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# Semi-synthesis and anti-proliferative activity evaluation of novel analogues of Honokiol

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ABSTRACT

A series of honokiol analogues were synthesized by modifying the 5- and/or 3′-position(s) of honokiol to assess their anti-tumor effects. Some compounds exerted more potent anti-proliferative activities than those of honokiol on K562 leukemia cells, A549 alveolar basal epithelial cells, SPC-A1 adenocarcinoma cells and A2780 human ovarian carcinoma cells in vitro. Compounds **2b**, **3a**, and **3c** displayed most potent anti-proliferative activities against these tested cell strains and their anti-drug resistance effects were evaluated in vitro on cisplatin-resistant A2780 human ovarian carcinoma cells. The structure–activity relationship was also proposed.



Honokiol, a significant bioactive component extracted from the root, stem bark and the seeds cones of Magnolia officinalis, demonstrates various biological activities such as anti-oxidative,[1] anti-arrhythmic,[2] anti-inflammatory,[3] anti-thrombocytic,[4] anti-angiogenesis,[5] anti-tumor,[6] anxiolytic effects,[7] and anti-HIV activity[8]. Recent studies in our laboratory also indicate that honokiol induces apoptosis in tumor cells, inhibits angiogenesis and has synergistic anti-tumor activities combined with chemotherapy agents and radiotherapy in vitro and in vivo.[9] These unusual combined biological properties encourage further structure modification to increase the potencies and understand the underlying mechanism. However, until now, only few analogues have been reported in the literatures.[10–13] Kong et al.[10] and Esumi et al.[11] reported that honokiol's biological effects are attributed to the bisphenol structure bearing allyl moieties. Accordingly, to further clarify a structure–activity relationship, make clear the action mechanism and improve the anti-proliferative potencies of these compounds, we now describe the semi-synthesis of a novel series of honokiol analogues with different groups at the 5- and/or 3′-positions and in vitro evaluation as potential inhibitors to various tumor cell strains.

We have reported approaches for the synthesis, HSCCC isolation and anti-proliferative effects evaluation of three C-formylated derivatives (**2a–c**) of honokiol in our previous Letter.[14] Since the formyl group usually has high reactivity toward many chemical reagents, the introduction of formyl groups (a formyl group) to the 5- and/or 3′-position(s) of honokiol provided us convenient approaches (see Scheme 1) to modify honokiol through such various kinds of chemical reactions as aldol condensation, Knovenagel condensation, Wittig reaction, and nucleophilic addition/elimination.

The oxime compounds[15] **3a–c** were prepared in parallel by respectively refluxing **2a–c** with hydroxylamine hydrochloride in the presence of triethylamine as catalyst in methanol for 3 h.

The aldol condensation of the formylated honokiols **2a–b** with 1.2 equiv ethyl cyanoacetate proceeded gradually in refluxing ethanol for 48 h[16] with 4 Å molecular sieves powder as catalyst to afford compounds **4a–b** in 85–88% yields. Of note, some salicylaldehydes were reported to undergo tandem Knoevenagel/Michael processes with 2.0 equiv ethyl cyanoacetate to produce compounds bearing a 4*H*-chromene moiety in the presence of 4Å molecular sieves as catalyst.[17] However, the above formylated derivatives of honokiol bearing a salicylaldehyde moiety did not trigger this reaction cascade, and terminated at Knoevenagel condensation step. The inertia to this reaction condition of the formylated honokiols could be interpreted as the steric-hindrance effects caused by the bulky biaryl structure.

