HETEROCYCLES, Vol. 87, No. 5, 2013, pp. 1099 - 1108. © 2013 The Japan Institute of Heterocyclic Chemistry
Received, 25th February, 2013, Accepted, 18th March, 2013, Published online, 26th March, 2013
DOI: 10.3987/COM-13-12690

ONE-POT SYNTHESIS OF (GUAIAZULEN-1-YL)FURAN DERIVATIVES FROM GUAIAZULENE AND 1,4-DIARYL-2-BUTENE-1,4-DIONES

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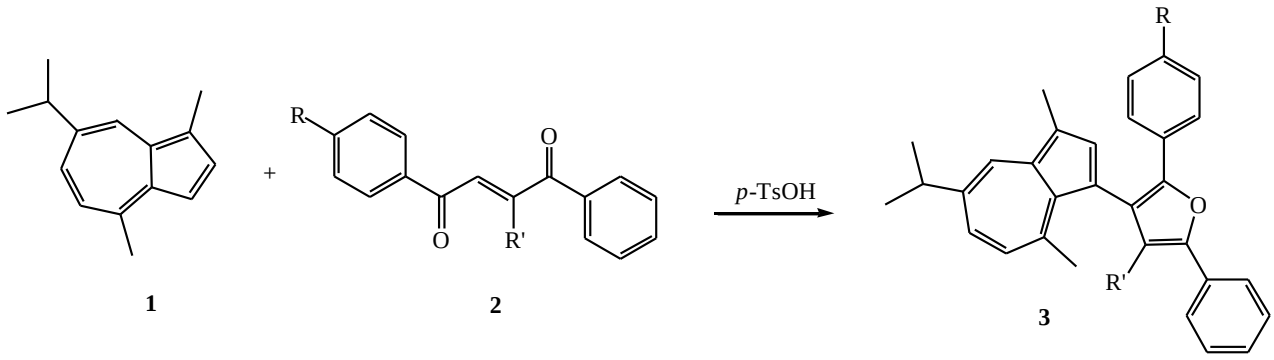
Abstract – A facile, convenient, efficient, and high yielding synthesis of 3-(guaiazulen-1-yl)furan derivatives (**3**) has been developed by the condensation of guaiazulene (**1**) with 1,4-diaryl-2-butene-1, 4-diones (**2**) as nucleophiles in the presence of *p*-toluenesulfonic acid as the catalyst.

Furans occupy an important place in the heterocyclic family of compounds because of their prevalence as a key structural component in a myriad of natural and pharmaceutical products.[1] Polyfunctionalized furans are of great importance because numerous interesting compounds bearing such a heterocyclic ring exhibit a wide array of activity and are also building blocks for organic synthesis.[2] While this has led to a myriad of impressive approaches for furan synthesis being developed over the years,[3] there remains a need for new methods for their construction with selective control substitution of patterns from starting materials and a catalytic system that are readily accessible, atom-economical, and low cost.

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.[4] Azulene derivatives have attracted interest in medicine as antiulcer drugs,[5] anticancer agents,[6] and as antioxidant therapeutics for neurodegenerative conditions.[7] 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.[8]

As part of our recent research,[9] we herein report a novel preparation of azulene substituted furans **3**

starting from guaiazulene **1** and 1,4-diaryl-2-butene-1,4-diones **2**,[10] *via* the integration of Friedel-Crafts alkylation and Paale-Knorr cyclization in the presence of *p*-toluenesulfonic acid (**Scheme 1**).



1 **2** **3**

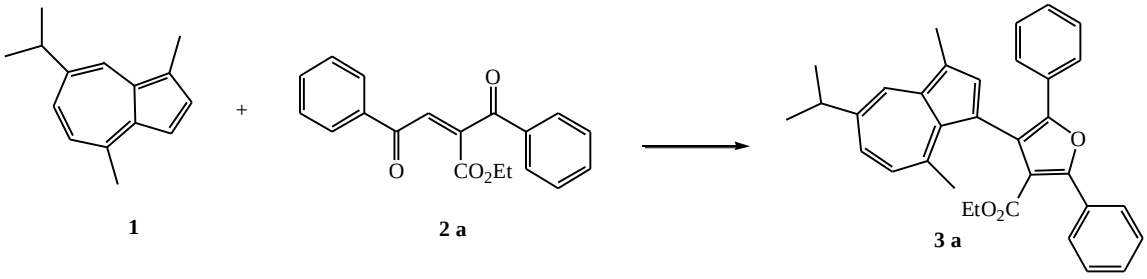
Scheme 1. Syntheses of 3-(guaiazulen-1-yl)furans

First, to optimize the conditions, we studied the effects of molar ratio, temperature, reaction time, and solvent. In a typical experiment, a mixture of guaiazulene (**1**) and ethyl 2-benzoyl-4-oxo-4-phenylbut-2-enoate (**2a**) was reacted and monitored by HPLC, and the results are summarized in Table 1.

