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Facile preparation of new unsymmetrical curcumin derivatives by solid-phase synthesis strategy

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Abstract—Seventeen unsymmetrical curcumin derivatives were synthesized in good yield and purity by a facile solid phase synthesis strategy.

Curcumin, a yellow pigment isolated from the root of *Curcuma longa* rhizomes, was widely used as food additive for many years. It has been found in the last decades that curcumin derivatives possess broad biological activities, such as antioxidant activity,[1] anti-imflammatory properties,[2] anti-HIV protease activity[3] and cancer preventive properties.[4,5] Although the poor solubility becomes a major problem in pharmacological test, a large number of curcumin derivatives were prepared and investigated by medicinal chemists owing to their excellent bioactivities along with low toxicity.

Synthetic curcumin derivatives could be simply obtained via one step coupling of 2 equiv aromatic aldehydes with 1 equiv acetylacetone.[6] The disadvantage is obvious, however, that the equal reactivity of the two terminal α-carbons (α-C) in acetylacetone provides the same chance when they are reacted with aldehydes, resulting in only symmetrical curcumin derivatives (Fig. 1, $Ar_1 = Ar_2$). The synthesis of unsymmetrical curcumin derivatives, which have different aromatic moieties ($Ar_1 \neq Ar_2$), needed more tricks. Early solution is by using excessive acetylacetone to react with aldehyde to form mono-aromatic ring substituted hexanone in the first step, then followed by condensation with another aromatic aldehyde.[7] This strategy is inconvenient in the practical operation when a way of parallel or combinatorial synthesis was proposed because of the low yield and the requirement of column chromatography for purification. To the best of our knowledge, despite the intensive chemical and pharmacological investigations of various symmetrical curcumin derivatives, studies on unsymmetrical curcumin compounds actually remain scarce. Herein, we first describe a facile solid-phase synthesis strategy to prepare the novel unsymmetrical curcumin derivatives in high purity and good yield, targeting on the diversity of curcumin derivatives for further activity screening.

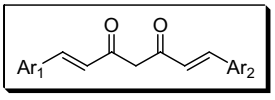

Figure 1. General structure of curcumin derivatives.

As efficient tools in rapid generation of diverse libraries of drug-like compounds, solid-phase synthesis and combinatorial chemistry have been well known in drug discovery. Our strategy is based on the 'pseudo-dilution effect', in which large size of the solid supports renders the resin-bound species inaccessible to each other and

