HETEROCYCLES, Vol. 102, No. 1, 2021, pp. 105 - 113. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 12th October, 2020, Accepted, 6th November, 2020, Published online, 12th November, 2020
DOI: 10.3987/COM-20-14362

A SIMPLE ROUTE FOR SYNTHESIS AND EVALUATION OF ANTIOXIDANT ACTIVITY OF (GUAIAZULEN-1-YL)FURANS

Si-Tong Guo,[†,a] Jiao Xu,[†,b,c] Xiao-Liang Zhang,[a] Xin-Shuang Xiong,[a] Lu Zhang,[a] Dao-Lin Wang,[a*] and Shu-Quan Zhang[c*]

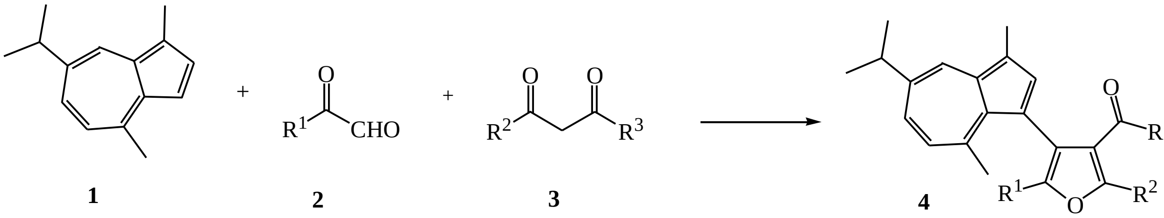
[a] College of Chemistry and Material Science, Bohai University, Jinzhou, China; [b] College of Jiamusi, Heilongjiang University of Chinese Medicine, Jiamusi, China; [c] Institute of economic crops, Heilongjiang Academy of Agricultural Sciences, Harbin, China. †These authors contributed equally to this work; *Corresponding authors E-mail: wangdaolin@sina.com; zsqhlj@126.com.

Abstract – An effective protocol for the synthesis of guaiazulene substituted furan derivatives via three-component reactions of guaiazulene, α-ketoaldehyde, and 1,3-dicarbonyl compound under mild conditions in good yield is reported. All of these compounds were evaluated for their antioxidant properties *in vitro* against lipid peroxidation and several compounds were found to have good activities.

Polysubstituted furans are among the most important heterocyclic compounds with widespread occurrence in nature.[1] Compounds featuring a furan skeleton exhibit diverse biological properties, such as anticancer,[2] anti-inflammatory,[3] anti-allergic,[4] hair-growth-stimulating[5] and immunosuppressive activities.[6] Furthermore, many polysubstituted furans have been widely used as important reaction intermediates in the total synthesis and synthetic industry.[7]

Guaiazulene is a known active component of the essential oil of *Guaiacum officinalis* L., and there are a number of reports describing the anti-allergenic and anti-inflammatory activities.[8] Azulene derivatives have attracted interest in medicine as antiulcer drugs,[9] anticancer agents,[10] and as antioxidant therapeutics for neurodegenerative conditions.[11] A variety of heterocycle-fused and substituted azulenes have so far been obtained on the viewpoints of chemical properties and physiological activities by several methods.[12]

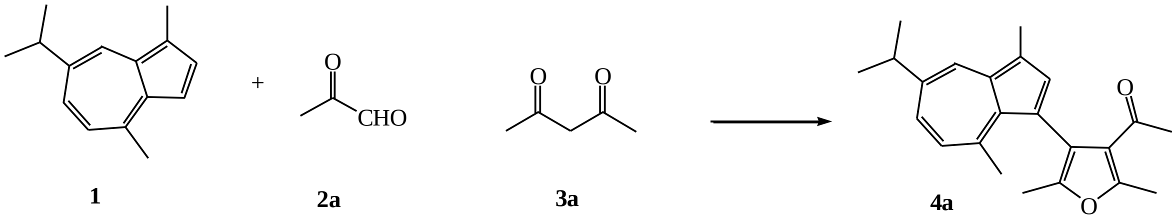
In recent years, our reserach group has reported the synthesis of new heteroarylazulene derivatives.[13] As part of a continuing effort in our laboratory toward the development of azulene chemistry,[14] we became interested in exploring the reactivity and synthetic application of guaiazulene[15] to guaiazulene substituted furan derivatives[16] via multicomponent reaction of guaiazulene, α-ketoaldehyde, and 1,3-dicarbonyl compound under mild conditions (Scheme 1). To our interest, this may be a novel series of compounds, possessing antioxidant activity against lipid peroxidation. In this paper, we report the synthesis and antioxidant activities of (guaiazulen-1-yl)furans.