The initial reaction of guaiazulene (**1**) and ethyl 2-benzoyl-4-oxo-4-phenylbut-2-enoate (**2a**) at an ambient temperature in dichloromethane did not give any product until *p*-toluenesulfonic acid was added into the reaction mixture and stirred for 12 h. After the reaction was completed, the mixture was purified by flash column chromatography to give pure product, ethyl 2,5-diphenyl-4-(guaiazulen-1-yl)furan-3-carboxylate (**3a**), whose structure was characterized by ^{1}H NMR, ^{13}C NMR, IR spectra and elemental analysis.

The reaction of **1** and **2a** was optimized by screening the solvent such as dichloromethane, 1,2-dichloroethane, ethanol, acetonitrile, acetic acid, toluene and tetrahydrofuran, changing the amount of *p*-toluenesulfonic acid and the ratio of **1**/**2a**. It was found, when 15 mol % *p*-toluenesulfonic acid was used, the reaction best proceeded smoothly and gave the product **3a** in 87% yield (Table 1, entry 5). Increasing the amount of *p*-toluenesulfonic acid to 20 mol %, the yield of **3a** was not further improved (Table 1, entry 6). Furthermore, we also tested the catalytic activity of different catalysts in this reaction, but the desired product **3a** was obtained in lower yields, such as phosphoric acid, trifluoroacetic acid, sulphuric acid, methanesulfonic acid, indium chloride, aluminum chloride, zinc chloride, and iron chloride.

Table 1. Optimization of reaction conditions on the synthesis of ethyl 2,5-diphenyl-4-(guaiazulen-1-yl)-furan-3-carboxylate (**3a**)



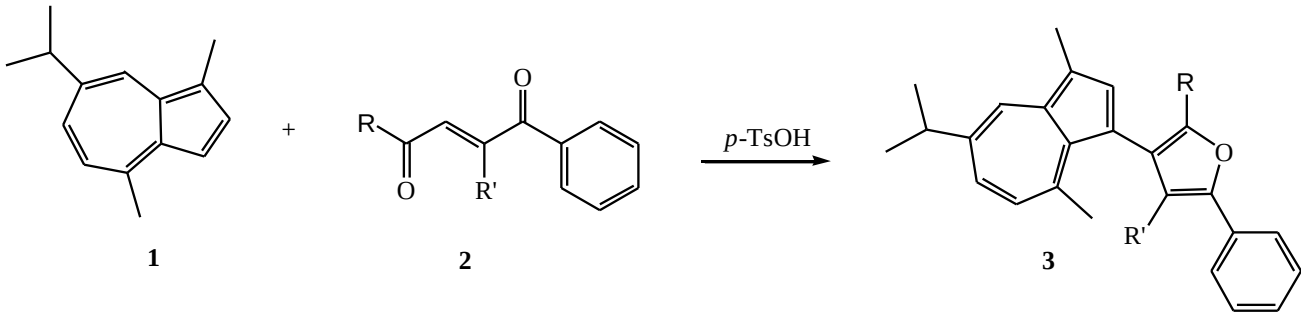
1 **2 a** **3 a**

Entry	Molar ratio	*p*-TsOH (mol%)	Solvent	Temp / ºC	Time / h	Yield / %
1	1:1.2	0	CH_2Cl_2	25	12	0
2	1:1.0	10	CH_2Cl_2	25	12	38
3	1:1.2	10	CH_2Cl_2	40	4	73
4	1:1.2	15	CH_2Cl_2	40	3	87
5	1:1.2	20	CH_2Cl_2	40	3	85
6	1:1.2	15	CH_2ClCH_2Cl	80	7	73
7	1:1.2	15	EtOH	80	12	65
8	1:1.2	15	AcOH	80	4	78
9	1:1.2	15	MeCN	80	8	64
10	1:1.2	15	toluene	100	10	57
11	1:1.5	15	THF	50	12	43

[a] Yield of isolated products.