Keywords: Solid-phase synthesis; Unsymmetrical curcumin derivatives.
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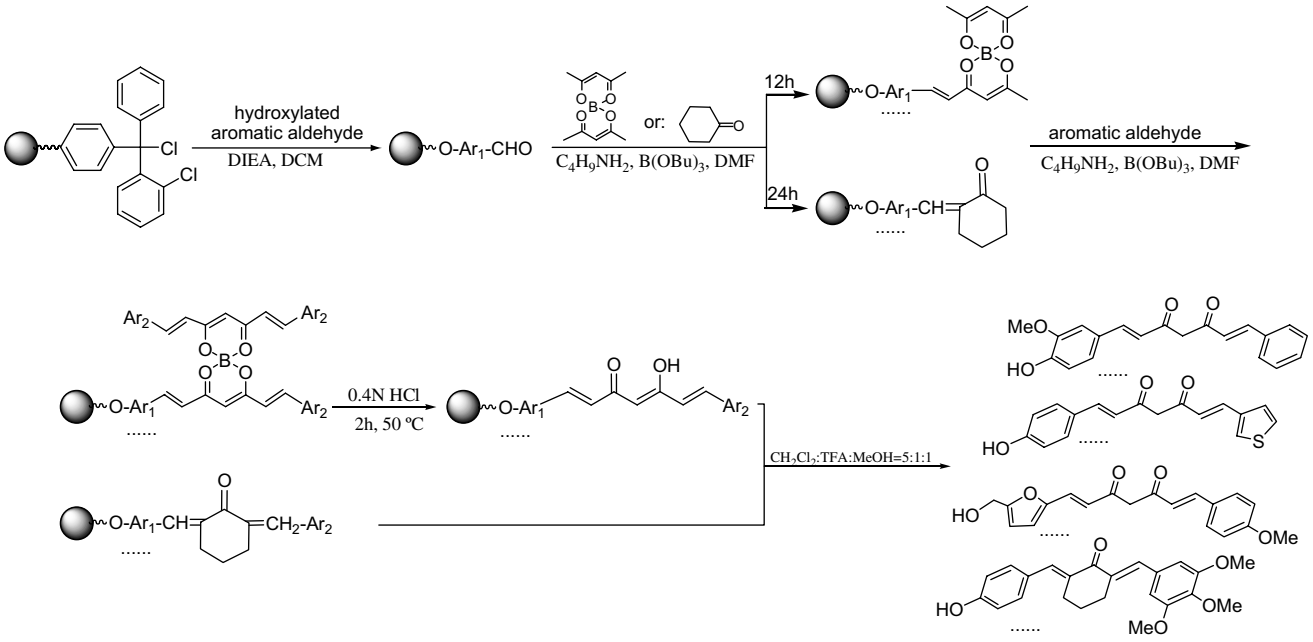
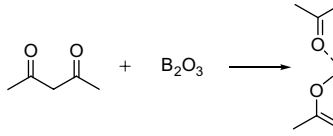
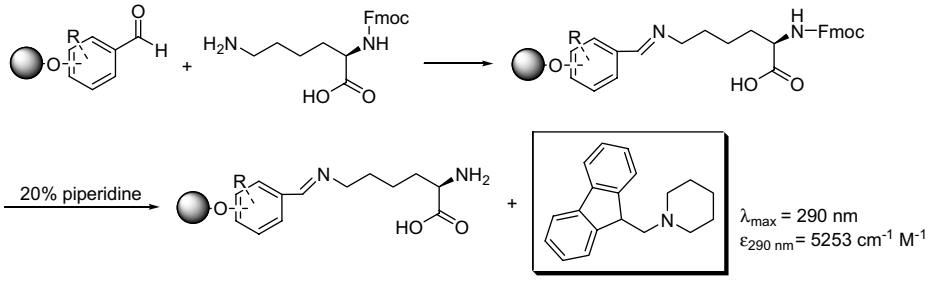


Scheme 1. Parallel synthesis of unsymmetrical curcumin derivatives.

then, cross reactions can be avoided[8,9] while good regio selectivity can be achieved in the reaction. The whole procedure began with loading aromatic aldehydes to a solid support, followed by coupling a methylene-protected acetylacetone to the resin-bound aldehyde group through the well known Claisen–Schimidt condensation reaction. In this way, only one terminal α-C of acetylacetone was linked to the resin-bound aldehyde group, leaving the other terminal α-C for alternative aromatic aldehyde condensation (Scheme 1). The active methylene of acetylacetone was protected with a boric-acetylacetone complex (Scheme 2), by forming a stable enol configuration to avoid the Knoevenagel reaction.[6] Briefly, excessive acetylacetone and boric anhydride (B_2O_3) were mixed at 70 °C to produce the methylene protected boric-acetylacetone complex as a white insoluble powder. A mixture of the white powder, tributyl borate and catalytic amount of butylamine in DMF was added to the aldehyde-bound resin and the mixture was shaken at 50 °C for 12 h. This step was monitored by IR based on the fact that the resin-bound aldehyde groups of *p*-hydroxybenzaldehyde and vanillin show typical IR absorption at 1687 cm^{-1} and 1694 cm^{-1}, respectively. The resin was then split into several parts,



Scheme 2. Protection of methylene of acetylacetone.



Scheme 3. The determination of the loading value by Fmoc detection.

