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Synthesis and topoisomerase II inhibitory and cytotoxic activity of oxiranylmethoxy- and thiiranylmethoxy-chalcone derivatives

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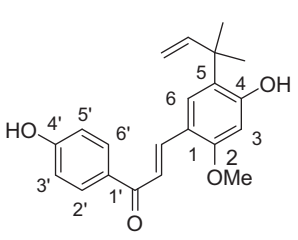
ABSTRACT

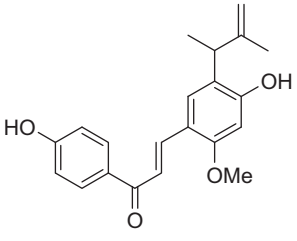
In order to find potential anticancer drug candidate targeting topoisomerases enzyme, we have designed and synthesized oxiranylmethoxy- and thiiranylmethoxy-retrochalcone derivatives and evaluated their pharmacological activity including topoisomerases inhibitory and cytotoxic activity. Of the compounds prepared compound **25** showed comparable or better cytotoxic activity against cancer cell lines tested. Compound **25** inhibited MCF7 (IC_{50}: 0.49 ± 0.21 μM) and HCT15 (IC_{50}: 0.23 ± 0.02 μM) carcinoma cell growth more efficiently than references. In the topoisomerases inhibition test, all the compounds were inactive to topoisomerase I but moderate inhibitors to topoisomerase II enzyme. Especially, compound **25** inhibited topoisomerase II activity with comparable extent to etoposide at 100 μM concentrations. Correlation between cytotoxicity and topoisomerase II inhibitory activity implies that compound **25** can be a possible lead compound for anticancer drug impeding the topoisomerase II function.

Topoisomerases are essential cellular enzymes necessary for cell proliferation by solving topological hurdles during DNA replication process.[1] Topoisomerase enzymes are divided into two types, type I and II, depending on the DNA cleavage pattern. Topoisomerase I mediates the breaking and rejoining of single strand of DNA duplex to relax the supercoiled condition of chromosomes. On the other hand, topoisomerase II produces the relaxation of DNA double helices by scissoring and rejoining two strands. These critical role of topoisomerase enzymes during the proliferative process introduced topoisomerases to be one of the major targets for anticancer drug development. To date, numerous compounds have been reported to inhibit topoisomerases inhibitory activity. Among these compounds, normal chalcone were reported to inhibit only topoisomerase II, but not I, while retrochalcone was found to inhibit topoisomerase I.[2] Retrochalcones,[3] missing 2′ and 6′-hydroxy group from normal chalcone core, are unusual phenolic compound family and *Glycyrrhiza inflata* is a major source for these compounds. Recently, licochalcone A (**1**) and E (**2**), members of retrochalcone, have shown potent topoisomerase I inhibitory activity.[4]

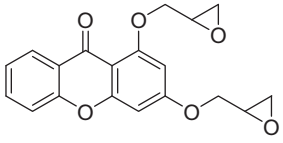
Previously we reported that substitution of epoxide (**3**) or thioepoxide (**4**) on the xanthone derivatives could engender the selectivity on the topoisomearase I and II enzyme function.[5]



Licochalcone A (1)



Licochalcone E (2)



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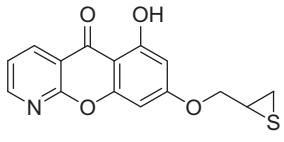

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In order to extend the scaffold of the anticancer drug candidates targeting topoisomerase enzyme, we have designed and synthesized chalcone derivatives substituted with epoxide or thioepoxide groups.