Compounds **5a–c** were synthesized in parallel by, respectively, heating **2a–c** with 2,4-thiazolidinedione in acetic acid in the presence of β-alanine as catalyst at 100 °C for 12 h.[18] The six Schiff base

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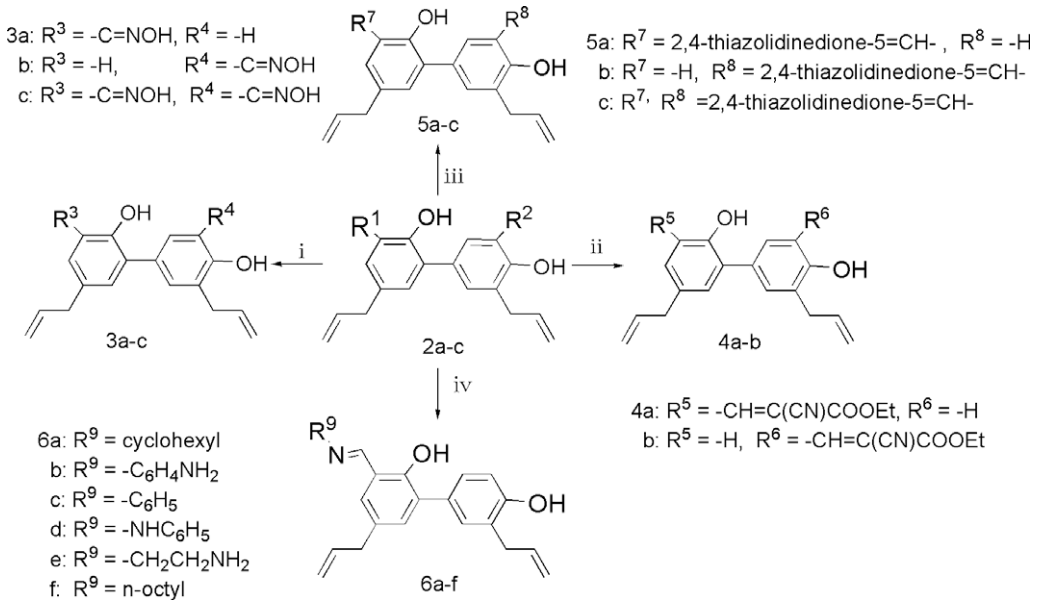



**Scheme 1.** Synthesis of compounds **3a–c**, **4a–b**, **5a–c**, **6a–f**. Reagents and conditions: (i) hydroxylamine hydrochloride, triethylamine, methanol, reflux, 3 h; (ii) ethyl cyanoacetate, 4 Å molecular sieves powder, anhydrous ethanol, reflux, 48 h; (iii) 2,4-thiazolidinedione, acetic acid, β-alanine, 100 °C,12 h; (iv) ethanol, reflux, 2 h.

derivatives **6a–f** were prepared similarly by refluxing **2a** with the corresponding amine in ethanol for 2 h.[19]

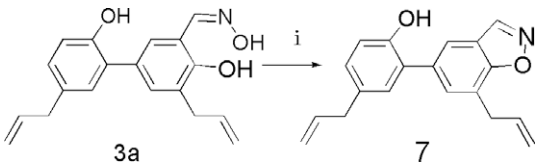
Intramolecularly cyclodehydration of the oxime **3a** afforded compound **7** by stirring with thionyl chloride and pyridine at 0 °C for 2 h[20] (see Scheme 2).

All of the compounds described except **2a–c** were purified by flash chromatography and their purities were above 98.5% by HPLC. The structures of all honokiol analogues were identified by ESI-HRMS, $^{1}$H NMR and $^{13}$C NMR. The two isomers, 3′-formylhonokiol and 5-formylhonokiol, were further characterized unambiguously by heteronuclear multiple-bond correlation (HMBC) spectra (see Supplementary data).

The anti-proliferative activity assessment was performed by standard procedure which was described detailed in our previous Letter.[14] The $IC_{50}$ values of honokiol and its analogues were listed in Table 1.

