

## ONE-POT SYNTHESIS OF 3-(GUAIAZULEN-3-YL)DIHYDRO-1H-INDOL-4(5H)-ONES VIA DOMINO REACTION

Lu Zhang, Dao-Lin Wang,\* Jin-Juan Xing, and Lin Liu

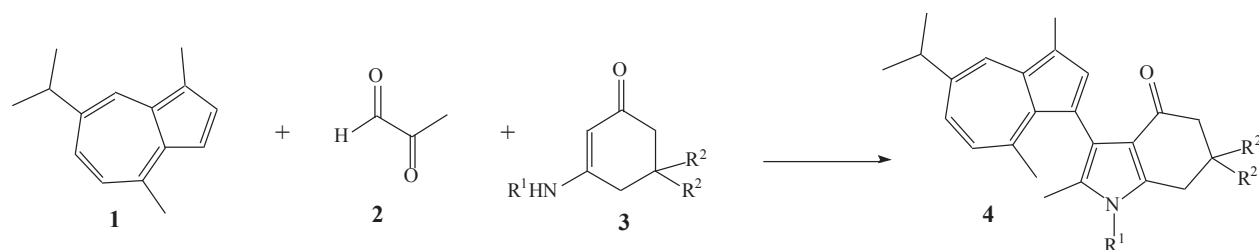
College of Chemistry and Chemical Engineering, Bohai University, Jinzhou, China; \*Corresponding authors E-mail: wangdaolin@sina.com

**Abstract** – A facile and efficient one-pot procedure for the preparation of 3-(guaiazulen-1-yl)dihydro-1*H*-indol-4(5*H*)-ones by a catalyst-free, three-component reaction of guaiazulene, methylglyoxal and enaminones under mild conditions in good yield is reported.

The indole nucleus is probably the most well-known heterocyclic compound, a common and important feature of a variety of natural products and medicinal agents.<sup>1</sup> Compounds carrying the indole moiety exhibit antibacterial and antifungal activities.<sup>2</sup> It is used as an important skeleton in organic synthesis<sup>3</sup> and is also utilized in other important fields, such as medicinal chemistry.<sup>4</sup> As a consequence, a number of methods have been reported for the construction of indoles.<sup>5</sup> Recently, some functionalized indoles have been synthesized by using different starting materials.<sup>6</sup>

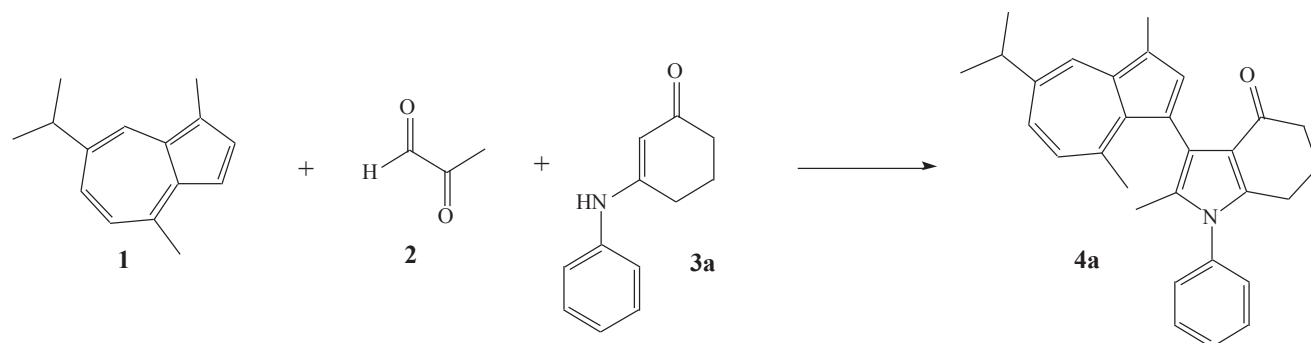
Azulene has a dipole moment whose negative end is directed toward the five-membered ring.<sup>7</sup> The effect of this polarized  $\pi$ -electron system on the structure and properties of azulenyl peptides is interesting in medicine as antiulcer drugs,<sup>8</sup> anticancer agents,<sup>9</sup> and as antioxidant therapeutics for neurodegenerative conditions.<sup>10</sup> Various efficient synthetic methods have been developed for azulene derivatives.<sup>11</sup> Thus, preparation and reactivities of a number of heterocycle-fused azulenes have already been revealed by many research groups.<sup>12</sup>