Table 1. The loading value of the first aldehyde onto resin (mmol/g)

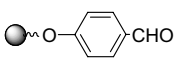
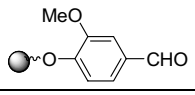
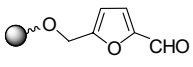
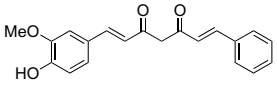
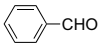
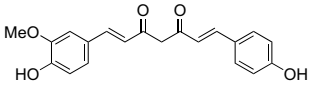
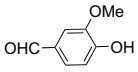
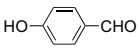
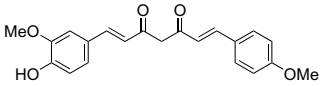
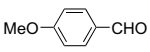
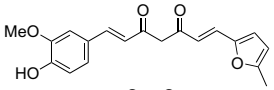
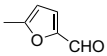
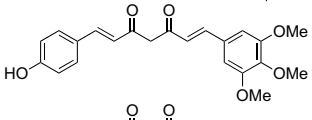
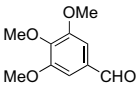
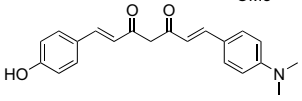
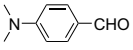
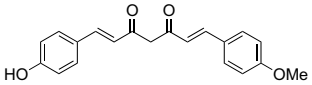
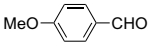
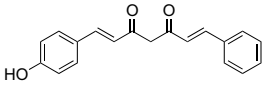
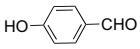
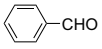
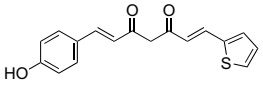
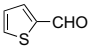
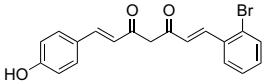
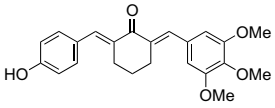
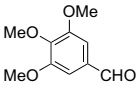
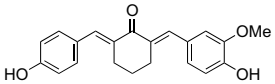
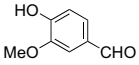
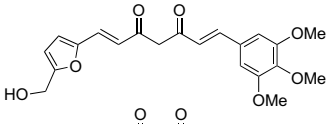
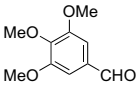
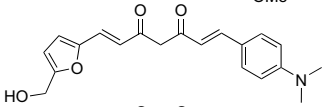
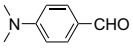
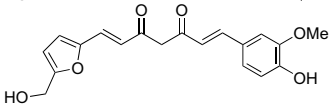
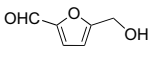
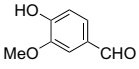
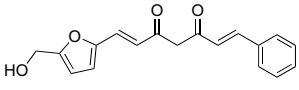
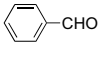
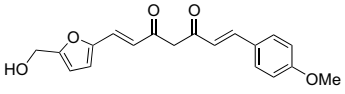
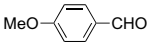
On-resin aldehyde			
LV (mmol/g)	0.48	0.64	0.73

Table 2. Compounds obtained from parallel solid-phase synthesis using CLTR as solid support

Compound	Structure	1st aldehyde	Ketone	2nd aldehyde	Purity (%)[a]	Yield (%)[b]	
						Y_o	Y_{lv}
1a					89	29	95
1b					97	30	99
1c					98	30	99
1d					90	29	96
2a					95	40	99
2b					95	38	96
2c					95	38	96
2d					97	40	99
2e					92	38	95
2f					90	38	94
2g					98	40	99
2h					90	38	95
3a					90	44	96
3b					92	44	97
3c					93	44	96
3d					89	43	94
3e					94	44	96

[a] Calculated from HPLC and the integral peaks were selected 5 min later, conditions as mentioned in Figure 2.
[b] Y_o: yield based on the original substitution. Y_{lv}: yield based on loading level of the first aldehyde on resin.

to each part different aromatic aldehydes and tributyl borates, and catalytic butylamine were added at 50 °C, and the resin was shaken for 12 h. After the resin was washed and dried under N_2, the boric-acetylacetone complex was decomposed with 0.4 N HCl at 50 °C for 2 h; the final products were cleaved using DCM/TFA/MeOH (5:1:1) from the washed and dried resins, and dried under a vacuum. All products were characterized without further purification except for the elemental analysis (EA).

