Synthesis and Antiproliferative Effect of Novel Curcumin Analogues

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Novel curcumin analogues with *α*,*β*-unsaturated ketone moiety and/or *α*,*β*-saturated ketone structure were synthesized from curcumin *via* alkylation at the central carbon and the phenolic hydroxy groups, and hydrogenation of *α*,*β*-unsaturated ketone moiety. The antiproliferative activities were tested in five human solid tumor cell lines *in vitro*. Most of the compounds exhibited increased antiproliferative activities comparing with that of curcumin. Structure–activity relationship (SAR) analysis revealed that the *α*,*β*-unsaturated ketone structure was not required for antiproliferative activity of these curcumin analogues. Among these compounds, 1,7-bis(3-methoxy-4-(3-(4-methylpiperazinyl-1-yl)propoxy)phenyl)-4,4-dibenzylheptane-3,5-dione (16f) was the most effective one with IC_{50} value below 1 μM, which was 9- to 81-fold more potent than curcumin.

Key words curcumin; curcumin analogue; antiproliferation

Curcumin (Fig. 1) is one of the bioactive components of *Curcuma longa* Linn. (Turmeric) and has been found to possess antiproliferative activity against different cancer cell lines.[1)] To improve its antitumor effects, a great of efforts have been put to modify its structure,[2,3)] and several curcumin derivatives and analogues, such as dimethoxycurcumin,[4,5)] 4-ethoxycarbonylethylcurcumin (ECECur),[6)] hydrazinocurcumin,[7)] EF24,[8,9)] and FLLL32[10–12)] were discovered to be more active compounds (Fig. 2).

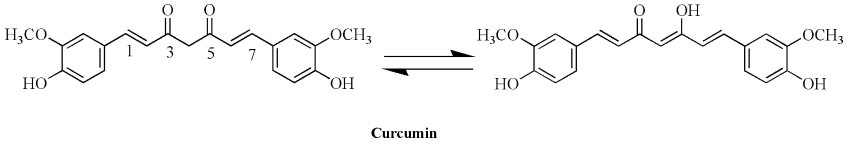
Since the conjugated *α*,*β*-unsaturated diketone moiety in curcumin skeleton is believed to play an important role in mediating the antitumor activity,[13,14)] most analogues synthesized before retained *α*,*β*-unsaturated ketone moiety.[6,7,15–22)] However, a few of reports showed that analogues with broken *α*,*β*-unsaturated diketone moiety also have antitumor activity.[10–12,23–25)] For further investigation of the effects of *α*,*β*-unsaturated ketone moiety, in this communication, two series of curcumin derivatives (**10a–f**, **11a–f**, **12a–f** and **13a–f** with *α*,*β*-unsaturated ketone moieties, and **16a–f** with a *α*,*β*-saturated ketone moiety, Fig. 3) were synthesized and tested for their antiproliferative activities in five human carcinoma cell lines. In the target compounds, dialkylation at C-4 position was aimed to block the conjugation of the diketone moieties, and hydrogenation of compounds **13a–f** was proposed to explore the impact of the olefin double bonds. In addition, modification on the phenolic hydroxy groups might be of benefit to physical stability as well as metabolism behavior,[5)] and introduction of the terminal hydrophilic amino groups in the side chains was carried out in anticipation of improved water solubility or/and antitumor activity.[26,27)]

Results and Discussion

Chemistry The synthetic routes of the target compounds were outlined in Chart 1 and in Chart 2. For regio-selective alkylation at the C-4 position of curcumin to get the intermediates **4** and **5**, the phenolic hydroxyl groups were protected via acetylation, followed by alkylation at the central carbon of intermediate **1** with methyl iodide or benzyl bromide, subsequent deprotection of the acetyl groups. The heptadiene moiety in the intermediate **5** was hydrogenized to obtain **14**. The resulting compound **4** or **5**, **14** was coupled with 1,2-dibromoethane or 1-bromo-3-chloropropane to yield halo-substituted intermediate **6**–**9** and **15**, respectively. Nucleophilic substitution of intermediate **6**, or **7**, **8**, **9**, **15** with various heterocyclic or aliphatic secondary amines afforded the target compounds.

Biological Activity The growth inhibitory effects of the target compounds and intermediates **4**–**9**, **14** were evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay in five human carcinoma cell lines including human breast adenocarcinoma (MCF-7), human hepatocellular carcinoma (HepG2), human colorectal carcinoma (HCT116), human lung carcinoma (A549), and human fibrosarcoma (HT-1080). The IC_{50} values for 48 h exposure were summarized in Table 1.

As shown in Table 1, the intermediate **4** exhibited greater growth inhibitory potency than curcumin in all the tested cell lines and the intermediate **5** had the similar antiproliferative activity as that of curcumin, suggesting that alkylation at the C-4 position of curcumin was of benefit to antiproliferative activity to some extent.[11)] The impact of the characteristic of the *O*-alkylated side chains in the halo-substituted intermedi-



Curcumin

Fig. 1. The Keto-Enlo Tautomeric Structure of Curcumin

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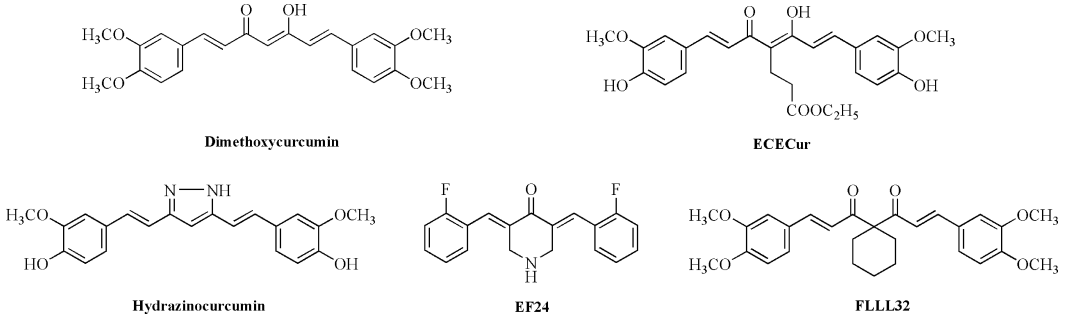


Fig. 2. The Structures of More Active Curcumin Analogues

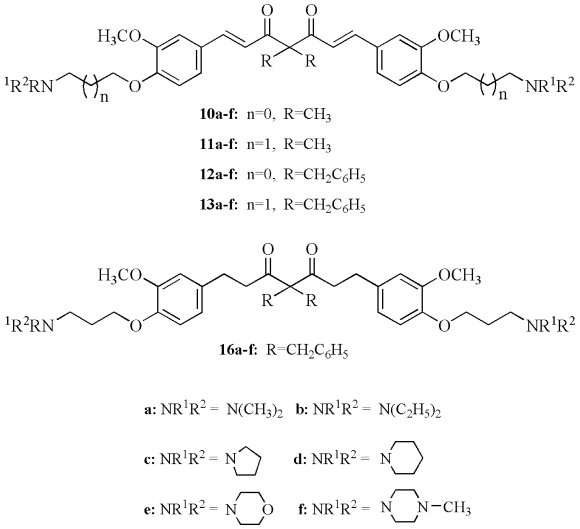


Fig. 3. The Structures of the Target Compounds

ates on cytotoxicity was uncertain since the intermediate **6** possessed similar cytotoxic property in comparison with the intermediate **4** whereas the intermediates **7**, **8** and **9** showed dramatically decreased antiproliferative activity.