First the starting chalcone and retrochalcone were prepared employing with the known methods.[6] Chalcone compounds were subsequently reacted with epichlorohydrin (3 equiv) or epit-

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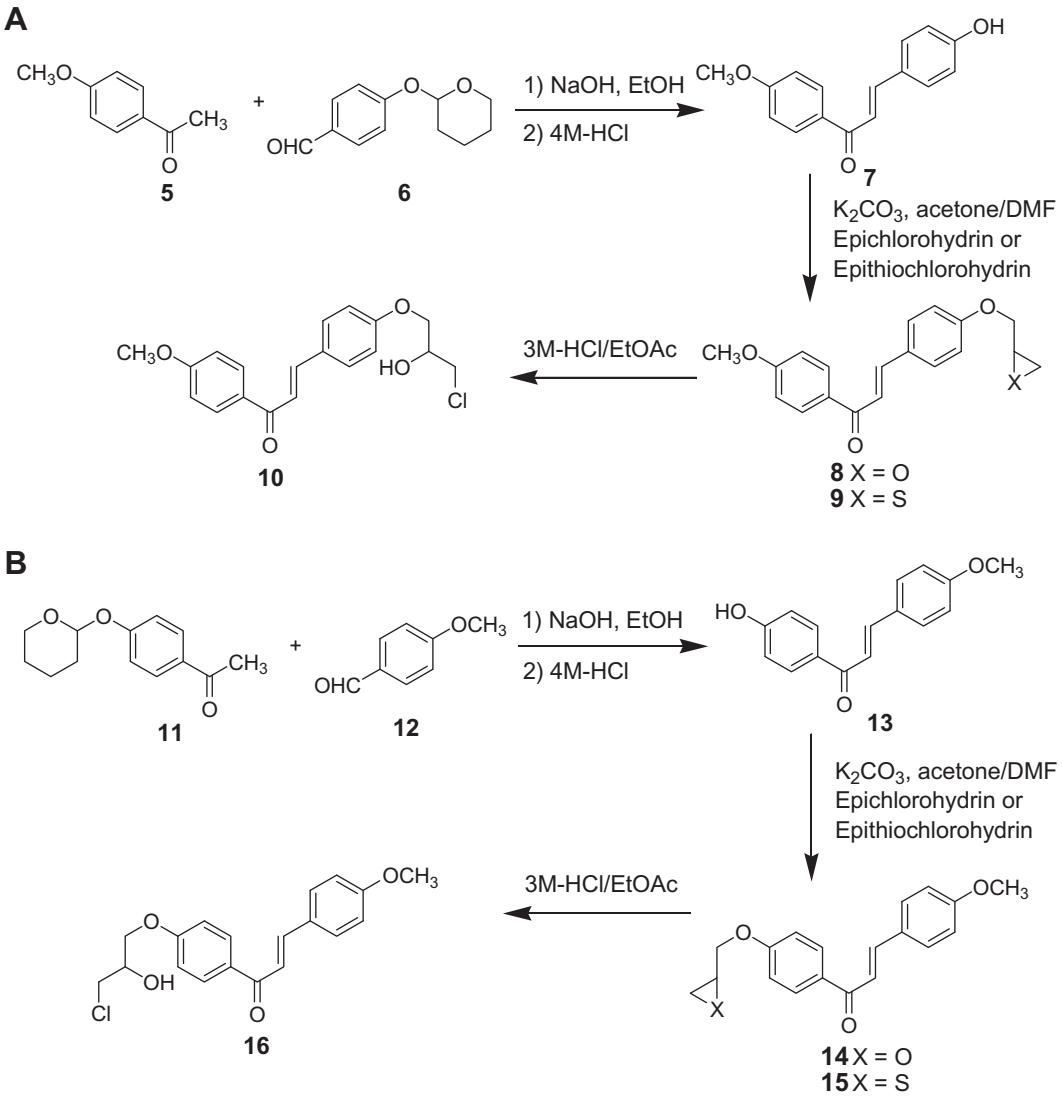
hiochlrohydrin (1.5 equiv) under K_2CO_3 basic condition in the acetone and DMF (1:1) to give oxiranylmethoxy- and thiiranylmethoxy-chalcone derivatives **8**, **9**, **14** and **15**. Chlorohydrin compounds **10** and **16** were generated after treatment of corresponding epoxide compounds **8** and **14** with 3 M HCl in aqueous EtOAc (Scheme 1).

