, 2H), 8.13 ppm (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 68.9, 70.5, 101.4, 106.1, 114.7, 115.1, 117.9, 118.2, 124.2, 127.1, 127.5, 127.8, 128.4, 128.7, 132.5, 135.7, 157.8, 161.2, 163.0, 163.1, 177.8 ppm; LRMS (ESI) m/z 385 [M^++H, 100]; HRMS (ESI) calcd for $C_{25}H_{21}O_4$ [M^++H] 385.1440, found 385.1457.

6-Benzyloxy-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (55): This compound was obtained from chalcone **35** (0.63 g, 1.63 mmol) and I_2 (cat, 15 mg) as a white solid (0.40 g, 64%) according to general procedure II: mp: 145–146 °C; ^{1}H NMR ($CDCl_3$): δ = 4.62 (d, J = 5.6 Hz, 2H), 5.16 (s, 2H), 5.33 (dd, J = 1.2, 10.2 Hz, 1H), 5.45 (dd, J = 1.2, 17.4 Hz, 1H), 6.02–6.12 (m, 1H), 6.73 (s, 1H), 7.03 (d, J = 8.8 Hz, 2H), 7.33–7.51 (m, 7H), 7.70 (d, J = 2.8 Hz, 1H), 7.87 ppm (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 68.9, 70.6, 105.5, 106.1, 115.1, 118.2, 119.4, 124.0, 124.2, 124.5, 127.6, 127.9, 128.1, 128.6, 132.5, 136.3, 151.1, 156.0, 161.3, 163.2, 178.1 ppm; LRMS (ESI) m/z 385 [M^++H, 100]; HRMS (ESI) calcd for $C_{25}H_{21}O_4$ [M^++H] 385.1440, found 385.1441.

5-Benzyloxy-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (56): This compound was obtained from chalcone **36** (1.55 g, 4.02 mmol) and I_2 (cat, 35 mg) as a white solid (0.79 g, 51%) according to general procedure II: mp: 150–151 °C; ^{1}H NMR ($CDCl_3$): δ = 4.60 (d, J = 5.6 Hz, 2H), 5.28 (s, 2H), 5.33 (dd, J = 1.2, 10.2 Hz, 1H), 5.45 (dd, J = 1.2, 17.4 Hz, 1H), 6.00–6.10 (m, 1H), 6.63 (s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 7.29 (dd, J = 7.2, 7.2 Hz, 1H), 7.39 (dd, J = 7.2, 7.6 Hz, 2H), 7.48 (dd, J = 8.0, 8.4 Hz, 1H), 7.62 (d, J = 7.6 Hz, 2H), 7.82 ppm (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 68.9, 70.9, 107.7, 108.5, 110.4, 115.1, 118.1, 123.8, 126.6, 127.6, 127.7, 128.5, 132.5, 132.6, 133.4, 133.6, 158.2, 158.5, 161.1, 161.1, 178.1 ppm; LRMS (ESI) m/z 385 [M^++H, 100]; HRMS (ESI) calcd for $C_{25}H_{21}O_4$[M^++H] 385.1440, found 385.1445.

5,7-Dimethoxy-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (57): This compound was obtained from chalcone **37** (1.20 g, 3.53 mmol) and I_2 (cat, 30 mg) as a pale-yellow solid (0.86 g, 72%) according to general procedure II: mp: 171–172 °C; ^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3H), 3.92 (s, 3H), 4.59 (d, J = 5.6 Hz, 2H), 5.33 (dd, J = 1.2, 10.2 Hz, 1H), 5.45 (dd, J = 1.2, 17.4 Hz, 1H), 6.00–6.10 (m, 1H), 6.34 (d, J = 2.4 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 6.57 (s, 1H), 6.99 (d, J = 8.8 Hz, 2H), 7.79 ppm (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 55.7, 56.3, 68.9, 92.8, 96.0, 107.6, 109.1, 115.0, 118.1, 123.9, 127.5, 132.5, 159.8, 160.6, 160.8, 161.0, 163.9, 177.6 ppm; LRMS (ESI) m/z 339 [M^++H, 100], 361 [M^++Na, 5]; HRMS (ESI) calcd for $C_{20}H_{19}O_5$ [M^++H] 339.1232, found 339.1248.

5,7-Dibenzyloxy-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (58): This compound was obtained from chalcone **38** (0.52 g, 1.06 mmol) and I_2 (cat, 10 mg) as a white solid (0.36 g, 69%) according to general procedure II: mp: 147–148 °C; ^{1}H NMR ($CDCl_3$): δ = 4.57 (d, J = 5.6 Hz, 2H), 5.05 (s, 2H), 5.08 (s, 2H), 5.33 (dd, J = 1.2, 10.2 Hz, 1H), 5.45 (dd, J = 1.2, 17.4 Hz, 1H), 6.00–6.09 (m, 1H), 6.46 (d, J = 2.0 Hz, 1H), 6.55 (s, 1H), 6.60 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 7.26–7.43 (m, 8H), 7.62 (d, J = 7.6 Hz, 2H), 7.77 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 68.9, 70.4, 70.7, 94.2, 98.3, 107.6, 109.7, 115.0, 118.1, 123.9, 126.5, 127.6, 128.4, 128.5, 128.7, 128.9, 132.5, 135.7, 136.4, 159.6, 159.6, 160.7, 161.0, 162.8, 177.3 ppm; LRMS (ESI) m/z 491 [M^++H, 100], 513 [M^++Na, 26]; HRMS (ESI) calcd for $C_{32}H_{27}O_5$ [M^++H] 491.1858, found 491.1859.

6-Ethyl-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (59): This compound was obtained from chalcone **39** (9.30 g, 30 mmol) and I_2 (cat, 0.25 g) as a pale-yellow solid (6.65 g, 72%) according to general procedure II: mp: 119–121 °C; ^{1}H NMR ($CDCl_3$): δ = 1.20 (t, J = 7.6 Hz, 3H), 2.66 (q, J = 7.6 Hz, 2H), 4.49 (d, J = 5.2 Hz, 2H), 5.26 (dd, J = 1.2, 10.4 Hz, 1H), 5.38 (dd, J = 1.6, 17.4 Hz, 1H), 5.93–6.05 (m, 1H), 6.60 (s, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 1H), 7.39 (dd, J = 2.0, 8.4 Hz, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.92 ppm (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 15.3, 28.2, 68.8, 105.8, 115.0, 117.7, 118.0, 123.5, 123.6, 124.0, 127.7, 132.5, 133.6, 141.1, 154.4, 161.2, 163.0, 178.3 ppm; LRMS (ESI) m/z 307 [M^++H, 100], 329 [M^++Na, 14]; HRMS (ESI) calcd for $C_{20}H_{18}O_3$ [M^++H] 307.1334, found 307.1338.

6-Methyl-8-nitro-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (60): This compound was obtained from chalcone **40** (0.70 g, 2.06 mmol) and I_2 (cat, 20 mg) as a yellow solid (0.53 g, 76%) according to general procedure II: mp: 142–145 °C; ^{1}H NMR ($CDCl_3$): δ = 2.52 (s, 3H), 4.60 (d, J = 5.2 Hz, 2H), 5.33 (dd, J = 1.2, 10.4 Hz, 1H), 5.44 (dd, J = 1.6, 17.4 Hz, 1H), 5.99–6.08 (m, 1H), 6.77 (s, 1H), 7.01 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.8 Hz, 2H), 8.18 (d, J = 2.0 Hz, 1H), 8.27 ppm (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 20.7, 68.9, 105.6, 115.3, 118.3, 122.7, 125.4, 128.4, 130.5, 131.4, 132.3, 134.8, 138.1, 146.7, 161.9, 163.6, 176.2 ppm; LRMS (ESI) m/z 338 [M^++H,

100], 360 [M^++Na, 16]; HRMS (ESI) calcd for $C_{19}H_{16}NO_5$ [M^++H] 338.1028, found 338.1039.

General procedure III for the dimerization of flavone monomers to flavone dimers 61–80: *Step (a)*: A catalytic amount of [Pd(PPh$_3$)$_4$] (2–3 mol%) was added to a round-bottom flask charged with allyl-protected flavones **41**–**60** (1 equiv), K_2CO_3 (4 equiv), and MeOH at reflux. The reaction mixture was stirred at reflux for 4 h. During heating, the reaction mixture turned from pale brown to deep brown. When TLC indicated complete consumption of starting material, the reaction mixture was filtered to remove excess K_2CO_3. The filtrate was poured into a beaker containing H_2O, and the solution was acidified to pH 3–4 using 1 M HCl at 0 °C. An off-white solid was formed which was collected by suction filtration to furnish allyl-deprotected compound. This was brought to the next step without further purification. *Step (b)*: The product of step (a) (2 equiv) was added to a round-bottom flask charged with tetra(ethylene glycol) dimesylate (1 equiv), K_2CO_3 (2.5 equiv), and DMF. The reaction mixture was stirred at reflux for 3 h. During heating, the reaction mixture slowly turned from deep brown to a milky color. When TLC indicated complete consumption of starting material, the reaction mixture was poured into a separating funnel containing H_2O. The mixture was continuously extracted with CH_2Cl_2. If the mixture could not be separated into two layers, a small amount of 1 M HCl was added. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give a crude reaction mixture. Purification of the flavone dimer was performed by flash column chromatography on silica gel with 10–20% acetone in CH_2Cl_2 as eluent to furnish the desired product.

1,13-Bis[4′-(4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (61). For step (a), 4′-hydroxyflavone (2.28 g, 95%) was obtained from allyl-protected flavone **41** (2.80 g, 10 mmol), K_2CO_3 (5.56 g), and a catalytic amount of [Pd(PPh$_3$)$_4$] (0.23 g) according to general procedure III(a). For step (b), the title compound **61** was obtained from 4′-hydroxyflavone (0.48 g, 2.0 mmol), tetra(ethylene glycol) dimesylate (0.35 g, 1.0 mmol), and K_2CO_3 (0.35 g) as a pale-yellow solid (0.38 g, 60%) according to general procedure III(b): mp: 129–131 °C; ^{1}H NMR ($CDCl_3$): δ = 3.62–3.67 (m, 8H), 3.79 (t, J = 4.8 Hz, 4H), 4.06 (t, J = 4.4 Hz, 4H), 6.57 (s, 2H), 6.87 (d, J = 8.8 Hz, 4H), 7.26 (dd, J = 7.6, 7.6 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.53 (ddd, J = 1.2, 8.8, 8.8 Hz, 2H), 7.68 (d, J = 8.8 Hz, 4H), 8.20 ppm (dd, J = 1.2, 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 67.3, 69.2, 70.4, 70.5, 105.6, 114.6, 117.6, 123.5, 123.5, 124.7, 125.1, 127.5, 133.3, 155.7, 161.3, 162.8, 177.9 ppm; LRMS (ESI) *m/z* 635 [M^++H, 100], 658 [M^++Na, 2]; HRMS (ESI) calcd for $C_{38}H_{35}O_9$ [M^++H] 635.2281, found 635.2260.

1,13-Bis[4′-(7-fluoro-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (62). For step (a), 7-fluoro-4′-hydroxyflavone (290 mg, 91%) was obtained from allyl-protected flavone **42** (370 mg, 1.25 mmol), K_2CO_3 (690 mg), and a catalytic amount of [Pd(PPh$_3$)$_4$] (18 mg) according to general procedure III(a). For step (b), the title compound **62** (150 mg, 45%) was obtained from 7-fluoro-4′-hydroxyflavone (260 mg, 1.0 mmol), tetra(ethylene glycol) dimesylate (175 mg, 0.50 mmol), and K_2CO_3 (180 mg) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 3.68–3.75 (m, 8H), 3.87 (t, J = 4.8 Hz, 4H), 4.16 (t, J = 4.4 Hz, 4H), 6.64 (s, 2H), 6.98 (d, J = 8.8 Hz, 4H), 7.06 (ddd, J = 2.0, 8.4, 8.4 Hz, 2H), 7.10 (dd, J = 2.0, 8.4 Hz, 2H), 7.77 (d, J = 8.8 Hz, 4H), 8.17 ppm (dd, J = 6.4, 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 67.6, 69.5, 70.6, 70.8, 104.6 (d, J = 25.2 Hz, C6), 106.0, 113.8 (d, J = 22.5 Hz, C8), 115.0, 120.6 (d, J = 2.1 Hz, C10), 123.6, 127.8, 128.0 (d, J = 10.6 Hz, C5), 157.0 (d, J = 13.3 Hz, C9), 161.7, 163.5, 165.5 (d, J = 253.0 Hz, C7), 177.3 ppm; LRMS (ESI) *m/z* 671 [M^++H, 18], 693 [M^++Na, 100]; HRMS (ESI) calcd for $C_{38}H_{33}O_9F_2$ [M^++H] 671.2093, found 671.2072.