In our current procedure, 2-chlorotrityl chloride resin (CLTR, substitution value: 1.0 mmol/g), which was widely used in peptide synthesis,[10] was chosen as the solid support. The phenolic or hydroxyl group in the first aldehydes was anchored onto CLTR in the presence of 2.5 equiv of DIEA (diisopropylethylamine) in DCM through S_N1 nucleophilic substitutions. The unreacted sites of resins were then capped by MeOH.

The loading value of the first building block onto the solid support is critical to the practicability of a solid phase synthesis strategy, and it should be properly determined. In our work, the loading value of the first aldehyde onto the resin was determined by a modified Fmoc detection method[11,12] (Scheme 3), which was well used in solid phase peptide synthesis. Nα-Fmoc protected lysine reacted with resin-bound aldehyde in trimethyl orthoformate (TMOF) to produce an on-resin Schiff base. Twenty percent piperidine in DMF (3 ml) was utilized to remove Fmoc group from the resin, and UV absorbance of Fmoc–piperidine adduct was recorded at 290 nm. The loading value was then calculated by the equation: LV (mmol/g) $= A_{290}$/(mg of resin × 1.75). In this work, the loading value was determined as up to 0.73 mmol/g that afforded satisfactory results in the practical works (Table 1).

When cyclohexanone was used in replacing acetylacetone, the monoketone curcumin derivatives[4] were obtained via the similar procedure, except that the protection/deprotection process was omitted.

A total of 17 unsymmetrical curcumin derivatives listed in Table 2 were designed and synthesized parallelly according to the above procedure.[13] Products except **1a**–**c**, **2c**, **2d**, and **2h**[14,15] were identified as new compounds based on the best of our knowledge, and they were characterized by ^{1}HNMR, EA, HRMS, ESI/EI-MS[16] and HPLC (Fig. 2, Table 2).

It should be noted that the symmetrical derivatives $Ar_2CHCHCOCH_2COCHCHAr_2$ were also formed during the second aldehyde condensation (Scheme 1). These byproducts were not determined and collected, but washed away in the boric-acetylacetone complex decomposition step in the current works.

In summary, we have developed a facile solid-phase strategy and conveniently synthesized 17 unsymmetrical curcumin derivatives in good yield and high purity. Compared to the classical liquid-phase protocol, which needs complicated purification processing even in some symmetrical curcumin derivatives synthesis, the described strategy seems to be more efficient and can readily be adopted to combinatorial chemistry to generate more novel unsymmetrical curcumin diversities as well as the symmetrical ones. Extensive works of constructing a curcuminoid-conjugated peptide library targeting on anti-tumor studies are actively underway in our laboratory.

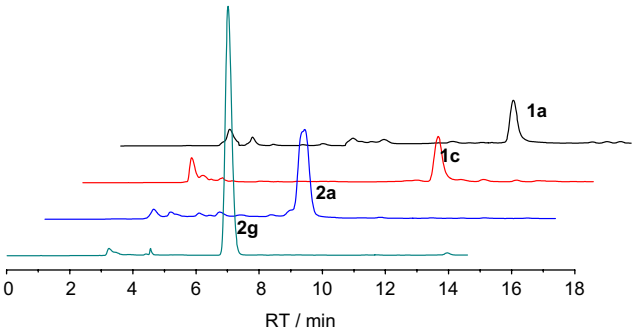


Figure 2. Representative HPLC spectrum of curcumin derivatives Conditions: BDS HYPERSIL C18 column (250 mm × 4.6 mm) at 254 nm. Gradient: MeOH in H_2O variating from 70% to 90% over 20 min, flow rate: 1 mL/min.