Scheme 1. One-pot synthesis of guaiazulene substituted furan derivatives

First, to optimize the conditions, we initially evaluated the three-component reaction of guaiazulene **1**, methylglyoxal **2a**, and acetylacetone **3a** (Scheme 2). The reaction mixture, which was composed of a 1:1:1 mixture of **1, 2a**, 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.

The initial reaction of guaiazulene **1**, methylglyoxal **2a**, and acetylacetone **3a** was attempted with stirring for 24 h at 25 °C in HOAc (Table 1, Entry 1). After the reaction was completed, the mixture was purified by flash column chromatography to give pure product, 3-acetyl-2,5-dimethyl-4-(guaiazulen-1-yl)furan (**4a**), whose structure was characterized by ^{1}H NMR, ^{13}C NMR, IR spectra and elemental analysis.



Scheme 2. Synthesis of 3-acetyl-2,5-dimethyl-4-(guaiazulen-1-yl)furan (**4a**)

After the above observation, the reaction was carried out under neat conditions at 100 °C without and with different acid catalysts such as *p*-toluenesulfonic acid (*p*-TsOH), trifluoroacetic acid (TFA), and sulfamic acid (SA) each 10 mol% in HOAc (entries 2–5). The maximum yield was obtained using *p*-TsOH (entry 3). It was found that when the reaction was carried out without any catalyst the yield of product was very low (Table 1, entries 1 and 2). Although a lower catalyst loading of 5 mol% accomplished this condensation (entry 6), 10 mol% of *p*-TsOH was optimal in terms of reaction time and isolated yield (entry 3). Increasing the amount from 10 to 15 mol% has no effect on the product yield and reaction time (entry 7). A higher reaction temperature (110 °C) did not make a significant effect in the yield of product (entry 8).

In addition, various solvents such as EtOH, and MeCN were screened for the optimal reaction conditions. The best catalytic activity was observed in HOAc compared to other organic solvents (entries 9 and 10). From these optimization results, we found that HOAc (at 100 °C) is the most effective solvent media, and *p*-TsOH was the best catalyst for this one-pot three-component synthesis.

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

Entry	Catalyst / (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	none	HOAc	25	24	31
2	none	HOAc	100	11	42
3	*p*-TsOH (10)	HOAc	100	5	88
4	TFA (10)	HOAc	100	6	70
5	SA (10)	HOAc	100	10	74
6	*p*-TsOH (5)	HOAc	100	8	75
7	*p*-TsOH (15)	HOAc	100	5	85
8	*p*-TsOH (10)	HOAc	110	4	82
9	*p*-TsOH (10)	EtOH	80	13	78
10	*p*-TsOH (10)	MeCN	80	12	65

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

With the optimized reaction conditions in hand, we next surveyed the substrate scope of α-ketoaldehyde, and 1,3-dicarbonyl compound for the synthesis of guaiazulene substituted furans (see Scheme 1), and the results are summarized in Table 2.

Table 2. Synthesis of guaiazulene substituted furan derivatives **4**

Entry	R^1	R^2	R^3	Time (h)	Product	Yield (%)
1	Me	Me	Me	5	**4a**	88
2	Me	Me	OMe	5	**4b**	90
3	Me	Me	OEt	6	**4c**	85
4	Ph	Me	Me	7	**4d**	90
5	Ph	Me	OMe	6	**4e**	86
6	Ph	Me	OEt	5	**4f**	87
7	Me	CH_2-	-CH_2CH_2	8	**4g**	90
8	Me	CH_2-	-$C(Me)_2CH_2$	7	**4h**	92

As shown in Table 2, 1,3-dicarbonyl compounds such as acetylacetone (**3a**), methyl acetoacetate (**3b**), ethyl acetoacetate (**3c**), cyclohexane-1,3-dione (**3d**), and 5,5-dimethylcyclohexane-1,3-dione (**3e**) were suitable partners for α-ketoaldehyde (such as methylglyoxal (**2a**) and phenylglyoxal (**2a**)) to afford the desired disubstituted furan products (**4a-h**) in high yields. The structures of all the synthesized compounds were established by IR, NMR, MS spectroscopy and elemental analysis.