On the other hand, domino reactions have emerged as an effective tool for the assembly of complex cyclic structures by the combination of two or more distinct reactions into a one-pot transformation.<sup>13</sup> Recently, our research group has reported the synthesis of new heteroarylazulene derivatives.<sup>14</sup> In a continuation of our previous work,<sup>15</sup> we became interested in exploring the reactivity and synthetic application of guaiazulene to 3-(guaiazulen-1-yl)dihydro-1*H*-indol-4(5*H*)-one derivatives (**4**) by a catalyst-free, three-component reaction of guaiazulene (**1**), methylglyoxal (**2**) and enaminones (**3**) *via* domino alkylation–Michael addition–intramolecular cyclization (Scheme 1).



**Scheme 1.** Three-component synthesis of 3-(guaiazulen-1-yl)dihydro-1*H*-indol-4(5*H*)-ones **4**

We initially evaluated the three-component reaction of the guaiazulene (**1**), methylglyoxal (**2**) and 3-(phenylamino)cyclohex-2-enone (**3a**) (Scheme 2). The reaction mixture, which was composed of a 1:1:1 mixture of **1**, **2**, and **3a**, was tested under a variety of different conditions. The effects of solvent and temperature were evaluated for this reaction, and the results are summarized in Table 1. It was found that when the reaction was carried out in water without any catalyst the yield of product was very low (Table 1, entry 1). After the above observation, we also examined the influence of solvents such as toluene, MeCN, EtOH, and DMF without catalysts, and the desired product **4a** was obtained in 43–64% yield (Table 1, entries 2–5). In order to make the reaction more efficient, next we employed the model reaction in AcOH at 100 °C, and to our delight the desired product was attained in 78% yield within 6 h (Table 1, entry 6). Inspired by these results, the model reaction was performed in the mixture of H<sub>2</sub>O and AcOH (1:9) at 100 °C to furnish the desired product **4a** in 86% yield within 5 h (Table 1, entry 7). Increasing (20 and 50 vol%) or decreasing (5 vol%) the volume ratio of H<sub>2</sub>O/AcOH did not improve the product yield (Table 1, entries 8–10). When the reaction mixture was tested in EtOH/AcOH and MeCN/AcOH (10 vol%) at reflux for 7–8 h, the desired product **4a** was obtained in 70–72% yield (Table 1, entries 11, 12). From these optimization results, we found that H<sub>2</sub>O/AcOH (1:9 at 100 °C) is the most effective solvent media for this one-pot three-component synthesis.



**Scheme 2.** Synthesis of 2-methyl-3-(guaiazulen-1-yl)-6,7-dihydro-1-phenyl-1*H*-indol-4(5*H*)-one **4a**

**Table 1.** Optimizing the reaction conditions for the synthesis of **4a**\*

Entry	Solvent	Temperature	Time (h)	Yield (%)
1	H <sub>2</sub> O	100	24	18
2	toluene	100	13	43
3	MeCN	80	9	52
4	EtOH	80	10	54
5	DMF	100	8	64
6	AcOH	100	6	78
7	H <sub>2</sub> O:AcOH(1:9)	100	5	86
8	H <sub>2</sub> O:AcOH(1:4)	100	5	86
9	H <sub>2</sub> O:AcOH(1:1)	100	5	83
10	H <sub>2</sub> O:AcOH(1:19)	100	6	80
11	EtOH:AcOH(1:9)	reflux	8	70
12	MeCN:AcOH(1:9)	reflux	7	72

\* Reaction conditions: guaiazulene (**1**, 1.0 mmol), methylglyoxal (**2**, 1.0 mmol) and enaminone (**3a**, 1.0 mmol), solvent (20 mL).