1,13-Bis[4′-(6-fluoro-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (63). For step (a), 6-fluoro-4′-hydroxyflavone (250 mg, 93%) was obtained from allyl-protected flavone **43** (310 mg, 1.05 mmol), K_2CO_3 (580 mg), and a catalytic amount of [Pd(PPh$_3$)$_4$] (25 mg) according to general procedure III(a). For step (b), the title compound **63** (145 mg, 44%) was obtained from 6-fluoro-4′-hydroxyflavone (240 mg, 0.94 mmol), tetra(ethylene glycol) dimesylate (173 mg, 0.49 mmol), and K_2CO_3 (185 mg) as a white solid according to general procedure III(b): mp: 147–149 °C; ^{1}H NMR ($CDCl_3$): δ = 3.66–3.75 (m, 8H), 3.88 (t, J = 4.8 Hz, 4H), 4.17 (t, J = 4.8 Hz, 4H), 6.68 (s, 2H), 6.99 (d, J = 8.8 Hz, 4H), 7.37 (ddd, J = 2.0, 8.4, 8.4 Hz, 2H), 7.50 (dd, J = 4.4, 9.2 Hz, 2H), 7.79 (d, J = 8.8 Hz, 4H), 7.81 ppm (dd, J = 4.4, 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 67.6, 69.5, 70.7, 70.8, 105.3, 110.6 (d, J = 23.5 Hz, C5), 115.0, 119.9 (d, J = 7.9 Hz, C10), 121.7 (d, J = 25.2 Hz, C7), 123.7, 124.9 (d, J = 7.2 Hz, C8), 127.9, 152.2 (d, J = 1.4 Hz, C9), 159.5 (d, J = 245.2 Hz, C6), 161.7, 163.6, 177.4 ppm; LRMS (ESI) *m/z* 671 [M^++H, 50], 693 [M^++Na, 100]; HRMS (ESI) calcd for $C_{38}H_{33}O_9F_2$ [M^++H] 671.2093, found 671.2076.

1,13-Bis[4′-(6-chloro-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (64). For step (a), 6-chloro-4′-hydroxyflavone (0.24 g, 86%) was obtained from allyl-protected flavone **44** (0.32 g, 1.0 mmol), K_2CO_3 (0.57 g), and a catalytic amount of [Pd(PPh$_3$)$_4$] (25 mg) according to general procedure III(a). For step (b), the title compound **64** (33 mg, 41%) was obtained from 6-chloro-4′-hydroxyflavone (60 mg, 0.22 mmol), tetra(ethylene glycol) dimesylate (40 mg, 0.11 mmol), and K_2CO_3 (50 mg) as a yellow solid according to general procedure III(b): mp: 180–182 °C; ^{1}H NMR ($CDCl_3$): δ = 3.70–3.76 (m, 8H), 3.90 (t, J = 4.8 Hz, 4H), 4.18 (t, J = 4.8 Hz, 4H), 6.70 (s, 2H), 7.00 (d, J = 8.8 Hz, 4H), 7.47 (dd, J = 8.8 Hz, 2H), 7.60 (dd, J = 2.8, 8.8 Hz, 2H), 7.81 (d, J = 8.8 Hz, 4H), 8.14 ppm (d, J = 2.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 67.6, 69.5, 70.7, 70.8, 105.9, 115.0, 119.6, 123.6, 124.8, 125.1, 127.9, 131.0, 133.7, 154.4, 161.8, 163.5, 177.0 ppm; LRMS (ESI) *m/z* 704 [M^++H, 10], 726 [M^++Na, 16]; HRMS (ESI) calcd for $C_{38}H_{33}O_9Cl_2$ [M^++H] 703.1502, found 703.1505.

1,13-Bis[4′-(6-bromo-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (65). For step (a), 6-bromo-4′-hydroxyflavone **114** (0.42 g, 80%) was obtained from allyl-protected flavone **45** (0.59, 1.7 mmol), K_2CO_3 (0.91 g), and a catalytic amount of [Pd(PPh$_3$)$_4$] (40 mg) according to general procedure III(a). For step (b), the title compound **65** (110 mg, 49%) was obtained from 6-bromo-4′-hydroxyflavone (180 mg, 0.57 mmol), tetra(ethylene glycol) dimesylate (100 mg, 0.29 mmol), and K_2CO_3 (110 mg) as a yellow solid according to general procedure III(b): mp: 184–186 °C; ^{1}H NMR ($CDCl_3$): δ = 3.69–3.75 (m, 8H), 3.88 (t, J = 4.8 Hz, 4H), 4.17 (t, J = 4.8 Hz, 4H), 6.68 (s, 2H), 6.98 (d, J = 8.8 Hz, 4H), 7.38 (d, J = 9.2 Hz, 2H), 7.71 (dd, J = 2.4, 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 4H), 8.27 ppm (d, J = 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 67.6, 69.5, 70.6, 70.8, 106.0, 115.0, 119.8, 123.6, 125.1, 127.9, 128.2, 136.5, 154.8, 161.8, 163.5, 176.9 ppm; LRMS (ESI) *m/z* 793 [M^++H, 7], 815 [M^++Na, 20]; HRMS (ESI) calcd for $C_{38}H_{33}O_9Br_2$ [M^++H] 791.0491, found 791.0506.

1,13-Bis[4′-(6,8-dichloro-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (66). For step (a), 6,8-dichloro-4′-hydroxyflavone (0.59 g, 95%) was obtained from allyl-protected flavone **46** (0.70 g, 2.0 mmol), K_2CO_3 (1.15 g), and a catalytic amount of [Pd(PPh$_3$)$_4$] (50 mg) according to general procedure III(a). For step (b), the title compound **66** (32 mg, 48%) was obtained from 6,8-dichloro-4′-hydroxyflavone (52 mg, 0.17 mmol), tetra(ethylene

glycol) dimesylate (30 mg, 0.09 mmol), and K_2CO_3 (38 mg) as a white solid according to general procedure III(b): mp: 147–148 °C; ^{1}H NMR ($CDCl_3$): δ = 3.70–3.76 (m, 8H), 3.90 (t, J = 4.8 Hz, 4H), 4.18 (t, J = 4.8 Hz, 4H), 6.71 (s, 2H), 7.00 (d, J = 8.8 Hz, 4H), 7.67 (d, J = 2.4 Hz, 2H), 7.85 (d, J = 8.8 Hz, 4H), 8.03 ppm (d, J = 2.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 67.7, 69.5, 70.7, 70.8, 105.6, 115.1, 123.1, 123.8, 124.2, 125.6, 128.1, 130.7, 133.5, 150.2, 162.0, 163.3, 176.2 ppm; LRMS (ESI) m/z 773 [M^++H, 29], 795 [M^++Na, 100]; HRMS (ESI) calcd for $C_{38}H_{31}O_9Cl_4$ [M^++H] 771.0722, found 771.0730.

1,13-Bis[4′-(6,8-dibromo-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (67). For step (a), 6,8-dibromo-4′-hydroxyflavone (130 mg, 95%) was obtained from allyl-protected flavone **47** (150 mg, 0.34 mmol), K_2CO_3 (200 mg), and a catalytic amount of [$Pd(PPh_3)_4$] (10 mg) according to general procedure III(a). For step (b), the title compound **67** (58 mg, 43%) was obtained from 6,8-dibromo-4′-hydroxyflavone (110 mg, 0.28 mmol), tetra(ethylene glycol) dimesylate (50 mg, 0.14 mmol), and K_2CO_3 (65 mg) as a pale-yellow solid according to general procedure III(b): mp: 186–187 °C; ^{1}H NMR ($CDCl_3$): δ = 3.70–3.76 (m, 8H), 3.90 (t, J = 4.8 Hz, 4H), 4.18 (t, J = 4.8 Hz, 4H), 6.71 (s, 2H), 7.00 (d, J = 8.8 Hz, 4H), 7.87 (d, J = 8.8 Hz, 4H), 7.97 (d, J = 2.4 Hz, 2H), 8.23 ppm (d, J = 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 67.7, 69.4, 70.7, 70.8, 105.4, 112.8, 115.0, 118.2, 122.8, 125.8, 127.6, 128.0, 138.9, 151.4, 162.0, 163.1, 175.9 ppm; LRMS (ESI) m/z 951 [M^++H, 32], 973 [M^++Na, 25]; HRMS (ESI) calcd for $C_{38}H_{30}O_9Br_4$ [M^++H] 946.8702, found 946.8859.

1,13-Bis[4′-(7-methyl-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (68). For step (a), 7-methyl-4′-hydroxyflavone (0.39 g, 94%) was obtained from allyl-protected flavone **48** (0.48 g, 1.6 mmol), K_2CO_3 (0.91 g), and a catalytic amount of [$Pd(PPh_3)_4$] (40 mg) according to general procedure III(a). For step (b), the title compound **68** (0.23 g, 61%) was obtained from 7-methyl-4′-hydroxyflavone (0.28 g, 1.1 mmol), tetra(ethylene glycol) dimesylate (0.20 g, 0.57 mmol), and K_2CO_3 (0.21 g) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 2.45 (s, 6H), 3.68–3.75 (m, 8H), 3.87 (t, J = 4.8 Hz, 4H), 4.16 (t, J = 4.8 Hz, 4H), 6.66 (s, 2H), 6.98 (d, J = 8.8 Hz, 4H), 7.16 (d, J = 8.0 Hz, 2H), 7.28 (s, 2H), 7.79 (d, J = 8.4 Hz, 4H), 8.03 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 21.8, 67.6, 69.5, 70.7, 70.8, 105.9, 114.9, 117.7, 121.5, 124.1, 125.2, 126.5, 127.8, 144.9, 156.2, 161.5, 163.0, 178.3 ppm; LRMS (ESI) m/z 663 [M^++H, 97], 685 [M^++Na, 100]; HRMS (ESI) calcd for $C_{40}H_{39}O_9$ [M^++H] 663.2594, found 663.2588.

1,13-Bis[4′-(6-methyl-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (69). For step (a), 6-methyl-4′-hydroxyflavone (0.37 g, 95%) was obtained from allyl-protected flavone **49** (0.45 g, 1.5 mmol), K_2CO_3 (0.85 g), and a catalytic amount of [$Pd(PPh_3)_4$] (40 mg) according to general procedure III(a). For step (b), the title compound **69** (57 mg, 42%) was obtained from 6-methyl-4′-hydroxyflavone (100 mg, 0.40 mmol), tetra(ethylene glycol) dimesylate (72 mg, 0.21 mmol), and K_2CO_3 (80 mg) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 6H), 3.69–3.75 (m, 8H), 3.88 (t, J = 4.8 Hz, 4H), 4.16 (t, J = 4.8 Hz, 4H), 6.69 (s, 2H), 6.98 (d, J = 8.4 Hz, 4H), 7.39 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 1.2, 8.6 Hz, 2H), 7.81 (d, J = 8.4 Hz, 4H), 7.94 ppm (s, 2H); ^{13}C NMR ($CDCl_3$): δ = 20.9, 67.6, 69.5, 70.6, 7.08, 105.9, 114.9, 117.6, 123.4, 124.1, 124.9, 127.8, 134.8, 135.0, 154.3, 161.5, 163.1, 178.4 ppm; LRMS (ESI) m/z 663 [M^++H, 79], 685 [M^++Na, 100]; HRMS (ESI) calcd for $C_{40}H_{39}O_9$ [M^++H] 663.2594, found 663.2586.