Next, with the optimized reaction conditions established, the scope of the reaction with respect to 1, 4-enedione (**2a**) and various 1, 4-enediones (ethyl 2-benzoyl-4-oxo-4-arylbut-2-enoates or 4-aryl-1,2-diphenyl-2-butene-1,4-diones) (**2**) was investigated (Table 2). The reactions with 1, 4-enediones bearing electrondonating groups (entries 2-4 and 11-13) at the aromatic ring proceeded smoothly to give the desired products in high yields. Good yields were also obtained with haologenated substrates (entries 5, 6 and 14). The position of the substituents on the phenyl ring of 1, 4-enediones affected the reaction yield slightly. The sterically hindered (1-naphthyl) R substituents all reacted efficiently to afford the desired products in good yield (entry 7). Besides, the heteroaryl groups for R were also investigated, such as 2-thienyl and 2-furyl group, the corresponding product (**3h** and **3i**) could be obtained in 83 and 85% yields, respectively (entries 8 and 9).

Table 2. Synthesis of 3-(guaiazulen-1-yl)furan derivatives 3*



1 **2** **3**

Entry	R	R’	Time (h)	Product **3**	Yield [a] (%)
1	C_6H_5	CO_2Et	6	**3a**	93
2	4-MeC_6H_4	CO_2Et	6	**3b**	90
3	4-$MeOC_6H_4$	CO_2Et	5	**3c**	95
4	4-HOC_6H_4	CO_2Et	5	**3d**	88
5	4-ClC_6H_4	CO_2Et	7	**3e**	81
6	4-FC_6H_4	CO_2Et	8	**3f**	83
7	1-naphthyl	CO_2Et	10	**3g**	86
8	2-thienyl	CO_2Et	8	**3h**	83
9	2-furyl	CO_2Et	8	**3i**	85
10	C_6H_5	C_6H_5	6	**3j**	90
11	4-MeC_6H_4	C_6H_5	7	**3k**	86
12	4-$MeOC_6H_4$	C_6H_5	5	**3l**	91
13	4-HOC_6H_4	C_6H_5	6	**3m**	90
14	4-FC_6H_4	C_6H_5	6	**3n**	80

[a] Yield of isolated products.

In summary, we have developed an efficient methodology for the synthesis of 3-(guaiazulen-1-yl)furan derivatives by the condensation of guaiazulene with 1,4-diaryl-2-butene-1,4-diones as nucleophiles in the presence of *p*-toluenesulfonic acid as the catalyst, *via* the integration of Friedel-Crafts alkylation and Paale-Knorr cyclization reactions.

ACKNOWLEDGEMENT

This work was partially supported by the Science and Technology Department of Liaoning Province (No.2011220022), and the Innovation Talent Program of Heilongjiang University of Chinese Medicine.

EXPERIMENTAL

All melting points were determined on a Yanako MP-3 apparatus and are uncorrected. ^{1}HNMR spectra were obtained on a Bruker-400 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standards. IR spectra were recorded on Shimadzu IR-740 spectrophotometer as KBr pellets. HRMS spectra were obtained with a Bruker micro TOF-Q 134 instrument.

General experimental procedure

p-TsOH (0.1 mmol) was added to a solution of guaiazulene **1** (1 mmol) and appropriate 1,4-diaryl-2-butene-1,4-dione **2** (1.2 mmol) in CH_2Cl_2 (25 mL). Then the mixture was refluxed for the appropriate time (Table 1) and monitored to completion by TLC. After completion of the reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with EtOAc (3 x 10 mL), dried, and purified by column chromatography on silica gel using *n*-hexane / EtOAc as eluent to afford the corresponding products. The physical and spectra data of the compounds **3** are as follows:

Ethyl 2,5-diphenyl-4-(guaiazulen-1-yl)furan-3-carboxylate (**3a**): Blue scaly crystals (from EtOAc). mp 79-81 ºC; IR (KBr, cm^{-1}): *v* 1684 (C=O). ^{1}H-NMR($CDCl_3$): δ 1.24 (6H, d, *J* = 6.6 Hz, CH($\underline{CH_3}$)$_2$), 1.30 (3H, t, *J* = 7.2 Hz, OCH$_2\underline{CH_3}$), 2.25 (3H, s, CH_3), 2.69 (3H, s, CH_3), 2.98-3.05 (1H, m, $\underline{CH}(CH_3)_2$), 3.47 (2H, q, *J* = 7.2 Hz, $CO_2\underline{CH_2}CH_3$), 6.48 (1H, d, *J* = 10.2 Hz), 6.72-6.75 (5H, m), 6.99-7.01 (2H, m), 7.08-7.10 (3H, m), 7.59-7.61 (2H, m), 7.80 (1H, s). ^{13}C-NMR($CDCl_3$) : δ 12.8, 13.2, 24.7, 25.6, 29.7, 37.7, 60.5, 117.9, 118.5, 121.0, 124.0, 125.5, 126.5, 127.3, 128.2, 128.4, 128.9, 129.9, 130.4, 133.4, 134.1, 134.7, 138.1, 139.4, 139.8, 145.7, 149.2, 153.7, 164.8. *Anal*. Calcd for $C_{34}H_{32}O_3$: C 83.56, H 6.60. Found: C 83.68, H 6.73%.

Ethyl 4-(guaiazulen-1-yl)-5-(4-methylphenyl)-2-phenylfuran-3-carboxylate (**3b**): Blue scaly crystals (from EtOAc). mp 158-160 ºC; IR (KBr, cm^{-1}): *v* 1680 (C=O). ^{1}H-NMR($CDCl_3$): δ 1.28 (6H, d, *J* = 6.6 Hz, CH($\underline{CH_3}$)$_2$), 1.31 (3H, t, *J* = 7.2 Hz, OCH$_2\underline{CH_3}$), 2.16 (3H, s, CH_3), 2.53 (3H, s, CH_3), 2.57 (3H, s, CH_3), 2.97-3.04 (1H, m, $\underline{CH}(CH_3)_2$), 3.79 (2H, q, *J* = 7.2 Hz, $CO_2\underline{CH_2}CH_3$), 6.79 (1H, d, *J* = 10.0 Hz), 6.88 (2H, d, *J* = 8.0 Hz), 7.20 (2H, d, *J* = 8.0 Hz), 7.31-7.32 (1H, m), 7.36-7.39 (4H, m), 7.90-7.92 (2H, m), 8.11 (1H, s). ^{13}C-NMR($CDCl_3$): δ 13.0, 13.2, 21.2, 24.7, 25.8, 29.6, 37.8, 60.3, 117.9, 118.5, 121.3, 123.8, 125.5, 126.6, 127.6, 127.7, 128.3, 128.8, 129.0, 130.0, 133.2, 134.3, 134.9, 137.4, 138.5, 139.6, 139.8, 146.1, 149.6, 153.6, 164.8. *Anal*. Calcd for $C_{35}H_{34}O_3$: C 83.63, H 6.82. Found: C 83.79, H 6.95%.

Ethyl 3-(guaiazulen-1-yl)-5-(4-methoxyphenyl)-2-phenylfuran-3-carboxylate (**3c**): Blue scaly crystals (from EtOAc). mp 129-130 ºC; IR (KBr, cm^{-1}): *v* 1689 (C=O). ^{1}H-NMR($CDCl_3$): δ 0.85 (6H, d, *J* = 6.6

Hz, CH($\underline{CH_3}$)$_2$), 0.98 (3H, t, *J* = 7.2 Hz, OCH$_2\underline{CH_3}$), 2.21 (3H, s, CH$_3$), 2.26 (3H, s, CH$_3$), 2.65-2.72 (1H, m, $\underline{CH}$(CH$_3$)$_2$), 3.32 (3H, s, OCH$_3$), 3.45 (2H, q, *J* = 7.2 Hz, CO$_2\underline{CH_2}$CH$_3$), 6.29 (2H, d, *J* = 7.2 Hz), 6.47 (1H, d, *J* = 10.0 Hz), 6.91 (2H, d, *J* = 7.2 Hz), 7.05-7.07 (1H, m), 7.15-7.24 (4H, m), 7.57-7.59 (2H, m), 7.78 (1H, s). ^{13}C-NMR(CDCl$_3$): δ 12.9, 13.1, 24.7, 25.8, 29.7, 37.8, 55.1, 60.1, 113.8, 117.8, 118.7, 121.1, 123.6, 124.7, 126.4, 126.7, 127.5, 128.2, 128.7, 130.1, 133.4, 134.0, 134.7, 138.2, 139.5, 139.8, 145.9, 148.2, 152.9, 158.7, 164.5. *Anal*. Calcd for $C_{35}H_{34}O_4$: C 81.05, H 6.61. Found: C 81.16, H 6.74%.