It could be seen in Table 1 that the introduction of little hindrance groups such as formyl group or its oxime to the 5- and/or 3′-position(s) of honokiol (compounds **2a–c, 3a–c, 6e**) exhibited comparable or slightly more potent anti-proliferative activities than that of honokiol. Adversely, the potencies of compound **7** decreased almost threefold compared with compound **3a** after intramolecular cyclization between the hydroxy group at 2′-position and the oxime at 3′-position. The intramolecular cyclodehydration caused the loss of hydrogen atom at 2-position, likely prohibiting the formation of intermolecular hydrogen or ionic bond between 2′-hydroxy group and possible biomolecular targets.

This deduction meets, to some extent, the slightly decreased anti-proliferative effects of 3′-formylhonokiol (**2a**) in comparison to honkiol, whose $IC_{50}$ values for K562, SPC-A1, and A549 were




**Scheme 2.** Synthesis of compound **7**. Reagents and conditions: (i) thionyl chloride, pyridine, diethyl ether, reflux, 2 h.

38.8, 38.4 and 41.8 μM, respectively. In 3′-formylhonokiol (**2a**), 2′-hydroxy group can form intramolecular hydrogen bond with 3′-formyl group and the hydrogen bond would decrease its ability to interact with biological target molecules.

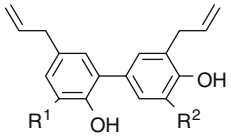
The above results suggest that 2′-hydroxy group is pharmacophoric moiety in the suppression of tumor cells growth.

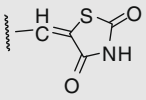
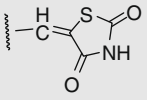
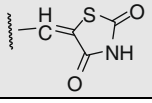
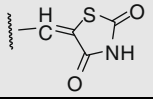
As to 5-formylhonokiol (**2b**), its inhibitory activities on some tumor cell strains are increased by about twofold although intramolecular hydrogen bond could be formed between 4-hydroxy group and 5-formyl group. From this finding it can be assumed that a proton donor at 4-position is unfavorable for the biological activities. Derivatives with depletion of hydrogen atom in 4-hydroxy group are necessary to be synthesized to evaluate the anti-proliferative activities in vitro. The synthesis of these analogues is under progress in our group.

Introduction of a bulky subsituent to the 5- and/or 3′-position(s) of honokiol (compounds **4a–b, 5a–c**) led to decreased effects conspicuously. Thus 2,4-thiazolidinedione, widely thought to be a pharmacophore in some effective inhibitors of phosphatidylinositol 3-kinase (PI3K),[21] a signaling transduction molecule involved in many tumors, was subject to reacted with the formylated honokiols **2a–c** through Knoevenagel condensation to produce compounds **5a–c,** whose $IC_{50}$ values for all tested tumor cells increased significantly. As the assay used herein is cell-based, no statement can be made on the mechanism underlying the observed low inhibitory effects against the tested tumor cell strains so far. Therefore in order to be able to evaluate the potential of these compounds as PI3K inhibitors, it will be necessary perform a cell-free assay on direct PI3K inhibition.

The anti-proliferative effects of the introduction of substituted phenyl groups (compounds **6b–d**) or aliphatic substituents (compounds **6a, 6f**) to the 5- and/or 3′-position(s) of honokiol by imine bond formation starting from the formylated honokiols **2a–c** were also evaluated. Analogues with substituted phenyl group retained partial or full anti-proliferative activities except compound **6d**, while aliphatic ones conspicuously decreased the effects in vitro, especially for compound **6f**, whose $IC_{50}$ values for the three tested tumor cell strains were all above 40 μg/mL. Of note, compound **6d** displayed no anti-proliferative effects at our maximum tested concentration (40 μg/mL), sharply contrast with other phenyl substi-