Compared to the halo-substituted intermediates, most of the target compounds bearing various heterocyclic or aliphatic amino moieties exhibited increased antiproliferative activities. The target compounds (**10a**–**f**) derived from **6** were less active than **6**. The target compounds (**11a**–**f**, **12a**–**f** and **13a**–**f**) derived from **7**, **8**, and **9** showed more potent activity than that of the three intermediates, respectively, suggesting that the terminal amino moieties introduced into the *O*-alkyl side chains contributed to the improved antiproliferative activities. Compounds **12a**–**f** and **13af** with 4,4-dibenzyl substitution were more potent than compounds **10a**–**f** and **11a**–**f** with 4,4-dimethyl substitution, which suggested that sterically large substitution at C-4 position might favor the enhancement of cytotoxic activity.

The intermediate **14** exhibited the similar antiproliferative activity as that of curcumin and that of the intermediate **5**, suggesting that the diketone moiety, but not α,β-unsaturated diketone moiety, is required for the antiproliferative activity. More intriguing, it was found that compounds **16a**–**f** with α,β-saturated ketone moiety were more active than compounds **13a**–**f** with α,β-unsaturated ketone moieties. The most potent compound **16f** inhibited cell growth with IC_{50} values below 1 μM, which was 9- to 81-fold more potent than curcumin.

Conclusion

Two series of novel curcumin analogues, a total of 30 title compounds bearing *O*-aminoalkyl moieties were synthesized and evaluated for their antiproliferative activity against five human carcinoma cell lines *in vitro*. Most of them possessed moderate to excellent growth inhibitory activity against one or more cell lines. Compound **12c**, **13c**, **13d** and **16f** showed dramatically increased antiproliferative effects in all five cell lines as compared with curcumin.

Preliminary structure–activity relationships revealed that the terminal amino moieties of the *O*-alkyl side chains were critical for improving antiproliferative activity, and that the conjugated α, β-unsaturated diketone moiety and the olefin double bonds had no significant influence on growth inhibitory effect. Moreover, sterically large substitution at the central carbon of curcumin skeleton was favorable to improving cytotoxic activity.

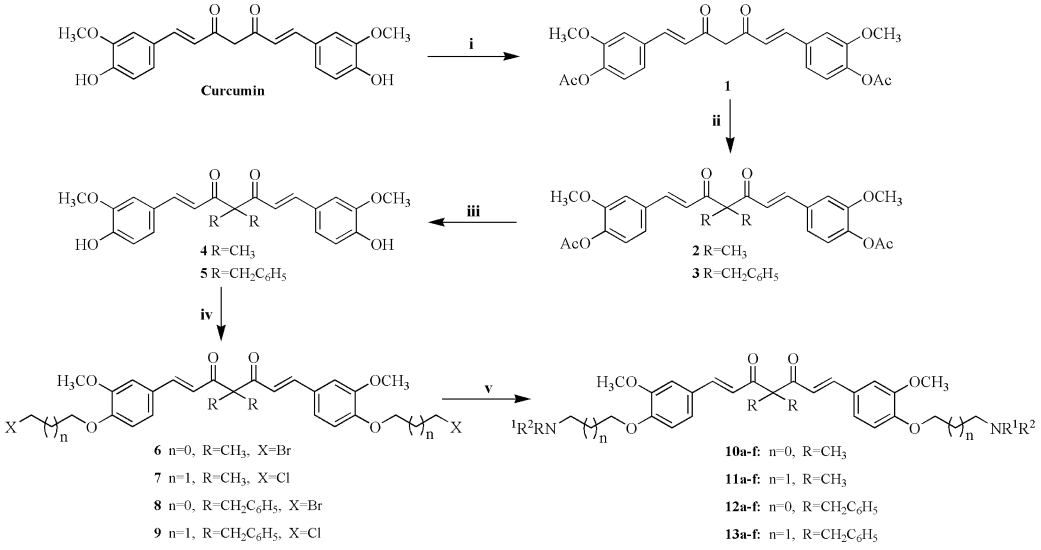
Experimental

Reagents and General Procedures Melting points were determined with a Yanaco micro melting point apparatus and were uncorrected. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Bruker ARX-300 spectrometer or a Bruker AV-600 spectrometer. The coupling constants were recorded in hertz (Hz) and chemical shifts were reported in parts per million (δ, ppm) downfield from tetramethylsilane (TMS). High-resolution mass spectra (HR-MS) were recorded on a high-resonance electrospray time-of-flight mass spectrometer LC/MSD QTOF 6520 (Agilent). All reagents and solvents (analytical grade) were commercially available and used without further purification.

Preparation of 1,7-Bis(4-acetoxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (1) To a solution of curcumin (2.50 g, 6.8 mmol) in methylene chloride (30 mL), acetic anhydride (1.9 mL, 20.4 mmol) and pyridine (1.7 mL, 20.4 mmol) were added. The mixture was refluxed for 2 h and then concentrated under reduced pressure. To the residue, methanol (50 mL) was added to give **1** as a yellow solid, 98% yield, mp 155–157°C. [lit. 154–155°C].[28)]

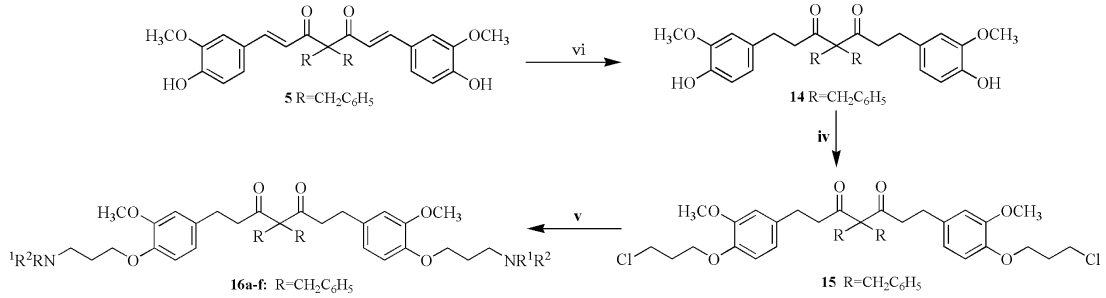
General Procedure for the Preparation of Compounds 2 and 3 To a stirred solution of **1** (4.5 g, 10.0 mmol) and potassium carbonate (3.5 g, 25.0 mmol) in dry acetone (30 mL), iodomethane or benzyl bromide (25 mmol) was added. The mixture was refluxed overnight and then cooled to room temperature. The filtrate was collected by filtration and concentrated under reduced pressure. The residue was crystallized from acetone-ethanol to give **2** and **3**, respectively.