Ethyl 4-(guaiazulen-1-yl)-5-(4-hydrophenyl)-2-phenylfuran-3-carboxylate (**3d**):

Blue scaly crystals (from EtOH). mp 169-172 ºC; IR (KBr, cm^{-1}): *v* 1690 (C=O). ^{1}H-NMR(CDCl$_3$): δ 0.84 (6H, d, *J* = 6.6 Hz, CH($\underline{CH_3}$)$_2$), 0.97 (3H, t, *J* = 7.2 Hz, OCH$_2\underline{CH_3}$), 2.12 (3H, s, CH$_3$), 2.24 (3H, s, CH$_3$), 2.64-2.71 (1H, m, $\underline{CH}$(CH$_3$)$_2$), 3.43 (2H, q, *J* = 7.2 Hz, CO$_2\underline{CH_2}$CH$_3$), 6.19 (2H, d, *J* = 6.8 Hz), 6.46 (1H, d, *J* = 10.4 Hz), 6.91 (2H, d, *J* = 7.2 Hz), 6.91-6.93 (2H, m), 7.02-7.05 (3H, m), 7.55-7.57 (2H, m), 7.77 (1H, s). ^{13}C-NMR(CDCl$_3$): δ 13.0, 13.3, 24.7, 25.8, 29.5, 37.8, 60.5, 114.1, 117.6, 118.5, 121.4, 123.3, 123.9, 127.3, 126.7, 128.2, 128.5, 128.8, 130.0, 133.9, 134.1, 134.8, 138.4, 139.7, 140.3, 146.1, 149.5, 153.5, 155.3, 165.1. *Anal*. Calcd for $C_{34}H_{32}O_4$: C 80.93, H 6.39. Found: C 81.12, H 6.52%.

Ethyl 5-(4-chlorophenyl)-4-(guaiazulen-1-yl)-2-phenylfuran-3-carboxylate (**3e**): Blue scaly crystals (from EtOH). mp 112-114 ºC; IR (KBr, cm^{-1}): *v* 1694 (C=O). ^{1}H-NMR(CDCl$_3$): δ 1.26 (6H, d, *J* = 6.6 Hz, CH($\underline{CH_3}$)$_2$), 1.44 (3H, t, *J* = 7.2 Hz, OCH$_2\underline{CH_3}$), 2.59 (3H, s, CH$_3$), 2.66 (3H, s, CH$_3$), 3.08-3.09 (1H, m, $\underline{CH}$(CH$_3$)$_2$), 3.87 (2H, q, *J* = 7.2 Hz, CO$_2\underline{CH_2}$CH$_3$), 6.89 (1H, d, *J* = 10.4 Hz), 7.10 (2H, d, *J* = 8.2 Hz), 7.28 (2H, d, *J* = 8.2 Hz), 7.41-7.43 (2H, m), 7.49-7.52 (3H, m), 7.90-7.92 (2H, m), 8.13 (1H, s). ^{13}C-NMR(CDCl$_3$): δ 13.1, 13.4, 24.7, 25.6, 29.5, 37.7, 60.4, 119.3, 121.4, 123.9, 126.6, 126.8, 127.2, 128.3, 128.5, 128.9, 129.1, 129.8, 133.2, 133.6, 134.2, 134.5, 138.6, 139.8, 139.9, 145.6, 148.2, 154.1, 164.5. *Anal*. Calcd for $C_{34}H_{31}ClO_3$: C 78.07, H 5.97. Found: C 78.16, H 6.14%.