1,13-Bis[4′-(7-methoxy-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (70). For step (a), 7-methoxy-4′-hydroxyflavone (0.28 g, 80%) was obtained from allyl-protected flavone **50** (0.40 g, 1.3 mmol), K_2CO_3 (0.72 g), and a catalytic amount of [$Pd(PPh_3)_4$] (30 mg) according to general procedure III(a). For step (b), the title compound **70** (0.14 g, 47%) was obtained from 7-methoxy-4′-hydroxyflavone (0.22 g, 0.82 mmol), tetra(ethylene glycol) dimesylate (0.15 g, 0.43 mmol), and K_2CO_3 (0.16 g) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 3.69–3.75 (m, 8H), 3.88 (t, J = 4.8 Hz, 4H), 3.91 (s, 6H), 4.17 (t, J = 4.8 Hz, 4H), 6.65 (s, 2H), 6.90 (d, J = 2.0 Hz, 2H), 6.93 (dd, J = 2.0, 9.0 Hz, 2H), 6.99 (d, J = 8.8 Hz, 4H), 7.80 (d, J = 8.4 Hz, 4H), 8.07 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 55.8, 67.6, 69.5, 70.7, 70.8, 100.3, 105.9, 114.2, 114.9, 117.6, 124.1, 126.9, 127.7, 157.8, 161.4, 162.9, 164.0, 177.8 ppm; LRMS (ESI) m/z 695 [M^++H, 63], 717 [M^++Na, 100]; HRMS (ESI) calcd for $C_{40}H_{39}O_{11}$ [M^++H] 695.2492, found 695.2495.

1,13-Bis[4′-(6-methoxy-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (71). For step (a), 6-methoxy-4′-hydroxyflavone (0.29 g, 90%) was obtained from allyl-protected flavone **51** (0.37 g, 1.2 mmol), K_2CO_3 (0.66 g), and a catalytic amount of [$Pd(PPh_3)_4$] (30 mg) according to general procedure III(a). For step (b), the title compound **71** (0.15 g, 42%) was obtained from 6-methoxy-4′-hydroxyflavone (0.28 g, 1.0 mmol), tetra(ethylene glycol) dimesylate (0.18 g, 0.51 mmol), and K_2CO_3 (0.18 g) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 3.69–3.75 (m, 8H), 3.87 (s, 6H), 3.88 (t, J = 4.8 Hz, 4H), 4.16 (t, J = 4.8 Hz, 4H), 6.70 (s, 2H), 6.98 (d, J = 8.8 Hz, 4H), 7.25 (dd, J = 2.8, 9.0 Hz, 2H), 7.43 (d, J = 9.2 Hz, 2H), 7.53 (d, J = 2.8 Hz, 2H), 7.80 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 55.9, 67.6, 69.5, 70.7, 70.8, 104.7, 105.3, 114.9, 119.3, 123.5, 124.3, 127.8, 150.9, 156.8, 161.5, 163.1, 178.1 ppm; LRMS (ESI) m/z 695 [M^++H, 47], 717 [M^++Na, 100]; HRMS (ESI) calcd for $C_{40}H_{39}O_{11}$ [M^++H] 695.2492, found 695.2493.

1,13-Bis[4′-(5-methoxy-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (72). For step (a), 5-methoxy-4′-hydroxyflavone (0.27 g, 76%) was obtained from allyl-protected flavone **52** (0.41 g, 1.3 mmol), K_2CO_3 (0.73 g), and a catalytic amount of [$Pd(PPh_3)_4$] (30 mg) according to general procedure III(a). For step (b), the title compound **72** (0.14 g, 50%) was obtained from 5-methoxy-4′-hydroxyflavone (0.22 g, 0.82 mmol), tetra(ethylene glycol) dimesylate (0.14 g, 0.40 mmol), and K_2CO_3 (0.14 g) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 3.68–3.72 (m, 8H), 3.86 (t, J = 4.8 Hz, 4H), 3.95 (s, 6H), 4.14 (t, J = 4.8 Hz, 4H), 6.61 (s, 2H), 6.77 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.8 Hz, 4H), 7.06 (d, J = 8.4 Hz, 2H), 7.51 (dd, J = 8.0, 8.4 Hz, 2H), 7.77 ppm (d, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ = 56.4, 67.5, 69.5, 70.6, 70.8, 106.3, 107.5, 110.0, 114.8, 123.6, 127.6, 133.5, 158.1, 159.6, 161.0, 161.3, 178.2 ppm; LRMS (ESI) m/z 695 [M^++H, 29], 717 [M^++Na, 100]; HRMS (ESI) calcd for $C_{40}H_{39}O_{11}$[M^++H] 695.2492, found 695.2497.

1,13-Bis[4′-(6,7-dimethoxy-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (73). For step (a), 6,7-dimethoxy-4′-hydroxyflavone (0.31 g, 86%) was obtained from allyl-protected flavone **53** (0.41 g, 1.2 mmol), K_2CO_3 (0.67 g), and a catalytic amount of [$Pd(PPh_3)_4$] (30 mg) according to general procedure III(a). For step (b), the title compound **73** (0.13 g, 47%) was obtained from 6,7-dimethoxy-4′-hydroxyflavone (0.22 g, 0.74 mmol), tetra(ethylene glycol) dimesylate (0.13 g, 0.37 mmol), and K_2CO_3 (0.14 g) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 3.67–3.71 (m, 8H), 3.85 (t, J = 4.8 Hz, 4H), 3.89 (s, 6H), 3.95 (s, 6H), 4.12 (t, J = 4.8 Hz, 4H), 6.60 (s, 2H), 6.85 (s, 2H), 6.92 (d, J = 8.8 Hz, 4H), 7.40 (s, 2H), 7.71 ppm (d, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ = 56.1, 56.3, 67.5, 69.4, 70.6, 70.7, 99.5, 104.0, 105.3, 114.8, 116.9, 124.0, 127.5, 147.3, 151.9, 154.1, 161.2, 162.5,

177.3 ppm; LRMS (ESI) *m/z* 755 [M^++H, 48], 777 [M^++Na, 100]; HRMS (ESI) calcd for $C_{42}H_{43}O_{13}$ [M^++H] 755.2704, found 755.2693.

1,13-Bis[4′-(7-benzyloxy-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (74). For step (a), 7-benzyloxy-4′-hydroxyflavone (0.42 g, 98%) was obtained from allyl-protected flavone **54** (0.48 g, 1.3 mmol), K_2CO_3 (0.69 g), and a catalytic amount of [$Pd(PPh_3)_4$] (30 mg) according to general procedure III(a). For step (b), the title compound **74** (0.15 g, 33%) was obtained from 7-benzyloxy-4′-hydroxyflavone (0.38 g, 1.1 mmol), tetra(ethylene glycol) dimesylate (0.19 g, 0.54 mmol), and K_2CO_3 (0.19 g) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 3.70–3.76 (m, 8H), 3.89 (t, J = 4.8 Hz, 4H), 4.18 (t, J = 4.8 Hz, 4H), 5.17 (s, 4H), 6.64 (s, 2H), 6.99–7.03 (m, 8H), 7.36–7.47 (m, 10H), 7.80 (d, J = 8.8 Hz, 4H), 8.10 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 67.6, 69.5, 70.5, 70.7, 70.9, 101.4, 106.1, 114.6, 114.9, 117.9, 124.2, 127.0, 127.5, 127.7, 128.3, 128.7, 135.8, 157.7, 161.4, 162.9, 163.1, 177.7 ppm; LRMS (ESI) *m/z* 847 [M^++H, 12], 869 [M^++Na, 100]; HRMS (ESI) calcd for $C_{52}H_{47}O_{11}$ [M^++H] 847.3118, found 847.3116.

1,13-Bis[4′-(6-benzyloxy-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (75). For step (a), 6-benzyloxy-4′-hydroxyflavone (0.18 g, 77%) was obtained from allyl-protected flavone **55** (0.26 g, 0.68 mmol), K_2CO_3 (0.37 g), and a catalytic amount of [$Pd(PPh_3)_4$] (20 mg) according to general procedure III(a). For step (b), the title compound **75** (63 mg, 40%) was obtained from 6-benzyloxy-4′-hydroxyflavone (120 mg, 0.35 mmol), tetra(ethylene glycol) dimesylate (65 mg, 0.19 mmol), and K_2CO_3 (80 mg) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 3.69–3.75 (m, 8H), 3.88 (t, J = 4.8 Hz, 4H), 4.16 (t, J = 4.8 Hz, 4H), 5.10 (s, 4H), 6.68 (s, 2H), 6.99 (d, J = 8.8 Hz, 4H), 7.29–7.45 (m, 14H), 7.65 (d, J = 2.8 Hz, 2H), 7.80 ppm (d, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ = 67.6, 69.5, 70.5, 70.7, 70.9, 105.4, 106.1, 115.0, 119.4, 123.9, 124.2, 124.4, 127.6, 127.8, 128.1, 128.6, 136.3, 151.0, 156.0, 161.5, 163.0, 178.0 ppm; LRMS (ESI) *m/z* 847 [M^++H, 22], 869 [M^++Na, 100]; HRMS (ESI) calcd for $C_{52}H_{47}O_{11}$ [M^++H] 847.3118, found 847.3110.

1,13-Bis[4′-(5-benzyloxy-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (76). For step (a), 5-benzyloxy-4′-hydroxyflavone (0.32 g, 94%) was obtained from allyl-protected flavone **56** (0.38 g, 0.99 mmol), K_2CO_3 (0.95 g), and a catalytic amount of [$Pd(PPh_3)_4$] (25 mg) according to general procedure III(a). For step (b), the title compound **76** (0.17 g, 50%) was obtained from 5-benzyloxy-4′-hydroxyflavone (0.27 g, 0.78), tetra(ethylene glycol) dimesylate (0.14 g, 0.40 mmol), and K_2CO_3 (0.14 g) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 3.70–3.76 (m, 8H), 3.89 (t, J = 4.8 Hz, 4H), 4.19 (t, J = 4.8 Hz, 4H), 5.27 (s, 4H), 6.61 (s, 2H), 6.80 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.8 Hz, 4H), 7.08 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 7.2 Hz, 2H), 7.40 (dd, J = 7.2, 7.2 Hz, 4H), 7.47 (dd, J = 8.4, 8.4 Hz, 2H), 7.62 (d, J = 7.2 Hz, 4H), 7.80 ppm (d, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ = 67.6, 69.5, 70.7, 70.8, 107.7, 108.4, 110.4, 114.9, 115.0, 123.9, 126.6, 127.6, 127.7, 128.5, 133.3, 136.6, 158.2, 158.5, 161.0, 161.3, 178.0 ppm; LRMS (ESI) *m/z* 847 [M^++H, 12], 869 [M^++Na, 100]; HRMS (ESI) calcd for $C_{52}H_{47}O_{11}$ [M^++H] 847.3118, found 847.3102.

1,13-Bis[4′-(5,7-dimethoxy-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (77). For step (a), 5,7-dimethoxy-4′-hydroxyflavone (0.29 g, 76%) was obtained from allyl-protected flavone **57** (0.43 g, 1.3 mmol), K_2CO_3 (0.70 g), and a catalytic amount of [$Pd(PPh_3)_4$] (30 mg) according to general procedure III(a). For step (b), the title compound **77** (91 mg, 42%) was obtained from 5,7-dimethoxy-4′-hydroxyflavone (160 mg, 0.54 mmol), tetra(ethylene glycol) dimesylate (100 mg, 0.29 mmol), and K_2CO_3 (120 mg) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 3.66–3.72 (m, 8H), 3.84 (t, J = 4.8 Hz, 4H), 3.86 (s, 6H), 3.89 (s, 6H), 4.13 (t, J = 4.8 Hz, 4H), 6.28 (d, J = 2.0 Hz, 2H), 6.46 (d, J = 2.0 Hz, 2H), 6.51 (s, 2H), 6.93 (d, J = 9.2 Hz, 4H), 7.71 ppm (d, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ = 55.6, 56.2, 67.5, 69.4, 70.6, 70.7, 92.7, 95.9, 107.3, 108.9, 114.8, 123.7, 127.4, 159.6, 160.4, 160.6, 161.1, 163.8, 177.5 ppm; LRMS (ESI) *m/z* 755 [M^++H, 52], 777 [M^++Na, 24]; HRMS (ESI) calcd for $C_{42}H_{43}O_{13}$ [M^++H] 755.2704, found 755.2710.