1,7-Bis(4-acetoxy-3-methoxyphenyl)-4,4-dimethyl-hep-



Reagents and conditions: (i) $(CH_3CO)_2O$, pyridine, methylene chloride, reflux, 2 h; (ii) CH_3I or $C_6H_5CH_2Br$, K_2CO_3, acetone, reflux, overnight; (iii) NaOH, methanol; rt., 2 h; (iv) $BrCH_2CH_2Br$ or $ClCH_2CH_2CH_2Br$, K_2CO_3, acetonitrile, reflux, 6 h; (v) HNR^1R^2, acetonitrile, reflux, 5 h.

Chart 1. Synthesis of the Target Compounds **10a–f**, **11a–f**, **12a–f** and **13a–f**



Reagents and conditions: (vi) H_2/Pd–C, ethanol, rt., 12 h.

Chart 2. Synthesis of the Target Compounds **16a–f**

ta-1,6-diene-3,5-dione (**2**): Yellow solid, 75% yield, mp 160–163°C. ^{1}H-NMR (300 MHz) δ: 1.48 (6H, s), 2.30 (6H, s), 3.85 (6H, s), 6.70 (2H, d, J=15.6 Hz), 7.02 (2H, d, J=8.1 Hz), 7.06 (2H, d, J=1.8 Hz), 7.13 (2H, dd, J=1.8, 8.1 Hz), 7.68 (2H, d, J=15.6 Hz). HR-MS m/z: 481.1857 (Calcd for $C_{27}H_{29}O_8$: 481.1862).

1,7-Bis(4-acetoxy-3-methoxyphenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**3**): Yellow solid, 88% yield, mp 178–179°C. ^{1}H-NMR (600 MHz) δ: 2.29 (6H, s), 3.38 (4H, s), 3.81 (6H, s), 6.53 (2H, d, J=15.6 Hz), 6.91 (2H, d, J=1.8 Hz), 6.99 (2H, d, J=8.4 Hz), 7.03 (2H, dd, J=1.8, 8.4 Hz), 7.11 (4H, m), 7.18 (2H, m), 7.22 (4H, m), 7.68 (2H, d, J=15.6 Hz). HR-MS m/z: 633.2483 (Calcd for $C_{39}H_{37}O_8$: 633.2488).

General Procedure for the Preparation of Compounds 4 and 5 To a solution of intermediate **2** or **3** (7.9 mmol) in methanol (20 mL), sodium hydroxide (0.7 g, 17.4 mmol) was added. The mixture was stirred for 2 h at room temperature, and then evaporated to dryness *in vacuo*. The residue was dissolved in methylene chloride (30 mL), followed by neutralization with acetic acid. Then water (50 mL) was added and the organic phase was separated. The aqueous phase was extracted with methylene chloride (2×20 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was crystallized from petroleum ether–ethyl acetate to give **4** and **5**.

1,7-Bis(4-hydroxy-3-methoxyphenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**4**): Yellow solid, 74% yield, mp 136–138°C. ^{1}H-NMR (300 MHz) δ: 1.47 (6H, s), 3.91 (6H, s), 6.62 (2H, d, J=15.6 Hz), 6.89 (2H, d, J=8.4 Hz), 6.99 (2H, d, J=1.8 Hz), 7.09 (2H, dd, J=1.8, 8.4 Hz), 7.66 (2H, d, J=15.6 Hz); HR-MS m/z: 397.1646 (Calcd for $C_{23}H_{25}O_6$: 397.1651).

1,7-Bis(4-hydroxy-3-methoxyphenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**5**): Yellow solid, 91% yield, mp 115–117°C. ^{1}H-NMR (600 MHz): δ 3.38 (4H, s), 3.86 (6H, s), 6.54 (2H, d, J=15.6 Hz), 6.86 (4H, m), 7.03 (2H, dd, J=1.8, 7.8 Hz), 7.10 (4H, m), 7.17 (2H, m), 7.21 (4H, m), 7.69 (2H, d, J=15.6 Hz). HR-MS m/z: 549.2272 (Calcd for $C_{35}H_{33}O_6$: 549.2277).

Preparation of 1,7-Bis(4-hydroxy-3-methoxyphenyl)-4,4-dibenzylheptane-3,5-dione (14) To a solution of compound **5** (5.5 g, 0.01 mol) in ethanol (50 mL) was added 10% Pd–C (0.5 g). After degassing, the mixture was hydrogenated at room temperature and at atmospheric pressure for 12 h. Then, methylene chloride (10 mL) was added to dissolve the precipitate, and the reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give **14** as a white solid, 65% yield, mp 73–75°C. ^{1}H-NMR (300 MHz) δ: 2.55

Table 1. Antiproliferative Activities of These Synthetic Curcumin Derivatives in Five Solid Tumor Cell Lines