Ethyl 5-(4-fluorophenyl)-4-(guaiazulen-1-yl)-2-phenylfuran-3-carboxylate (**3f**): Blue scaly crystals (from EtOAc). mp 137-139 ºC; IR (KBr, cm^{-1}): *v* 1698 (C=O). ^{1}H-NMR(CDCl$_3$): δ 1.25 (6H, d, *J* = 6.6 Hz, CH($\underline{CH_3}$)$_2$), 1.38 (3H, t, *J* = 7.2 Hz, OCH$_2\underline{CH_3}$), 2.37 (3H, s, CH$_3$), 2.66 (3H, s, CH$_3$), 3.08-3.10 (1H, m, $\underline{CH}$(CH$_3$)$_2$), 3.86 (2H, q, *J* = 7.2 Hz, CO$_2\underline{CH_2}$CH$_3$), 6.83 (1H, d, *J* = 10.4 Hz), 6.90 (2H, d, *J* = 8.4 Hz), 7.29 (2H, d, *J* = 8.4 Hz), 7.34-7.36 (2H, m), 7.42-7.44 (3H, m), 7.97-7.99 (2H, m), 8.20 (1H, s). ^{13}C-NMR(CDCl$_3$): δ 12.9, 13.4, 24.6, 25.8, 29.4, 37.7, 60.5, 115.3, 117.9, 118.9, 121.5, 123.9, 126.6, 126.7, 127.3, 127.5, 128.3, 129.0, 129.9, 133.7, 134.1, 134.7, 138.6, 139.7, 139.8, 146.4, 148.5, 153.9, 162.0, 164.6. *Anal*. Calcd for $C_{34}H_{31}FO_3$: C 78.07, H 5.97. Found: C 78.15, H 6.13%.

Ethyl 4-(guaiazulen-1-yl)-5-(1-naphthyl)-2-phenylfuran-3-carboxylate (**3g**): Blue scaly crystals (from EtOAc). mp 78-80 ºC; IR (KBr, cm^{-1}): *v* 1682 (C=O). ^{1}H-NMR($CDCl_3$): *δ* 1.44 (6H, d, *J* = 6.6 Hz, CH($\underline{CH_3}$)$_2$), 1.37 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 2.48 (3H, s, CH_3), 2.64 (3H, s, CH_3), 2.89-2.796 (1H, m, $\underline{CH}(CH_3)_2$), 3.82 (2H, q, *J* = 7.2 Hz, $CO_2\underline{CH_2}CH_3$), 6.74 (1H, d, *J* = 9.6 Hz), 7.09-7.18 (2H, m), 7.24-7.27 (3H, m), 7.33-7.39 (4H, m), 7.62 (1H, d, *J* = 8.0 Hz), 7.74 (1H, d, *J* = 8.0 Hz), 7.92-7.94 (2H, m), 8.01 (1H, s), 8.28 (1H, d, *J* = 8.4 Hz). ^{13}C-NMR($CDCl_3$): *δ* 12.8, 13.3, 24.6, 25.9, 29.6, 37.9, 60.9, 118.2, 121.3, 123.8, 125.0, 125.9, 126.5, 126.4, 127.3, 127.7, 128.2, 128.3, 128.8, 128.9, 129.1, 129.9, 131.7, 133.5, 133.6, 134.2, 134.5, 138.4, 139.7, 139.9, 145.3, 149.5, 154.8, 165.2. *Anal*. Calcd for $C_{38}H_{34}O_3$: C 84.73, H 6.36. Found: C 84.86, H 6.52%.

Ethyl 4-(guaiazulen-1-yl)-2-phenyl-5-(2-thienyl)furan-3-carboxylate (**3h**): Blue scaly crystals (from EtOAc). mp 126-127 ºC; IR (KBr, cm^{-1}): *v* 1678 (C=O). ^{1}H-NMR($CDCl_3$): *δ* 1.24 (6H, d, *J* = 6.6 Hz, CH($\underline{CH_3}$)$_2$), 1.36 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 2.59 (3H, s, CH_3), 2.66 (3H, s, CH_3), 2.11-2.18 (1H, m, $\underline{CH}(CH_3)_2$), 3.89 (2H, q, *J* = 7.2 Hz, $CO_2\underline{CH_2}CH_3$), 5.66 (1H, d, *J* = 2.4 Hz), 6.20 (1H, d, *J* = 2.4 Hz), 6.90 (1H, d, *J* = 10.4 Hz), 7.28-7.30 (3H, m), 7.46-7.49 (3H, m), 7.98-7.99 (2H, m), 8.19 (1H, s). ^{13}C-NMR($CDCl_3$) δ(ppm): 12.8, 13.2, 24.6, 25.9, 29.7, 37.6, 60.4, 117.4, 118.8, 121.0, 121.1, 124.2, 125.3, 127.4, 126.5, 128.2, 128.9, 129.9, 131.3, 133.2, 134.1, 134.7, 138.3, 139.5, 139.7, 145.3, 147.1, 153.6, 164.7. *Anal*. Calcd for $C_{32}H_{30}O_3S$: C 77.70, H 6.11. Found: C 77.84, H 6.26%.