1,13-Bis[4′-(5,7-dibenzyloxy-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (78). For step (a), 5,7-dibenzyloxy-4′-hydroxyflavone (0.14 g, 73%) was obtained from allyl-protected flavone **58** (0.21 g, 0.43 mmol), K_2CO_3 (0.24 g), and a catalytic amount of [$Pd(PPh_3)_4$] (10 mg) according to general procedure III(a). For step (b), the title compound **78** (76 mg, 56%) was obtained from 5,7-dibenzyloxy-4′-hydroxyflavone (110 mg, 0.24 mmol), tetra(ethylene glycol) dimesylate (45 mg, 0.13 mmol), and K_2CO_3 (50 mg) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 3.69–3.77 (m, 8H), 3.88 (t, J = 4.8 Hz, 4H), 4.15 (t, J = 4.8 Hz, 4H), 5.07 (s, 4H), 5.17 (s, 4H), 6.43 (d, J = 2.0 Hz, 2H), 6.53 (s, 2H), 6.58 (d, J = 2.0 Hz, 2H), 6.96 (d, J = 8.8 Hz, 4H), 7.26–7.42 (m, 16H), 7.60 (d, J = 7.6 Hz, 4H), 7.74 ppm (d, J = 8.8 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ = 67.6, 69.6, 70.4, 70.6, 70.7, 70.8, 94.1, 98.2, 107.6, 109.7, 114.8, 123.9, 126.5, 127.5, 127.5, 127.6, 128.3, 128.5, 128.7, 135.7, 136.4, 159.6, 159.6, 160.5, 161.2, 162.7, 177.2 ppm; LRMS (ESI) *m/z* 1060 [M^++H, 19], 1082 [M^++Na, 22]; HRMS (ESI) calcd for $C_{66}H_{59}O_{13}$ [M^++H] 1059.3956, found 1059.3994.

1,13-Bis[4′-(6-ethyl-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (79). For step (a), 6-ethyl-4′-hydroxyflavone (0.49 g, 91%) was obtained from allyl-protected flavone **59** (0.62 g, 2.0 mmol), K_2CO_3 (1.2 g), and a catalytic amount of [$Pd(PPh_3)_4$] (50 mg) according to general procedure III(a). For step (b), the title compound **79** (0.37 g, 54%) was obtained from 6-ethyl-4′-hydroxyflavone (0.54 g, 2.0 mmol), tetra(ethylene glycol) dimesylate (0.35 g, 1.0 mmol), and K_2CO_3 (0.40 g) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 1.24 (t, J = 7.6 Hz, 6H), 2.70 (q, J = 7.6 Hz, 4H), 3.67–3.73 (m, 8H), 3.85 (t, J = 4.8 Hz, 4H), 4.14 (t, J = 4.8 Hz, 4H), 6.65 (s, 2H), 6.96 (d, J = 8.8 Hz, 4H), 7.38 (d, J = 8.4 Hz, 2H), 7.44 (dd, J = 2.4, 8.6 Hz, 2H), 7.78 (d, J = 8.8 Hz, 4H), 7.95 ppm (d, J = 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 15.4, 28.3, 67.6, 69.5, 70.6, 70.8, 105.9, 114.9, 117.7, 123.5, 123.6, 124.1, 127.8, 133.7, 141.2, 154.4, 161.5, 163.0, 178.4 ppm; LRMS (ESI) *m/z* 692 [M^++H, 37], 714 [M^++Na, 48]; HRMS (ESI) calcd for $C_{42}H_{43}O_9$ [M^++H] 691.2907, found 691.2873.

1,13-Bis[4′-(6-methyl-8-nitro-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (80). For step (a), 6-methyl-8-nitro-4′-hydroxyflavone (0.19 g, 63%) was obtained from allyl-protected flavone **60** (0.34 g, 1.0 mmol), K_2CO_3 (0.56 g), and a catalytic amount of [$Pd(PPh_3)_4$] (25 mg) according to general procedure III(a). For step (b), the title compound **80** (82 mg, 38%) was obtained from 6-methyl-8-nitro-4′-hydroxyflavone (160 mg, 0.54 mmol), tetra(ethylene glycol) dimesylate (100 mg, 0.29 mmol), and K_2CO_3 (110 mg) as a pale-yellow solid according to general procedure III(b): mp: 145–146 °C; ^{1}H NMR ($CDCl_3$): δ = 2.49 (s, 6H), 3.68–3.75 (m, 8H), 3.88 (t, J = 4.8 Hz, 4H), 4.15 (t, J = 4.8 Hz, 4H), 6.68 (s, 2H), 6.96 (d, J = 8.8 Hz, 4H), 7.84 (d, J = 8.4 Hz, 4H), 8.13 (d, J = 2.4 Hz, 2H), 8.19 ppm (d, J = 1.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 20.7, 67.7, 69.5, 70.7, 70.8, 105.5, 115.1, 122.7, 125.3, 128.3, 130.5, 131.4, 134.7, 138.0, 146.6, 162.1, 163.4, 176.0 ppm; LRMS (ESI) *m/z*

754 [M^++H, 6], 776 [M^++Na, 7]; HRMS (ESI) calcd for $C_{40}H_{37}N_2O_{13}$ [M^++H] 753.2296, found 753.2288.

1,13-Bis[4′-(5-hydroxy-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (81). A round-bottom flask was charged with compound **76** (150 mg, 1.77 mmol), a catalytic amount of Pd (60 mg, 10% on activated charcoal), and $CHCl_3$ (20 mL). The reaction mixture was stirred vigorously under H_2 atmosphere at balloon pressure and room temperature for 14 h. When TLC indicated complete consumption of the starting material, the charcoal was removed by suction filtration. The pale-yellow filtrate was purified by passing through a short pad of silica gel to furnish the desired product (97 mg, 82%) as a white foam: ^{1}H NMR ($CDCl_3$): δ = 3.70–3.75 (m, 8H), 3.89 (t, J = 4.8 Hz, 4H), 4.19 (t, J = 4.8 Hz, 4H), 6.61 (s, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 9.2 Hz, 4H), 7.50 (dd, J = 8.4, 8.4 Hz, 2H), 7.82 (d, J = 9.2 Hz, 4H), 12.64 ppm (s, 2H); ^{13}C NMR ($CDCl_3$): δ = 67.7, 69.5, 70.7, 70.9, 104.5, 106.8, 110.7, 111.3, 115.0, 123.5, 128.1, 135.1, 156.3, 160.7, 161.9, 164.4, 183.4 ppm; LRMS (ESI) *m/z* 667 [M^++H, 5], 689 [M^++Na, 100]; HRMS (ESI) calcd for $C_{38}H_{35}O_{11}$ [M^++H] 667.2179, found 667.2180.

***trans*-3-(4-Allyloxyphenyl)-2-methyl-1-(2-hydroxyphenyl)propenone (83)**: This compound (2.62 g, 89%) was obtained from 4-allyloxybenzaldehyde (1.62 g, 10 mmol), acetophenone **82** (1.50 g, 10 mmol), and KOH (20 mL) as a yellow solid according to general procedure I: mp: 89–91 °C; ^{1}H NMR ($CDCl_3$): δ = 2.28 (s, 3H), 4.59 (d, J = 5.2 Hz, 2H), 5.32 (dd, J = 1.6, 10.2 Hz, 1H), 5.44 (dd, J = 1.6, 17.4 Hz, 1H), 6.02–6.09 (m, 1H), 6.88 (dd, J = 7.2, 7.2 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 8.8, 2H), 7.48 (dd, J = 7.2, 7.2 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 11.82 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 15.3, 68.8, 114.8, 117.9, 118.3, 118.4, 119.2, 128.2, 131.3, 132.8, 132.8, 133.6, 135.7, 139.1, 158.8, 162.8, 203.8 ppm; LRMS (ESI) *m/z* 295 [M^++H, 100], 317 [M^++Na, 10]; HRMS (ESI) calcd for $C_{19}H_{19}O_3$ [M^++H] 295.1334, found 295.1339.

3-Hydroxy-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (84): Excess H_2O_2 (35%, 6 mL) was added dropwise to a well-stirred solution of chalcone **21** (0.77 g, 2.75 mmol) in excess KOH (3 M solution in 96% EtOH, 20 mL) at 0 °C. The reaction mixture was stirred vigorously at 0 °C for 30 min, and then at room temperature for 30 min. When TLC indicated complete consumption of the starting material, the reaction mixture was acidified to pH 5 with 1 M HCl at ice-bath temperature. The precipitate formed was collected by suction filtration. The obtained solid was washed with *n*-hexane and crystallized from MeOH to afford the desired 3-hydroxyflavone **84** (0.49 g, 61%) as an off-white solid: mp: 156–157 °C; ^{1}H NMR ($CDCl_3$): δ = 4.61 (d, J = 5.2 Hz, 2H), 5.32 (dd, J = 1.2, 10.2 Hz, 1H), 5.47 (dd, J = 1.6, 17.4 Hz, 1H), 6.04–6.11 (m, 1H), 7.04 (br, 1H), 7.05 (d, J = 9.2 Hz, 2H), 7.39 (dd, J = 7.6, 7.6 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.67 (ddd, J = 1.6, 8.4, 8.4 Hz, 1H), 8.22 (d, J = 8.8 Hz, 2H), 8.24 ppm (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 68.8, 114.8, 118.0, 118.1, 120.7, 123.6, 124.3, 125.3, 129.5, 132.7, 133.3, 137.6, 145.3, 155.2, 160.0, 173.1 ppm; LRMS (ESI) *m/z* 295 [M^++H, 100], 317 [M^++Na, 22]; HRMS (ESI) calcd for $C_{18}H_{15}O_4$ [M^++H] 295.0970, found 295.0981.

3-Methyl-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (85): This compound (0.41 g, 69%) was obtained from chalcone **83** (0.60 g, 2.0 mmol) and I_2 (cat, 20 mg) as a pale-yellow solid according to general procedure II: mp: 101–102 °C; ^{1}H NMR ($CDCl_3$): δ = 2.17 (s, 3H), 4.60 (d, J = 5.2 Hz, 2H), 5.31 (dd, J = 0.8, 10.4 Hz, 1H), 5.44 (dd, J = 1.2, 17.4 Hz, 1H), 6.01–6.09 (m, 1H), 7.02 (d, J = 8.8 Hz, 2H), 7.35 (dd, J = 7.6, 7.6 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.59 (dd, J = 7.6, 7.6 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 8.22 ppm (dd, J = 1.6, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 11.9, 68.9, 114.5, 116.8, 117.8, 118.0, 122.4, 124.6, 125.8, 125.8, 130.5, 132.7, 133.2, 156.0, 160.0, 161.0, 178.9 ppm; LRMS (ESI) *m/z* 293 [M^++H, 100], 315 [M^++Na, 7]; HRMS (ESI) calcd for $C_{19}H_{17}O_3$ [M^++H] 293.1178, found 293.1182.

3-Methoxy-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (86): A round-bottom flask was charged with flavone **84** (0.17 g, 0.58 mmol), Me_2SO_4 (0.10 g, 0.79 mmol), K_2CO_3 (0.16 g), and acetone (20 mL). The reaction mixture was stirred at reflux for 2 h. When TLC indicated complete consumption of **84**, the reaction mixture was poured into a separating funnel containing H_2O. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give a crude mixture. Purification of the crude mixture by passing through a short pad of silica gel furnished the desired product (0.15 g, 84%) as a white solid: mp: 82–83 °C; ^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3H), 4.62 (d, J = 5.2 Hz, 2H), 5.32 (dd, J = 1.2, 10.2 Hz, 1H), 5.47 (dd, J = 1.6, 17.4 Hz, 1H), 6.04–6.11 (m, 1H), 7.03 (d, J = 8.8 Hz, 2H), 7.39 (dd, J = 7.6, 7.6 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.64 (dd, J = 1.6, 8.4 Hz, 1H), 8.10 (d, J = 9.2 Hz, 2H), 8.25 ppm (d, J = 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 59.9, 68.8, 114.7, 117.8, 118.1, 123.3, 124.2, 124.5, 125.7, 130.2, 132.6, 133.2, 140.8, 155.1, 155.5, 160.5, 174.9 ppm; LRMS (ESI) *m/z* 309 [M^++H, 100], 331 [M^++Na, 71]; HRMS (ESI) calcd for $C_{19}H_{17}O_4$ [M^++H] 309.1127, found 309.1137.

