Improved Synthesis of Asymmetric Curcuminoids and Their Assessment as Antioxidants

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Abstract: In this paper, the syntheses of twelve asymmetric curcumin analogs using Pabon’s method are reported. Generally, the previously reported yields of asymmetric curcuminoids, such as 9a (53%), 9c (38%), and 9l (38%), have been moderate or low. Herein, we propose that the low yields were due to the presence of water and n-BuNH2 in the reaction media. To prove this formulated hypothesis, we have demonstrated that the yields can be improved by adding molecular sieves (MS) (4 Å) to the reaction mixture, thus reducing the interference of water. Therefore, improved yields (41–76%) were obtained, except for 9b (36.7%), 9g (34%), and 9i (39.5%). Furthermore, compounds 9b, 9d, 9e, 9f, 9g, 9h, 9i, 9j, and 9l are reported herein for the first time. The structures of these synthetic compounds were determined by spectroscopic and mass spectrometry analyses. The free radical scavenging ability of these synthetic asymmetric curcuminoids was evaluated and compared to that of the positive control butylated hydroxytoluene (BHT). Among the synthesized asymmetric curcuminoids, compounds 9a (IC50 = 37.57 ± 0.89 μM) and 9e (IC50 = 37.17 ± 1.76 μM) possessed effective 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging abilities, and compounds 9b (IC50 = 11.36 ± 0.65 μM) and 9i (IC50 = 10.91 ± 0.77 μM) displayed potent 2,2’-azinobis-(3-ethylbenzthiazoline-6-sulphonate) (ABTS) radical scavenging abilities comparable to that of curcumin (IC50 = 10.14 ± 1.04 μM). Furthermore, all the synthetic asymmetric curcuminoids were more active than BHT.

Keywords: asymmetric curcuminoids; curcuminoids; Pabon’s method; 2,4-pentanedione

1. Introduction

Turmeric is an orange-yellow powder that is obtained from the rhizomes of the natural plant Curcuma longa, and is used as a spice and traditional herbal medicine in South Asian countries like India and China. Although turmeric has been used for thousands of years, its major constituent curcumin was discovered in 1815 [1]. Thereafter, the structure of curcumin was determined [2], and it was synthesized [3] in the 1910s. The active components of turmeric that are used for medicinal purposes and as food additives for human health [4] are called curcuminoids. Their biological activities have attracted increasing attention from many researchers since the 1970s [5], and research on curcuminoids has grown rapidly since the 1990s [6]. The most abundant constituents of curcuminoids isolated from Curcuma longa are curcumin (CUR, curcumin I), demethoxycurcumin (DMC, curcumin II), and bisdemethoxycurcumin (BDMC, curcumin III), with contents of approximately 60–75%, 15–30%, and 3–15% yields, respectively (Figure 1) [7,8]. However, their
contents vary depending on their origin and species [8]. Curcumin possesses a bis-α,β-unsaturated framework, which equilibrates in either a keto form or a keto-enol form in solution (Figure 2). This phenomenon is called tautomerism, which is dependent on solvent, temperature, and pH, and is determined by detailed NMR analysis [8]. Neutral or acidic conditions favor the keto-enol form, whereas the keto form is dominant under alkaline conditions [9]. Among the aforementioned curcuminoids, DMC has an asymmetric structure.

Figure 1. The most abundant constituents of natural curcuminoids.

Figure 2. Tautomerism of curcumin under different pH values.

Natural curcuminoids and their synthetic derivatives exhibit a wide range of biological activities and are safe for consumers [10,11]. They possess anti-Alzheimer’s disease (AD) [12–15], anti-bacterial [16], anti-cancer [17–23], anti-inflammatory [12,24–31], and antioxidant properties [20,25,27,29], and are used in therapeutic treatments [9,32–35]. Curcuminoids have recently been used to synthesize diazepine derivatives, such as α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (AMPARs), which are involved in neurodegenerative diseases [36]. However, the limitations of using curcuminoids as pharmacological agents are due to their insolubility in water, instability, poor absorption, and rapid metabolism, which prevent their bioavailability. Furthermore, curcuminoids have been linked to over 100 cellular targets, limiting their use as therapeutic agents [12]. Therefore, improvements in the synthesis of curcuminoids are still underway, with the aim of obtaining oral bioavailable analogs [37,38].

The syntheses of symmetric or asymmetric curcumin analogs were performed using Pabon’s method [39] or modified versions of Pabon’s method [12,40,41]. Symmetric curcuminoids are generally prepared by treating 2,4-pentanedione and B2O3 in EtOAc, followed by the addition of two equivalents of the corresponding aldehydes, (BuO)3B and n-BuNH2, to yield 2 (Figure 3, path a). Following the same procedure, monosubstituted intermediate 3 was synthesized by adding one equivalent of aldehyde in the first step [9,12,42,43]. This intermediate can be either isolated or directly subjected to one-pot treatment with another equivalent of different aldehydes to afford 4 (Figure 3, path b). The drawback of asymmetric curcuminoid synthesis is low yields (<38–2%) [15,44]. Therefore, the synthesis of symmetric curcuminoids is more convenient, and their biological activities have been reported more routinely than those of asymmetric ones.
Oxidative stress is caused by an imbalance between free radical production and quenching. Active free radicals can react strongly with biomacromolecules, including DNA, carbohydrates, proteins, and membrane lipids, causing oxidative damage [45]. Furthermore, reactive oxygen species (ROS) play a vital role in many diseases, including atherosclerosis, cancer, mitochondrial diseases, and chronic diseases [46]. The property of hydrogen donation under oxidation allows curcumin to serve as a scavenger for most ROS [9,26,34]. Therefore, the ability to remove ROS can reduce cancer risk. In the pursuit of better oxidants than curcumin, we found that asymmetric curcumin analogs are relatively underexplored compared to symmetric ones. Therefore, the class of asymmetric curcuminoids reported here was evaluated for their antioxidant ability, and compared with curcumin and BHT as positive controls.