Bisoxiranylmethoxy- and bisthiiranylmethoxy-chalcone derivatives were prepared with excess amounts of epichlorohydrin (6 equiv) or epithiochlrohydrin (4 equiv) under K_2CO_3 or Cs_2CO_3 basic condition (Scheme 2). Analytical data of the compounds prepared were described in the reference section.[7]

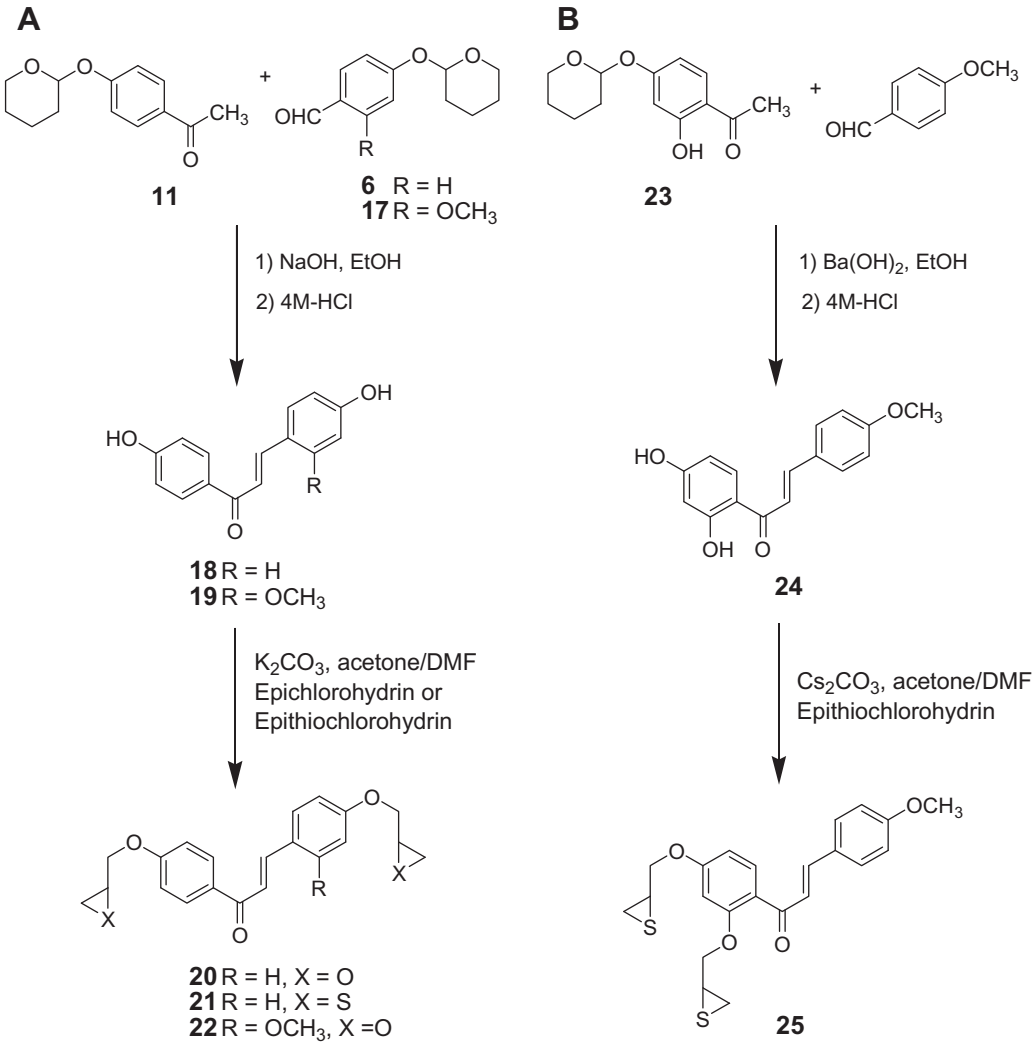
All the compounds prepared were evaluated for the cytotoxicity against several human cancer cell lines using adriamycin, etoposide and camptothecin as references. Typical MTT assay procedure was employed for the test.[5c] The result is indicated in Table 1. Most compounds showed moderate cytotoxic activity on the cancer cell lines tested. Of the compounds, compound **25** showed most potent cytotoxic activity over the tested cancer cell lines. Compound **25** inhibited MCF7 (IC_{50}: 0.49 ± 0.21 μM) and HCT15 (IC_{50}: 0.23 ± 0.02 μM) carcinoma cell growth more efficiently than references.