3-Benzyloxy-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (87): A round-bottom flask was charged with flavone **84** (0.15 g, 0.51 mmol), benzyl bromide (0.11 g, 0.64 mmol), K_2CO_3 (0.14 g), and DMF (10 mL). The reaction mixture was stirred at reflux for 1 h. When TLC indicated complete consumption of **84**, the reaction mixture was poured into a separating funnel containing H_2O. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give a crude mixture which was subjected to crystallization from MeOH to afford the desired flavone (0.13 g, 66%) as a white solid: mp: 102–103 °C; ^{1}H NMR ($CDCl_3$): δ = 4.62 (d, J = 5.2 Hz, 2H), 5.12 (s, 2H), 5.34 (dd, J = 1.2, 10.2 Hz, 1H), 5.47 (dd, J = 1.6, 17.4 Hz, 1H), 6.06–6.10 (m, 1H), 6.98 (d, J = 8.8 Hz, 2H), 7.26–7.28 (m, 3H), 7.36–7.88 (m, 2H), 7.39 (dd, J = 8.4, 8.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.66 (ddd, J = 1.6, 8.4, 8.4 Hz, 1H), 8.03 (d, J = 9.2 Hz, 2H), 8.29 ppm (d, J = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 68.8, 73.9, 114.4, 117.9, 118.1, 123.4, 124.2, 124.6, 125.7, 128.0, 128.2, 128.8, 130.5, 132.7, 133.2, 136.7, 139.3, 155.2, 156.3, 160.4, 174.9 ppm; LRMS (ESI) *m/z* 385 [M^++H, 100], 407 [M^++Na, 67]; HRMS (ESI) calcd for $C_{25}H_{21}O_4$ [M^++H] 385.1440, found 385.1454.

1,13-Bis[4′-{(3-methoxy)-4*H*-chromen-4-on-2-yl}phenyl]-1,4,7,10,13-pentaoxatridecane (88). For step (a), 3-methoxy-4′-hydroxyflavone (90 mg, 86%) was obtained from allyl-protected flavone **86** (120 mg, 0.39 mmol), K_2CO_3 (220 mg), and a catalytic amount of [$Pd(PPh_3)_4$] (15 mg) according to general procedure III(a). For step (b), the title compound **88** (39 mg, 49%) was obtained from 3-methoxy-4′-hydroxyflavone (60 mg, 0.22 mmol), tetra(ethylene glycol) dimesylate (40 mg, 0.11 mmol), and K_2CO_3 (50 mg) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 3.71–3.78 (m, 8H), 3.87 (s, 6H), 3.91 (t, J = 4.8 Hz, 4H), 4.21 (t, J = 4.4 Hz, 4H), 7.03 (d, J = 9.2 Hz, 4H), 7.39 (dd, J = 7.2, 7.2 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.65 (dd, J = 8.4, 8.4 Hz, 2H), 8.09 (d, J = 9.2 Hz, 4H), 8.24 ppm (d, J = 9.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 59.9, 67.5, 69.6, 70.7, 70.9, 114.6, 117.8, 123.4, 124.2, 124.6, 125.7, 130.2, 133.3, 140.8, 155.1, 155.5, 160.7, 175.0 ppm; LRMS (ESI) *m/z* 695 [M^++H, 34], 717 [M^++Na, 72]; HRMS (ESI) calcd for $C_{40}H_{39}O_{11}$ [M^++H] 695.2492, found 695.2480.

1,13-Bis[4′-(3-benzyloxy-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (89). For step (a), 3-benzyloxy-4′-hydroxyflavone (0.18 g, 91%) was obtained from allyl-protected flavone **87** (0.22 g, 0.57 mmol), K_2CO_3 (0.32 g), and a catalytic amount of [$Pd(PPh_3)_4$] (15 mg) according to general procedure III(a). For step (b), the title compound **89** (90 mg, 41%) was obtained from 3-benzyloxy-4′-hydroxyflavone (170 mg, 0.49 mmol), tetra(ethylene glycol) dimesylate (90 mg, 0.26 mmol), and K_2CO_3 (100 mg) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 3.72–3.77 (m, 8H), 3.90 (t, J = 4.8 Hz, 4H), 4.19 (t, J = 4.4 Hz, 4H), 5.10 (s, 4H), 6.96 (d, J = 8.8 Hz, 4H), 7.25–7.27 (m, 6H), 7.35–7.38 (m, 6H), 7.48 (d, J = 8.4 Hz, 2H), 7.63 (dd, J = 8.4, 8.4 Hz, 2H), 8.01 (d, J = 8.8 Hz, 4H), 8.26 ppm (d, J = 9.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 67.5, 69.6, 70.7, 70.9, 73.9, 114.3, 117.8, 123.5, 124.1, 124.5, 125.7, 128.0, 128.2, 128.8, 130.5, 133.2, 136.7, 139.2, 155.1, 156.2, 160.6, 174.9 ppm; LRMS (ESI) *m/z* 847 [M^++H, 38], 869 [M^++Na, 100]; HRMS (ESI) calcd for $C_{52}H_{47}O_{11}$ [M^++H] 847.3118, found 847.3146.

1,13-Bis[4′-(3-hydroxy-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (90). A round-bottom flask was charged with compound **89** (50 mg, 0.06 mmol), a catalytic amount of Pd (40 mg, 10% on activated charcoal), and $CHCl_3$ (20 mL). The reaction mixture was stirred vigorously under H_2 atmosphere at balloon pressure and room temperature for 14 h. When TLC indicated complete consumption of the starting material, the charcoal was removed by suction filtration. The pale-yellow filtrate was purified by passing through a short pad of silica gel to furnish the debenzylated product (31 mg, 79%) as a white foam: ^{1}H NMR ($CDCl_3$): δ = 3.67–3.77 (m, 8H), 3.90 (t, J = 4.8 Hz, 4H), 4.18 (t, J = 4.4 Hz, 4H), 7.00 (s, 2H), 7.02 (d, J = 8.8 Hz, 4H), 7.36 (dd, J = 7.6, 7.6 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.65 (dd, J = 7.6, 7.6 Hz, 2H), 8.15–8.20 ppm (m, 6H); ^{13}C NMR ($CDCl_3$): δ = 67.5, 69.6, 70.7, 70.8, 114.6, 118.1, 120.6, 123.6, 124.3, 125.3, 129.4, 133.3, 137.6, 145.2, 155.1, 160.2, 173.0 ppm; LRMS (ESI) *m/z* 667 [M^++H, 51], 689 [M^++Na, 87]; HRMS (ESI) calcd for $C_{38}H_{35}O_{11}$ [M^++H] 667.2179, found 667.2161.

1,13-Bis[4′-(3-methyl-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (91). For step (a), 3-methyl-4′-hydroxyflavone (0.18 g, 69%) was obtained from allyl-protected flavone **85** (0.30 g, 1.0 mmol), K_2CO_3 (0.57 g), and a catalytic amount of [$Pd(PPh_3)_4$] (25 mg) according to general procedure III(a). For step (b), the title compound **91** (78 mg, 46%) was obtained from 3-methyl-4′-hydroxyflavone (120 mg, 0.48 mmol), tetra(ethylene glycol) dimesylate (90 mg, 0.26 mmol), and K_2CO_3 (100 mg) as a white foam according to general procedure III(b): ^{1}H NMR ($CDCl_3$): δ = 2.11 (s, 6H), 3.66–3.72 (m, 8H), 3.85 (t, J = 4.8 Hz, 4H), 4.15 (t, J = 4.4 Hz, 4H), 6.97 (d, J = 8.8 Hz, 4H), 7.28 (dd, J = 7.6, 7.6 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.52 (dd, J = 7.6, 7.6 Hz, 2H), 7.53 (d, J = 8.4 Hz, 4H), 8.15 ppm (dd, J = 1.6, 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 11.9, 67.5, 69.5, 70.6, 70.8, 114.3, 116.7, 117.7, 122.3, 124.5, 125.7, 125.8, 130.5, 133.1, 155.9, 160.2, 160.7, 178.7 ppm; LRMS (ESI) *m/z* 663 [M^++H, 100], 685 [M^++Na, 16]; HRMS (ESI) calcd for $C_{40}H_{39}O_9$ [M^++H] 663.2594, found 663.2582.

1,13-Bis[4′-(5,7-dihydroxy-6,8-dibromo-4*H*-chromen-4-on-2-yl)-phenyl]-1,4,7,10,13-pentaoxatridecane (95). Excess Br_2 (0.5 mL) was added dropwise to a well-stirred solution of compound **92** (41 mg, 0.06 mmol) in CH_2Cl_2 (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 48 h. When TLC indicated complete consumption of starting material, the reaction mixture was diluted with CH_2Cl_2, washed with 0.1% $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and evaporated to give the desired product (53 mg, 89%) as a pale-yellow solid: mp: 204–206 °C; ^{1}H NMR ([D_6]DMSO): δ = 3.55–3.59 (m, 8H), 3.76 (t, J = 4.8 Hz, 4H), 4.09 (t, J = 4.8 Hz, 4H), 6.93 (s, 2H), 7.02 (d, J = 8.8 Hz, 4H), 7.93 (d, J = 9.2 Hz, 4H), 13.77 ppm (s, 2H); ^{13}C NMR ([D_6]DMSO): δ = 68.0, 69.2, 70.3, 70.4, 88.6, 103.6, 105.1, 115.4, 122.5, 128.7, 152.3, 157.4, 162.3, 163.8, 181.6 ppm; LRMS and HRMS data were not obtained owing to the poor solubility of this compound in common organic solvents.

1,13-Bis[4′-(5,7-diacetyloxy-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (96). Excess Ac_2O (0.5 mL) was added dropwise to well-stirred solution of compound **92** (32 mg, 0.05 mmol) in pyridine (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 24 h. When TLC indicated complete consumption of starting material, the reaction mixture was poured into a separating funnel containing 1 M HCl. The mixture was continuously extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give a crude reaction mixture. Purification of the flavone dimer was performed by flash column chromatography on silica gel with 5–10% acetone in CH_2Cl_2 as eluent to furnish the desired product (32 mg, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$): δ = 2.33 (s, 6H), 2.42 (s, 6H), 3.68–3.74 (m, 8H), 3.87 (t, J = 4.8 Hz, 4H), 4.16 (t, J = 4.8 Hz, 4H), 6.53 (s, 2H), 6.80 (d, J = 2.0 Hz, 2H), 6.99 (d, J = 8.8 Hz, 4H), 7.29 (d, J = 2.4 Hz, 2H), 7.76 ppm (d, J = 9.2 Hz, 4H); ^{13}C NMR ($CDCl_3$): δ = 21.0, 21.1, 67.6, 69.5, 70.7, 70.9, 107.1, 108.9, 113.4, 114.8, 115.0, 123.3, 127.8, 150.1, 153.7, 157.5, 161.7, 162.4, 168.0, 169.4, 176.3 ppm; LRMS (ESI) *m/z* 867 [M^++H, 80], 889 [M^++Na, 100]; HRMS (ESI) calcd for $C_{46}H_{43}O_{17}$ [M^++H] 867.2500, found 867.2524.

6-(1-imidazolyl)-2-(4′-allyloxyphenyl)-4*H*-chromen-4-one (97): A reaction vessel was charged with CuI (114 mg, 3 mol%), L-lysine (87 mg, 6 mol%), imidazole (2.04 g, 30 mmol), K_3PO_4 (1.26 g, 6.0 mmol) and flavone **45** (1.07 g, 3.0 mmol). The reaction mixture was irradiated by microwave for 3 min to increase the reaction temperature to 140 °C; further irradiation at this temperature was continued for 10 h. When TLC indicated complete consumption of starting material, the reaction mixture was cooled to room temperature and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give a crude reaction mixture which was subjected to flash column chromatography on silica gel with 10–20% acetone in CH_2Cl_2 as eluent to furnish the desired product (0.16 g, 15%) as an off-white solid: mp: 170–171 °C; ^{1}H NMR ($CDCl_3$): δ = 4.64 (d, J = 5.2 Hz, 2H), 5.35 (dd, J = 2.4, 10.2 Hz, 1H), 5.46 (dd, J = 2.0, 17.2 Hz, 1H), 6.02–6.13 (m, 1H), 6.79 (s, 1H), 7.06 (d, J = 9.2 Hz, 2H), 7.28 (s, 1H), 7.41 (s, 1H), 7.69–7.75 (m, 2H), 7.92 (d, J = 9.0 Hz, 2H), 7.98 (s, 1H), 8.23 ppm (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 69.0, 106.0, 115.3, 117.4, 118.3, 120.0, 123.6, 124.9, 126.4, 128.1, 130.9, 132.4, 134.4, 154.7, 161.7, 163.9, 177.3 ppm; LRMS *m/z* 345 [M^++H, 78]; HRMS calcd for $C_{21}H_{17}N_2O_3$ [M^++H] 345.1239, found 345.1232.