2. Results and Discussion

2.1. Chemistry

The syntheses of the asymmetric curcumin analogs are shown in Schemes 1 and 2. Monosubstituted intermediate 6 was prepared in the first step in order to synthesize asymmetric curcuminoids (Scheme 1). In this way, compound 6 was synthesized via Pabon’s method in moderate yield (45%) [22], and symmetric curcumin 7 was isolated as a by-product (6%) [16]. However, the yields of monosubstituted intermediates during the preparation of asymmetric curcuminoids have not been reported in the literature [14–16,21,42]. Monosubstituted 6 was therefore used as the starting material for condensation with another equivalent of the corresponding aldehydes 8a–l by employing the aforementioned procedure (Scheme 2). Unfortunately, these reactions are not clean, and repeated column chromatography purification is required to afford compounds 7, 9a–l, and 10a–l. The corresponding yields are listed in Table 1.
Scheme 1. Pabon’s method for the synthesis of monosubstituted intermediate 6.

Scheme 2. Pabon’s method for the synthesis of asymmetric curcumin analogues 9a–l.

Table 1. Yields of products for the synthesis of asymmetric curcumin analogues 9a–l from compound 6 in condensation with aldehydes 8a–l in Scheme 2.

| Entry | Aldehyde | Compound | Yield%  | Compound | Yield%  | Compound | Yield%  |
|-------|----------|----------|---------|----------|---------|----------|---------|
| 1     | 8a       | 7        | 12 (9.2 \(^a\)) | 9a       | 28 (58 \(^a\)) | 10a      | 2 (NA \(^a\)) |
| 2     | 8b       | 7        | 8 (9.5 \(^a\))   | 9b       | 27 (36.7 \(^a\)) | 10b      | 3 (NA \(^a\)) |
| 3     | 8c       | 7        | 7 (12 \(^a\))    | 9c       | 22 (73 \(^a\))   | 10c      | 3 (NA \(^a\)) |
| 4     | 8d       | 7        | 14.3 (3.8 \(^a\)) | 9d       | 12.5 (20 \(^a\)) | 10d      | NA (NA \(^a\)) |
| 5     | 8e       | 7        | 8.4 (6 \(^a\))   | 9e       | 28.9 (51.6 \(^a\)) | 10e      | 3 (NA \(^a\)) |
| 6     | 8f       | 7        | 10 (12.7 \(^a\)) | 9f       | 34.8 (49.2 \(^a\)) | 10f      | 4 (NA \(^a\)) |
| 7     | 8g       | 7        | 9.4 (2.5 \(^a\)) | 9g       | 31.1 (34 \(^a\)) | 10g      | 9 (NA \(^a\)) |
| 8     | 8h       | 7        | 10.6 (3.1 \(^a\)) | 9h       | 36.8 (44.7 \(^a\)) | 10h      | 11 (NA \(^a\)) |
| 9     | 8i       | 7        | 11.6 (NA \(^a\)) | 9i       | 37.8 (52.1 \(^a\)) | 10i      | 9 (NA \(^a\)) |
| 10    | 8j       | 7        | 11 (22.2 \(^a\)) | 9j       | 20.7 (40.9 \(^a\)) | 10j      | 8 (NA \(^a\)) |
| 11    | 8k       | 7        | 17.5 (14 \(^a\)) | 9k       | 11.2 (48.6 \(^a\)) | 10k      | 11 (NA \(^a\)) |
| 12    | 8l       | 7        | 18.5 (25.4 \(^a\)) | 9l       | 28.8 (39.5 \(^a\)) | 10l      | 5 (NA \(^a\)) |

\(^a\): Isolated yield by the improved method. NA = Was not obtained from column purification.
The results shown in Table 1 are interesting. The combined yields of compounds 7, 9a–l, and 10a–l were low to moderate (~27–59%, entries 1–12) [47]. Symmetric curcumin analogs 7 and 10a–l (except 10d) were isolated during the synthesis of asymmetric curcumin analogs. Additionally, asymmetric curcumin analogs 9a–l were obtained in low yields (~11–38%) throughout this study, which is consistent with the results reported in the literature [16]. We were interested in this phenomenon and proposed a plausible mechanism for the formation of by-products 7 and 10a–l, as shown in Figure 4.

Figure 4. Plausible mechanism of the formation of by-products 7 and compounds 10a–l for the synthesis of asymmetric curcuminoids 9a–l.