**Table 1**
$IC_{50}$ values of Honokiol and its analogues against various tumor cells




| Entry | $R^1$ | $R^2$ | MW | $IC_{50}$ (μM) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | K562 | SPC-A1 | A549 | A2780 | A2780/*cis* |
| **1** | –H | –H | 272 | 21.1 | 36.1 | 35.0 | 30.5 | 41.2 |
| **2a** | –CHO | –H | 294 | 38.8 | 38.4 | 41.8 | n.t.[a] | n.t. |
| **3a** | –CH=N–OH | –H | 309 | 20.7 | 45.0 | 40.4 | 33.0 | 37.2 |
| **4a** | –CH=C(CN)COOEt | –H | 389 | 95.1 | 92.5 | 87.4 | n.t. | n.t. |
| **5a** |  | –H | 393 | 91.6 | >101.8 | 91.6 | n.t. | n.t. |
| **7** | –CH=N–O– | –H | 291 | 78.4 | 77.3 | 65.6 | n.t. | n.t. |
| **6a** | –CH=N–cyclohexyl | –H | 375 | 90.7 | 88.0 | 93.3 | n.t. | n.t. |
| **6b** | –CH=N–$C_6H_5NH_2$ | –H | 384 | 29.2 | 40.1 | 38.8 | n.t. | n.t. |
| **6c** | –CH=N–$C_6H_5$ | –H | 369 | 32.2 | 40.7 | 39.8 | n.t. | n.t. |
| **6d** | –CH=N–N–$C_6H_5$ | –H | 384 | >104.2 | >104.2 | >104.2 | n.t. | n.t. |
| **6e** | –CH=N–$CH_2CH_2NH_2$ | –H | 336 | 42.6 | 50.3 | 41.1 | n.t. | n.t. |
| **6f** | –CH=N–Hexyl(n) | –H | 377 | >106.1 | >106.1 | >106.1 | n.t. | n.t. |
| **2b** | –H | –CHO | 294 | 11.9 | 25.5 | 41.8 | 16.7 | 22.4 |
| **3b** | –H | –CH=N–OH | 309 | 24.9 | 53.1 | 39.5 | n.t. | n.t. |
| **4b** | –H | –CH=C(CN)COOEt | 389 | 47.6 | 62.0 | 57.6 | n.t. | n.t. |
| **5b** | –H |  | 393 | 81.4 | >101.8 | >101.8 | n.t. | n.t. |
| **2c** | –CHO | –CHO | 322 | 36.0 | 45.3 | 55.0 | n.t. | n.t. |
| **3c** | –CH=N–OH | –CH=N–OH | 352 | 21.5 | 43.8 | 32.4 | 20.2 | 29.3 |
| **5c** |  |  | 520 | >76.9 | >76.9 | >76.9 | n.t. | n.t. |

[a] n.t.: not tested. Values are geometric means of at least two experiments with six data points in each experiment.

tuted derivatives. More studies should be conducted to investigate whether the introduced phenyl moiety play a part in the suppression of these tumor cell strains.

Additionally, honokiol had been reported to overcome conventional drug resistance in human multiple myeloma by induction of caspase-dependent and -independent apoptosis.[22] Herein we chose three compounds (**2b**, **3a**, and **3c**) with most potent inhibitory effects on the tested cell strains to evaluate their activities on cisplatin-sensitive and -resistant A2780 human ovarian carcinoma cells in order to investigate their anti-drug resistance effects against cisplatin-resistant tumor cells. Two of the tested compounds (**2b** and **3c**) displayed more potent inhibitory activities than those of honokiol on A2780/cis cells as well as on A2780. This observation suggests that honokiol and some semi-synthetic analogues can overcome cisplatin-resistant human ovarian carcinoma cells.

In conclusion, 18 analogues[23] have been synthesized by introduction of diverse groups to the 5- or 3′-position(s) of honokiol and the anti-proliferative activities have been evaluated in vitro. The structure–activity data acquired show that the hydroxy groups, especially 2′-hydroxy play a crucial role on anti-proliferative activities, and imply that the introduction of a formyl group to the 5-position of honokiol enhances the potencies. The discovery of compounds **2b**, **3a**, and **3c**, especially **2b**, provides a new insight on the synthesis and anti-proliferative evaluation of new honokiol analogues. As a result of the above findings, the formyl group or its oxime, especially at the 5-position would be envisaged in order to implement a more successful modification of honokiol in order to generate more potent analogues.