Topoisomerases relaxation inhibitory activities were evaluated using human topoisomerase I and II (Topogen) with camptothecin and etoposide as positive controls.[5c] Data were analyzed and evaluated with LabWork 4.5 Software to calculate the inhibition ratio. Test results were indicated in Figure 1 and Table 2. In the topoisomerase I relaxation assay, none of the compounds were active. This observation is conflict on the previous reports that retrochalcones are efficient topoisomerase I inhibitor,[2] which means that substituents on the retrochalcones affect the topoisomerase I inhibitory activity. But most compounds inhibited topoisomerase II function moderately. Compound **25** was most active inhibitor on topoisomerase II enzyme with comparable extent to etoposide at 100 μM concentration. This observation suggests that proximity of the two thiiranylmethoxy groups enhance the inhibitory function of the chalcone compound on topoisomerase II.

In conclusion, we have designed and synthesized 10 oxiranylmethoxy- and thiiranylmethoxy-chalcone derivatives and evaluated their pharmacological activity. Most compounds showed moderate cytotoxicity and topoisomerase II inhibitory activity but were inactive to topoisomerase I function. Compound **25** exhibited consistent pharmacological activity between cytotoxicity and topoisomerase II inhibition, which implicates the topoisomerase II inhibition of the compound **25** on the cytotoxicity. Our findings suggest that elaborate optimization of the chalcone structure with oxiranylmethoxy- and thiiranylmethoxy-groups can produce po-



Scheme 1. Synthetic methods for mono-epoxide analogues.



Scheme 2. Synthetic methods for bis-epoxide analogues.

Table 1
Result of cytotoxicity of compounds synthesized against various cancer cells

Compound/cells	IC_{50}[a] (μM)			
	MCF	K562	DU145	HCT15
Adriamycin	1.69 ± 0.12	1.33 ± 0.11	1.75 ± 0.24	1.25 ± 0.13
Etoposide	1.98 ± 0.28	1.21 ± 0.16	1.44 ± 0.50	2.03 ± 0.24
Camptothecin	2.43 ± 0.31	0.59 ± 0.02	0.61 ± 0.13	0.80 ± 0.15
8	10.86 ± 0.14	33.47 ± 0.19	36.89 ± 1.38	30.43 ± 0.51
9	11.46 ± 0.17	32.49 ± 1.40	>50	28.42 ± 0.48
14	11.64 ± 0.26	27.95 ± 1.61	43.30 ± 1.26	27.13 ± 0.94
15	23.58 ± 0.29	>50	19.41 ± 0.25	10.08 ± 1.11
10	29.15 ± 3.00	29.07 ± 1.65	>50	20.55 ± 1.62
16	18.45 ± 0.16	16.23 ± 3.06	>50	20.46 ± 1.17
20	3.87 ± 0.00	7.27 ± 0.73	>50	18.50 ± 0.86
21	21.71 ± 0.70	13.39 ± 1.16	>50	12.19 ± 0.68
22	3.64 ± 0.02	13.66 ± 0.78	>50	4.82 ± 0.14
25	0.49 ± 0.21	7.60 ± 0.38	1.07 ± 0.59	0.23 ± 0.02

[a] Each data point represents mean ± SD from three different experiments performed in triplicate.