First, compound 6 was complexed with B_2O_3 to form compound 11, and then reacted with aldehydes 8a–l in the presence of (BuO)_3B and n-BuNH_2 to afford the target compounds 9a–l. Conversely, compound 11 may be hydrolyzed in the presence of trace amounts of water. Therefore, 11 underwent an accessible 1,4-addition with water to afford 12, followed by hydrogen abstraction to afford 13. Notably, compound 5 was recovered during this step. Compound 13 was deprotonated by n-BuNH_2 via a retro aldol process to convert back to intermediate 14, which is suspected to immediately recombine with hydrolyzed 5 to yield 7 in a faster manner [34]. Intermediate 14 also reacted with aldehydes 8a–l to yield 10a–l at a relatively slower rate. It has been reported that the removal of water in the reaction can increase curcumin yield [34].

The formation of intermediate 14 is most likely derived from the retro aldol reaction of boronic complex 11, because its conjugated system serves as a Michael acceptor. Compound 11 was hydrolyzed by n-BuNH_2; otherwise, compound 7 was not obtained. This evidence supports the hypothesis that the low yields of asymmetric curcuminoids are due to the presence of water. Notably, compound 10l has previously been used to kill Gram-positive bacteria efficiently via a photodynamic method [48]. Spectroscopy data for compounds
7 and 10a–c, and 10f–l were compared with previously reported ones [48], except for compound 10e.

To prove the hypothesis of the retro aldol reaction of compound 13 proposed herein, the identities of water and n-BuNH₂ must be clarified. Therefore, a control experiment was designed by adding an MS of 4 Å to the reaction mixture (see Experimental Section 3.4). It was concluded that the yields of compounds 9a–l were enhanced, although symmetric curcumin 7 was inevitably formed in every case (see parentheses in Table 1). However, no 10a–l was isolated by column chromatography in either case in the control experiment. This proves that the removal of water from the reaction mixture favors the target molecules. It is crucial to enhance the yields of compounds 9a–l and reduce the formation of compounds 10a–l.

2.2. Pharmacology/Biology

2.2.1. DPPH Free-Radical Scavenging Activity of Compounds 9a–l

DPPH, a kind of stable free radical, accepts an electron or hydrogen radical in order to be reduced to a pale-yellow molecule [49]. The changes in absorbance can be used to determine the antioxidant capacity of the sample. The inhibitory activity data of the compounds 9a–l as regards DPPH radical scavenging are shown in Figure 5 and Table 2. The commercially available antioxidant BHT was used as the positive control. From the results of the DPPH radical scavenging assay, the following conclusions can be drawn: (a) compounds 9a–l exhibited potent DPPH radical scavenging activities and were more effective than the positive control, BHT (IC₅₀ = 122.78 ± 0.96 µM); (b) compounds 9a (with 4-fluorophenyl moiety) and 9e (with 3-fluorophenyl moiety) showed the strongest DPPH radical scavenging activity among the synthesized compounds, with IC₅₀ values of 37.57 ± 0.89 and 37.17 ± 1.76 µM, respectively, and displayed more effective inhibition than their analog 9h (with 2-fluorophenyl moiety); (c) compounds 9b, 9c, 9f, and 9g (with 4-chlorophenyl, 4-bromophenyl, 3-chlorophenyl, and 3-bromophenyl moieties, respectively) exhibited more effective inhibition than their analogs, 9i and 9j (with 2-chlorophenyl and 2-bromophenyl moieties, respectively); (d) compound 9k (with thiophen-2-yl moiety) displayed more effective inhibition than its analog 9l (with 5-methylthiophen-2-yl moiety).

2.2.2. ABTS Radical Cation Scavenging Activity of Compounds 9a–l

Potassium persulfate converts ABTS into the blue ABTS radical cation, and it becomes colorless when neutralized by antioxidants [50]. The inhibitory activity data of the compounds 9a–l in terms of ABTS radical scavenging, using BHT as the positive control, are shown in Figure 5 and Table 2. From the results of the ABTS radical scavenging assay, the following conclusions can be drawn: (a) compounds 9a–l showed stronger ABTS radical scavenging activities than BHT (IC₅₀ = 71.94 ± 1.81 µM); (b) compound 9i proved the most effective among the synthesized compounds, with IC₅₀ = 10.91 ± 0.77 µM, in the scavenging of the ABTS free radicals; (c) compounds 9h and 9i (with 2-fluorophenyl and 2-chlorophenyl moieties, respectively) displayed more effective inhibition than their analogs 9a, 9b, 9e, and 9f (with 4-fluorophenyl, 4-chlorophenyl, 3-fluorophenyl, and 3-chlorophenyl moieties, respectively); (d) compound 9g (with 3-bromophenyl moiety) showed stronger ABTS inhibitory action than its analogs 9c and 9j (with 4-bromophenyl and 2-bromophenyl moieties, respectively); (e) compound 9k (with thiophen-2-yl moiety) exhibited more effective inhibition than its analog 9l (with 5-methylthiophen-2-yl moiety).
Figure 5. Bars show (A) DPPH and (B) ABTS radical scavenging activity at different concentrations (12.5, 25, 50, 100 µM) of compounds 9a–l, curcumin, and BHT. Bars represent mean ± SD of three experiments. Bars marked with different letters are significantly different (a p < 0.05; b p < 0.01; c p < 0.001 compared to control).