## Acknowledgment

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.06.071.

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15. *Typical procedure for the synthesis of the oxime derivatives* **3a–c**: Compound **3a** was prepared as follows. The solution of 3′-formylhonokiol (**2a**) (0.1 mmol), methanol (2 mL), and hydroxylammonium chloride (0.5 mmol) was bufferd to a pH of 8 with triethylamine and then heated under reflux for 3 h. The mixture was poured into distilled water (10 mL), filtered, washed with distilled water (3 × 5 mL), and dried in vacuo at 50 °C for 24 h. The product was yellowish white solid with a yield of 90% in purity of 99%.
16. *Typical procedure for the synthesis of compounds* **4a–b**: 3′-Formylhonokiol (**2a**) (0.1 mmol) was mixed with ethanol (2 mL) and ethyl cyanoacetate (0.2 mmol) in a reaction tube of 10 mL. 4 Å molecular sieves power (20 mg) was added and stirred under reflux for 48 h, then filtered and evaporated. The resulting colorless oil was columned using an eluent of 25% ethyl acetate in petroleum ether (v/v). The product was yellow solid with a yield of 85% in purity of 99%).
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18. *Typical procedure for the synthesis of compounds* **5a–c**: 3′-Formylhonokiol (**2a**) (0.1 mmol) was dissolved in 2 mL acetic acid. 2,4-Thiazolidinedione (0.2 mmol) and β-alanine (0.2 mmol) were added and left the mixture to stir at 100 °C for 12 h. The reaction mixture was poured into distilled water (5 mL), filtered, washed with distilled water (10 × 5 mL), and dried in vacuo at 50 °C for 24 h. The product was yellow solid with a yield of 92% in purity of 99%.
19. *Typical procedure for the synthesis of the Schiff base derivatives* **6a–f**: 3′-Formylhonokiol (**2a**) (0.1 mmol) was dissolved in ethanol (2 mL) and the corresponding amine (0.2 mmol) was added and left to stir under reflux for 2 h. The reaction mixture was evaporated to afford brown oily residue. This residue was columned to get clear yellow oil with a yield of 86% in purity of 98.5%.
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23. *Spectral data for the honokiol anologues*:
*Compound* **3a**: $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ (ppm), 11.64 (s, 1H), 10.41 (s, 1H), 9.52 (s, 1H), 8.39 (s, 1H), 7.24 (q, $J$ = 2.0, 8.0 Hz, 1H), 7.22 (d, $J$ = 2.0 Hz, 1H), 7.14 (d, $J$ = 2.0 Hz, 1H) , 7.06 (d, $J$ = 2.0 Hz, 1H), 6.86 (d, $J$ = 8.0 Hz, 1H), 5.91–6.04 (m, 2H), 5.00–5.11 (m, 4H), 3.33 (t, $J$ = 6.4, 11.2 Hz, 4H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), $\delta$ (ppm), 154.45, 152.33, 152.13, 151.68, 138.28, 137.56, 131.80, 131.17, 131.00, 129.22, 129.00, 128.74, 128.36, 125.90, 117.94, 116.17, 115.84, 114.92, 34.30; MS: $m/z$ 309.1365 (M+).