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13. *General procedure*: A mixture of 6 equiv of 1st aromatic aldehyde and 2.5 equiv of DIEA in DCM was added to a pre-swollen resin (1.0 mmol/g) at rt and reacted for 12 h. After washed with DCM, the resin was capped with DCM/MeOH/DIEA (80:15:5) for 2×15 min and dried. To synthesize β-diketone curcumin derivatives, 20 equiv of acetylacetone and 15 equiv of boric anhydride (B_2O_3) were first mixed in DMF for 1 h at 70 °C. The resultant white powder and 15 equiv of tributyl borate were added to the aldehyde-bound resin in DMF, and 2 equiv of butylamine as catalyst at 50 °C for 12 h. The resin was then washed with DMF five times and split into several parts. To each part, 15 equiv of another aldehyde, 10 equiv of tributyl borate, and 1 equiv of butylamine were added at 50 °C. After 12 h, 0.4 N HCl was used to decompose the acetylacetone–boron complex at 60 °C for 2 h. The resin was washed with DMF, MeOH, and dried under N_2. The final products were cleaved with DCM/TFA/MeOH (5:1:1). For monoketone curcumin derivatives, the procedure does not include the composition/decomposition of the acetylacetone–boron complex. Each step is allowed to be repeated two or more times if necessary.
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16. **1a**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 3.95 (s, 3H), 5.84 (s, 1H, enol), 6.50 (d, 1H, $J = 16$ Hz), 6.62 (d, 1H, $J = 16$ Hz), 6.93 (d, 1H, $J = 8$ Hz), 7.06 (s, 1H), 7.12 (d, 1H, $J = 8$ Hz), 7.37–7.40 (m, 3H), 7.55 (d, 2H, $J = 8$ Hz), 7.61 (d, 1H, $J = 16$ Hz), 7.65 (d, 1H, $J = 16$ Hz). ESI-MS m/z: 321.1 $(M-H)^{-\cdot}$. **1b**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 3.88 (s, 3H), 5.72 (s, 1H, enol), 6.41 (d, 1H, $J = 16$ Hz), 6.42 (d, 1H, $J = 16$ Hz), 6.78 (d, 2H, $J = 8.5$ Hz), 6.86 (d, 1H, $J = 8$ Hz), 6.98 (d, 1H, $J = 1.5$ Hz), 7.05 (dd, 1H, $J = 8$, 1.5 Hz), 7.39 (d, 2H, $J = 8.5$ Hz), 7.52 (d, 1H, $J = 16$ Hz), 7.54 (d, 1H, $J = 16$ Hz). ESI-MS m/z: 337.0 $(M-H)^{-\cdot}$. **1c**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 3.85 (s, 3H), 3.95 (s, 3H), 5.79 (s, 1H, enol), 6.47 (d, 1H, $J = 16$ Hz), 6.49 (d, 1H, $J = 16$ Hz), 6.91 (d, 2H, $J = 8.5$ Hz), 6.93 (d, 1H, $J = 8$ Hz), 7.05 (d, 1H, $J = 2$ Hz), 7.12 (dd, 1H, $J = 8$, 2 Hz), 7.50 (d, 2H, $J = 9$ Hz), 7.59 (d, 1H, $J = 16$ Hz), 7.62 (d, 1H, $J = 16.5$ Hz). ESI-MS m/z: 351.1 $(M-H)^{-\cdot}$. **1d**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 2.37 (s, 3H), 3.94 (s, 3H), 5.75 (s, 1H, enol), 6.09 (d, 1H, $J = 3$ Hz), 6.43 (d, 1H, $J = 16$ Hz), 6.46 (d, 1H, $J = 16$ Hz), 6.51 (d, 1H, $J = 3.5$ Hz), 6.92 (d, 1H, $J = 8$ Hz), 7.03 (s, 1H), 7.11 (dd, 1H, $J = 8$, 2 Hz), 7.34 (d, 1H, $J = 16$ Hz), 7.57 (d, 1H, $J = 16$ Hz). ESI-MS m/z: 325.0 $(M-H)^{-\cdot}$. Elem. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.68; H, 5.90. **2a**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 3.89 (s, 3H), 3.90 (s, 6H), 5.82 (s, 1H, enol), 6.49 (d, 1H, $J = 15$ Hz), 6.52 (d, 1H, $J = 15$ Hz), 6.78 (s, 2H), 6.86 (d, 2H, $J = 8.5$ Hz), 7.45 (d, 2H, $J = 8.5$ Hz), 7.56 (d, 2H, $J = 15.5$ Hz), 7.61 (d, 2H, $J = 16$ Hz). ESI-MS m/z: 381.0 $(M-H)^{-\cdot}$. Elem. Anal. Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 68.85; H, 6.03. **2b**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 3.05 (s, 6H), 5.76 (s, 1H, enol), 6.43 (d, 1H, $J = 16$ Hz), 6.47 (d, 1H, $J = 15.5$ Hz), 6.68 (d, 2H, $J = 9$ Hz), 6.85 (d, 2H, $J = 8.5$ Hz), 7.44–7.47 (m, 4H), 7.58 (d, 1H, $J = 16$ Hz), 7.62 (d, 1H, $J = 15.5$ Hz). ESI-MS m/z: 334.19 $(M-H)^{-\cdot}$. HRMS-EI m/z: calcd for $C_{21}H_{21}O_3N$, 335.1516; found 335.1520. **2c**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 3.85 (s, 3H), 5.78 (s, 1H, enol), 6.48 (d, 1H, $J = 16$ Hz), 6.50 (d, 1H, $J = 16$ Hz), 6.87 (d, 2H, $J = 8.5$ Hz), 6.92 (d, 2H, $J = 8.5$ Hz), 7.45 (d, 2H, $J = 9$ Hz), 7.51 (d, 2H, $J = 9$ Hz), 7.60 (d, 1H, $J = 16$ Hz), 7.62 (d, 1H, $J = 16$ Hz). ESI-MS m/z: 321.17 $(M-H)^{-\cdot}$. **2d**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 5.82 (s, 1H,enol), 6.50 (d, 1H, $J = 16$ Hz), 6.62 (d, 1H, $J = 16$ Hz), 6.87 (d, 2H, $J = 8.5$ Hz), 7.38–7.40 (m, 3H), 7.46 (d, 2H, $J = 8.5$ Hz), 7.55–7.57 (m, 2H), 7.62 (d, 1H, $J = 16$ Hz), 7.65 (d, 1H, $J = 16$ Hz). ESI-MS m/z: 291.1 $(M-H)^{-\cdot}$. **2e**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 5.76 (s, 1H, enol), 6.41 (d, 1H, $J = 15.5$ Hz), 6.48 (d, 1H, $J = 15.5$ Hz), 6.85 (d, 2H, $J = 8.5$ Hz), 7.06 (dd, 1H, $J = 5$, 4 Hz), 7.26 (d, 1H, $J = 4$ Hz), 7.38 (d, 1H, $J = 5$ Hz), 7.46 (d, 2H, $J = 8.5$ Hz), 7.61 (d, H, $J = 16$ Hz), 7.76 (d, 1H, $J = 16$ Hz). ESI-MS m/z 297.0 $(M-H)^{-\cdot}$. Elem. Anal. Calcd for $C_{17}H_{14}O_3S$: C, 68.44; H, 4.73. Found: C, 68.31; H, 4.95. **2f**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 5.86 (s, 1H, enol), 6.51 (d, 1H, $J = 16$ Hz), 6.56 (d, 1H, $J = 16$ Hz), 6.86 (d, 2H, $J = 8.5$ Hz), 7.21 (td, 1H, $J = 8$, 1.5 Hz), 7.33 (t, 1H, $J = 7.5$ Hz), 7.47 (d, 2H, $J = 8.5$ Hz), 7.61–7.65 (m, 3H), 7.99 (d, 1H, $J = 15.5$ Hz). ESI-MS m/z 369.0, 371.0 $(M-H)^{-\cdot}$. Elem. Anal. Calcd for $C_{19}H_{15}O_3Br$: C, 61.47; H, 4.07. Found: C, 61.35; H, 4.34. **2g**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 1.82 (penta, 2H, $J = 6$ Hz), 2.92–2.94 (m, 4H), 6.70 (s, 2H), 6.90 (d, 2H, $J = 8.5$ Hz), 7.39 (d, 2H, $J = 8.5$ Hz), 7.72 (s, 1H), 7.76 (s, 1H). ESI-MS m/z 379.2 $(M-H)^{-\cdot}$. Elem. Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.35; H, 6.34. **2h**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 1.81 (penta, 2H, $J = 6.5$ Hz), 2.87–2.96 (m, 4H), 3.90 (s, 3H), 6.88 (d, 2H, $J = 8.5$ Hz), 6.92 (d, 1H, $J = 8.5$ Hz), 6.99 (d, 1H, $J = 1.5$ Hz), 7.03 (dd, 1H, $J = 8.5$, 1.5 Hz), 7.36 (d, 2H, $J = 9$ Hz), 7.70 (s, 1H), 7.71 (s, 1H). ESI-MS m/z: 335.27 $(M-H)^{-\cdot}$. **3a**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 3.89 (s, 3H), 3.91 (s, 6H), 4.67 (s, 2H), 5.79 (s, 1H, enol), 6.39 (d, 1H, $J = 3.5$ Hz), 6.52 (d, 1H, $J = 15.5$ Hz), 6.53 (d, 1H, $J = 15.5$ Hz), 6.57 (d, 1H, $J = 3.5$ Hz), 6.78 (s, 2H), 7.38 (d, 1H, $J = 16$ Hz), 7.57 (d, 1H, $J = 16$ Hz). EI-MS m/z: 386 $(M^{+\cdot})$, 368, 337, 234. Elem. Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.15; H, 5.98. Compound **3b**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 3.05 (s, 6H), 4.66 (s, 2H), 5.74 (s, 1H, enol), 6.38 (d, 1H, $J = 4$ Hz), 6.46 (d, 1H, $J = 15.5$ Hz), 6.51 (d, 1H, $J = 15.5$ Hz), 6.53 (d, 1H, $J = 3.5$ Hz), 6.82 (br d, 2H), 7.34 (d, 1H, $J = 15.5$ Hz), 7.48 (d, 2H, $J = 9$ Hz), 7.62 (d, 1H, $J = 15$ Hz). EI-MS m/z: 339 $(M^{+\cdot})$, 243, 174. HRMS-EI m/z: calcd for $C_{20}H_{21}O_4N$, 339.1465; found, 339.1461. **3c**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 3.94 (s, 3H), 4.66 (s, 2H), 5.75 (s, 1H, enol), 6.38 (d, 1H, $J = 3.5$ Hz), 6.47 (d, 1H, $J = 16$ Hz), 6.50 (d, 1H, $J = 16$ Hz), 6.55 (d, 1H, $J = 2$ Hz), 6.92 (d, 1H, $J = 8.5$ Hz), 7.04 (d, 2H, $J = 1.5$ Hz), 7.11 (dd, 1H, $J = 8$, 2 Hz), 7.36 (d, 1H, $J = 15.5$ Hz), 7.58 (d, 1H, $J = 15.5$ Hz). EI-MS m/z: 342 $(M^{+\cdot})$, 324, 293, 217, 177. Elem. Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.66; H, 5.53. **3d**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 4.66 (s, 2H), 5.79 (s, 1H, enol), 6.39 (d, 1H, $J = 3$ Hz), 6.53 (d, 1H, $J = 15.5$ Hz), 6.57 (d, 1H, $J = 3.5$ Hz), 6.61 (d, 1H, $J = 15.5$ Hz), 7.37–7.40 (m, 4H), 7.54–7.56 (m, 2H), 7.65 (d, 1H, $J = 16$ Hz). EI-MS m/z: 296 $(M^{+\cdot})$, 278, 265, 131. Elem. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.74; H, 5.75. Compound **3e**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 3.84 (s, 3H), 4.66 (s, 2H), 5.75 (s, 1H, enol), 6.38 (d, ^{1}H, $J = 3$ Hz), 6.49 (d, 1H, $J = 16$ Hz), 6.51 (d, 1H, $J = 15.5$ Hz), 6.55 (d, 1H, $J = 3.5$ Hz), 6.91 (d, 2H, $J = 8.5$ Hz), 7.36 (d, 1H, $J = 15$ Hz), 7.50 (d, 2H, $J = 9$ Hz), 7.61 (d, 1H, $J = 16$ Hz). EI-MS m/z: 326 $(M^{+\cdot})$, 308, 161. Elem. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.71; H, 5.97.