Table 2. DPPH and ABTS radical scavenging activity of compounds 9a–l, curcumin and BHT.

| Compounds | DPPH Radical IC_{50} (µM) | ABTS Radical Cation IC_{50} (µM) |
|-----------|--------------------------|-------------------------------|
| 9a        | 37.57 ± 0.89 *           | 18.79 ± 1.58 *                |
| 9b        | 40.55 ± 6.04 *           | 22.05 ± 0.51 *                |
| 9c        | 49.22 ± 7.57 *           | 17.47 ± 1.09 *                |
| 9d        | 54.47 ± 4.08 *           | 46.17 ± 1.62 *                |
| 9e        | 37.17 ± 1.76 *           | 19.55 ± 0.08 *                |
| 9f        | 40.74 ± 0.97 **          | 17.91 ± 1.21 *                |
| 9g        | 40.47 ± 1.71 **          | 14.18 ± 1.44 *                |
| 9h        | 41.81 ± 3.11 *           | 11.36 ± 0.65 **               |
| 9i        | 48.12 ± 8.70 *           | 10.91 ± 0.77 **               |
| 9j        | 66.67 ± 8.60             | 22.80 ± 0.26 *                |
| 9k        | 42.18 ± 4.75 *           | 15.05 ± 0.01 *                |
| 9l        | 63.77 ± 10.92 *          | 20.19 ± 1.08 *                |
| curcumin  | 28.56 ± 4.12 **          | 10.14 ± 1.04 **               |
| BHT b     | 122.78 ± 0.96 *          | 71.94 ± 1.81 *                |

Results are presented as averages ± SD (n = 3). a Concentration necessary for 50% inhibition (IC_{50}). b Butylated hydroxytoluene (BHT) was used as a positive control. * p < 0.05 compared with the control. ** p < 0.01 compared with the control.

3. Materials and Methods

3.1. General Procedures

All chemicals were purchased from the Uni-Onward Corporation in Taiwan and used without further purification. Ethyl acetate was dried over CaH_2 and distilled before use. Flash column chromatography was performed on 230–400 mesh SiO_2 gel (SiliaFlash® P60,
40–63 µm 60 Å; SiliCycle® Inc., Quebec City, QC, Canada). Structural determinations were based on 1H and 13C nuclear magnetic resonance spectroscopy (NMR) data and were recorded on a Bruker 600 MHz Ultrashield instrument. The chemical shifts were reported in parts per million (ppm) relative to the residual of the solvents: 1H (7.26 ppm) and 13C (77.0 ppm) for CDCl3, and 1H (4.78 ppm) and 13C (49.15 ppm) for CD3OD. Melting points were measured using an MP-2D apparatus and were uncorrected. The molecular weights of the compounds were determined by high-resolution mass spectrometry (HRMS) using a TMS-700 instrument in the electrospray ionization (ESI) mode. MS 4 Å was oven-dried overnight at 100 °C before use.

3.2. Synthesis of Monosubstituted 6 (Pabon’s Method)

An oven-dried flask was charged with a mixture of 2,4-pentanedione (1.09 mL, 10.60 mmol) and B2O3 (0.5130 g, 7.33 mmol) in dry EtOAc (4.0 mL), and then heated at 85 °C for 30 min. A mixture of compound 5 (0.807 g, 5.30 mmol) and (BuO)3B (0.372 mL, 1.38 mmol) in EtOAc (3.0 mL) was stirred at ambient temperature for 30 min before this mixture was added to the aforementioned solution. This mixture was heated at 85 °C for 30 min, and n-BuNH2 (0.21 mL, 2.12 mmol) and EtOAc (1.0 mL) were added to the mixture using a syringe pump at 0.5 mL/h. The reaction was monitored by TLC till completion (18–24 h, depending on the aldehydes used; the reaction time for aldehyde 8d was 48 h). The mixture was then cooled to 50 °C, followed by the addition of 2 N HCl (5.5 mL) and stirring for 30 min. Then the mixture was diluted in H2O and extracted with EtOAc. The organic layer was dried (MgSO4), concentrated, and purified using flash column chromatography.

3.3. Synthesis of Asymmetric Curcumin Analogs

Compound 6 (1 equivalent) was reacted with B2O3 (0.5 equivalent), (BuO)3B (2 equivalent), and n-BuNH2 (1 equivalent) by Pabon’s method, except that different aldehydes (2 equivalents) were used. The organic layer was purified by flash column chromatography to obtain compounds 7, 9a–l, and 10a–l.

3.4. Controlled Experiment

A mixture of compound 6 (1 equivalent), B2O3 (0.5 equivalent), and MS 4 Å (3.5-fold w/w relative to the amount of compound 6) in dry EtOAc was heated at 85 °C for 30 min. We then followed the procedure described in Section 3.2. The crude mixture was purified using column chromatography. Please note that using more than 3.5 times the amount of MS 4 Å gave rise to low yields of compounds 9a–l.

3.5. Biological Assay

3.5.1. Materials

2,2-Diphenyl-1-picrylhydrazyl (DPPH) was obtained from the Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). 2,2’-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Potassium peroxodisulfate was obtained from SHOWA Chemical Co., Ltd. (Chuo-ku, Japan).