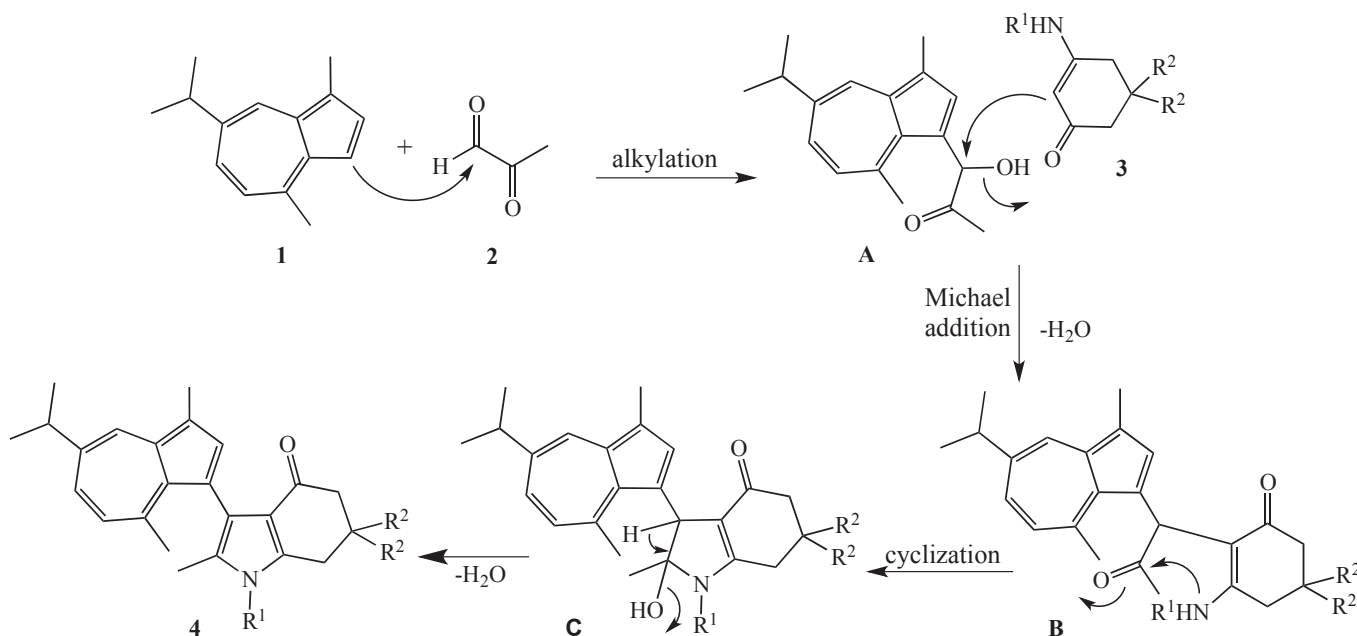
With this optimized procedure in hand, a range of 3-(guaiazulen-1-yl)dihydro-1*H*-indol-4(5*H*)-ones were synthesized by the one-pot condensation of guaiazulene with methylglyoxal and enaminones (see Table 2).

**Table 2.** Synthesis of 3-(guaiazulen-1-yl)dihydro-1*H*-indol-4(5*H*)-ones **4**

Entry	R <sup>1</sup>	R <sup>2</sup>	Time (h)	Product ( <b>4</b> )	Yield (%)
1	C <sub>6</sub> H <sub>5</sub>	H	5	<b>4a</b>	86
2	3-MeC <sub>6</sub> H <sub>4</sub>	H	5	<b>4b</b>	82
3	4-ClC <sub>6</sub> H <sub>4</sub>	H	4	<b>4c</b>	80
4	C <sub>6</sub> H <sub>5</sub>	Me	5	<b>4d</b>	83
5	3-MeC <sub>6</sub> H <sub>4</sub>	Me	4	<b>4e</b>	85
6	4-ClC <sub>6</sub> H <sub>4</sub>	Me	5	<b>4f</b>	83
7	benzyl	H	2	<b>4g</b>	90
8	<i>n</i> -propyl	H	3	<b>4h</b>	88
9	<i>n</i> -butyl	H	3	<b>4i</b>	82

It was found that aliphatic and phenyl groups, bearing either electron-withdrawing or electron-donating groups on the enaminone ring, were tolerated under the reaction conditions, leading to the final products in satisfactory yields (up to 90%). To the best of our knowledge, this new procedure provides the first example of an efficient synthesis for the 3-(guaiazulen-1-yl)dihydro-1*H*-indol-4(5*H*)-one derivatives. The structures of all the synthesized compounds were established by IR, NMR, MS spectroscopy and elemental analysis.