Oxidative stress may initiate molecular events in the cancer formation, and reduction of oxidative stress may protect against carcinogenesis.[17] The azulene scaffold is widely found among natural products and synthetic compounds, which exhibit a range of important biological activities.[18] Different functional groups and heterocyclic moieties attached to the azulene nucleus have been shown to modulate the antioxidant ability of the resulting compounds.[19]

All of the synthetic new compounds **4a-h** were subjected to antioxidant activity screening against lipid peroxidation *in vitro*, using magnesium lithospermate B (MLB) as reference drug. The IC_{50} values for these active compounds were listed in **Table 3**. Lipid peroxidation was evaluated by measuring the malondialdehyde (MDA) concentration using the TBA test.[20]

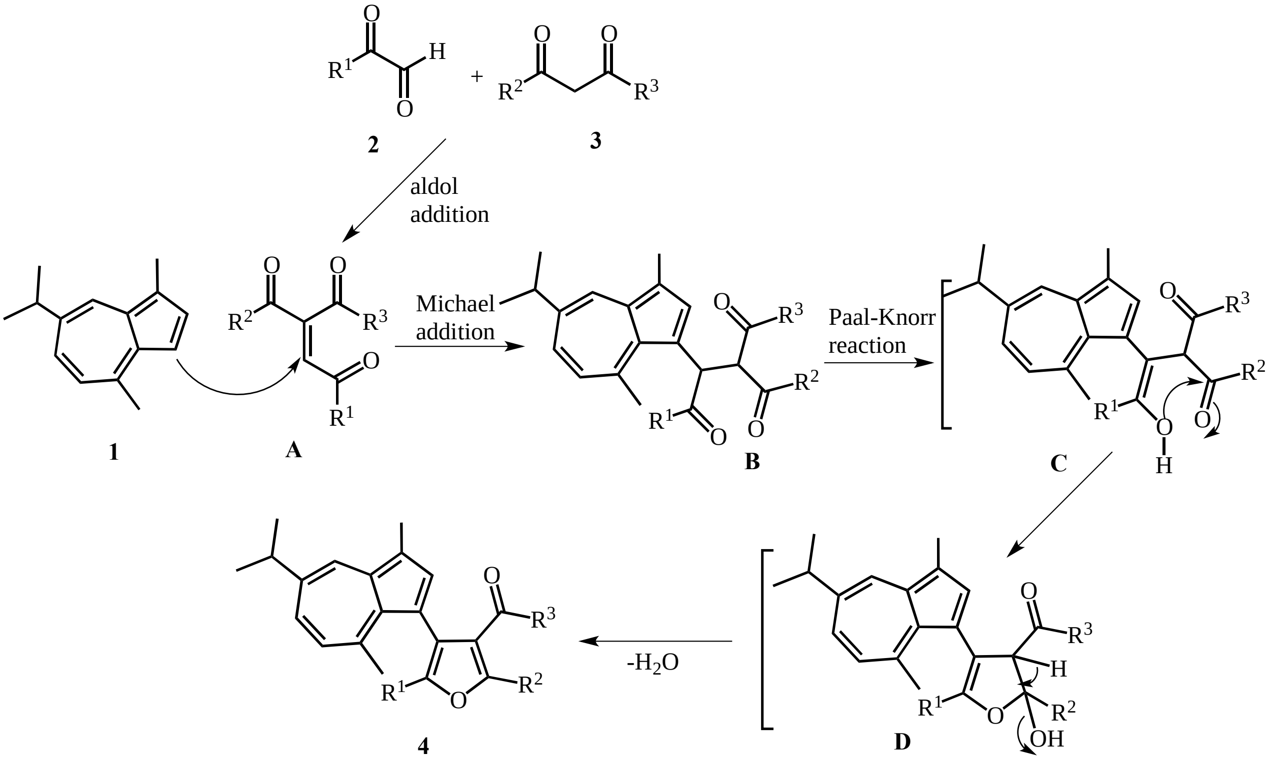
Table 3. Antioxidant activity against lipid peroxidation of compounds (IC_{50} at µg/mL)*

Compound	IC_{50}	Compound	IC_{50}	Compound	IC_{50}
4a	18	**4d**	16	**4g**	11
4b	3.9	**4e**	6.1	**4h**	15
4c	4.3	**4f**	5.0	**MLB**	2.5

* Compound was dissolved in DMSO (solvent expressed no antioxidant activity).