*Compound* **4a**: $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ (ppm), 8.55 (s, 1H) , 7.49 (d, $J$ = 2.0 Hz, 1H), 7.35 (m, 1H), 7.33 (d, $J$ = 2.0 Hz, 1H), 7.31 (d, $J$ = 2.0 Hz, 1H), 6.90 (d, $J$ = 8.4 Hz, 1H), 5.93–6.11 (m, 2H), 5.12–5.21 (m, 4H), 4.41 (q, $J$ = 7.2, 14.4 Hz, 2H), 3.47 (t, $J$ = 8.0, 16.0 Hz, 4H), 1.41 (t, $J$ = 7.2, 14.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$ (ppm), 163.22, 157.18, 154.54, 150.49, 149.27, 136.60, 136.37, 136.20, 135.94, 131.16, 130.21, 126.74, 127.47, 127.06, 125.95, 118.26, 117.69, 116.99, 116.37, 115.77, 61.95, 39.21, 34.76, 14.19; MS: $m/z$ 389.1627 (M+).
*Compound* **5a**: $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ (ppm), 8.07 (s, 1H), 7.14 (s, 1H), 7.13 (s, 1H), 7.12 (s, 1H), 6.86 (d, $J$ = 2.0 Hz, 1H), 6.85 (d, $J$ = 2.0 Hz, 1H), 5.90–6.00 (m, 2H), 5.00–5.13 (m, 4H), 3.32 (t, $J$ = 7.2, 7.6 Hz, 4H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), $\delta$ (ppm), 168.62, 167.66, 154.73, 152.03, 137.93, 137.38, 133.60, 132.44, 131.75, 130.99, 128.74, 128.65, 128.39, 126.52, 126.32, 123.17, 122.98, 116.54, 116.01, 115.22, 34.29, 21.39; MS: $m/z$ 393.1035 (M+).
*Compound* **6a**: $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ (ppm), 8.37 (s, 1H), 7.40 (q, $J$ = 1.6, 5.6 Hz, 1H) 7.36 (d, $J$ = 1.6 Hz, 1H), 7.17 (d, $J$ = 1.6 Hz, 1H), 7.01 (d, $J$ = 1.6 Hz, 1H), 6.86 (d, $J$ = 5.6 Hz, 1H), 5.94–6.09 (m, 2H), 5.15–5.22 (m, 2H), 3.47 (d, $J$ = 4.0 Hz, 2H), 3.36 (d, $J$ = 4.0 Hz, 2H), 3.24 (s, 1H), 1.36–1.82 (m, 10H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$ (ppm), 162.43, 157.39, 153.44, 137.69, 136.60, 133.26, 131.32, 130.58, 129.77, 129.56, 129.41, 128.89, 124.87, 118.68, 116.47, 115.71, 115.58, 39.26, 35.42, 34.28, 34.28, 30.95, 25.49, 24.32; MS: $m/z$ 375.2198 (M+).
*Compound* **6b**: $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ (ppm), 8.61 (s, 1H), 6.58–7.42 (m, 9H), 5.95–6.09 (m, 2H), 5.11–5.22 (m, 4H), 3.47 (d, $J$ = 4.0 Hz, 2H), 3.38 (d, $J$ = 4.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$ (ppm), 158.75, 156.59, 153.48, 145.81, 139.09, 137.59, 136.61, 133.59, 131.36, 130.42, 130.37, 130.09, 129.56, 128.86, 125.09, 122.34, 122.27, 119.44, 116.45, 115.84, 115.68, 115.68, 115.58, 39.28, 35.31; MS: $m/z$ 384.1838 (M+).
*Compound* **6c**: $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ (ppm), 8.66 (s, 1H), 6.88–7.44 (m, 10H), 5.96–6.10 (m, 2H), 5.09–5.24 (m, 4H), 3.48 (d, $J$ = 4.0 Hz, 2H), 3.40 (d, $J$ = 4.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$ (ppm),162.71, 156.81, 153.55, 148.24, 137.43, 136.50, 134.43, 131.39, 130.90, 130.32, 130.28, 129.73, 129.42, 129.33, 128.91, 126.91, 124.98, 121.15, 121.15, 119.12, 116.57, 115.98, 115.63, 39.22, 35.37; MS: $m/z$ 369.1729 (M+).