Compd.	IC_{50} (μM)				
	MCF-7	HepG2	HCT116	A549	HT1080
4	8.14	5.88	6.31	7.25	5.18
5	31.09	26.45	35.85	27.72	15.50
14	33.66	35.98	31.73	35.32	49.50
6	6.36	7.96	7.48	31.88	5.42
7	42.45	72.23	>100	>100	>100
8	>100	>100	>100	>100	>100
9	>100	>100	>100	>100	>100
10a	7.62	>100	47.48	39.60	4.87
10b	>100	>100	94.36	>100	63.53
10c	30.04	34.92	7.42	41.15	4.98
10d	43.48	35.76	8.54	48.54	4.16
10e	32.54	45.92	7.68	73.30	0.06
10f	19.32	41.08	9.26	43.45	5.30
11a	0.79	7.25	42.94	33.05	5.15
11b	6.24	6.65	32.33	7.72	0.68
11c	32.00	44.63	43.58	34.37	0.68
11d	2.18	36.80	53.23	43.93	5.26
11e	28.39	70.67	96.86	>100	39.12
11f	7.11	44.80	8.64	38.34	3.98
12a	6.21	2.64	6.50	5.88	5.86
12b	5.89	72.01	46.97	43.44	35.49
12c	0.03	5.17	4.80	5.41	0.47
12d	4.81	5.38	39.60	47.04	6.14
12e	7.54	58.37	94.47	72.54	41.05
12f	4.76	5.42	7.61	5.75	4.92
13a	4.71	5.98	8.13	5.87	5.89
13b	5.22	28.96	42.81	39.17	8.21
13c	4.71	0.64	5.10	4.26	5.94
13d	0.74	0.66	4.93	0.72	4.66
13e	6.47	43.88	45.23	46.94	44.14
13f	0.64	5.79	6.31	5.93	4.75
16a	0.76	5.73	5.91	5.49	10.72
16b	0.87	0.38	0.59	0.50	10.27
16c	0.70	0.93	7.88	4.55	4.81
16d	2.46	4.70	7.35	4.88	4.84
16e	6.78	6.55	7.94	5.47	6.09
16f	0.71	0.51	0.78	0.51	0.63
Curcumin	28.03	37.37	43.31	41.35	5.96

a) These cells were treated with a variety of concentrations of each compound for 48 h and the concentrations (IC_{50}s) which inhibit 50% of cell growth were calculated.

(4H, m), 2.69 (4H, m), 3.31 (4H, s), 3.83 (6H, s), 6.55 (4H, m), 6.79 (2H, d, J=8.4 Hz), 6.93 (4H, m), 7.21 (6H, m). HR-MS m/z: 553.2585 (Calcd for $C_{35}H_{37}O_6$: 553.2592).

General Procedure for the Preparation of Compounds 6, 7, 8, 9 and 15 To a solution of **4** or **5**, **14** (12.0 mmol) in acetonitrile (50 mL), potassium carbonate (5.0 g, 36.0 mmol) was added. The mixture was stirred at 70°C, and then 1,2-dibromoethane or 1-bromo-3-chloropropane (36.0 mmol) diluted with acetonitrile (5 mL) was added dropwise. The mixture was refluxed for 6 h, and concentrated under reduced pressure. To the residue, methylene chloride (50 mL) and water (50 mL) were added. The organic phase was separated and the aqueous phase was extracted with methylene chloride (3×20 mL). The combined organic phase was dried over anhydrous sodium sulfate and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography with petroleum ether–ethyl acetate as gradient elute to give **6**, **7**, **8**, **9** and **15**.

1,7-Bis(4-(2-bromoethoxy)-3-methoxyphenyl)-4,4-dimethylhepta-1,6-diene-3,5-dione (**6**): Yellow solid, 42% yield, mp 93–95°C. ^{1}H-NMR (300 MHz) δ: 1.48 (6H, s), 3.65 (4H, t, J=6.6 Hz), 3.88 (6H, s), 4.34 (4H, t, J=6.6 Hz), 6.65 (2H, d, J=15.6 Hz), 6.85 (2H, d, J=8.1 Hz), 7.02 (2H, d, J=1.5 Hz), 7.10 (2H, dd, J=1.5, 8.1 Hz), 7.67 (2H, d, J=15.6 Hz). HR-MS m/z: 609.0482 (Calcd for $C_{27}H_{31}Br_2O_6$: 609.0487).

1,7-Bis(4-(3-chloropropoxy)-3-methoxyphenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**7**): Yellow solid, 50% yield, mp 90–91°C. ^{1}H-NMR (300 MHz) δ: 1.48 (6H, s), 2.28 (4H, m), 3.75 (4H, t, J=6.0 Hz), 3.87 (6H, s), 4.18 (4H, t, J=6.0 Hz), 6.65 (2H, d, J=15.6 Hz), 6.86 (2H, d, J=8.4 Hz) 7.00 (2H, d, J=1.8 Hz), 7.11 (2H, dd, J=1.8, 8.4 Hz), 7.68 (2H, d, J=15.6 Hz). HR-MS m/z: 549.1805 (Calcd for $C_{29}H_{35}Cl_2O_6$: 549.1810).

1,7-Bis(4-(2-bromoethoxy)-3-methoxyphenyl)-4,4-dibenzylhepta-1,6-diene-3,5-dione (**8**): Yellow solid, 71% yield, mp 156–157°C. ^{1}H-NMR (300 MHz) δ: 3.38 (4H, s), 3.64 (4H, t, J=6.6 Hz), 3.85 (6H, s), 4.33 (4H, t, J=6.6 Hz), 6.52 (2H, d, J=15.6 Hz), 6.82 (2H, d, J=8.4 Hz), 6.87 (2H, d, J=1.8 Hz), 7.03 (2H, dd, J=1.8, 8.4 Hz), 7.10 (4H, m), 7.20 (6H, m), 7.67 (2H, d, J=15.6 Hz). HR-MS m/z: 761.1108 (Calcd for $C_{39}H_{39}Br_2O_6$: 761.1113).

1,7-Bis(4-(3-chloropropoxy)-3-methoxyphenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**9**): Yellow solid, 78% yield, mp 106–108°C. ^{1}H-NMR (300 MHz) δ: 2.27 (4H, m), 3.38 (4H, s), 3.74 (4H, t, J=6.0 Hz), 3.83 (6H, s), 4.17 (4H, t, J=6.0 Hz), 6.53 (2H, d, J=15.3 Hz), 6.84 (2H, d, J=8.4 Hz), 6.87 (2H, d, J=1.8 Hz), 7.05 (2H, dd, J=1.8, 8.4 Hz), 7.11 (4H, m), 7.20 (6H, m), 7.68 (2H, d, J=15.3 Hz). HR-MS m/z: 701.2431 (Calcd for $C_{41}H_{43}Cl_2O_6$: 701.2436).

1,7-Bis(4-(3-chloropropoxy)-3-methoxyphenyl)-4,4-dibenzylheptane-3,5-dione (**15**): White solid, 75% yield, mp 95–97°C. ^{1}H-NMR (300 MHz) δ: 2.25 (4H, m), 2.58 (4H, m), 2.71 (4H, m), 3.31 (4H, s), 3.75 (4H, t, J=6.0 Hz), 3.82 (6H, s), 4.11 (4H, t, J=6.0 Hz), 6.59 (4H, m), 6.79 (2H, d, J=8.7 Hz), 6.94 (4H, m), 7.21 (6H, m). HR-MS m/z: 705.2744 (Calcd for $C_{41}H_{47}Cl_2O_6$: 705.2751).