Ethyl 5-(2-furyl)-4-(guaiazulen-1-yl)-2-phenylfuran-3-carboxylate (**3i**): Blue scaly crystals (from EtOAc). mp 122-124 ºC; IR (KBr, cm^{-1}): *v* 1684 (C=O). ^{1}H-NMR($CDCl_3$): *δ* 1.25 (6H, d, *J* = 6.6 Hz, CH($\underline{CH_3}$)$_2$), 1.38 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 2.60 (3H, s, CH_3), 2.68 (3H, s, CH_3), 2.15-2.19 (1H, m, $\underline{CH}(CH_3)_2$), 3.90 (2H, q, *J* = 7.2 Hz, $CO_2\underline{CH_2}CH_3$), 6.78-6.79 (1H, m), 6.81-6.83 (1H, m), 6.92 (1H, d, *J* = 10.2 Hz), 7.27-7.39 (3H, m), 7.47-7.49 (3H, m), 7.97-7.98 (2H, m), 8.22 (1H, s). ^{13}C-NMR($CDCl_3$) δ(ppm): 13.0, 13.2, 24.5, 25.9, 29.6, 37.8, 60.4, 111.8, 111.9, 112.1, 118.2, 121.3, 123.7, 125.7, 126.0, 128.2, 130.2, 133.5, 134.0, 134.8, 138.1, 139.6, 139.8, 143.3, 143.4, 144.7, 145.8, 146.8, 149.2, 163.7. *Anal*. Calcd for $C_{32}H_{30}O_4$: C 80.31, H 6.32. Found: C 80.49, H 6.46%.

3-(Guaiazulen-1-yl)-2,4,5-triphenylfuran (**3j**): Blue scaly crystals (from EtOAc). mp 61-63 ºC; ^{1}H-NMR($CDCl_3$): *δ* 2.50 (3H, s, CH_3), 2.69 (3H, s, CH_3), 2.98-3.02 (1H, m, $\underline{CH}(CH_3)_2$), 6.86 (1H, d, *J* = 10.4 Hz), 7.14-7.18 (4H, m), 7.30-7.34 (5H, m), 7.46 (1H, d, *J* = 8.2 Hz), 7.64-7.68 (2H, m), 8.04 (1H, s). ^{13}C-NMR($CDCl_3$): *δ* 13.0, 24.6, 25.8, 29.8, 37.9, 118.1, 121.3, 124.3, 124.7, 125.5, 126.0, 126.2, 126.6, 128.1, 128.3, 128.5, 129.6, 129.7, 130.5, 133.1, 133.2, 134.3, 134.7, 137.2, 138.4, 139.6, 139.9, 144.7,

145.4, 146.8. *Anal*. Calcd for $C_{37}H_{32}O$: C 90.21, H 6.55. Found: C 90.37, H 6.68%.

4,5-Diphenyl-3-(guaiazulen-1-yl)-2-(4-methylphenyl)furan (**3k**): Blue scaly crystals (from EtOAc). mp 67-69 ºC; ^{1}H-NMR($CDCl_3$): δ 1.25 (6H, d, J = 6.6 Hz, CH($\underline{CH_3}$)$_2$), 2.25 (3H, s, CH_3), 2.50 (3H, s, CH_3), 2.68 (3H, s, CH_3), 2.97-3.02 (1H, m, $\underline{CH}$(CH_3)$_2$), 6.85 (1H, d, J = 10.4 Hz), 6.98 (2H, d, J = 7.6 Hz), 7.14-7.18 (2H, m), 7.24-7.29 (4H, m), 7.30-7.34 (4H, m), 7.63-7.68 (4H, m), 8.50 (1H, d, J = 8.2 Hz), 8.03 (1H, s). ^{13}C-NMR($CDCl_3$): δ 12.8, 21.2, 24.6, 25.8, 29.7, 37.8, 116.4, 122.7, 124.7, 124.8, 125.6, 126.4, 127.1, 127.9, 128.0, 128.2, 128.5, 129.2, 129.4, 129.8, 130.9, 132.7, 133.4, 134.2, 134.8, 137.1, 137.5, 138.1, 139.8, 146.1, 148.3, 150.0. *Anal*. Calcd for $C_{38}H_{34}O$: C 90.08, H 6.76. Found: C 90.15, H 6.83%.