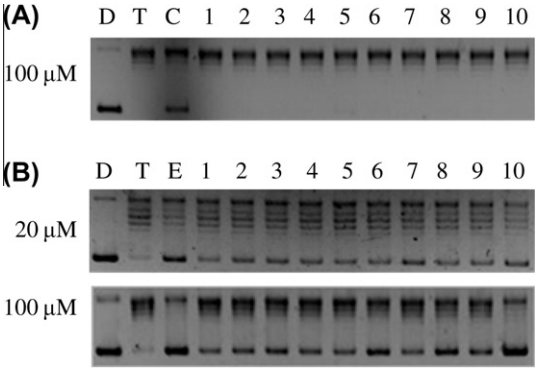


Figure 1. Topoisomerase I (A) and II (B) inhibitory activities of compounds. Compounds were examined in a final concentration of 20 and 100 μM, respectively, as designated. (A) Lane D: pBR322 only, Lane T: pBR322 + Topo I, Lane C: pBR322 + Topo I + camptothecin, Lanes **1**–**10**: pBR322 + Topo I + compounds in order of **8**, **9**, **14**, **15**, **10**, **16**, **20**, **21**, **22**, and **25**. (B) Lane D: pBR322 only, Lane T: pBR322 + Topo II, Lane E: pBR322 + Topo II + etoposide, Lanes 1–10: pBR322 + Topo II + compounds as the same as the order of (A).

tential anticancer drug candidates targeting on topoisomerase II enzyme. But topoisomerase II inhibitory activities of compound **25** might not directly related to the corresponding cytotoxicities, which implies that we can't exclude the possibility that additional targets can be involved in the mechanism of action of compound **25**.

Table 2
Topoisomerase I and II inhibitory activities of compounds

Compound	Topo I (% inhibition)	Topo II (% inhibition)	
	100 μM	100 μM	20 μM
Camptothecin	64.30	—	—
Etoposide	—	61.85	38.03
8	0.0	22.03	15.18
9	0.0	31.55	15.50
14	0.0	28.79	17.58
15	0.0	31.55	14.75
10	0.0	30.10	14.01
16	0.0	34.88	16.27
20	0.0	33.46	19.34
21	0.0	34.65	18.01
22	0.0	28.52	13.96
25	0.0	61.00	20.77

The values of % inhibition are the means from at least three independent experiments. The mark '—' indicates that the experiment was not performed.