General Procedure for the Preparation of Target Compounds 10a–f, 11a–f, 12a–f, 13a–f and 16a–f To a solution of halo-substituted intermediate **6**, or **7**, **8**, **9**, **15** (2.0 mmol) in acetonitrile (10 mL), a heterocyclic or aliphatic secondary amine (20.0 mmol) was added. The mixture was refluxed for 5 h and concentrated under reduced pressure. The residue was dissolved in methylene chloride (20 mL) and washed with water (3×30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography with dichloromethane–methanol as gradient elute to afford the corresponding target compounds **10a–f**, **11a–f**, **12a–f**, **13a–f** and **16a–f**.

1,7-Bis(4-(2-dimethylaminoethoxy)-3-methoxyphenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**10a**): Yellow oil, 38% yield. ^{1}H-NMR (300 MHz) δ: 1.47 (6H, s), 2.40 (12H, s), 2.86 (4H, t, J=5.7 Hz), 3.86 (6H, s), 4.17 (4H, t, J=5.7 Hz), 6.64 (2H, d, J=15.6 Hz), 6.85 (2H, d, J=8.4 Hz), 6.99 (2H, s), 7.10 (2H, d, J=8.4 Hz), 7.67 (2H, d, J=15.6 Hz). HR-MS m/z: 539.3166 (Calcd for $C_{31}H_{43}N_2O_6$: 539.3121).

1,7-Bis(4-(2-diethylaminoethoxy)-3-methoxyphenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**10b**): Yellow oil, 45% yield. ^{1}H-NMR (300 MHz) δ: 1.05 (12H, t, J=7.2 Hz), 1.47

(6H, s), 2.62 (8H, q, *J*=7.2 Hz), 2.91 (4H, t, *J*=6.9 Hz), 3.87 (6H, s), 4.10 (4H, t, *J*=6.9 Hz), 6.64 (2H, d, *J*=15.6 Hz), 6.85 (2H, d, *J*=8.4 Hz), 6.99 (2H, d, *J*=1.5 Hz), 7.10 (2H, dd, *J*=1.5, 8.4 Hz), 7.67 (2H, d, *J*=15.6 Hz). HR-MS *m/z*: 595.3742 (Calcd for $C_{35}H_{51}N_2O_6$: 595.3747).

1,7-Bis(3-methoxy-4-(2-pyrrolidin-1-yl-ethoxy)phenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**10c**): Yellow oil, 57% yield. ^{1}H-NMR (300 MHz) *δ*: 1.47 (6H, s), 1.80 (8H, m), 2.63 (8H, m), 2.95 (4H, t, *J*=6.3 Hz), 3.87 (6H, s), 4.17 (4H, t, *J*=6.3 Hz), 6.64 (2H, d, *J*=15.3 Hz), 6.85 (2H, d, *J*=8.4 Hz), 7.00 (2H, d, *J*=1.5 Hz), 7.10 (2H, dd, *J*=1.5, 8.4 Hz), 7.67 (2H, d, *J*=15.3 Hz). HR-MS *m/z*: 591.3429 (Calcd for $C_{35}H_{47}N_2O_6$: 591.3434).

1,7-Bis(3-methoxy-4-(2-piperidin-1-yl-ethoxy)phenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**10d**): Yellow oil, 60% yield. ^{1}H-NMR (300 MHz) *δ*: 1.46 (10H, m), 1.59 (8H, m), 2.50 (8H, m), 2.80 (4H, t, *J*=6.6 Hz), 3.87 (6H, s), 4.16 (4H, t, *J*=6.6 Hz), 6.64 (2H, d, *J*=15.6 Hz), 6.85 (2H, d, *J*=8.4 Hz), 6.99 (2H, d, *J*=1.8 Hz), 7.10 (2H, dd, *J*=1.8, 8.4 Hz), 7.67 (2H, d, *J*=15.6 Hz). HR-MS *m/z*: 619.3742 (Calcd for $C_{37}H_{51}N_2O_6$: 619.3747).

1,7-Bis(3-methoxy-4-(2-morpholinoethoxy)phenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**10e**): Yellow oil, 71% yield. ^{1}H-NMR (600 MHz) *δ*: 1.47 (6H, s), 2.58 (8H, m), 2.83 (4H, t, *J*=6.0 Hz), 3.71 (8H, m), 3.87 (6H, s), 4.17 (4H, t, *J*=6.0 Hz), 6.64 (2H, d, *J*=15.6 Hz), 6.85 (2H, d, *J*=8.4 Hz), 7.00 (2H, d, *J*=1.8 Hz), 7.10 (2H, dd, *J*=1.8, 8.4 Hz), 7.67 (2H, d, *J*=15.6 Hz). HR-MS *m/z*: 623.3327 (Calcd for $C_{35}H_{47}N_2O_8$: 623.3332).

1,7-Bis(3-methoxy-4-(2-(4-methylpiperazinyl-1-yl)ethoxy)-phenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**10f**): Yellow oil, 70% yield. ^{1}H-NMR (300 MHz) *δ*: 1.47 (6H, s), 2.28 (6H, s), 2.45 (12H, s), 2.61 (8H, s), 3.87 (6H, s), 4.15 (4H, t, *J*=5.7 Hz), 6.64 (2H, d, *J*=15.6 Hz), 6.84 (2H, d, *J*=8.1 Hz), 7.00 (2H, s), 7.10 (2H, d, *J*=8.1 Hz), 7.67 (2H, d, *J*=15.6 Hz). HR-MS *m/z*: 649.3960 (Calcd for $C_{37}H_{53}N_4O_6$: 649.3965).

1,7-Bis(3-methoxy-4-(3-dimethylaminopropoxy)phenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**11a**): Yellow oil, 40% yield. ^{1}H-NMR (300 MHz) *δ*: 1.47 (6H, s), 2.02 (4H, m), 2.24 (12H, s), 2.45 (4H, t, *J*=7.2 Hz), 3.87 (6H, s), 4.09 (4H, t, *J*=6.6 Hz), 6.64 (2H, d, *J*=15.6 Hz), 6.86 (2H, d, *J*=8.4 Hz), 7.00 (2H, s), 7.10 (2H, d, *J*=8.4 Hz), 7.68 (2H, d, *J*=15.6 Hz). HR-MS *m/z*: 567.3429 (Calcd for $C_{33}H_{47}N_2O_6$: 567.3434).

1,7-Bis(3-methoxy-4-(3-diethylaminopropoxy)phenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**11b**): Yellow oil, 53% yield. ^{1}H-NMR (300 MHz) *δ*: 1.01 (12H, t, *J*=7.2 Hz), 1.47 (6H, s), 1.98 (4H, m), 2.57 (12H, m), 3.87 (6H, s), 4.08 (4H, t, *J*=6.9 Hz), 6.64 (2H, d, *J*=15.6 Hz), 6.85 (2H, d, *J*=8.4 Hz), 7.00 (2H, d, *J*=1.5 Hz), 7.10 (2H, dd, *J*=1.5, 8.4 Hz), 7.68 (2H, d, *J*=15.6 Hz). HR-MS *m/z*: 623.4055 (Calcd for $C_{37}H_{55}N_2O_6$: 623.4060).