3.5.2. DPPH Radical Scavenging Assay

The DPPH radical-scavenging activity of each compound was measured as previously described [51]. Briefly, the DPPH solution (400 µM, dissolved in ethanol, 100 µL) and different concentrations (6.25, 12.5, 25, 50, 100, and 200 µM) of each compound (dissolved in ethanol, 100 µL) were mixed in a 96-well microplate. After incubation in the dark at room temperature for 30 min, the absorbance was measured at 520 nm using an ELISA plate reader (µQuant; Tecan Group Ltd., Switzerland) (µQuant). The DPPH radical scavenging activity was determined using the following formula:

DPPH radical inhibiting activity (%) = (Ac − At)/Ac × 100,
Here, Ac and At are the absorbances of the control (untreated group) and test sample, respectively. Commercially available BHT was used as a positive control. All half-maximal inhibitory concentration (IC\(_{50}\)) values of the tested activities were determined using linear regression of the percentage of remaining radicals against the sample concentration.

### 3.5.3. ABTS Cation Radical Scavenging Activity

The ABTS cation radical scavenging activity was determined using the reference method [50]. The mixture of 28 mM ABTS solution and 9.6 mM potassium peroxydisulfate (1/1, v/v) was incubated in the dark at room temperature for 16 h to prepare the ABTS cation solution. The solution was diluted with ethanol to obtain an absorbance of 0.70 ± 0.02 at 740 nm. Different concentrations of extracts (10 \(\mu\)L) were then mixed with the working solution (190 \(\mu\)L) and incubated at room temperature for 6 min. ABTS cation radical scavenging activity was determined by calculating the decrease in absorbance measured at 740 nm using the following equation:

\[
\text{ABTS radical inhibiting activity (\%)} = \left( \frac{\text{Ac} - \text{At}}{\text{Ac}} \right) \times 100.
\]

Commercially available BHT was used as a positive control. All the IC\(_{50}\) values of the tested activities were determined using linear regression of the percentage of remaining radicals against the sample concentration.

### 3.5.4. Statistical Analysis

All data are expressed as mean ± standard deviation (SD). Statistical analysis was performed using Student's \(t\)-test. A probability of \(\leq 0.05\) or less was considered statistically significant. All experiments were performed at least three times.

### 3.6. Synthetic Compounds

The following reactions were all conducted under the Section 3.4.

#### 3.6.1. (E)-6-(4-Hydroxy-3-methoxyphenyl)hex-5-ene-2,4-dione (6)

Purification by flash chromatography (EtOAc:Hexane = 1:4–1:2–1:1; EtOAc:Hexane = 1:2, \(R_f = 0.6\)) afforded a yellow solid. Yield: 45%. \(\text{Literature}\ [22, 23] 45\% ; [23] 50\% \). Mp 147–149°C (\(\text{Literature}\ [22, 23] 146–147\°C\)). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.53 (d, \(J = 15.8\) Hz, 1H), 7.08 (dd, \(J = 8.2, 1.7\) Hz, 1H), 7.00 (d, \(J = 1.7\) Hz, 1H), 6.92 (d, \(J = 8.2\) Hz, 1H), 6.32 (d, \(J = 15.8\) Hz, 1H), 3.93 (s, 3H), 2.17 (s, 3H).

\(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 196.9, 177.9, 147.7, 146.8, 140.0, 127.7, 122.6, 120.3, 114.8, 109.5, 100.7, 55.9, 26.8. HRMS (ESI) calculated for C\(_{13}\)H\(_{13}\)O\(_4\) [M–H]\(^+\) 233.0814. Found: 233.0817.

#### 3.6.2. (1E,6E)-1-(4-Fluorophenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (9a)

Purification by flash chromatography (EtOAc:Hexane = 1:3–1:1; EtOAc:Hexane = 1:2, \(R_f = 0.3\)) afforded an orange-red solid. Yield: 58% \(\text{Literature}\ [16] 53\% \). Mp 154–155°C (\(\text{Literature}\ [16] 146–147\°C\)). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.60 (d, \(J = 15.7\) Hz, 2H), 7.53 (dd, \(J = 8.6, 5.4\) Hz, 2H), 7.13 (dd, \(J = 8.2, 1.6\) Hz, 1H), 7.08 (t, \(J = 8.5\) Hz, 2H), 7.05 (d, \(J = 1.6\) Hz, 1H), 6.93 (d, \(J = 8.0\) Hz, 1H), 6.59 (d, \(J = 15.8\) Hz, 1H), 6.53 (d, \(J = 15.8\) Hz, 1H), 5.89 (s, 1H), 5.81 (s, 1H), 3.95 (s, 3H).

\(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 184.3, 182.1, 163.7 \(J_C-F = 249.0\) Hz), 148.0, 146.8, 141.1, 138.8, 131.3, 129.8 \(J_C-F = 7.5\) Hz), 127.6, 123.8, 123.0, 121.7, 115.9 \(J_C-F = 22.5\) Hz), 114.8, 109.6, 101.5, 56.0. HRMS (ESI) calculated for C\(_{20}\)H\(_{18}\)FO\(_4\) [M+H]\(^+\) 341.1184. Found: 341.1184.