6-Phenyl-2-(4′-hydroxyphenyl)-4*H*-chromen-4-one (100): Bromoflavone **98** was prepared according to general procedure III(a) from compound **45**. A reaction vessel was charged with [$Pd(PPh_3)_4$] (55 mg, 5 mol%), phenylboronic acid (226 mg, 1.89 mmol), Cs_2CO_3 (0.62 g), flavone **98** (300 mg, 0.95 mmol), and H_2O (2 mL). The reaction mixture was irradiated by microwave for 3 min to increase the temperature to 85 °C; further irradiation was continued at this temperature for 6 h. When TLC indicated complete consumption of starting material, the reaction mixture was cooled to room temperature and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give a crude reaction mixture which was recrystallized from acetone to furnish the desired compound (145 mg, 49%) as a yellow solid: mp: 278–280 °C; ^{1}H NMR ([D_6]DMSO): δ = 6.92 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 7.42

(dd, J=7.2, 7.2 Hz, 1H), 7.51 (d, J=7.6, Hz, 1H), 7.52 (d, J=7.6, Hz, 1H), 7.76 (d, J=7.6 Hz, 2H), 7.85 (d, J=8.8, 1H), 7.98 (d, J=8.4 Hz, 2H), 8.13 (dd, J=2.0, 7.6 Hz, 1H), 8.23 (d, J=2.0 Hz, 1H), 10.36 ppm (br, 1H); ^{13}C NMR (DMSO): δ=105.2, 116.4, 119.6, 121.9, 122.4, 124.0, 127.2, 128.3, 128.8, 129.6, 132.8, 137.6, 139.0, 155.5, 161.5, 163.5, 177.2 ppm; LRMS m/z 315 [M^++H, 68]; HRMS calcd for $C_{21}H_{15}O_3$ [M^++H] 315.1021, found 315.1033.

1,13-Bis[4′-{6-(1-imidazolyl)-4*H*-chromen-4-on-2-yl}phenyl]-1,4,7,10,13-pentaoxatridecane (101). 4′-hydroxyflavone **99** (65 mg, 72%) was obtained from flavone **97** (100 mg, 0.29 mmol), [Pd(PPh$_3$)$_4$] (7 mg), and K_2CO_3 (161 mg) according to general procedure III(a). The title compound **101** (48 mg, 60%) was obtained from 4′-hydroxyflavone **99** (65 mg, 0.21 mmol), tetra(ethylene glycol) dimesylate (37 mg, 0.11 mmol), and K_2CO_3 (65 mg) as a pale-yellow solid according to general procedure III(b): mp: 107–108 °C; ^{1}H NMR ($CDCl_3$): δ=3.66–3.75 (m, 8H), 3.88 (t, J=4.8 Hz, 4H), 4.15 (t, J=4.8 Hz, 4H), 6.67 (s, 2H), 6.98 (d, J=8.8 Hz, 4H), 7.20 (s, 2H), 7.32 (s, 2H), 7.60 (d, J=9.2 Hz, 2H), 7.66 (dd, J=2.8, 8.8 Hz, 2H), 7.79 (d, J=8.8 Hz, 4H), 7.92 (d, J=8.0 Hz, 2H), 8.08 ppm (d, J=2.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=67.7, 69.5, 70.6, 73.4, 105.8, 115.1, 117.1, 118.1, 119.9, 123.4, 124.7, 126.3, 127.9, 130.8, 134.3, 135.5, 154.5, 161.9, 163.6, 177.2 ppm; LRMS m/z 767 [M^++H, 59]; HRMS calcd for $C_{44}H_{38}N_4O_9$ [M^++H] 767.2717, found 767.2755.

1,13-Bis[4′-(6-phenyl-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (102). This compound was obtained from 4′-hydroxyflavone **100** (100 mg, 0.32 mmol), tetra(ethylene glycol) dimesylate (55 mg, 0.16 mmol), and K_2CO_3 (90 mg) as a pale-yellow crystal (75 mg, 60%) according to the general procedure III(b) as described above: mp: 122–123 °C; ^{1}H NMR ($CDCl_3$): δ=3.67–3.77 (m, 8H), 3.91 (t, J=4.8 Hz, 4H), 4.19 (t, J=4.8 Hz, 4H), 6.78 (s, 2H), 7.02 (d, J=8.8 Hz, 4H), 7.38 (d, J=7.2 Hz, 2H), 7.43 (dd, J=7.2, 7.2 Hz, 2H), 7.79 (d, J=8.8 Hz, 4H), 7.92 (d, J=8.0 Hz, 2H), 8.08 ppm (d, J=2.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=67.7, 69.5, 70.7, 70.8, 106.0, 115.0, 118.4, 123.4, 123.8, 124.0, 127.1, 127.7, 128.0, 128.9, 132.4, 138.2, 139.2, 155.5, 161.7, 163.4, 178.3 ppm; LRMS (ESI) m/z 787 [M^++H, 58]; HRMS calcd for $C_{50}H_{43}O_9$ [M^++H] 787.2907, found 787.2897.

1,13-Bis[2′-(4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (103). The title compound **103** was obtained from 2′-hydroxyflavone (0.24 g, 1.0 mmol), tetra(ethylene glycol) dimesylate (0.18 g, 0.5 mmol), and K_2CO_3 (0.20 g) as a white solid (0.18 g, 55%) according to general procedure III(b): mp: 69–71 °C; ^{1}H NMR ($CDCl_3$): δ=3.68 (s, 4H), 3.69 (s, 4H), 3.88 (t, J=4.8 Hz, 4H), 4.21 (t, J=4.8 Hz, 4H), 7.00 (d, J=8.4 Hz, 2H), 7.07 (dd, J=7.6, 7.5 Hz, 2H), 7.14 (s, 2H), 7.35–7.43 (m, 4H), 7.50 (d, J=8.4 Hz, 2H), 7.65 (dd, J=7.9, 7.4 Hz, 2H), 7.85 (d, J=7.7 Hz, 2H), 8.19 ppm (d, J=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=68.2, 69.4, 70.6, 70.9, 112.3, 112.7, 112.9, 118.0, 120.9, 121.1, 123.8, 124.8, 125.5, 125.5, 129.2, 132.3, 133.5, 156.4, 157.1, 160.9, 178.7 ppm; LRMS (ESI) m/z 635 [M^++H, 100]; HRMS (ESI) calcd for $C_{38}H_{35}O_9$ [M^++H] 635.2281, found 635.2275.

1,13-Bis[3′-(4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (104). The title compound **104** was obtained from 3′-hydroxyflavone (0.48 g, 2.0 mmol), tetra(ethylene glycol) dimesylate (0.35 g, 1.0 mmol), and K_2CO_3 (0.35 g) as a white solid (0.33 g, 52%) according to general procedure III(b): mp: 89–91 °C; ^{1}H NMR ($CDCl_3$): δ=3.69–3.73 (m, 8H), 3.86 (t, J=4.3 Hz, 4H), 4.14 (t, J=4.4 Hz, 4H), 6.72 (s, 2H), 7.00 (d, J=7.5 Hz, 2H), 7.28–7.47 (m, 8H), 7.48 (d, J=8.4 Hz, 2H), 7.62 (dd, J=8.0, 7.4 Hz, 2H), 8.14 ppm (d, J=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=67.6, 69.6, 70.6, 70.8, 107.6, 107.6, 112.5, 117.6, 118.0, 118.7, 123.8, 125.1, 125.5, 130.0, 132.9, 133.7, 156.1, 159.1, 163.0, 178.3 ppm; LRMS (ESI) m/z 635 [M^++H, 100]; HRMS (ESI) calcd for $C_{38}H_{35}O_9$ [M^++H] 635.2281, found 635.2279.

1-[4′-(4*H*-chromen-4-on-2-yl)phenyl]-13-hydroxy-1,4,7,10,13-pentaoxatridecane (105). 4′-hydroxyflavone was prepared from compound **41** as general procedure III(a). A round-bottom flask was charged with 4′-hydroxyflavone (0.80 g, 3.36 mmol, 1 equiv), tetra(ethylene glycol) dimesylate (1.18 g, 3.37 mmol, 1 equiv), K_2CO_3 (0.93 g), and DMF (20 mL). The reaction mixture was stirred at reflux for 4 h. During heating, the reaction mixture slowly turned from deep brown to a milky color. When TLC indicated complete consumption of starting material, the reaction mixture was poured into a separating funnel containing H_2O. The mixture was continuously extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give a brown crude reaction mixture of flavonoid dimer **61** and monomer **105**. The integration of proton signal at 6.7 ppm indicated the ratio of compound **61** to **105** is about 1.5:1. Flash column chromatography on silica gel with 10–20% acetone in CH_2Cl_2 as eluent furnished compound **61** first, and then the desired product **105** (0.40 g, 29%) as a pale-brown oil: ^{1}H NMR ($CDCl_3$): δ=2.97 (br, 1H), 3.56 (t, J=4.8 Hz, 4H), 3.62–3.70 (m, 10H), 3.83 (t, J=4.8 Hz, 2H), 4.15 (t, J=4.8 Hz, 2H), 6.67 (s, 1H), 6.97 (d, J=8.8 Hz, 2H), 7.34 (dd, J=7.2, 7.2 Hz, 1H), 7.47 (d, J=8.4 Hz, 1H), 7.61 (dd, J=7.2, 7.2 Hz, 1H), 7.79 (d, J=9.2 Hz, 2H), 8.14 ppm (dd, J=1.2, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=61.5, 67.4, 69.3, 70.1, 70.3, 70.4, 70.6, 72.4, 105.9, 114.8, 117.8, 123.6, 123.8, 124.9, 125.4, 127.8, 133.4, 155.9, 161.4, 163.2, 178.2 ppm; LRMS (ESI) m/z 415 [M^++H, 46], 437 [M^++Na, 100]; HRMS (ESI) calcd for $C_{23}H_{27}O_7$ [M^++H] 415.1757, found 415.1772.

1-[4′-(4*H*-chromen-4-on-2-yl)phenyl]-13-methanesulfonyl-1,4,7,10,13-pentaoxatridecane (106). A round-bottom flask was charged with flavone **105** (0.21 g, 0.51 mmol), triethylamine (3 mL), and CH_2Cl_2 (10 mL) at 0 °C. Excess methanesulfonyl chloride (1.0 mL, 8.77 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min, and then at room temperature for 2 h. During addition, the reaction mixture turned milky. When TLC indicated complete consumption of starting material, the reaction mixture was filtered through a short pad of silica gel to remove ammonium salt. The pale-brown filtrate was washed with 0.1% $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give a crude brown oil (0.25 g, 100%), which was pure enough for the next step.

1-[4′-(4*H*-chromen-4-on-2-yl)phenyl]-13-[4′-(5-benzyloxy-7-methoxymethylphenyl-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (110). Substituted 4′-hydroxyflavone **107** was prepared as previously reported.[60] A round-bottom flask was charged with flavone **107** (0.18 g, 0.45 mmol), mesylate **106** (0.23 g, 0.47 mmol), K_2CO_3 (0.13 g), and DMF (10 mL). The reaction mixture was stirred at reflux for 3 h. During heating, the reaction mixture slowly turned from deep brown to a milky color. When TLC indicated complete consumption of starting material, the reaction mixture was poured into a separating funnel containing H_2O. The mixture was continuously extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give a crude reaction mixture. Purification of the flavone dimer was performed by flash column chromatography on silica gel with 10–20% acetone in CH_2Cl_2 as eluent to furnish the desired product (0.21 g, 59%) as a pale-brown oil: ^{1}H NMR ($CDCl_3$): δ=3.47 (s, 3H), 3.68–3.74 (m, 8H), 3.86 (t, J=4.8 Hz, 4H), 4.15 (t, J=4.8 Hz, 4H), 5.20 (s, 4H), 6.46 (d, J=2.0 Hz, 1H), 6.55 (s, 1H), 6.69 (s, 1H), 6.71 (d, J=2.0 Hz, 1H), 6.96 (d, J=8.0 Hz, 2H), 6.98 (d, J=8.4 Hz, 2H), 7.28 (d, J=7.6 Hz, 1H), 7.34–7.40 (m, 3H), 7.48 (d, J=8.4 Hz,

1H), 7.60–7.62 (m, 3H), 7.75 (d, J=9.2 Hz, 2H), 7.81 (d, J=8.8 Hz, 2H), 8.16 ppm (d, J=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=56.3, 67.5, 69.5, 70.6, 70.8, 94.2, 95.9, 98.6, 106.0, 107.4, 110.0, 114.8, 114.9, 117.9, 123.7, 123.9, 124.9, 125.4, 126.5, 127.5, 127.8, 128.5, 133.5, 136.3, 156.0, 159.3, 159.5, 160.6, 161.2, 161.5, 163.2, 177.3, 178.2 ppm; LRMS (ESI) m/z 801 [M^++H, 45], 823 [M^++Na, 61]; HRMS (ESI) calcd for $C_{47}H_{45}O_{12}$ [M^++H] 801.2911, found 801.2915.