1,7-Bis(3-methoxy-4-(3-pyrrolidin-1-yl-propoxy)-phenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**11c**): Yellow oil, 72% yield. ^{1}H-NMR (300 MHz) *δ*: 1.47 (6H, s), 1.80 (8H, m), 2.08 (4H, m), 2.56 (8H, m), 2.65 (4H, t, *J*=7.2 Hz), 3.87 (6H, s), 4.11 (4H, t, *J*=6.6 Hz), 6.64 (2H, d, *J*=15.3 Hz), 6.86 (2H, d, *J*=8.4 Hz), 7.00 (2H, d, *J*=1.8 Hz), 7.10 (2H, dd, *J*=1.8, 8.4 Hz), 7.67 (2H, d, *J*=15.3 Hz). HR-MS *m/z*: 619.3742 (Calcd for $C_{37}H_{51}N_2O_6$: 619.3747).

1,7-Bis(3-methoxy-4-(3-piperidin-1-yl)propoxy)phenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**11d**): Yellow oil, 78% yield. ^{1}H-NMR (300 MHz) *δ*: 1.42 (4H, m), 1.47 (6H, s), 1.57 (8H, m), 2.02 (4H, m), 2.38 (8H, s), 2.45 (4H, t, *J*=7.2 Hz), 3.87 (6H, s), 4.09 (4H, t, *J*=6.6 Hz), 6.64 (2H, d, *J*=15.6 Hz), 6.86 (2H, d, *J*=8.4 Hz,), 7.00 (2H, d, *J*=1.5 Hz), 7.10 (2H, dd, *J*=1.5, 8.4 Hz), 7.67 (2H, d, *J*=15.6 Hz). HR-MS *m/z*: 647.4055 (Calcd for $C_{39}H_{55}N_2O_6$: 647.4060).

1,7-Bis(3-methoxy-4-(3-morpholinopropoxy)phenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**11e**): Yellow oil, 69% yield. ^{1}H-NMR (300 MHz) *δ*: 1.47 (6H, s), 2.01 (4H, m), 2.49 (12H, m), 3.71 (8H, m), 3.87 (6H, s), 4.10 (4H, t, *J*=6.3 Hz), 6.64 (2H, d, *J*=15.6 Hz), 6.86 (2H, d, *J*=8.4 Hz), 7.00 (2H, s), 7.10 (2H, d, *J*=8.4 Hz), 7.67 (2H, d, *J*=15.6 Hz). HR-MS *m/z*: 651.3640 (Calcd for $C_{37}H_{51}N_2O_8$: 651.3645).

1,7-Bis(3-methoxy-4-(3-(4-methylpiperazinyl-1-yl)propoxy)-phenyl)-4,4-dimethyl-hepta-1,6-diene-3,5-dione (**11f**): Yellow oil, 63% yield. ^{1}H-NMR (300 MHz) *δ*: 1.47 (6H, s), 2.02 (4H, m), 2.28 (6H, s), 2.46 (20H, m), 3.87 (6H, s), 4.10 (4H, t, *J*=6.6 Hz), 6.64 (2H, d, *J*=15.6 Hz), 6.86 (2H, d, *J*=8.4 Hz), 7.00 (2H, d, *J*=1.8 Hz), 7.10 (2H, dd, *J*=1.8, 8.4 Hz), 7.68 (2H, d, *J*=15.6 Hz). HR-MS *m/z*: 677.4273 (Calcd for $C_{39}H_{57}N_4O_6$: 677.4278).

1,7-Bis(4-(2-dimethylaminoethoxy)-3-methoxyphenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**12a**): Yellow oil, 42% yield. ^{1}H-NMR (300 MHz) *δ*: 2.36 (12H, m), 2.83 (4H, t, *J*=6.0 Hz), 3.38 (4H, s), 3.83 (6H, s), 4.14 (4H, t, *J*=6.0 Hz), 6.53 (2H, d, *J*=15.3 Hz), 6.82 (2H, d, *J*=8.1 Hz), 6.86 (2H, d, *J*=1.2 Hz), 7.04 (2H, dd, *J*=1.2, 8.1 Hz), 7.10 (4H, m), 7.19 (6H, m), 7.68 (2H, d, *J*=15.3 Hz) HR-MS *m/z*: 691.3742 (Calcd for $C_{43}H_{51}N_2O_6$: 691.3747).

1,7-Bis(4-(2-diethylaminoethoxy)-3-methoxyphenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**12b**): Yellow oil, 48% yield. ^{1}H-NMR (300 MHz) *δ*: 1.06 (12H, t, *J*=6.9 Hz), 2.65 (8H, q, *J*=6.9 Hz), 2.93 (4H, t, *J*=6.6 Hz), 3.38 (4H, s), 3.83 (6H, s), 4.11 (4H, t, *J*=6.6 Hz), 6.53 (2H, d, *J*=15.3 Hz), 6.83 (2H, d, *J*=8.4 Hz), 6.86 (2H, d, *J*=1.5 Hz), 7.05 (2H, dd, *J*=1.5, 8.4 Hz), 7.10 (4H, m), 7.19 (6H, m), 7.68 (2H, d, *J*=15.3 Hz). HR-MS *m/z*: 747.4368 (Calcd for $C_{47}H_{59}N_2O_6$: 747.4373).

1,7-Bis(3-methoxy-4-(2-pyrrolidin-1-yl-ethoxy)phenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**12c**): Yellow oil, 67% yield. ^{1}H-NMR (300 MHz) *δ*: 1.80 (8H, m), 2.64 (8H, s), 2.96 (4H, t, *J*=6.6 Hz), 3.38 (4H, s), 3.83 (6H, s), 4.17 (4H, t, *J*=6.6 Hz), 6.53 (2H, d, *J*=15.3 Hz), 6.83 (2H, d, *J*=8.4 Hz), 6.86 (2H, d, *J*=1.8 Hz), 7.04 (2H, dd, *J*=1.8, 8.4 Hz), 7.10 (4H, m), 7.19 (6H, m), 7.68 (2H, d, *J*=15.3 Hz). HR-MS *m/z*: 743.4055 (Calcd for $C_{47}H_{55}N_2O_6$: 743.4060).