The proposed mechanism of the process is summarized in Scheme 3. First, alkylation of guaiazulene **1** with methylglyoxal **2** is proposed to give intermediate **A**. Michael addition of enaminone **3** to intermediate **A** then occurs to provide intermediate **B**, which undergoes intramolecular cyclization and dehydration to form the desired product **4**.



**Scheme 3.** Reasonable mechanism for the product **4**

In summary, we have demonstrated for the efficient method for the synthesis of 3-(guaiazulen-1-yl)-dihydro-1*H*-indol-4(5*H*)-ones from guaiazulene, methylglyoxal and enaminones through domino alkylation–Michael addition–intramolecular cyclization. This approach offers an effective route for the construction of heteroarylazulene frameworks in a one-step process from commercially available starting materials.

## EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The NMR spectra were recorded with a Bruker Avance 400 spectrometer (400 MHz for <sup>1</sup>H and 100 MHz for <sup>13</sup>C) using TMS an internal reference. IR spectra were measured on Shimadzu FTIR-8300 spectrophotometer. C, H and N analyses

were performed by a HP-MOD 1106 microanalyzer. LC-MS analyses were performed on waters Q-TOF micro mass spectrometer. The preparation of enaminones (**3**)<sup>16</sup> were according to the literature procedure. All other chemicals used in this study were commercially available.

**Typical Procedure for the Preparation of 3-(Guaiazulen-1-yl)dihydro-1*H*-indol-4(5*H*)-ones.** A solution of guaiazulene **1** (1 mmol), methylglyoxal **2** (1 mmol), and enaminones **3** (1 mmol) in H<sub>2</sub>O/AcOH (20 mL, 1:9) was heated at 100 °C. After completion monitored by TLC, the reaction mixture was allowed to cool to room temperature, and then water (40 mL) was added to the mixture. EtOAc (50 mL) was added to the mixture. The organic layer was washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The residue was recrystallized from isopropanol to afford the corresponding products **4a-i**.

**2-Methyl-3-(guaiazulen-1-yl)-6,7-dihydro-1-phenyl-1*H*-indol-4(5*H*)-one (4a):** Blue crystals. mp 40-42 °C; IR (KBr):  $\nu$  1656 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.38 (d, *J* = 6.8 Hz, 6H), 1.77 (s, 3H), 2.08-2.11 (m, 2H), 2.38-2.40 (m, 2H), 2.53 (s, 3H), 2.63-2.65 (m, 2H), 2.68 (s, 3H), 3.09-3.17 (m, 1H), 6.91 (d, *J* = 10.8 Hz, 1H), 7.37-7.43 (m, 3H), 7.55-7.64 (m, 4H), 8.19 (s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  193.6, 145.6, 142.9, 140.6, 138.9, 138.1, 137.5, 134.2, 133.4, 133.0, 129.5, 129.2, 128.5, 127.7, 126.1, 123.9, 121.0, 120.1, 118.9, 38.9, 37.9, 25.4, 24.8, 24.7, 23.9, 23.1, 13.1, 11.0. MS (ESI) *m/z*: 422 [M+H]<sup>+</sup>. *Anal.* Calcd for C<sub>30</sub>H<sub>31</sub>NO: C 85.47, H 7.41, N 3.32. Found: C 85.51, H 7.46, N 3.35.

**2-Methyl-3-(guaiazulen-1-yl)-6,7-dihydro-1-(3-methylphenyl)-1*H*-indol-4(5*H*)-one (4b):** Blue crystals. mp 54-57 °C; IR (KBr):  $\nu$  1647 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.36 (d, *J* = 6.8 Hz, 6H), 1.78 (s, 3H), 2.09-2.12 (m, 2H), 2.42-2.43 (m, 2H), 2.45 (s, 3H), 2.50 (s, 3H), 2.63-2.64 (m, 2H), 2.67 (s, 3H), 3.01-3.08 (m, 1H), 6.81 (d, *J* = 10.8 Hz, 1H), 7.10-7.12 (m, 2H), 7.26-7.28 (m, 2H), 7.41 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.52 (s, 1H), 8.12 (s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  193.6, 145.6, 142.9, 140.5, 139.5, 138.8, 138.1, 137.4, 134.1, 133.4, 132.9, 129.2, 129.1, 128.2, 126.1, 123.9, 121.1, 119.9, 118.8, 38.8, 37.8, 25.4, 24.7, 23.8, 23.1, 21.3, 19.4, 13.1, 11.0. MS (ESI) *m/z*: 436 [M+H]<sup>+</sup>. *Anal.* Calcd for C<sub>31</sub>H<sub>33</sub>NO: C 85.48, H 7.64, N 3.22. Found: C 85.54, H 7.69, N 3.23.