#### 3.6.3. (1(E,6E)-1-(4-Chlorophenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (9b)

Purification by flash chromatography (EtOAc:Hexane = 1:3–1:1; EtOAc:Hexane = 1:2, \(R_f = 0.4\)) afforded a red solid. Yield: 36.7%. Mp 115–120°C. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.61 (d, \(J = 15.4\) Hz, 1H), 7.58 (d, \(J = 15.4\) Hz, 1H), 7.47 (d, \(J = 8.5\) Hz, 2H), 7.36 (d, \(J = 8.5\) Hz,
2H), 7.12 (dd, J = 8.2, 1.7 Hz, 1H), 7.05 (d, J = 1.7 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.56 (d, J = 15.8 Hz, 1H), 6.49 (d, J = 15.8 Hz, 1H), 5.92 (s, 1H), 5.81 (s, 1H), 3.94 (s, 3H). 13C NMR (150 MHz, CDCl3) δ 184.7, 181.5, 148.0, 146.8, 141.3, 138.6, 135.8, 133.6, 129.2, 127.5, 124.5, 123.1, 121.7, 114.9, 109.7, 101.7, 56.0. HRMS (ESI) calculated for C20H18ClO4 [M+H]+: 357.0894. Found: 357.0905.

3.6.4. (1E,6E)-1-(4-Bromophenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (9d)

Purification by flash chromatography (EtOAc:Hexane = 1:3–1:1; EtOAc:Hexane = 1:2, Rf = 0.46) afforded an orange solid. Yield: 73% (literature [16] 32%; [44] 38%). Mp 113–116 °C (literature [16] 148–149 °C). 1H NMR (600 MHz, CDCl3) δ 7.61 (d, J = 15.8 Hz, 1H), 7.57 (d, J = 15.8 Hz, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 7.13 (dd, J = 8.2, 1.4 Hz, 1H), 7.05 (d, J = 1.3 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.58 (d, J = 15.8 Hz, 1H), 6.49 (d, J = 15.8 Hz, 1H), 5.89 (s, 1H), 5.81 (s, 1H), 3.93 (s, 3H). 13C NMR (150 MHz, CDCl3) δ 184.8, 181.4, 148.1, 146.8, 141.3, 138.6, 134.0, 132.1, 129.4, 127.5, 124.6, 124.1, 123.1, 121.8, 114.9, 109.7, 101.7, 56.0. HRMS (ESI) calculated for C20H18BrO4 [M+H]+: 401.0383. Found: 401.0383.

3.6.5. (1E,6E)-1-(4-Hydroxy-3-methoxyphenyl)-7-(4-nitrophenyl)hepta-1,6-diene-3,5-dione (9e)

Purification by flash chromatography (EtOAc:Hexane = 1:3–1:1; EtOAc:Hexane = 1:2, Rf = 0.45) afforded an orange-red solid. Yield: 20% (27% based on the recovery of compound 6). Mp 149–151 °C. 1H NMR (600 MHz, CDCl3) δ 8.25 (d, J = 8.8, 2H), 7.68 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 15.8 Hz, 1H), 7.65 (d, J = 15.8 Hz, 1H), 7.15 (dd, J = 8.3, 1.9 Hz, 1H), 7.07 (d, J = 1.9 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 15.8 Hz, 1H), 6.53 (d, J = 15.8 Hz, 1H), 5.88 (s, 1H), 5.87 (s, 1H), 3.96 (s, 3H). 13C NMR (150 MHz, CDCl3) δ 186.4, 179.0, 148.3, 148.1, 146.9, 142.2, 141.4, 136.7, 128.4 (2 X), 127.9, 127.4, 124.2 (2 X), 123.3, 121.8, 114.9, 109.7, 102.4, 56.0. HRMS (ESI) calculated for C20H16NO6 [M–H]–: 366.0978. Found: 366.0975.

3.6.6. (1E,6E)-1-(3-Fluorophenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (9e)

Purification by flash chromatography (EtOAc:Hexane = 1:3–1:1; EtOAc:Hexane = 1:2, Rf = 0.5) afforded an orange solid. Yield: 51.6%. Mp 154–155 °C. 1H NMR (600 MHz, CD2OD) δ 7.58 (d, J = 15.8 Hz, 1H), 7.54 (d, J = 15.8 Hz, 1H), 7.40–7.37 (m, 1H), 7.34 (d, J = 8.0, 1.8 Hz, 1H), 7.18 (d, J = 1.8 Hz, 1H), 7.10–7.06 (m, 2H), 6.81 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 15.8 Hz, 1H), 6.61 (d, J = 15.8 Hz, 1H), 5.99 (s, 1H), 3.89 (s, 3H). 13C NMR (150 MHz, CD2OD) δ 187.2, 181.8, 164.6 (JCF = 243.0 Hz), 150.7, 149.4, 143.2, 139.5, 139.1 (JC,F = 7.5 Hz), 131.7 (JC,F = 7.5 Hz), 128.4, 126.5, 125.3, 124.4, 117.5 (JC,F = 21.0 Hz), 116.6, 115.0 (JC,F = 23.0 Hz), 111.9, 102.7, 56.5. HRMS (ESI) calculated for C20H18FO4 [M+H]+: 341.1189. Found: 341.1189.