Among the compounds, **4b** exhibited the most potent antioxidant activity with IC_{50} value of 3.9 µg/mL. Yet compounds **4c**, **4e** and **4f** also showed significant antioxidant activities, and they all possessed methoxy or ethoxy group at R^3. The antioxidant activities of compounds **4a**, **4d**, **4g** and **4h**, whose alkoxy groups at R^3 were replaced by methyl or mthylene group, were reduced. So, R^3 with alkoxy group was crucial for the antioxidant activity.

The proposed mechanism of the process is summarized in Scheme 3. First, an aldol-type addition of α-ketoaldehyde **2** to 1,3-dicarbonyl compounds **3** occurred, enabling the formation of an intermediate **A**. The following Michael addition of guaiazulene **1** to intermediate **A** then occurs to provide trione **B**, which undergoes Paal-Knorr reaction to form the desired product **4**.



Scheme 3. Proposed mechanism for the synthesis of 4-(guaiazulen-1-yl)furans **4**

In summary, we have demonstrated for the efficient method for the synthesis of guaiazulene substituted furan derivatives via three-component reactions of guaiazulene, α-ketoaldehyde, and 1,3-dicarbonyl compound in good yield. This approach offers an effective route for the construction of heteroarylazulene frameworks in a one-step process from commercially available starting materials. In addition, the lead compounds emerging with the potent antioxidant activity in this study (such as **4b**) will be further structurally modified towards the discovery of a compound with optimal combined antioxidant and anticancer activities.

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 ^{1}H and 100 MHz for ^{13}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. All other chemicals used in this study were commercially available.

General experimental procedure

A mixture of guaiazulene **1** (1.0 mmol), α-ketoaldehyde **2** (1.0 mmol), 1,3-dicarbonyl compound **3** (1.0 mmol) and *p*-TsOH (0.1 mmol) was dissolved in HOAc (20 mL). and 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_2SO_4 and evaporated to dryness. The residue was recrystallized from isopropanol to afford the corresponding products **4a-h**.

3-Acetyl-2,5-dimethyl-4-(guaiazulen-1-yl)furan (4a): Blue scaly crystals. mp 58-60 °C; IR (KBr): *ν* 1646 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.11 (s, 1H), 7.31-7.35 (m, 1H), 7.29 (s, 1H), 6.93 (d, *J* = 10.8 Hz, 1H), 3.70-3.78 (m, 1H), 3.06 (s, 3H), 2.56 (s, 3H), 2.45 (s, 2H), 1.80(s, 3H), 1.36 (d, *J* = 7.2 Hz, 6H), 1.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 196.26, 165.89, 144.50, 139.82, 138.80, 138.34, 134.71, 133.73, 132.89, 127.22, 125.03, 124.88, 117.20, 113.78, 37.65, 29.74, 28.05, 24.57, 22.07, 15.78, 14.84, 13.12. MS (ESI) *m/z*: 335 $[M+H]^+$. *Anal.* Calcd for $C_{23}H_{26}O_2$: C 82.60, H, 7.84. Found: C 82.63, H 7.87.

Methyl 2,5-dimethyl-4-(guaiazulen-1-yl)furan-3-carboxylate (4b): Blue scaly crystals. mp 65-67 °C; IR (KBr,): *ν* 1647 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.16 (s, 1H), 7.45 (s, 1H), 7.33 (d, *J* = 10.8 Hz, 1H), 6.88 (d, *J* = 10.8 Hz, 1H), 3.53 (s, 3H), 3.05-3.11 (m, 1H), 2.68 (s, 3H), 2.64 (s, 3H), 2.61 (s, 3H), 2.05 (s, 3H), 1.38 (d, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.02, 156.97, 147.60, 145.42, 140.20, 139.32, 137.89, 134.47, 133.29, 130.98, 128.91, 126.44, 123.90, 120.16, 118.30, 50.91, 37.86, 30.56, 25.59, 24.69, 14.32, 12.98, 11.84. MS (ESI) *m/z*: 351 $[M+H]^+$. *Anal.* calcd for $C_{23}H_{26}O_3$: C 78.83, H 7.48. Found: C 78.85, H 7.51.