**2-Methyl-3-(guaiazulen-1-yl)-6,7-dihydro-1-(4-chlorophenyl)-1*H*-indol-4(5*H*)-one (4c):** Blue crystals. mp 60-62 °C; IR (KBr):  $\nu$  1655 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.35 (d, *J* = 6.8 Hz, 6H), 1.79 (s, 3H), 2.10-2.15 (m, 2H), 2.44-2.46 (m, 2H), 2.48 (s, 3H), 2.62-2.64 (m, 2H), 2.66 (s, 3H), 3.01-3.06 (m, 1H), 6.81 (d, *J* = 10.8 Hz, 1H), 7.26-7.28 (m, 3H), 7.49-7.52 (m, 3H), 8.13 (s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  193.5, 145.5, 142.7, 140.4, 139.0, 138.1, 136.0, 134.4, 134.2, 133.4, 133.1, 129.7, 129.0, 128.9, 126.1, 123.9, 120.6, 120.3, 119.3, 38.7, 37.8, 25.4, 24.6, 23.8, 23.0, 19.4, 13.1, 10.9. MS (ESI) *m/z*: 457 [M+H]<sup>+</sup>. *Anal.* Calcd for C<sub>30</sub>H<sub>30</sub>ClNO: C 79.02, H 6.63, N 3.07. Found: C 79.07, H 6.65, N 3.11.

**2-Methyl-3-(guaiazulen-1-yl)-6,7-dihydro-6,6-dimethyl-1-phenyl-1*H*-indol-4(5*H*)-one (4d):** Blue crystals. mp 43-45 °C; IR (KBr):  $\nu$  1652 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  1.09 (s, 3H), 1.12 (s,

3H), 1.36 (d,  $J = 6.8$  Hz, 6H), 1.80 (s, 3H), 2.31-2.39 (m, 2H), 2.44-2.48 (m, 2H), 2.55 (s, 3H), 2.68 (s, 3H), 3.02-3.09 (m, 1H), 6.83 (d,  $J = 10.4$  Hz, 1H), 7.27-7.32 (m, 3H), 7.48-7.54 (m, 4H), 8.14 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  193.0, 145.6, 141.9, 140.5, 138.9, 138.1, 137.5, 134.2, 133.5, 133.0, 129.5, 129.3, 128.5, 127.8, 126.2, 123.9, 120.9, 119.0, 118.7, 52.8, 37.8, 36.9, 35.3, 29.2, 27.8, 25.3, 24.7, 19.4, 13.1, 11.0. MS (ESI)  $m/z$ : 450  $[\text{M}+\text{H}]^+$ . *Anal.* Calcd for  $\text{C}_{32}\text{H}_{35}\text{NO}$ : C 85.48, H 7.85, N 3.12. Found: C 85.54, H 7.89, N 3.14.

**2-Methyl-3-(guaiazulen-1-yl)-6,7-dihydro-6,6-dimethyl-1-(3-methylphenyl)-1H-indol-4(5H)-one (4e):**

Blue crystals. mp 88-90 °C; IR (KBr):  $\nu$  1648  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.10 (s, 3H), 1.12 (s, 3H), 1.37 (d,  $J = 6.8$  Hz, 6H), 1.79 (s, 3H), 2.30-2.35 (m, 2H), 2.52 (s, 3H), 2.54 (s, 3H), 2.60-2.66 (m, 2H), 3.02-3.09 (m, 1H), 6.83 (d,  $J = 10.4$  Hz, 1H), 7.10-7.13 (m, 2H), 7.27-7.30 (m, 2H), 7.41-7.43 (m, 1H), 7.54 (s, 1H), 8.13 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  192.9, 145.6, 141.9, 140.5, 139.6, 138.8, 138.1, 137.4, 134.1, 133.5, 133.0, 129.3, 129.2, 129.2, 128.3, 126.1, 124.8, 123.9, 123.0, 118.9, 118.6, 100.7, 52.9, 37.8, 36.9, 35.3, 29.2, 27.9, 25.3, 24.7, 21.4, 19.4, 13.1, 11.0. MS (ESI)  $m/z$ : 464  $[\text{M}+\text{H}]^+$ . *Anal.* Calcd for  $\text{C}_{33}\text{H}_{37}\text{NO}$ : C 85.48, H 8.04, N 3.02. Found: C 85.53, H 8.06, N 3.05.