1-[4′-(4*H*-chromen-4-on-2-yl)phenyl]-13-[4′-(5-hydroxy-7-methoxymethylphenyl-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (111). A round-bottom flask was charged with compound **110** (150 mg, 0.19 mmol), a catalytic amount of Pd (25 mg, 10% on activated charcoal), and $CHCl_3$ (20 mL). The reaction mixture was stirred vigorously under H_2 atmosphere at balloon pressure and room temperature for 14 h. When TLC indicated complete consumption of the starting material, the charcoal was removed by suction filtration. The pale-yellow filtrate was purified by passing through a short pad of silica gel to furnish the deprotected product (110 mg, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$): δ=3.48 (s, 3H), 3.69–3.74 (m, 8H), 3.87 (t, J=4.8 Hz, 4H), 4.15 (t, J=4.8 Hz, 4H), 5.20 (s, 2H), 6.40 (d, J=2.0 Hz, 1H), 6.50 (s, 1H), 6.59 (d, J=2.4 Hz, 1H), 6.69 (s, 1H), 6.96 (d, J=8.0 Hz, 2H), 6.98 (d, J=8.4 Hz, 2H), 7.36 (dd, J=7.6, 7.6 Hz, 1H), 7.50 (d, J=7.6 Hz, 1H), 7.69 (dd, J=7.6, 7.6 Hz, 1H), 7.43 (d, J=8.8 Hz, 2H), 7.80 (d, J=8.8 Hz, 1H), 8.16 (d, J=7.6 Hz, 1H), 12.71 ppm (br, 1H); ^{13}C NMR ($CDCl_3$): δ=56.3, 67.6, 69.4, 70.6, 70.8, 94.1, 94.2, 99.9, 104.1, 105.9, 106.0, 114.9, 117.8, 123.3, 123.7, 123.9, 125.0, 125.5, 127.8, 127.9, 128.1, 133.5, 156.0, 157.3, 161.5, 161.7, 161.8, 162.8, 163.2, 163.8, 178.2, 182.3 ppm; LRMS (ESI) m/z 711 [M^++H, 52], 733 [M^++Na, 60]; HRMS (ESI) calcd for $C_{40}H_{39}O_{12}$ [M^++H] 711.2442, found 711.2452.

1-[4′-(4*H*-chromen-4-on-2-yl)phenyl]-13-[4′-(5,7-dihydroxyphenyl-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (112). A round-bottom flask was charged with compound **111** (90 mg, 0.13 mmol), 6 M HCl (10 mL), and THF (10 mL). The reaction mixture was stirred at room temperature for 1 h. When TLC indicated complete consumption of **111**, the reaction mixture was poured into a separating funnel containing H_2O. The mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give a crude mixture. Purification of the crude mixture by passing through a short pad of silica gel furnished the desired product (62 mg, 73%) as a pale-yellow oil: ^{1}H NMR ($CDCl_3$): δ=3.69–3.74 (m, 8H), 3.83 (t, J=4.8 Hz, 4H), 4.01 (t, J=4.8 Hz, 2H), 4.06 (t, J=4.8 Hz, 2H), 6.17 (d, J=1.6 Hz, 1H), 6.28 (d, J=2.0 Hz, 1H), 6.30 (s, 1H), 6.64 (s, 1H), 6.68 (d, J=8.8 Hz, 2H), 6.86 (d, J=9.2 Hz, 2H), 7.35 (dd, J=7.6, 7.6 Hz, 1H), 7.43 (d, J=7.6 Hz, 1H), 7.46 (d, J=8.8 Hz, 2H), 7.63 (ddd, J=1.6, 7.6, 7.6 Hz, 1H), 7.70 (d, J=8.8 Hz, 2H), 8.12 ppm (dd, J=1.6, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=67.4, 67.5, 69.5, 69.5, 70.6, 94.2, 99.7, 103.4, 104.5, 105.5, 114.5, 114.8, 117.9, 122.9, 123.4, 123.5, 125.1, 125.4, 127.3, 127.8, 133.7, 156.0, 157.3, 161.3, 161.6, 161.7, 163.2, 163.6, 178.6, 182.0 ppm; LRMS (ESI) m/z 667 [M^++H, 88], 689 [M^++Na, 44]; HRMS (ESI) calcd for $C_{38}H_{35}O_{11}$ [M^++H] 667.2179, found 667.2167.

1-[4′-(4*H*-chromen-4-on-2-yl)phenyl]-13-[4′-(7-methylphenyl-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (113). Substituted 4′-hydroxyflavone **108** was prepared according to general procedure III(a) from compound **48**. A round-bottom flask was charged with flavone **108** (58 mg, 0.23 mmol), mesylate **106** (110 mg, 0.22 mmol), K_2CO_3 (70 mg), and DMF (10 mL). The reaction mixture was stirred at reflux for 3 h. When TLC indicated complete consumption of starting material, the reaction mixture was poured into a separating funnel containing H_2O. The mixture was continuously extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give a crude reaction mixture. Purification of the flavone dimer was performed by flash column chromatography on silica gel with 10–20% acetone in CH_2Cl_2 as eluent to furnish the desired product (55 mg, 38%) as a colorless oil: ^{1}H NMR ($CDCl_3$): δ=2.48 (s, 3H), 3.64–3.76 (m, 8H), 3.87 (t, J=4.8 Hz, 4H), 4.18 (t, J=4.8 Hz, 4H), 6.68 (s, 1H), 6.71 (s, 1H), 7.01 (d, J=8.8 Hz, 2H), 7.02 (d, J=8.8 Hz, 2H), 7.24 (d, J=7.6 Hz, 1H), 7.31 (s, 1H), 7.38 (dd, J=7.6, 7.6 Hz, 1H), 7.51 (d, J=8.0 Hz, 1H), 7.66 (dd, J=7.6, 7.6 Hz, 1H), 7.81 (d, J=8.8 Hz, 2H), 7.84 (d, J=8.8 Hz, 2H), 8.06 (d, J=8.0 Hz, 1H), 8.19 ppm (d, J=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=21.8, 67.6, 69.5, 70.7, 70.9, 106.1, 106.1, 115.0, 115.0, 117.7, 117.9, 121.6, 123.8, 124.1, 124.2, 125.0, 125.3, 125.6, 126.5, 127.8, 127.9, 133.5, 144.8, 156.1, 156.2, 161.5, 161.6, 163.0, 163.2, 178.3, 178.3 ppm; LRMS (ESI) m/z 649 [M^++H, 6], 671 [M^++Na, 100]; HRMS (ESI) calcd for $C_{39}H_{37}O_9$ [M^++H] 649.2438, found 649.2419.

1-[4′-(4*H*-chromen-4-on-2-yl)phenyl]-13-[4′-(7-benzyloxyphenyl-4*H*-chromen-4-on-2-yl)phenyl]-1,4,7,10,13-pentaoxatridecane (114). Substituted 4′-hydroxyflavone **109** was prepared according to general procedure III(a) from compound **54**. A round-bottom flask was charged with flavone **109** (51 mg, 0.15 mmol), mesylate **106** (72 mg, 0.15 mmol), K_2CO_3 (50 mg), and DMF (10 mL). The reaction mixture was stirred at reflux for 3 h. When TLC indicated complete consumption of starting material, the reaction mixture was poured into a separating funnel containing H_2O. The mixture was continuously extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give a crude reaction mixture. Purification of the flavone dimer was performed by flash column chromatography on silica gel with 10–20% acetone in CH_2Cl_2 as eluent to furnish the desired product (48 mg, 44%) as a colorless oil: ^{1}H NMR ($CDCl_3$): δ=3.68–3.75 (m, 8H), 3.87 (t, J=4.8 Hz, 4H), 4.13–4.17 (m, 4H), 5.13 (s, 2H), 6.62 (s, 1H), 6.68 (s, 1H), 6.95–6.99 (m, 6H), 7.34–7.48 (m, 7H), 7.61 (dd, J=7.6, 7.6 Hz, 1H), 7.76 (d, J=8.8 Hz, 2H), 7.80 (d, J=8.8 Hz, 2H), 8.07 (d, J=8.4 Hz, 1H), 8.24 ppm (d, J=7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=67.6, 69.5, 70.4, 70.7, 70.8, 101.4, 106.0, 106.0, 114.6, 114.9, 115.0, 117.9, 123.8, 124.0, 124.1, 125.0, 125.5, 126.9, 127.5, 127.7, 127.9, 128.3, 128.7, 133.5, 135.7, 156.0, 157.7, 161.4, 161.6, 162.8, 163.0, 163.2, 177.6, 178.2 ppm; LRMS (ESI) m/z 741 [M^++H, 11], 763 [M^++Na, 100]; HRMS (ESI) calcd for $C_{45}H_{41}O_{10}$ [M^++H] 741.2700, found 741.2684;

Biology

Materials for biological studies: DMSO, VP ($C_{27}H_{38}N_2O_4$), DOX ($C_{27}H_{29}NO_{11}$), vinblastine ($C_{46}H_{58}N_4O_9$), and paclitaxel ($C_{47}H_{51}NO_{14}$) were purchased from Sigma–Aldrich. Dulbecco's modified Eagle's medium (DMEM), RPMI 1640, trypsin-EDTA, and penicillin/streptomycin were obtained from Gibco BRL. Fetal bovine serum (FBS) was purchased from HyClone Laboratories. MTS and phenazine methosulfate (PMS) were purchased from Promega. Both human breast cancer cell lines MDA435/LCC6 and MDA435/LCC6MDR were kindly provided by Dr. Robert Clarke (Georgetown University, Washington DC, USA).

Cell culture: MDA435/LCC6 is an estrogen-independent human breast cancer cell line. MDA435/LCC6MDR was generated by transducing a retroviral vector containing human MDR1 cDNA.[68] MDA435/LCC6 (both wild-type and MDR subtype) cells were maintained in DMEM supplemented with 10% FBS as previously described.[60] Cells were cultured at 37 °C in a humidified atmosphere

with 5% CO_2. A solution of 0.05% trypsin-EDTA was used to detach the MDA435/LCC6 (both wild-type and MDR subtype) cells.

Cell proliferation assay: The cytotoxicity of MDA435/LCC6MDR and MDA435/LCC6 cells was measured as described previously.[60]

Doxorubicin accumulation: A volume of 2.5 mL (10^5 cells mL^{-1}) MDA435/LCC6 (both wild-type and MDR subtype) cells were seeded in each well of 6-well plates. At confluence, the culture medium was removed. Fresh DMEM (2 mL) with modulators was added, and cells were incubated for 30 min at 37 °C. DOX (final concentration: 20 μM) was then added and incubated for 2 h at 37 °C. The cells were then harvested by trypsin-mediated detachment, and cell pellets were washed with cold phosphate-buffered saline (PBS, 3×) with an Eppendorf microcentrifuge. Cells were lysed with 0.3 M HCl in 50% EtOH, and sonicated using a Sonics Vibracell 130 sonicator at 50% maximum intensity for one cycle of 30 s. After centrifugation at 10000 rpm for 3 min, the supernatant was saved. The fluorescence of DOX was measured using a spectrofluorimeter (λ_{ex} = 470 nm, λ_{em} = 585 nm).