Ethyl 2,5-dimethyl-4-(guaiazulen-1-yl)furan-3-carboxylate (4c): Blue scaly crystals. mp 50-52 °C; IR (KBr): *ν* 1632 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.18 (s, 1H), 7.43 (s, 1H), 7.33 (d, *J* = 10.4 Hz, 1H), 6.88 (d, *J* = 10.4 Hz, 1H), 3.92-4.00 (m, 2H), 3.06-3.10 (m, 1H), 2.69 (s, 3H), 2.66 (s, 3H), 2.54 (s, 3H), 2.11 (s, 3H), 1.39 (d, *J* = 6.8 Hz, 6H), 0.79 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 164.57, 156.93, 147.26, 145.49, 140.27, 139.24, 137.92, 134.42, 134.00, 133.20, 130.86, 126.38, 123.77, 119.77, 118.54, 59.35, 37.87, 25.63, 24.71, 24.68, 14.18, 13.56, 12.94, 11.89. MS (ESI) *m/z*: 365 $[M+H]^+$. *Anal*. calcd for $C_{24}H_{28}O_3$: C 79.09, H 7.74. Found: C 79.11, H 7.75.

3-Acetyl-4-(guaiazulen-1-yl)-2-methyl-5-phenylfuran (4d): Blue scaly crystals. mp 78-80 °C; IR (KBr): ν 1641 cm^{-1} (C=O). ^1HNMR (400 MHz, $CDCl_3$): *δ* 8.24 (s, 1H), 7.45 (s, 1H), 7.38 (d, *J* = 10.4 Hz, 1H), 7.23-7.27 (m, 2H), 7.10-7.14 (m, 3H), 6.92 (d, *J* = 10.8 Hz, 1H), 3.09-3.15 (m, 1H), 2.75 (s, 3H), 2.67 (s, 3H), 2.55 (s, 3H), 1.57 (s, 3H), 1.41 (d, *J* = 6.8 Hz, 6H). ^{13}CNMR (100 MHz, $CDCl_3$): *δ* 196.59, 157.60, 147.10, 145.91, 140.19, 139.48, 138.29, 135.30, 134.04, 133.70, 130.80, 128.34, 127.18, 126.82, 126.03, 125.64, 124.51, 120.30, 117.85, 37.87, 30.26, 25.86, 24.64, 14.95, 13.00. MS (ESI) *m/z*: 397 $[M+H]^+$. *Anal.* calcd for $C_{28}H_{28}O_2$: C 84.81, H 7.12. Found: C 84.89, H 7.14.

Methyl 4-(guaiazulen-1-yl)-2-methyl-5-phenylfuran-3-carboxylate (4e): Blue scaly crystals. mp 90-92 °C; IR (KBr): *ν* 1643 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.22 (s, 1H), 7.44 (s, 1H), 7.34 (d, *J* = 10.8 Hz, 1H), 7.25-7.27 (m, 2H), 7.11-7.14 (m, 3H), 6.88 (d, *J* = 10.4 Hz, 1H), 3.55 (s, 3H), 3.04-3.10

(m, 1H), 2.75 (s, 3H), 2.69 (s, 2H), 2.56 (s, 2H), 1.41 (d, J = 7.2 Hz, 5H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 164.53, 157.60, 147.59, 145.63, 139.51, 139.47, 138.23, 134.68, 133.61, 133.50, 130.93, 130.79, 128.84, 128.31, 126.81, 126.62, 124.83, 124.59, 121.43, 51.05, 37.90, 25.80, 24.75, 24.68, 14.59, 13.08. MS (ESI) m/z: 413 $[M+H]^+$. *Anal*. calcd for $C_{28}H_{28}O_3$: C 81.52, H 6.84. Found: C 81.54, H 6.85.