**2-Methyl-3-(guaiazulen-1-yl)-6,7-dihydro-6,6-dimethyl-1-(4-chlorophenyl)-1H-indol-4(5H)-one (4f):**

Blue crystals. mp 83-85 °C; IR (KBr):  $\nu$  1650  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.09 (s, 3H), 1.11 (s, 3H), 1.36 (d,  $J = 6.8$  Hz, 6H), 1.80 (s, 3H), 2.30-2.34 (m, 2H), 2.49 (s, 3H), 2.53-2.57 (m, 2H), 2.67 (s, 3H), 3.01-3.08 (m, 1H), 6.82 (d,  $J = 10.4$  Hz, 1H), 7.25-7.30 (m, 2H), 7.50-7.53 (m, 3H), 8.13 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  192.9, 145.5, 141.7, 140.4, 139.0, 138.1, 136.0, 134.5, 134.2, 133.5, 133.1, 129.7, 129.1, 129.1, 126.2, 123.9, 120.5, 119.3, 119.1, 52.8, 37.8, 36.9, 35.3, 29.2, 27.9, 25.3, 24.7, 19.4, 13.1, 11.0. MS (ESI)  $m/z$ : 485  $[\text{M}+\text{H}]^+$ . *Anal.* Calcd for  $\text{C}_{32}\text{H}_{34}\text{ClNO}$ : C 79.40, H 7.08, N 2.89. Found: C 79.45, H 7.14, N 2.93.

**2-Methyl-3-(guaiazulen-1-yl)-6,7-dihydro-1-benzyl-1H-indol-4(5H)-one (4g):**

Blue crystals. mp 48-50 °C; IR (KBr):  $\nu$  1659  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.36 (d,  $J = 6.4$  Hz, 6H), 1.87 (s, 3H), 2.14-2.16 (m, 2H), 2.42-2.44 (m, 2H), 2.45 (s, 3H), 2.66 (s, 3H), 2.75-2.77 (m, 2H), 3.03-3.07 (m, 1H), 6.77 (d,  $J = 10.8$  Hz, 1H), 7.01 (d,  $J = 7.2$  Hz, 2H), 7.27-7.38 (m, 4H), 7.47 (s, 1H), 8.12 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  193.4, 145.5, 142.5, 140.6, 138.8, 138.1, 136.9, 134.1, 133.4, 133.0, 128.9, 128.6, 127.6, 126.0, 125.6, 123.8, 121.1, 119.9, 119.2, 47.4, 38.6, 37.8, 25.4, 24.7, 24.7, 23.7, 22.2, 13.0, 10.2. MS (ESI)  $m/z$ : 436  $[\text{M}+\text{H}]^+$ . *Anal.* Calcd for  $\text{C}_{31}\text{H}_{33}\text{NO}$ : C 85.48, H 7.64, N 3.67. Found: C 85.53, H 7.69, N 3.68.

**2-Methyl-3-(guaiazulen-1-yl)-6,7-dihydro-1-(n-propyl)-1H-indol-4(5H)-one (4h):**

Blue crystals. mp 44-46 °C; IR (KBr):  $\nu$  1656  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.00 (t,  $J = 7.2$  Hz, 3H), 1.36 (d,  $J = 6.8$  Hz, 6H), 1.73-1.77 (m, 2H), 1.96 (s, 3H), 2.15-2.18 (m, 2H), 2.39 (s, 3H), 2.40-2.42 (m, 2H), 2.66 (s, 3H), 2.82-2.85 (m, 2H), 3.03-3.06 (m, 1H), 3.82 (t,  $J = 7.2$  Hz, 2H), 6.78 (d,  $J = 10.4$  Hz, 1H), 7.26 (d,  $J = 10.4$

Hz, 1H), 7.45 (s, 1H), 8.11 (s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 193.2, 145.6, 141.9, 140.6, 138.7, 138.0, 134.1, 133.3, 132.9, 128.1, 125.9, 123.8, 121.5, 119.6, 118.7, 45.7, 38.6, 37.8, 2.20, 24.7, 24.7, 24.0, 23.8, 22.4, 13.0, 11.2, 10.3. MS (ESI) *m/z*: 388 [M+H]<sup>+</sup>. *Anal.* Calcd for C<sub>27</sub>H<sub>33</sub>N: 83.68, H 8.58, N 3.61. Found: C 83.70, H 8.61, N 3.63.