*Compound* **6d**: $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ (ppm), 7.83 (s, 1H), 7.43–6.87 (m,10H), 6.07–5.94 (m, 2H), 5.24–5.06 (m, 4H), 3.48 (d, $J$ = 6.4 Hz, 2H), 3.35 (d, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$ (ppm), 153.50, 152.41, 143.31, 141.36, 137.58, 136.49, 131.45, 131.42, 130.75, 130.65, 129.48, 129.48, 129.20, 128.98, 128.19, 124.94, 120.81, 118.52, 116.62, 115.80, 115.64, 112.63, 112.63, 39.27, 35.44; MS: $m/z$ 385 (M+).
*Compound* **6e**: $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ (ppm), 8.33 (s, 1H), 7.36 (d, $J$ = 4.0 Hz, 1H), 7.35 (d, $J$ = 4.0 Hz, 1H), 7.16 (d, $J$ = 2.0 Hz, 1H), 6.97 (d, $J$ = 2.0 Hz, 1H), 6.84 (q, $J$ = 2.8, 8.0 Hz, 1H), 5.88–6.08 (m, 2H), 5.02–5.22 (m, 2H), 3.45 (d, $J$ = 6.4 Hz, 2H), 3.32 (d, $J$ = 6.4 Hz, 2H), 0.88 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$ (ppm), 166.81, 156.70, 153.51, 137.46, 136.60, 133.64, 131.30, 130.27, 130.20, 129.88, 129.43, 128.81, 125.10, 118.51, 116.40, 115.85, 115.54, 59.59, 35.28, 30.93; MS: $m/z$ 336.1838 (M+).
*Compound* **6f**: $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ (ppm), 9.90 (s, 1H), 8.33 (s, 1H) , 7.41–7.31 (m, 2H) , 7.18 (d, $J$ = 2.4 Hz, 1H), 7.01 (d, $J$ = 2.4 Hz, 1H), 6.88–6.84 (m, 1H), 6.09–5.94 (m, 2H), 5.23–5.05 (m, 4H), 3.59–3.31 (m, 6H), 1.66 (s, 2H), 1.30–1.23 (m, 11H), 0.87 (t, $J$ = 6.8, 13.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$ (ppm), 164.65, 157.45, 153.43, 137.64, 136.60, 133.36, 131.32, 130.53, 129.76, 129.58, 129.45, 128.87, 124.90, 118.59, 116.45, 115.75, 115.58, 59.21, 39.26, 35.37, 31.83, 30.82, 29.70, 29.31, 29.19, 27.15, 18.83; MS: $m/z$ 378 (M+).
*Compound* **7**: $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ (ppm), 8.71 (s, 1H), 7.72 (q, $J$ = 2.4, 8.4 Hz, 1H), 7.68 (d, $J$ = 2.4 Hz, 1H), 7.52 (s, 1H), 7.43 (s, 1H), 7.03 (d, $J$ = 8.4 Hz, 1H), 5.99–6.10 (m, 2H), 5.12–5.23 (m, 4H), 3.53 (q, $J$ = 6.0, 12.6 Hz, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$ (ppm), 159.00, 154.58, 146.32, 137.12, 136.67, 136.25, 130.37, 129.38, 128.01, 127.72, 125.92, 123.98, 122.44, 119.21, 116.69, 116.44, 116.30, 39.81, 35.24; MS: $m/z$ 291.1259 (M+).