Ethyl 4-(guaiazulen-1-yl)-2-methyl-5-phenylfuran-3-carboxylate (4f): Blue scaly crystals. mp 87-88 °C; IR (KBr): ν 1649 cm^{-1} (C=O). ^{1}HNMR (400 MHz, $CDCl_3$: δ 8.16 (s, 1H), 7.41 (s, 1H), 7.32-7.35 (m, 2H), 7.10-7.16 (m, 3H), 3.87-3.92 (m, 2H), 3.06-3.13 (m, 1H), 2.75 (s, 3H), 2.66 (s, 2H), 2.56 (s, 3H), 1.40 (d, J = 6.8 Hz, 6H), 0.69 (t, J = 7.2 Hz, 3H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 164.25, 157.70, 147.17, 145.64, 139.56, 139.39, 138.28, 134.54, 133.85, 133.29, 130.91, 130.85, 128.82, 128.30, 126.76, 126.45, 124.70, 124.63, 121.28, 59.48, 37.87, 25.77, 24.70, 24.66, 14.37, 13.35, 12.99. MS (ESI) m/z: 427 $[M+H]^+$. *Anal.* calcd for $C_{29}H_{30}O_3$: C 81.66, H 7.09. Found: C 81.69, H 7.12.

3-(Guaiazulen-1-yl)-2-methyl-6,7-dihydrobenzofuran-4(5*H*)-one (4g): Blue scaly crystals. mp 89-91 °C; IR (KBr): ν 1651 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.30 (d, J = 10.8 Hz, 1H), 7.20 (s, 1H), 6.91 (d, J = 10.8 Hz, 1H), 3.61-3.67 (m, 1H), 3.07 (s, 3H), 2.56 (s, 3H), 2.42-2.46 (m, 2H), 2.18-2.21 (m, 2H), 1.35 (d, J = 6.8 Hz, 6H), 1.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.55, 174.66, 144.84, 139.40, 138.80, 137.72, 134.54, 133.45, 133.04, 127.15, 124.30, 123.59, 118.09, 117.60, 37.63, 37.10, 27.76, 24.64, 24.59, 24.07, 22.39, 21.81, 15.65, 13.21. MS (ESI) m/z: 347 $[M+H]^+$. *Anal.* calcd for $C_{24}H_{26}O_2$: C 83.20, H 7.56. Found: C 83.24, H 7.59.

3-(Guaiazulen-1-yl)-2,6,6-trimethyl-6,7-dihydrobenzofuran-4(5*H*)-one (4h): Blue scaly crystals. mp 95-97 °C; IR (KBr): ν 1651 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.38 (d, J = 10.2 Hz, 1H), 7.28 (s, 1H), 6.90 (d, J = 10.2 Hz, 1H), 3.59-3.63 (m, 1H), 3.05 (s, 3H), 2.47 (s, 3H), 2.33-2.46 (m, 2H), 2.24 (s, 2H), 1.34 (d, J = 6.8 Hz, 6H), 1.29 (s, 3H), 1.19 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.87, 173.57, 144.83, 139.41, 138.73, 137.84, 134.53, 133.47, 133.04, 127.12, 124.31, 123.67, 117.89, 116.74, 37.87, 37.61, 34.00, 29.12, 28.90, 27.76, 24.62, 24.56, 22.57, 15.66, 13.22. MS (ESI) m/z: 375 $[M+H]^+$. *Anal*. calcd for $C_{26}H_{30}O_2$: C 83.38, H 8.07. Found: C 83.41, H 8.09.

REFERENCES

1. (a) F. M. Dean, *Adv. Heterocycl. Chem.*, 1982, **30**, 167; (b) H. Huang and P. Xie, in Stereoselective Multiple Bond Forming Transformations in Organic Synthesis, ed. by J. Rodriguez and D. Bonne, Wiley, 2015, pp. 9–44; (c) P. Vitale and A. Scilimati, *Curr. Org. Chem.*, 2013, **17**, 1986.
2. (a) A. Wadood, S. B. Jamal, M. Riaz, and A. Mir, *Pharm. Biol.*, 2014, **52**, 1170; (b) C. K. Naidu and Y. Suneetha, *Med. Chem. Res.*, 2014, **23**, 4724; (c) S. A. Galal, A. S. Abd El-All, M. M. Abdallah, and H. I. El-Diwani, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2420.
3. P. Yadav, P. Singh, and A. K. Tewari, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 2251.