4,5-Diphenyl-3-(guaiazulen-1-yl)-2-(4-methoxyphenyl)furan (**3l**): Blue scaly crystals (from EtOAc). mp 116-118 ºC; ^{1}H-NMR($CDCl_3$): δ 1.25 (6H, d, J = 6.6 Hz, CH($\underline{CH_3}$)$_2$), 2.41 (3H, s, CH_3), 2.73 (3H, s, CH_3), 2.95-2.99 (1H, m, $\underline{CH}$(CH_3)$_2$), 3.35 (3H, s, OCH_3), 6.77-6.79 (1H, m), 7.08 (1H, s), 7.12-7.19 (2H, m), 7.31-7.35 (5H, m), 7.50-7.57 (4H, m), 7.82-7.86 (2H, m), 7.96-7.98 (3H, m), 8.50 (1H, d, J = 8.2 Hz). ^{13}C-NMR($CDCl_3$): δ 13.0, 24.7, 25.7, 29.6, 37.9, 55.4, 114.6, 121.5, 124.1, 124.9, 125.5, 126.0, 126.5, 126.7, 128.0, 128.3, 128.7, 129.4, 129.6, 130.4, 133.3, 133.5, 134.2, 134.9, 137.4, 138.5, 139.7, 139.9, 144.6, 146.7, 147.2. *Anal*. Calcd for $C_{38}H_{34}O_2$: C 87.32, H 6.56. Found: C 87.47, H 6.71%.

4,5-Diphenyl-3-(guaiazulen-1-yl)-2-(4-hydrophenyl)furan (**3m**): Blue scaly crystals (from EtOAc). mp 93-95 ºC; IR (KBr, cm^{-1}): ν 3218 (OH). ^{1}H-NMR($CDCl_3$): δ 1.28 (6H, d, J = 6.6 Hz, CH($\underline{CH_3}$)$_2$), 2.52 (3H, s, CH_3), 2.67 (3H, s, CH_3), 3.01-3.05 (1H, m, $\underline{CH}$(CH_3)$_2$), 5.73 (1H, s, OH), 6.95 (1H, d, J = 10.0 Hz), 7.16-7.20 (2H, m), 7.31-7.37 (6H, m), 7.34-7.37 (4H, m), 7.64-7.66 (2H, m), 7.70 (2H, d, J = 8.0 Hz), 8.05 (1H, s). ^{13}C-NMR($CDCl_3$) δ(ppm): 13.1, 24.7, 25.8, 29.6, 37.8, 115.6, 121.5, 124.3, 125.2, 125.8, 126.3, 126.7, 128.0, 128.6, 128.8, 129.4, 129.7, 130.1, 130.5, 133.4, 133.8, 134.4, 134.8, 137.9, 138.2, 139.3, 139.8, 144.7, 146.8, 150.6. *Anal*. Calcd for $C_{37}H_{32}O_2$: C 87.37, H 6.34. Found: C 87.46, H 6.45%.

4,5-Diphenyl-2-(4-fluorophenyl)3-(guaiazulen-1-yl)furan (**3n**): Blue scaly crystals (from EtOAc). mp 83-85 ºC; ^{1}H-NMR($CDCl_3$): δ 1.23 (6H, d, J = 6.6 Hz, CH($\underline{CH_3}$)$_2$), 2.34 (3H, s, CH_3), 2.50 (3H, s, CH_3), 2.99-3.03 (1H, m, $\underline{CH}$(CH_3)$_2$), 6.64 (2H, d, J = 8.0 Hz), 6.84 (1H, d, J = 10.4 Hz), 7.15-7.19 (2H, m), 7.24-7.28 (4H, m), 7.31-7.34 (4H, m), 7.61-7.63 (2H, m), 7.67 (2H, d, J = 8.0 Hz), 8.03 (1H, s). ^{13}C-NMR($CDCl_3$) δ(ppm): 13.1, 24.6, 25.8, 29.6, 37.7, 115.7, 118.9, 121.5, 124.3, 125.0, 125.5, 126.0, 126.6, 128.2, 128.4, 128.8, 129.5, 129.8, 130.2, 130.5, 133.1, 133.9, 134.4, 134.8, 137.9, 138.5, 139.0, 139.6, 148.7, 146.9, 154.2. *Anal*. Calcd for $C_{37}H_{31}FO$: C 87.03, H 6.12. Found: C 87.14, H 6.25%.

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