3.6.7. (1E,6E)-1-(3-Chlorophenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (9f)

Purification by flash chromatography (EtOAc:Hexane = 1:3–1:1; EtOAc:Hexane = 1:2, Rf = 0.4) afforded an orange-red solid. Yield: 49.2%. Mp 67–71 °C. 1H NMR (600 MHz, CD2OD) δ 7.64 (s, 1H), 7.61 (d, J = 15.8 Hz, 1H), 7.55 (d, J = 16.1 Hz, 1H), 7.53 (d, J = 9.0 Hz, 1H), 7.40–7.35 (m, 2H), 7.21 (d, J = 1.5 Hz, 1H), 7.11 (dd, J = 8.4, 1.8 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 13.2 Hz, 1H), 6.65 (d, J = 15.8 Hz, 1H), 6.02 (s, 1H), 3.91 (s, 3H). 13C NMR (150 MHz, CD2OD) δ 187.3, 181.7, 150.8, 149.5, 143.2, 139.1, 138.8, 136.0, 131.5, 130.7, 128.7, 128.4, 127.5, 126.7, 124.0, 122.4, 116.6, 111.4, 102.7. HRMS (ESI) calculated for C20H18ClO4 [M+H]+: 357.0894. Found: 357.0893.
3.6.8. (1E,6E)-1-(3-Bromophenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (9g)

Purification by flash chromatography (EtOAc:Hexane = 1:3–1:1; EtOAc:Hexane = 1:2, 
Rp = 0.5) afforded an orange solid. Yield: 34%. Mp 74–78 °C. 1H NMR (600 MHz, CDCl3) δ 7.70 (s, 1H), 7.61 (d, J = 15.8 Hz, 1H), 7.55 (d, J = 15.8 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.13 (dd, J = 8.2, 1.8 Hz, 1H), 7.06 (d, J = 1.7 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.58 (d, J = 15.8 Hz, 1H), 6.50 (d, J = 15.8 Hz, 1H), 5.89 (s, 1H), 5.82 (s, 1H), 3.95 (s, 3H). 13C NMR (150 MHz, CDCl3) δ 185.2, 180.9, 148.1, 146.8, 141.5, 138.2, 137.3, 132.6, 130.5, 130.4, 127.5, 125.3, 123.2, 123.0, 121.8, 114.9, 109.7, 101.8, 56.0. HRMS (ESI) calculated for C21H18BrO4 [M+H]+ 401.0388. Found: 401.0381.

3.6.9. (1E,6E)-1-(2-Fluorophenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (9h)

Purification by flash chromatography (EtOAc:Hexane = 1:3–1:1; EtOAc:Hexane = 1:2, 
Rp = 0.5) afforded an orange-yellow solid. Yield: 44.7%. Mp 124–127 °C. 1H NMR (600 MHz, CDCl3) δ 7.75 (d, J = 16.0 Hz, 1H), 7.61 (d, J = 15.8 Hz, 1H), 7.55 (td, J = 7.6, 1.4 Hz, 1H), 7.36–7.31 (m, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.12 (dd, J = 8.2, 1.9 Hz, 1H), 7.10 (dd, J = 10.1, 8.4 Hz, 1H), 7.05 (d, J = 1.8 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 16.1 Hz, 1H), 6.50 (d, J = 15.8 Hz, 1H), 5.91 (s, 1H), 5.85 (s, 1H), 3.95 (s, 3H). 13C NMR (150 MHz, CDCl3) δ 184.9, 181.5, 161.4 (JCF = 253.5 Hz), 148.0, 146.8, 141.2, 132.7, 131.2 (JCF = 7.5 Hz), 129.2, 127.6, 126.6 (JCF = 6.0 Hz), 124.5, 123.2, 123.1, 121.8, 116.2 (JCF = 21.0 Hz), 114.8, 109.2, 101.7, 56.0. HRMS (ESI) calculated for C21H13FO4 [M+H]+ 341.1189. Found: 341.1189.

3.6.10. (1E,6E)-1-(2-Chlorophenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (9i)

Purification by flash chromatography (EtOAc:Hexane = 1:3–1:1; EtOAc:Hexane = 1:2, 
Rp = 0.33) afforded an orange-red solid. Yield: 52.1%. Mp 118–120 °C. 1H NMR (600 MHz, CDCl3) δ 8.30 (d, J = 15.8 Hz, 1H), 7.66–7.63 (m, 1H), 7.61 (d, J = 15.8 Hz, 1H), 7.43–7.40 (m, 1H), 7.30–7.26 (m, 2H), 7.12 (dd, J = 8.3, 1.3 Hz, 1H), 7.05 (s, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.59 (d, J = 15.8 Hz, 1H), 6.50 (d, J = 15.8 Hz, 1H), 5.95 (s, 1H), 5.86 (s, 1H), 3.93 (s, 3H). 13C NMR (150 MHz, CDCl3) δ 184.9, 181.3, 148.0, 146.8, 141.3, 135.7, 135.0, 133.3, 130.7, 130.2, 127.5, 127.0, 126.5, 123.1, 121.8, 116.2, 114.8, 109.6, 101.5, 55.9 HRMS (ESI) calculated for C21H13ClO4 [M+H]+ 357.0894. Found: 357.0891.