4. L. Vasamsetty, F. A. Khan, and G. Mehta, *Tetrahedron Lett*., 2014, **55**, 7068.
5. H. Shinonaga, Y. Kawamura, A. Ikeda, M. Aoki, N. Sakai, N. Fujimoto, and A. Kawashima, *Tetrahedron Lett*., 2009, **50**, 108.
6. A. Ladurner, A. G. Atanasov, E. H. Heiss, L. Baumgartner, S. Schwaiger, J. M. Rollinger, H. Stuppner, and V. M. Dirsch, *Biochem. Pharmacol*., 2012, **84**, 804.
7. W. S. Zhang, W. J. Xu, F. Zhang, and Y. Li, *Chin. J. Org. Chem.*, 2019, **39**, 1277.
8. H. Yamazaki, S. Irono, A. Uchida, H. Ohno, N. Saito, K. Kondo, K. Jinzenji, and T. Yamamoto, *Nippon Yakurigaku Zasshi* (*Jpn. J. Pharmacol*.), 1958, **54**, 362.
9. T. Yanagisawa, S. Wakabayashi, T. Tomiyama, M. Yasunami, and K. Takase, *Chem. Pharm. Bull*., 1988, **36**, 641.
10. (a) A. E. Asato, A. Peng, M. Z. Hossain, T. Mirzadegan, and J. S. Bertram, *J. Med. Chem*., 1993, **36**, 3137; (b) B. C. Hong, Y. F. Jiang, and E. S. Kumar, *Bioorg. Med. Chem. Lett*., 2001, **11**, 1981.
11. D. A. Becker, J. J. Ley, L. Echegoyen, and R. Alvarado, *J. Am. Chem. Soc*., 2002, **124**, 4678.
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. Ito, 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. Ito, M. Yasunami, and N. Morita, *Heterocycles*, 2013, **87**, 303; (e) S. Ito, S. Yamazaki, S. Kudo, R. Sekiguchi, J. Kawakami, M. Takahashi, T. Matsuhashi, K. Toyota, and N. Morita, *Tetrahedron*, 2014, **70**, 2796; (f) N. Takenaga, K. Fukazawa, M. Maruko, and K. Sato, *Heterocycles*, 2015, **90**, 113.
13. (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.
14. (a) G. Fischer, *Adv. Heterocyclic Chem*., 2009, **97**, 131; (b) S. Ito, T. Shoji, and N. Morita, *Synlett*, 2011, 2279; (c) J.-X. Dong and H.-L. Zhang, *Chin. Chem. Lett*., 2016, **27**, 1097; (d) T. Shoji and S. Ito, *Chem. Eur. J*., 2017, **23**, 16696; (e) H. Xin and X. Gao, *ChemPlusChem*., 2017, **82**, 945; (f) A. C. Razus and L. Birzan, *Monatsh. Chem*., 2019, **150**, 139; (g) L. Ou, Y. Zhou, B. Wu, and L. Zhu, *Chin. Chem. Lett*., 2019, **30**, 1903; (h) T. Shoji, T. Okujima, and S. Ito, *Int. J. Mol. Sci*., 2020, **21**, 7087.
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; (f) L. Zhang, D.-L, Wang, J.-J, Xing, and L. Liu, *Heterocycles*, 2019, **98**, 1547; (g) L. Zhang, D.-L, Wang, J.-J, Xing, and L. Liu, *Heterocycles*, 2019, **98**, 1555.

16. (a) M. Oda, T. Kajioka, K. Haramoto, R. Miyatake, and S. Kuroda, *Synthesis*, 1999, 1349; (b) M. Murai, S.-Y. Ku, N. D. Treat, M. J. Robb, M. L. Chabinyc, and C. Hawker, *J. Chem. Sci.*, 2014, **5**, 3753; (c) T. Shoji, M. Tanaka, S. Takagaki, K. Miura, A. Ohta, R. Sekiguchi, S. Ito, S. Mori, and T. Okujima, *Org. Biomol. Chem.*, 2018, **16**, 480.
17. W. Dröge, *Physiol. Rev.*, 2002, **82**, 47.
18. T. Shoji and S. Ito, *Adv. Heterocycl. Chem.*, 2018, **126**, 1.
19. (a) A. P. Kourounakis, E. A. Rekka, and P. Kourounakis, *J. Pharm. Pharmacol.*, 1997, **49**, 938; (b) H. Pratsinis and S. Haroutounian, *Nat. Prod. Lett.*, 2002, **16**, 201; (c) A. Capuzzo, A. Occhipinti, and M. E. Maffei, *Nat. Prod. Res.*, 2014, **28**, 2321.
20. X. J. Wu, Y. P. Wang, and W. Wang, *Acta Pharmacol. Sin.*, 2000, **21**, 855.