**2-Methyl-3-(guaiazulen-1-yl)-6,7-dihydro-1-(*n*-butyl)-1*H*-indol-4(5*H*)-one (4i):** Blue crystals. mp 39-41 °C; IR (KBr): ν 1653 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.01 (t, *J* = 7.2 Hz, 3H), 1.35 (d, *J* = 6.8 Hz, 6H), 1.43-1.47 (m, 2H), 1.68-1.72 (m, 2H), 1.95 (s, 3H), 2.15-2.17 (m, 2H), 2.41 (s, 3H), 2.43-2.45 (m, 2H), 2.66 (s, 3H), 2.82-2.85 (m, 2H), 3.04-3.06 (m, 1H), 3.84 (t, *J* = 7.6 Hz, 2H), 6.78 (d, *J* = 10.4 Hz, 1H), 7.25 (d, *J* = 10.4 Hz, 1H), 7.45 (s, 1H), 8.12 (s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 193.2, 145.6, 141.8, 140.6, 138.7, 138.0, 134.0, 133.3, 132.9, 128.1, 125.9, 123.8, 121.5, 119.6, 118.7, 44.0, 38.6, 37.8, 32.9, 25.2, 24.7, 24.7, 23.7, 22.4, 20.1, 13.9, 13.1, 10.2. MS (ESI) *m/z*: 402 [M+H]<sup>+</sup>. *Anal.* Calcd for C<sub>28</sub>H<sub>35</sub>NO: C 83.74, H 8.78, N 3.49. Found: C 83.78, H 8.80, N 3.53.

## REFERENCES

1. W. J. Houlihan, W. A. Remers, and R. K. Brown, *Indoles: Part I*; Wiley: New York, 1992.
2. R. J. Sundberg, *The Chemistry of Indoles*; Academic: New York, 1996.
3. (a) J. R. Fuchs and R. L. Funk, *Org. Lett.*, 2005, **7**, 677; (b) W.-L. Chen, Y.-F. Cai, X. Fu, X.-H. Liu, L.-L. Lin, and X.-M. Feng, *Org. Lett.*, 2011, **13**, 4910; (c) Y.-A. Qiu, W.-Q. Kong, C.-L. Fu, and S.-M. Ma, *Org. Lett.*, 2012, **14**, 6198.
4. (a) S. Wu, A. Fluxe, J. M. Janusz, J. B. Sheffer, G. Browning, B. Blass, K. Cobum, R. Hedges, M. Murawsky, B. Fang, G. M. Fadayel, M. Hare, and L. Djandjighian, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5859; (b) B. Pita, C. F. Masaguer, and E. Raviña, *Tetrahedron Lett.*, 2002, **43**, 7929.
5. (a) D. B. England, G. Merey, and A. Padwa, *Org. Lett.*, 2007, **9**, 3805; (b) X. Ban, Y. Pan, Y.-F. Lin, S.-Q. Wang, Y.-F. Du, and K. Zhao, *Org. Biomol. Chem.*, 2012, **10**, 3606; (c) J. T. Kuethe, A. Wong, and I. W. Davies, *Org. Lett.*, 2003, **5**, 3975.
6. (a) B. Jiang, M.-S. Yi, F. Shi, S.-J. Tu, S. Pindi, P. McDowell, and G. Li, *Chem. Commun.*, 2012, **48**, 808; (b) L.-P. Fu, Q.-Q. Shi, Y. Shi, B. Jiang, and S.-J. Tu, *ACS Comb. Sci.*, 2013, **15**, 135.
7. S. Aravinda, N. Shamala, C. Das, A. Sriranjini, I. L. Karle, and P. Balaram, *J. Am. Chem. Soc.*, 2003, **125**, 5308.
8. T. Yanagisawa, S. Wakabayashi, T. Tomiyama, M. Yasunami, and K. Takase, *Chem. Pharm. Bull.*, 1988, **36**, 641.
9. A. E. Asato, A. Peng, M. Z. Hossain, T. Mirzadegan, and J. S. Bertram, *J. Med. Chem.*, 1993, **36**, 3137.
10. D. A. Becker, J. J. Ley, L. Echegoyen, and R. Alvarado, *J. Am. Chem. Soc.*, 2002, **124**, 4678.