For flow cytometry experiments, cells were incubated at 37 °C for 15 min after adding flavonoid dimers. DOX was added to each tube at a final concentration of 10 μM, and the cells were incubated for 90 min at 37 °C. The cells were pelleted at 13000 rpm for 8 s using an Eppendorf microcentrifuge (model 5415C), and the supernatant was discarded. Ice-cold PBS (0.5 mL) was added to re-suspend the cells, and the cells were loaded into a BD Biosciences FACSAria flow cytometer. Fluorescence of DOX was measured using the PE channel (λ = 585 nm).

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[1] U. A. Germann, *Eur. J. Cancer* **1996**, *32*, 927–944.
[2] G. Szakacs, J. K. Paterson, J. A. Ludwig, C. Booth-Genthe, M. M. Gottesman, *Nat. Rev. Drug Discovery* **2006**, *5*, 219–234.
[3] C. J. Chen, J. E. Chin, K. Ueda, D. P. Clark, I. Pastan, M. M. Gottesman, I. B. Roninson, *Cell* **1986**, *47*, 381–389.
[4] C. Kast, V. Canfield, R. Levenson, P. Gros, *J. Biol. Chem.* **1996**, *271*, 9240–9248.
[5] R. J. Dawson, K. P. Locher, *Nature* **2006**, *443*, 180–185.
[6] M. F. Rosenberg, A. B. Kamis, R. Callaghan, C. F. Higgins, R. C. Ford, *J. Biol. Chem.* **2003**, *278*, 8294–8299.
[7] T. W. Loo, D. M. Clarke, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 3511–3516.
[8] Q. Qu, F. J. Sharom, *Biochemistry* **2001**, *40*, 1413–1422.
[9] C. Vigano, M. Julien, I. Carrier, P. Gros, J. M. Ruysschaert, *J. Biol. Chem.* **2002**, *277*, 5008–5016.
[10] T. Tsuruo, H. Iida, S. Tsukagoshi, Y. Sakurai, *Cancer Res.* **1981**, *41*, 1967–1972.
[11] T. Tsuruo, H. Iida, M. Nojiri, S. Tsukagoshi, Y. Sakurai, *Cancer Res.* **1983**, *43*, 2905–2910.
[12] V. Hollt, M. Kouba, M. Dietel, G. Vogt, *Biochem. Pharmacol.* **1992**, *43*, 2601–2608.
[13] T. Tsuruo, H. Iida, S. Tsukagoshi, Y. Sakurai, *Cancer Res.* **1982**, *42*, 4730–4733.
[14] R. Ganapathi, D. Grabowski, R. Turinic, R. Valenzuela, *Eur. J. Cancer Clin. Oncol.* **1984**, *20*, 799–806.
[15] T. Tsuruo, H. Iida, Y. Kitatani, K. Yokota, S. Tsukagoshi, Y. Sakurai, *Cancer Res.* **1984**, *44*, 4303–4307.
[16] W. T. Beck, M. C. Cirtain, C. J. Glover, R. L. Felsted, A. R. Safa, *Biochem. Biophys. Res. Commun.* **1988**, *153*, 959–966.
[17] L. M. Slater, P. Sweet, M. Stupecky, M. W. Wetzel, S. Gupta, *Br. J. Cancer* **1986**, *54*, 235–238.
[18] L. M. Slater, P. Sweet, M. Stupecky, S. Gupta, *J. Clin. Invest.* **1986**, *77*, 1405–1408.
[19] N. J. Chao, M. Aihara, K. G. Blume, B. I. Sikic, *Exp. Hematol.* **1990**, *18*, 1193–1198.
[20] P. R. Twentyman, N. E. Fox, D. J. White, *Br. J. Cancer* **1987**, *56*, 55–57.
[21] E. Solary, I. Velay, B. Chauffert, J. M. Bidan, D. Caillot, M. Dumas, H. Guy, *Cancer* **1991**, *68*, 1714–1719.
[22] K. Ueda, N. Okamura, M. Hirai, Y. Tanigawara, T. Saeki, N. Kioka, T. Komano, R. Hori, *J. Biol. Chem.* **1992**, *267*, 24248–24252.
[23] K. M. Barnes, B. Dickstein, G. B. Cutler, Jr., T. Fojo, S. E. Bates, *Biochemistry* **1996**, *35*, 4820–4827.
[24] D. J. Gruol, M. C. Zee, J. Trotter, S. Bourgeois, *Cancer Res.* **1994**, *54*, 3088–3091.
[25] R. Pirker, D. J. FitzGerald, M. Raschack, Z. Frank, M. C. Willingham, I. Pastan, *Cancer Res.* **1989**, *49*, 4791–4795.
[26] J. Hofmann, A. Wolf, M. Spitaler, G. Bock, J. Drach, C. Ludescher, H. Grunicke, *J. Cancer Res. Clin. Oncol.* **1992**, *118*, 361–366.
[27] P. R. Twentyman, N. M. Bleehen, *Eur. J. Cancer* **1991**, *27*, 1639–1642.
[28] U. A. Germann, P. J. Ford, D. Shlyakhter, V. S. Mason, M. W. Harding, *Anticancer. Drugs* **1997**, *8*, 141–155.
[29] U. A. Germann, D. Shlyakhter, V. S. Mason, R. E. Zelle, J. P. Duffy, V. Galullo, D. M. Armistead, J. O. Saunders, J. Boger, M. W. Harding, *Anticancer. Drugs* **1997**, *8*, 125–140.
[30] T. Yanagisawa, A. Newman, H. Coley, J. Renshaw, C. R. Pinkerton, K. Pritchard-Jones, *Br. J. Cancer* **1999**, *80*, 1190–1196.
[31] B. L. Lum, M. P. Gosland, *Hematol. Oncol. Clin. North. Am.* **1995**, *9*, 319–336.
[32] H. Thomas, H. M. Coley, *Cancer Control* **2003**, *10*, 159–165.
[33] C. H. Lee, *Curr. Med. Chem. Anti-Cancer Agents* **2004**, *4*, 43–52.
[34] R. Krishna, L. D. Mayer, *Eur. J. Pharm. Sci.* **2000**, *11*, 265–283.
[35] M. Hadjeri, M. Barbier, X. Ronot, A. M. Mariotte, A. Boumendjel, J. Boutonnat, *J. Med. Chem.* **2003**, *46*, 2125–2131.
[36] J. B. Harborne, *Prog. Clin. Biol. Res.* **1986**, *213*, 15–24.
[37] E. Middleton, Jr., C. Kandaswami, T. C. Theoharides, *Pharmacol. Rev.* **2000**, *52*, 673–751.
[38] E. Chieli, N. Romiti, F. Cervelli, R. Tongiani, *Life Sci.* **1995**, *57*, 1741–1751.
[39] G. Comte, J. B. Daskiewicz, C. Bayet, G. Conseil, A. Viornery-Vanier, C. Dumontet, A. Di Pietro, D. Barron, *J. Med. Chem.* **2001**, *44*, 763–768.
[40] J. W. Critchfield, C. J. Welsh, J. M. Phang, G. C. Yeh, *Biochem. Pharmacol.* **1994**, *48*, 1437–1445.
[41] G. Scambia, F. O. Ranelletti, P. B. Panici, R. De Vincenzo, G. Bonanno, G. Ferrandina, M. Piantelli, S. Bussa, C. Rumi, M. Cianfriglia, et al., *Cancer Chemother. Pharmacol.* **1994**, *34*, 459–464.
[42] A. F. Castro, G. A. Altenberg, *Biochem. Pharmacol.* **1997**, *53*, 89–93.
[43] S. Zhang, M. E. Morris, *J. Pharmacol. Exp. Ther.* **2003**, *304*, 1258–1267.
[44] J. Jodoin, M. Demeule, R. Beliveau, *Biochim. Biophys. Acta Mol. Cell Res.* **2002**, *1542*, 149–159.
[45] W. F. De Azevedo, Jr., H. J. Mueller-Dieckmann, U. Schulze-Gahmen, P. J. Worland, E. Sausville, S. H. Kim, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 2735–2740.
[46] G. Zapata-Torres, F. Opazo, C. Salgado, J. P. Munoz, H. Krautwurst, C. Mascayano, S. Sepulveda-Boza, R. B. Maccioni, B. K. Cassels, *J. Nat. Prod.* **2004**, *67*, 416–420.
[47] P. C. Ferriola, V. Cody, E. Middleton, Jr., *Biochem. Pharmacol.* **1989**, *38*, 1617–1624.
[48] M. Hagiwara, S. Inoue, T. Tanaka, K. Nunoki, M. Ito, H. Hidaka, *Biochem. Pharmacol.* **1988**, *37*, 2987–2992.
[49] T. Akiyama, J. Ishida, S. Nakagawa, H. Ogawara, S. Watanabe, N. Itoh, M. Shibuya, Y. Fukami, *J. Biol. Chem.* **1987**, *262*, 5592–5595.
[50] F. Sicheri, I. Moarefi, J. Kuriyan, *Nature* **1997**, *385*, 602–609.
[51] M. J. Robinson, A. H. Corbett, N. Osheroff, *Biochemistry* **1993**, *32*, 3638–3643.
[52] V. L. Zyma, N. S. Miroshnichenko, V. M. Danilova, E. En Gin, *Gen. Physiol. Biophys.* **1988**, *7*, 165–175.
[53] A. Di Pietro, C. Godinot, M. L. Bouillant, D. C. Gautheron, *Biochimie* **1975**, *57*, 959–967.
[54] T. Hirano, K. Oka, M. Akiba, *Life Sci.* **1989**, *45*, 1111–1117.

[55] P. Thiyagarajah, S. C. Kuttan, S. C. Lim, T. S. Teo, N. P. Das, *Biochem. Pharmacol.* **1991**, *41*, 669–675.
[56] S. Murakami, M. Muramatsu, K. Tomisawa, *J. Enzyme Inhib.* **1999**, *14*, 151–166.
[57] A. Di Pietro, G. Conseil, J. M. Pérez-Victoria, G. Dayan, H. Baubichon-Cortay, D. Trompier, E. Steinfels, J. M. Jault, H. de Wet, M. Maitrejean, G. Comte, A. Boumendjel, A. M. Mariotte, C. Dumontet, D. B. McIntosh, A. Goffeau, S. Castanys, F. Gamarro, D. Barron, *Cell Mol. Life Sci.* **2002**, *59*, 307–322.
[58] J. M. Pérez-Victoria, M. J. Chiquero, G. Conseil, G. Dayan, A. Di Pietro, D. Barron, S. Castanys, F. Gamarro, *Biochemistry* **1999**, *38*, 1736–1743.
[59] A. Boumendjel, A. Di Pietro, C. Dumontet, D. Barron, *Med. Res. Rev.* **2002**, *22*, 512–529.
[60] K. F. Chan, Y. Zhao, B. A. Burkett, I. L. Wong, L. M. Chow, T. H. Chan, *J. Med. Chem.* **2006**, *49*, 6742–6759.
[61] I. L. Wong, K. F. Chan, B. A. Burkett, Y. Zhao, Y. Chai, H. Sun, T. H. Chan, L. M. Chow, *Antimicrob. Agents Chemother.* **2007**, *51*, 930–940.
[62] M. Mammen, S. K. Choi, G. M. Whitesides, *Angew. Chem.* **1998**, *110*, 2908–2953; *Angew. Chem. Int. Ed.* **1998**, *37*, 2754–2794.
[63] S. J. Sucheck, A. L. Wong, K. M. Koeller, D. D. Boehr, K. Draker, P. Sears, G. D. Wright, C.-H. Wong, *J. Am. Chem. Soc.* **2000**, *122*, 5230–5231.
[64] J. Rao, J. Lahiri, L. Isaacs, R. M. Weis, G. M. Whitesides, *Science* **1998**, *280*, 708–711.
[65] E. Fan, Z. Zhang, W. E. Minke, Z. Hou, C. L. M. J. Verlinde, W. G. J. Hol, *J. Am. Chem. Soc.* **2000**, *122*, 2663–2664.
[66] M. M. Pires, C. A. Hrycyna, J. Chmielewski, *Biochemistry* **2006**, *45*, 11695–11702.
[67] P. Mistry, A. J. Stewart, W. Dangerfield, S. Okiji, C. Liddle, D. Bootle, J. A. Plumb, D. Templeton, P. Charlton, *Cancer Res.* **2001**, *61*, 749–758.
[68] F. Leonessa, D. Green, T. Licht, A. Wright, K. Wingate-Legette, J. Lippman, M. M. Gottesman, R. Clarke, *Br. J. Cancer* **1996**, *73*, 154–161.

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