3.6.11. (1E,6E)-1-(2-Bromophenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (9j)

Purification by flash chromatography (EtOAc:Hexane = 1:3–1:1; EtOAc:Hexane = 1:2, 
Rp = 0.4) afforded an orange diene. Yield: 40.9%. Mp 132–133 °C. 1H NMR (600 MHz, CD2OD) δ 7.93 (d, J = 15.8 Hz, 1H), 7.77 (d, J = 6.9, 1.0 Hz, 1H), 7.62 (dd, J = 7.6, 0.8 Hz, 1H), 7.60 (d, J = 15.9 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.24 (td, J = 8.6, 1.4 Hz, 1H), 7.20 (d, J = 1.6 Hz, 1H), 7.10 (dd, J = 8.2, 1.7 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 15.8 Hz, 1H), 6.64 (d, J = 15.8 Hz, 1H), 4.67 (s, 1H), 3.90 (s, 3H). 13C NMR (150 MHz, CD2OD) δ 187.8, 181.3, 150.9, 149.6, 143.5, 138.8, 136.4, 134.7, 132.3, 129.3, 129.0, 128.5, 127.9, 126.4, 124.6, 122.6, 116.8, 112.0, 56.6. HRMS (ESI) calculated for C21H18BrO4 [M+H]+ 401.0388. Found: 401.0403.

3.6.12. (1E,6E)-1-(4-Hydroxy-3-methoxyphenyl)-7-(thiophen-2-yl)hepta-1,6-diene-3,5-dione (9k)

Purification by flash chromatography (EtOAc:Hexane = 1:3–1:1; EtOAc:Hexane = 1:2, 
Rp = 0.31) afforded a red solid. Yield: 48.6% (literature [23] 38%). Mp 127–129 °C (literature [23] Mp 130–132 °C). 1H NMR (600 MHz, CDCl3) δ 7.76 (d, J = 15.5 Hz, 1H), 7.59 (d, J = 15.8 Hz, 1H), 7.38 (d, J = 5.1 Hz, 1H), 7.25 (s, 2H), 7.12 (dd, J = 8.2, 1.8 Hz, 1H), 7.06 (d, J = 8.6 Hz, 1H), 7.05 (dd, J = 8.2, 1.9 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.47 (d, J = 15.8 Hz, 1H), 6.41 (d, J = 15.5 Hz, 1H), 5.89 (s, 1H), 5.77 (s, 1H), 3.95 (s, 3H). 13C NMR (150 MHz, CDCl3) δ 183.9, 182.0, 147.9, 146.8, 140.9, 140.6, 132.8, 130.7, 128.2 (2 X), 127.6, 123.1, 123.0,
121.8, 114.8, 109.6, 101.5, 56.0. HRMS (ESI) calculated for C_{18}H_{17}O_{4}S [M+H]\textsuperscript{+} 329.0848. Found: 329.0851.

3.6.13. (1E,6E)-1-(4-Hydroxy-3-methoxyphenyl)-7-(5-methylthiophen-2-yl)hepta-1,6-diene-3,5-dione (9l)

Purification by flash chromatography (EtOAc:Hexane = 1:3–1:1; EtOAc:Hexane = 1:2, \( R_f = 0.35 \)) afforded an orange-red solid. Yield: 39.5%. Mp 155–157 °C. \( \text{^1} \text{H} \text{NMR (600 MHz, CDCl}_3 \)) \( \delta 7.68 (d, J = 15.4 \text{ Hz, 1H}), 7.57 (d, J = 15.7 \text{ Hz, 1H}), 7.11 (dd, J = 8.2, 1.6 \text{ Hz, 1H}), 7.06 (d, J = 3.5 \text{ Hz, 1H}), 7.04 (d, J = 1.6 \text{ Hz, 1H}), 6.93 (d, J = 8.2 \text{ Hz, 1H}), 6.71 (d, J = 3.3 \text{ Hz, 1H}), 6.46 (d, J = 15.7 \text{ Hz, 1H}), 6.27 (d, J = 15.4 \text{ Hz, 1H}), 5.74 (s, 1H), 3.93 (s, 3H), 2.51 (s, 3H). \( \text{^13} \text{C} \text{NMR (150 MHz, CDCl}_3 \)) \( \delta 183.3, 182.7, 147.9, 146.8, 144.0, 140.5, 138.6, 133.4, 131.6, 127.7, 126.7, 122.9, 121.8, 114.8, 109.6, 101.3, 56.0, 15.9. HRMS (ESI) calculated for C_{19}H_{19}O_{4}S [M+H]\textsuperscript{+} 343.1004. Found: 343.1010.

4. Conclusions

All conditions used for the synthesis of asymmetric curcumin analogues were similar, and their yields reported in the literature were low to moderate. Our results clearly indicate that the moderate yield of monosubstituted 6 is due to the competitive formation of bissubstituted 7. The subsequent step also involves the cleavage of 11 by water, mediated by n-BuNH\textsubscript{2}, to yield three different compounds, as shown in Figure 3. Our finding is crucial and provides the optimized conditions for the synthesis of asymmetric curcuminoids by adding MS 4Å. In conclusion, compound 9a–l possessed antioxidant potential and might be useful against free radical-induced disorders. It is worthy of note that symmetric 10l was previously investigated for its photodynamic killing of Gram-positive microbes under blue light, with great potential. Compounds 9a–l will be evaluated via their photodynamic effects on bacteria, and the results will be reported in due course. The synthetic compounds 9a–l showed more potent DPPH and ABTS radical scavenging activities than the known antioxidant BHT. The present study suggests that the bioactive synthetic compounds 9a–l (especially 9a, 9e, 9h and 9i) are worthy of further investigation, and should developed as candidates for the treatment or prevention of oxidative stress-related diseases.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27082547/s1. \( \text{^1} \text{H} \) and \( \text{^13} \text{C} \) NMR data for compounds 6, 9a–l and 10e.

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