1,7-Bis(3-methoxy-4-(2-piperidin-1-yl-ethoxy)phenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**12d**): Yellow oil, 73% yield; ^{1}H-NMR (300 MHz) *δ*: 1.44 (4H, m), 1.59 (8H, m), 2.50 (8H, m), 2.80 (4H, t, *J*=6.3 Hz), 3.38 (4H, s), 3.83 (6H, s), 4.15 (4H, t, *J*=6.3 Hz), 6.53 (2H, d, *J*=15.6 Hz), 6.82 (2H, d, *J*=8.4 Hz), 6.86 (2H, d, *J*=1.5 Hz), 7.04 (2H, dd, *J*=1.5, 8.4 Hz), 7.10 (4H, m), 7.19 (6H, m), 7.68 (2H, d, *J*=15.6 Hz). HR-MS *m/z*: 771.4368 (Calcd for $C_{49}H_{59}N_2O_{66}$: 771.4373).

1,7-Bis(3-methoxy-4-(2-morpholinoethoxy)phenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**12e**): Yellow oil, 69% yield; ^{1}H-NMR (300 MHz) *δ*: 2.58 (8H, m), 2.83 (4H, t, *J*=6.0 Hz), 3.38 (4H, s), 3.72 (8H, m), 3.83 (6H, s), 4.15 (4H, t, *J*=6.0 Hz), 6.53 (2H, d, *J*=15.3 Hz), 6.82 (2H, d, *J*=8.4 Hz), 6.86 (2H, d, *J*=1.5 Hz), 7.04 (2H, dd, *J*=1.5, 8.4 Hz), 7.10 (4H, m), 7.19 (6H, m.), 7.68 (2H, d, *J*=15.3 Hz). HR-MS *m/z*: 775.3953 (Calcd for $C_{47}H_{55}N_2O_8$: 775.3958).

1,7-Bis(3-methoxy-4-(2-(4-methylpiperazinyl-1-yl)ethoxy)-phenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**12f**): Yellow oil, 63% yield. ^{1}H-NMR (300 MHz) δ: 2.29 (6H, s), 2.50 (8H, s), 2.63 (8H, s), 2.84 (4H, t, J=6.0 Hz), 3.38 (4H, s), 3.83 (6H, s), 4.15 (4H, t, J=6.0 Hz), 6.53 (2H, d, J=15.6 Hz), 6.82 (2H, d, J=8.4 Hz), 6.86 (2H, d, J=1.5 Hz), 7.04 (2H, dd, J=1.5, 8.4 Hz), 7.10 (4H, m), 7.19 (6H, m), 7.68 (2H, d, J=15.6 Hz). HR-MS m/z: 801.4586 (Calcd for $C_{49}H_{61}N_4O_6$: 801.4591).

1,7-Bis(4-(3-dimethylaminopropoxy)-3-methoxyphenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**13a**): Yellow oil, 45% yield. ^{1}H-NMR (300 MHz) δ: 2.06 (4H, m), 2.30 (12H, s), 2.54 (4H, t, J=7.2 Hz), 3.38 (4H, s), 3.84 (6H, s), 4.07 (4H, t, J=6.6 Hz), 6.53 (2H, d, J=15.3 Hz), 6.82 (2H, d, J=8.4 Hz), 6.86 (2H, d, J=1.8 Hz), 7.04 (2H, dd, J=1.8, 8.4 Hz), 7.11 (4H, m), 7.19 (6H, m), 7.68 (2H, d, J=15.3 Hz). HR-MS m/z: 719.4055 (Calcd for $C_{45}H_{55}N_2O_6$: 719.4060).

1,7-Bis(4-(3-diethylaminopropoxy)-3-methoxyphenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**13b**): Yellow oil, 50% yield. ^{1}H-NMR (300 MHz) δ: 1.02 (12H, t, J=7.2 Hz), 1.98 (4H, m), 2.57 (8H, m), 2.63 (4H, m), 3.38 (4H, s), 3.83 (6H, s), 4.07 (4H, t, J=6.6 Hz), 6.54 (2H, d, J=15.4 Hz), 6.82 (2H, d, J=8.4 Hz), 6.86 (2H, d, J=1.8 Hz), 7.04 (2H, dd, J=1.8, 8.4 Hz), 7.10 (4H, m), 7.19 (6H, m), 7.68 (2H, d, J=15.4 Hz). HR-MS m/z: 775.4681 (Calcd for $C_{49}H_{63}N_2O_6$: 775.4686).

1,7-Bis(3-methoxy-4-(3-pyrrolidin-1-yl-propoxy)-phenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**13c**): Yellow oil, 68% yield. ^{1}H-NMR (300 MHz) δ: 1.80 (8H, s), 2.08 (4H, m), 2.59 (8H, s), 2.67 (4H, t, J=6.9 Hz), 3.38 (4H, s), 3.83 (6H, s), 4.09 (4H, t, J=6.6 Hz), 6.53 (2H, d, J=15.6 Hz), 6.83 (2H, d, J=8.4 Hz), 6.86 (2H, d, J=1.5 Hz), 7.04 (2H, dd, J=1.5, 8.4 Hz), 7.10 (4H, m), 7.19 (6H, m), 7.68 (2H, d, J=15.6 Hz). HR-MS m/z: 771.4368 (Calcd for $C_{49}H_{59}N_2O_6$: 771.4373).

1,7-Bis(3-methoxy-4-(3-piperidin-1-yl-propoxy)phenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**13d**): Yellow oil, 75% yield. ^{1}H-NMR (300 MHz) δ: 1.54 (4H, m), 1.77 (8H, m), 2.19 (4H, m), 2.86 (12H, m), 3.38 (4H, s), 3.82 (6H, s), 4.07 (4H, t, J=6.0 Hz), 6.53 (2H, d, J=15.3 Hz), 6.80 (2H, d, J=8.4 Hz), 6.85 (2H, d, J=1.5 Hz), 7.04 (2H, dd, J=1.5, 8.4 Hz), 7.10 (4H, m), 7.19 (6H, m), 7.68 (2H, d, J=15.3 Hz). HR-MS m/z: 799.4681 (Calcd for $C_{51}H_{63}N_2O_6$: 799.4686).

1,7-Bis(3-methoxy-4-(3-morpholinopropoxy)phenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**13e**): Yellow oil, 80% yield. ^{1}H-NMR (300 MHz) δ: 2.09 (4H, m), 2.65 (12H, m), 3.38 (4H, s), 3.77 (8H, m), 3.83 (6H, s), 4.08 (4H, t, J=6.3 Hz), 6.53 (2H, d, J=15.3 Hz), 6.81 (2H, d, J=8.4 Hz), 6.87 (2H, d, J=1.8 Hz), 7.04 (2H, dd, J=1.8, 8.4 Hz), 7.10 (4H, m), 7.19 (6H, m), 7.68 (2H, d, J=15.3 Hz). HR-MS m/z: 803.4266 (Calcd for $C_{49}H_{59}N_2O_6$: 803.4271).