*Compound* **3b**: $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ (ppm), 8.43 (s, 1H), 7.43 (d, $J$ = 2.4 Hz, 1H), 7.33 (d, $J$ = 2.0 Hz, 1H), 7.03 (d, $J$ = 2.4 Hz, 1H), 6.96 (q, $J$ = 2.0, 8.4 Hz, 1H), 6.87 (d, $J$ = 8.0 Hz, 1H), 5.92–6.04 (m, 2H), 5.02–5.13 (m, 4H), 3.41 (d, $J$ = 6.8 Hz, 2H), 3.35 (d, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), $\delta$ (ppm),153.31, 152.63, 151.67, 138.69, 137.00, 132.12, 130.87, 130.48, 130.28, 129.27, 128.45, 127.30, 126.62, 116.99, 116.28, 115.78, 33.88; MS: $m/z$ 309.1365 (M+).
*Compound* **4b**: $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ (ppm), 8.55 (s, 1H), 7.65 (d, $J$ = 2.0 Hz, 2H), 7.08 (d, $J$ = 8.0 Hz, 2H), 6.92 (d, $J$ = 8.0 Hz, 1H), 5.92–6.03 (m, 2H), 5.06–5.18 (m, 4H), 4.40 (q, $J$ = 7.2, 14.4 Hz, 2H), 3.63 (d, $J$ = 6.8 Hz, 2H), 3.36 (d, $J$ = 6.8 Hz, 2H), 1.26–1.41 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$ (ppm), 163.13, 156.90, 152.10, 151.07, 149.17, 137.53, 136.06, 134.76, 134.73, 132.67, 130.43, 129.62, 128.65, 128.10, 126.18, 117.98, 117.85, 117.40, 116.47, 115.83, 62.05, 39.32, 33.20, 14.21; MS: $m/z$ 389.1627 (M+).
*Compound* **5b**: $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ (ppm), 9.52 (d, $J$ = 4.0 Hz, 1H), 8.14 (s, 1H), 7.55 (d, $J$ = 2.0 Hz, 1H), 7.37 (d, $J$ = 2.0 Hz, 1H), 7.05 (d, $J$ = 2.0 Hz, 1H), 6.96 (q, $J$ = 2.0, 8.0 Hz, 1H), 6.86 (d, $J$ = 2.0 Hz, 1H) , 5.90–6.03 (m, 2H), 5.00–5.11 (m, 4H), 3.30 (d, $J$ = 6.8 Hz, 4H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), $\delta$ (ppm), 168.70, 167.74, 153.55, 152.76, 138.68, 136.95, 131.00, 130.96, 130.56, 130.16, 128.71, 128.67, 128.46, 127.28, 126.75, 123.05, 121.58, 116.48, 116.41, 116.17,34.32, 22.52; MS: $m/z$ 393.1035 (M+).
*Compound* **3c**: $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ (ppm), 8.44 (s, 1H), 8.40 (s, 1H), 7.46 (d, $J$ = 2.0 Hz, 1H), 7.35 (d, $J$ = 2.0 Hz,1H), 7.18 (d, $J$ = 2.0 Hz, 1H), 7.12 (d, $J$ = 2.0 Hz, 1H), 5.92–6.06 (m, 2H), 5.05–5.13 (m, 4H), 3.43 (d, $J$ = 6.8 Hz, 2H), 3.34 (d, $J$ = 6.8 Hz, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), $\delta$ (ppm), 153.64, 152.06, 151.55, 151.55, 138.15, 136.88, 132.11, 131.75, 131.34, 129.43, 129.39, 129.15, 128.28, 126.82, 117.97, 117.10, 116.34, 116.23, 33.85, 33.81; MS: $m/z$ 352.1423 (M+).
*Compound* **5c**: $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ (ppm), 8.13 (s, 1H), 8.10 (s, 1H), 7.42 (d, $J$ = 2.0 Hz, 1H), 7.32 (d, $J$ = 2.0 Hz, 1H), 7.18 (d, $J$ = 2.0 Hz, 1H), 7.15 (d, $J$ = 2.0 Hz, 1H), 5.93–6.05 (m, 2H), 5.04–5.23 (m, 2H), 3.46 (d, $J$ = 6.4 Hz, 2H), 3.38 (d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), $\delta$ (ppm), 168.65, 168.58, 167.68, 167.61, 154.09, 152.04, 137.84, 136.67 (2), 133.77, 133.25, 132.71, 130.63, 129.95, 128.79, 128.59, 128.50, 127.39, 127.16, 123.58, 123.32, 121.86, 116.66, 116.63, 34.29, 21.39; MS: $m/z$ 520.0763 (M+).