Acknowledgment

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7. *General synthetic procedure*: (a) Synthesis for compounds **8**, **9**, **14**, **15**, **20–22**, **25**: To a mixture of chalcone and K_2CO_3 or Cs_2CO_3 (1.1–2.2 equiv) in acetone/DMF (1:1) was added epi- or epithio-chlorohydrin(1.5–6.0 equiv). The reaction mixture was stirred at 70–80 °C (overnight) and poured into H_2O. If solid formed, solid was filtered, collected and dried. If solid was not formed, the mixture was extracted with ethyl acetate and then the organic layer was washed with brine and dried over Na_2SO_4. Solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography.
(b) *Synthesis for compounds* **10** and **16**: A mixture of compound **8** or **14** in aqueous 3 M HCl in ethyl acetate was stirred at rt (30 min). Solvent was removed under reduced pressure and H_2O was added to the residue. The mixture was extracted with CH_2Cl_2 (×2 times). Combined organic layer was washed with H_2O and brine and dried over Na_2SO_4. After evaporation of solvent, the residue was purified by silica gel column chromatography.
Compound **8**: Yield 63.8%; R_f: 0.27 (EtOAC/*n*-hexane = 1:1); mp 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (dd, *J* = 4.8, 2.8 Hz, 1H), 2.94 (dd, *J* = 8.8, 8.0 Hz, 1H), 3.36–3.40 (m, 1H), 3.90 (s, 3H), 4.00 (dd, *J* = 11.2, 5.6 Hz, 1H), 4.29 (dd, *J* = 11.2, 6.4 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 15.6 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 44.9, 50.1 (50.2), 55.6 (55.8), 69.0 (69.1), 114.0, 115.2, 120.0, 120.2, 128.6, 130.2, 130.4, 130.9, 131.0, 131.5, 143.7, 143.9, 160.5, 163.5, 188.9 ppm; EI-MS: *m*/*e* 310.2 [M]$^+$. *Compound* **9**: Yield 45.9%; R_f: 0.69 (EtOAC/*n*-hexane = 1:1); mp 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (d, *J* = 5.2 Hz, 1H), 2.64 (dd, *J* = 5.2 Hz, 1H), 3.28–3.31 (m, 1H), 3.90 (s, 3H), 3.98 (dd, *J* = 10.0, 6.8 Hz, 1H), 4.25 (dd, *J* = 10.0, 5.6 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 15.6 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 24.1, 31.4, 55.6 (55.7), 72.8 (72.9), 114.0, 115.1, 115.2, 120.1, 128.6, 130.4, 130.9, 131.0, 131.5, 143.7, 143.8, 160.4, 163.5, 188.9 ppm; EI-MS: *m*/*e* 326.1 [M]$^+$. *Compound* **10**: Yield 76.2%; R_f: 0.24 (EtOAC/*n*-hexane = 1:1); mp 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (d, *J* = 5.6 Hz, 1H), 3.75 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.80 (dd, *J* = 11.2, 7.2 Hz, 1H), 3.89 (s, 3H), 4.14–4.18 (m, 2H), 4.23–4.28 (m, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 15.6 Hz, 1H), 7.61 (dd, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 15.6 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 46.1, 55.6, 68.8, 70.0, 114.0, 115.2, 120.2, 128.8, 130.3, 130.4, 130.9, 131.0, 131.5, 143.7, 143.8, 160.2, 163.6, 189.0 ppm; EI-MS: *m*/*e* 346.1 [M]$^+$. *Compound* **14**:[8] Yield 74.6%; R_f: 0.42 (EtOAC/*n*-hexane = 1:1); mp 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79–2.80 (m, 1H), 2.93–2.95 (m, 1H), 3.39 (br s, 1H), 3.86 (s, 3H), 4.03 (dd, *J* = 10.8, 5.6 Hz, 1H), 4.33 (dd, *J* = 10.8, 2.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 15.6 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 44.8, 50.1 (50.2), 55.5 (55.7), 69.0 (69.1), 114.5, 114.6, 119.6, 119.8, 128.0, 130.3, 130.4, 130.9, 131.0, 132.0, 144.1, 144.2, 161.7, 162.2, 188.9 ppm; EI-MS: *m*/*e* 310.1 [M]$^+$. *Compound* **15**: Yield 34.8%; R_f: 0.41 (EtOAC/*n*-hexane = 1:2); mp 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (dd, *J* = 5.2, 1.2 Hz, 1H), 2.64 (dd, *J* = 6.0 Hz, 1H), 3.28–3.32 (m, 1H), 3.86 (s, 3H), 4.02 (dd, *J* = 10.0, 6.8 Hz, 1H), 4.27 (dd, *J* = 