1,7-Bis(3-methoxy-4-(3-(4-methylpiperazinyl-1-yl)propoxy)-phenyl)-4,4-dibenzyl-hepta-1,6-diene-3,5-dione (**13f**): Yellow oil, 75% yield. ^{1}H-NMR (300 MHz) δ: 2.02 (4H, m), 2.32 (6H, s), 2.52 (20H, m), 3.38 (4H, s), 3.83 (6H, s), 4.08 (4H, t, J=6.6 Hz), 6.54 (2H, d, J=15.6 Hz), 6.83 (2H, d, J=8.4 Hz), 6.87 (2H, d, J=1.8 Hz), 7.04 (2H, dd, J=1.8, 8.4 Hz), 7.10 (4H, m), 7.19 (6H, m), 7.68 (2H, d, J=15.6 Hz). HR-MS m/z: 829.4899 (Calcd for $C_{51}H_{65}N_4O_6$: 829.4904).

1,7-Bis(4-(3-dimethylaminopropoxy)-3-methoxyphenyl)-4,4-dibenzylheptane-3,5-dione (**16a**): Yellow oil, 49% yield. ^{1}H-NMR (300 MHz) δ: 1.95–2.04 (4H, m), 2.26 (12H, s), 2.47 (4H, t, J=7.2 Hz), 2.59 (4H, m), 2.70 (4H, m), 3.31 (4H, s), 3.82 (6H, s), 4.02 (4H, t, J=6.6 Hz), 6.58 (4H, m,), 6.78 (2H, d, J=8.7 Hz), 6.94 (4H, m), 7.21 (6H, m). HR-MS m/z: 723.4368 (Calcd for $C_{45}H_{59}N_2O_6$: 722.4375).

1,7-Bis(4-(3-diethylaminopropoxy)-3-methoxyphenyl)-4,4-dibenzylheptane-3,5-dione (**16b**): Yellow oil, 53% yield. ^{1}H-NMR (300 MHz) δ: 1.07 (12H, t, J=7.2 Hz), 2.00 (4H, m), 2.61 (12H, m), 2.68 (8H, m), 3.31 (4H, s), 3.81 (6H, s), 4.02 (4H, t, J=6.6 Hz), 6.58 (4H, m), 6.77 (2H, d, J=8.7 Hz), 6.94 (4H, m), 7.21 (6H, m). HR-MS m/z: 779.4994 (Calcd for $C_{49}H_{67}N_2O_6$: 779.5001).

1,7-Bis(3-methoxy-4-(3-pyrrolidin-1-yl-propoxy)-phenyl)-4,4-dibenzylheptane-3,5-dione (**16c**): Yellow oil, 66% yield. ^{1}H-NMR (300 MHz) δ: 1.81 (8H, m), 2.51 (4H, m), 2.58 (12H, m), 2.68 (8H, m), 3.31 (4H, s), 3.82 (6H, s), 4.04 (4H, t, J=6.6 Hz), 6.58 (4H, m), 6.78 (2H, d, J=8.7 Hz), 6.94 (4H, m), 7.21 (6H, m). HR-MS m/z: 775.4681 (Calcd for $C_{49}H_{63}N_2O_6$: 775.4688).

1,7-Bis(3-methoxy-4-(3-piperidin-1-yl-propoxy)phenyl)-4,4-dibenzylheptane-3,5-dione (**16d**): Yellow oil, 78% yield. ^{1}H-NMR (300 MHz) δ: 1.45 (4H, m), 1.59 (8H, m), 2.01 (4H, m), 2.40 (8H, m), 2.49 (4H, t, J=7.2 Hz), 2.59 (4H, m), 2.70 (4H, m), 3.31 (4H, s), 3.81 (6H, s), 4.02 (4H, t, J=6.6 Hz), 6.58 (4H, m), 6.78 (2H, d, J=8.7 Hz), 6.94 (4H, m), 7.21 (6H, m). HR-MS m/z: 803.4994 (Calcd for $C_{51}H_{67}N_2O_6$: 803.5001).

1,7-Bis(3-methoxy-4-(3-morpholinopropoxy)phenyl)-4,4-dibenzylheptane-3,5-dione (**16e**): Yellow oil, 84% yield. ^{1}H-NMR (300 MHz) δ: 1.99 (4H, m), 2.46 (8H, m), 2.51 (4H, t, J=6.9 Hz), 2.59 (4H, m), 2.71 (4H, m), 3.31 (4H, s), 3.71 (8H, m), 3.82 (6H, s), 4.03 (4H, t, J=6.6 Hz), 6.59 (4H, m), 6.78 (2H, d, J=8.7 Hz), 6.93 (4H, m), 7.21 (6H, m). HR-MS m/z: 807.4579 (Calcd for $C_{49}H_{64}N_2O_6$: 807.4586).

1,7-Bis(3-methoxy-4-(3-(4-methylpiperazinyl-1-yl)propoxy)-phenyl)-4,4-dibenzylheptane-3,5-dione (**16f**): Yellow oil, 73% yield. ^{1}H-NMR (300 MHz) δ: 1.99 (4H, m), 2.28 (6H, s), 2.52 (20H, m), 2.60 (8H, m), 3.31 (4H, s), 3.81 (6H, s), 4.02 (4H, t, J=6.6 Hz), 6.58 (4H, m), 6.78 (2H, d, J=8.7 Hz), 6.94 (4H, m), 7.21 (6H, m). HR-MS m/z: 833.5212 (Calcd for $C_{51}H_{69}N_4O_6$: 833.5219).

Antiproliferative Activity Assay The antiproliferative activity of curcumin analogues were evaluated with five human tumor cell lines by MTT assay. Briefly, approximately 5×10^3 cells (MCF-7, HepG2, HCT116, A549, and HT-1080) were suspended in 0.1 mL RPMI 1640 medium containing 10% fetal bovine serum (FBS) in triplicate in 96 well plate and 0.1 mL medium containing different concentrations of each analogue was added in each well and then incubated at 37°C for 48 h and then 0.1 mL of MTT solution (0.5 mg/mL) was added to each well. After 4 h incubated at 37°C, the mediums were removed carefully and 0.15 mL of dimethyl sulphoxide (DMSO) was added to dissolve the formazan crystals. The optical density (OD) values at 492 nm were measured with the enzyme-linked immunosorbent assay (ELISA) reader. The concentrations (IC_{50}s) which inhibited 50% of cell growth were calculated using Sigma plot10.

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