11. G. Fischer, *Adv. Heterocycl. Chem.*, 2009, **97**, 131.
12. (a) H. Matsuo, K. Fujimori, A. Ohta, A. Kakehi, M. Yasunami, and T. Nozoe, *Heterocycles*, 2003, **61**, 271; (b) M. Nishiura, I. Ueda, and K. Yamamura, *Heterocycles*, 2007, **74**, 951; (c) S. Itô, T. Okujima, S. Kikuchi, T. Shoji, N. Morita, T. Asao, T. Ikoma, S. Tero-Kubota, J. Kawakami, and A. Tajiri, *J. Org. Chem.*, 2008, **73**, 2256; (d) T. Shoji, E. Shimomura, Y. Inoue, M. Maruyama, A. Yamamoto, K. Fujimori, S. Itô, M. Yasunami, and N. Morita, *Heterocycles*, 2013, **87**, 303; (e) S. Itô, S. Yamazaki, S. Kudo, R. Sekiguchi, J. Kawakami, M. Takahashi, T. Matsushashi, K. Toyota, and N. Morita, *Tetrahedron*, 2014, **70**, 2796; (f) N. Takenaga, K. Fukazawa, M. Maruko, and K. Sato, *Heterocycles*, 2015, **90**, 113; (g) O. Sato, A. Sakai, M. Aoki, T. Kuramochi, and J. Nakayama, *Heterocycles*, 2012, **86**, 1253; (h) O. Sato, T. Saito, M. Iwase, and A. Sakai, *Heterocycles*, 2016, **93**, 714; (i) L. Zhang, D.-L. Wang, J.-J. Xing, and L. Liu, *Heterocycles*, 2019, **98**, DOI:10.3989/COM-19-14166.
13. (a) L. F. Tietze, G. Brasche, and K. M. Gericke, *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006; (b) L. F. Tietze, *Chem. Rev.*, 2006, **96**, 115; (c) R. Breinbauer, *Synthesis*, 2007, 794; (d) S. Indumathi, J. C. Menendez, and S. Perumal, *Curr. Org. Chem.*, 2013, **17**, 2038; (e) L. G. Voskressensky, A. A. Festa, and A. V. Varlamov, *Tetrahedron*, 2014, **70**, 551.
14. (a) D.-L. Wang, L.-N. Lin, S.-F. Li, W. Li, and Y.-F. Li, *Chin. J. Org. Chem.*, 2010, **30**, 1774; (b) D.-L. Wang, Y.-F. Li, J. Xu, W. Li, S.-F. Li, and L.-N. Lin, *Heterocycles*, 2011, **83**, 365; (c) D.-L. Wang, Q.-T. Cui, S.-S. Feng, and J.-Y. Yu, *Heterocycles*, 2012, **85**, 697; (d) D.-L. Wang, Z. Dong, Q.-T. Cui, F.-F. Yang, and W. Zhao, *Heterocycles*, 2013, **87**, 2343; (e) D.-L. Wang, J. Ma, X.-C. Shi, and J.-Y. Wu, *Heterocycles*, 2016, **92**, 133.
15. (a) D.-L. Wang, S.-F. Li, W. Li, Y. F.-Li, and L.-N. Lin, *Chin. Chem. Lett.*, 2011, **22**, 789; (b) D.-L. Wang, J.-Y. Yu, J. Xu, and Z. Dong, *Chin. J. Org. Chem.*, 2012, **32**, 1741; (c) D.-L. Wang, J.-Y. Yu, J. Xu, and Z. Dong, *Heterocycles*, 2013, **87**, 1099; (d) D.-L. Wang, Z. Dong, J. Xu, D. Li, and J.-Y. Yu, *Chin. Chem. Lett.*, 2013, **24**, 622; (e) Y. Liu, J. Xu, D.-L. Wang, W. Ma, and X.-W. Zhang, *Heterocycles*, 2018, **96**, 1445.
16. B. Datta, M. B. Madhusudana Reddy, and M. A. Pasha, *Synth. Commun.*, 2011, **41**, 2331.