10.0, 5.2 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 15.6 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 15.6 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 24.0, 31.2, 55.6, 72.9, 114.5, 114.6, 114.7, 119.7, 128.0, 130.4, 130.9, 131.0, 132.0, 144.2, 161.8, 162.2, 188.9 ppm; EI-MS: *m*/*e* 326.1 [M]$^+$. *Compound* **16**: Yield 76.2%; R_f: 0.27 (EtOAC/*n*-hexane = 1:1); mp 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (d, *J* = 6.4 Hz, 1H), 3.77 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.82 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.87 (s, 3H), 4.18 (d, *J* = 2.4 Hz, 1H), 4.19 (d, *J* = 1.6 Hz, 1H), 4.28 (quint, J = 5.6 Hz, 1H), 6.95 (dd, *J* = 6.8, 1.6 Hz, 2H), 7.01 (dd, *J* = 6.8, 1.6 Hz, 2H), 7.42 (d, *J* = 16.0 Hz, 1H), 7.61 (dd, *J* = 6.8, 2.4 Hz, 2H), 7.79 (d, *J* = 16.0 Hz, 1H), 8.04 (d, *J* = 6.8, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 46.1, 55.6 (55.7), 68.9, 69.9, 114.6, 127.9, 130.3, 130.4, 130.9, 131.0, 132.2, 144.4, 161.8, 162.0, 189.0 ppm; EI-MS: *m*/*e* 346.1 [M]$^+$. *Compound* **20**:[9] Yield 45.7%; R_f: 0.06 (EtOAC/*n*-hexane = 1:2); mp 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77–2.80 (m, 2H), 2.92–2.96 (m, 2H), 3.37–3.41 (m, 2H), 4.00 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.04 (dd, *J* = 10.8, 5.6 Hz, 1H), 4.30 (dd, *J* = 11.2, 3.2 Hz, 1H), 4.33 (dd, *J* = 10.8, 3.2 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 15.6 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 44.8, 50.1, 69.0, 114.6, 115.2, 115.3, 120.0, 128.5, 130.4, 130.9, 131.0, 132.0, 143.9, 160.5, 162.3, 188.9 ppm; EI-MS: *m*/*e* 352.2 [M]$^+$. *Compound* **21**: Yield 15.0%; R_f: 0.72 (EtOAC/*n*-hexane = 1:1); mp 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34–2.37 (m, 2H), 2.63–2.65 (m, 2H), 3.26–3.33 (m, 2H), 3.98 (dd, *J* = 10.8, 7.2 Hz, 1H), 4.02 (dd, *J* = 10.0, 6.8 Hz, 1H), 4.24 (dd, *J* = 10.0, 5.6 Hz, 1H), 4.28 (dd, *J* = 10.4, 5.6 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.99 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.43 (d, *J* = 15.6 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 24.0, 31.3, 72.8, 114.5, 115.1, 115.2, 119.9, 128.5, 130.3, 130.9, 131.0, 131.9, 143.9, 160.5, 162.2, 188.8 ppm; ESI-MS: *m*/*e* 385.3 [M+1]$^+$. *Compound* **22**: Yield 39.1%; R_f: 0.36 (EtOAC/*n*-hexane = 2:1); mp 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77–2.80 (m, 2H), 2.93–2.95 (m, 2H), 3.37–3.39 (m, 2H), 3.91 (s, 3H), 3.99 (dd, *J* = 10.8, 5.6 Hz, 1H), 4.03 (dd, *J* = 11.2, 6.0 Hz, 1H), 4.30 (dd, *J* = 11.2, 3.2 Hz, 1H), 4.33 (dd, *J* = 11.2, 3.2 Hz, 1H), 6.53 (d, *J* = 6.4 Hz, 1H), 6.55 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 15.6 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 8.02 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 44.9, 50.2, 55.8, 69.1, 99.4, 99.5, 106.0, 114.5, 118.0, 120.7, 120.8, 130.8, 132.3, 139.8, 160.5, 161.8, 162.1, 189.6 ppm; EI-MS: *m*/*e* 382.2 [M]$^+$. *Compound* **25**: Yield 3.5%; R_f: 0.735 (EtOAC/*n*-hexane = 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30–2.34 (m, 2H), 2.51 (d, *J* = 6.0 Hz, 1H), 2.59 (d, *J* = 6.0 Hz, 1H), 3.21–3.26 (m, 2H), 3.81 (s, 3H), 4.00 (dd, *J* = 10.0, 6.8 Hz, 1H), 4.08–4.18 (m, 3H), 6.44 (d, *J* = 2.0 Hz, 1H), 6.55 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 15.6 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 15.6 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 23.7, 23.9, 31.3, 55.6, 72.9, 73.4, 100.4, 100.5, 114.5, 123.3, 125.2, 128.2, 130.2, 130.3, 131.2, 142.3, 159.1, 161.5, 162.8, 190.5 ppm; ESI-MS: *m*/*e* 415.3 [M+1]$^+$.
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