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AN EFFICIENT SYNTHESIS OF 2-AMINO-4-(GUAIAZULEN-1-YL)-4*H*-CHROMENES *VIA* CYCLOADDITION OF 1-HYDROXY-2-(3-GUAIAZULENYLIUM)BENZENES WITH MALONONITRILE/ETHYL CYANOACETATE

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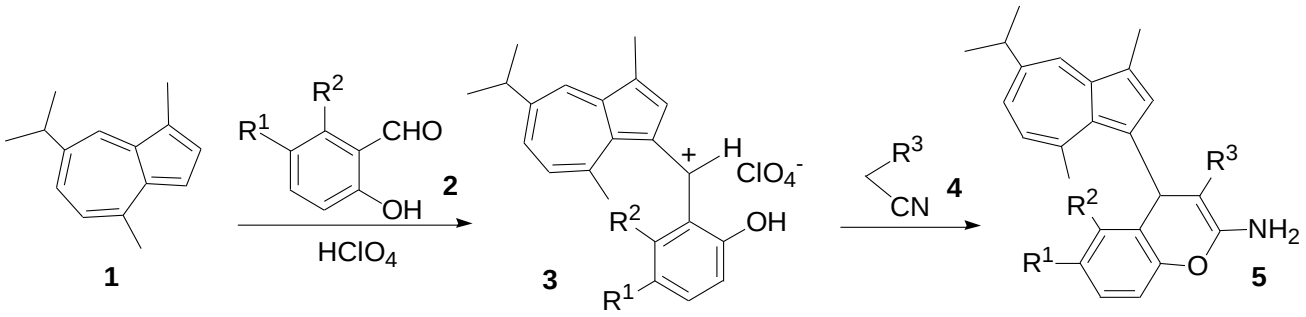
Abstract – An efficient two-step method developed for the synthesis of 2-amino-4-(guaiazulen-1-yl)-4*H*-chromenes is described. The construction of these compounds was achieved by the reaction of guaiazulene and 2-hydroxybenzaldehydes in the presence of perchloric acid, followed by cycloaddition of the resulting 1-hydroxy-2-(3-guaiazulenylmethylium)benzenes which allowed access to the title heterocycles.

Chromene frameworks are important structural components in biologically active and natural products.[1] They are currently explored as privileged structures in therapeutic agents and pharmacological relevance molecules.[2] Moreover, in recent years functionalized chromenes have played important role in the synthetic approaches to promising compounds in the field of medicinal chemistry.[3] Among the various structural patterns, 2-amino-4*H*-chromenes are considered as key cores in the synthesis of pigments,[4] agrochemicals,[5] cosmetics, and drugs.[6] The current interest in 2-amino-4-aryl-4*H*-chromenes bearing arises from their potential application in the treatment of selectively toxic to cancer cell lines.[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, 3-arylmethyleneguaiazulenim ion have been widely used as good stability 3-guaiazulenylmethylium ion in organic synthesis.[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 2-amino-4*H*-chromene derivatives *via* cycloaddition of 1-hydroxy-2-(3-guaiazulenylmethylium)benzenes with malononitrile/ethyl cyanoacetate under mild conditions (Scheme 1).

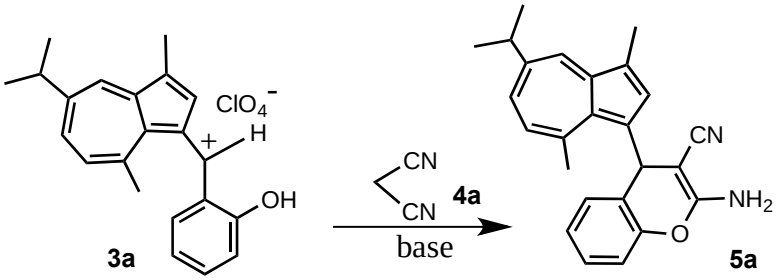


Scheme 1. Synthesis of 2-amino-4-(guaiazulen-1-yl)-4*H*-chromene derivatives

In this study, the key intermediate methyl cation compounds, 1-hydroxy-2-(3-guaiazulenylmethylium)-benzenes (**3**), were obtained by the condensation of guaiazulene (**1**) and 2-hydroxybenzaldehydes (**2**) (such as salicylaldehyde (**2a**), 2-hydroxy-5-methylbenzaldehyde (**2b**), 2-hydroxy-5-methoxybenzaldehyde (**2c**), 2,5-dihydroxybenzaldehyde (**2d**), 5-chloro-2-hydroxybenzaldehyde (**2e**), 5-bromo-2-hydroxybenzaldehyde (**2f**), and 2-hydroxy-1-naphthaldehyde (**2g**)) in the presence of perchloric acid with excellent yield (87~96%). The structures of the products **3** were established on the basis of elemental analysis and spectroscopic data. The compound **3a** was obtained as a dark-red powder. The IR spectrum showed that although a specific band (ν_{max} 3312 cm^{-1}) from hydroxy groups of **3a**, and specific bands (ν_{max} 1093 and 630 cm^{-1}) based on the counter anion (ClO_4^{-1}). The ^{1}H NMR spectrum for **3a** showed signals based on a 3-guaiazulenylmethylium ion unit with a similar resonance structure to the 3-guaiazulenylium ion form.[16] The chemical shifts (δ ppm) for the proton signal of the HC^+-α carbenium-ion center of **3a** at 9.23 in CF_3CO_2D.

First, we attempted to optimize the conditions for the reaction of 1-hydroxy-2-(3-guaiazulenylmethylium)benzene **3a** with malononitrile **4a** (Scheme 2). The reaction mixture, which was composed of a 1:1 mixture of **3a** and **4a** was tested under a variety of different conditions, and the results are summarized in Table 1. The initial reaction of 1-hydroxy-2-(3-guaiazulenylmethylium)benzene **3a** with malononitrile **4a** was set to stirr for 24 h at 25 °C in CH_2Cl_2 (Table 1, Entry 1). After the reaction was completed, the mixture was purified by recrystallized to give pure product, 2-amino-4-(guaiazulen-1-yl)-4*H*-chromene-3-carbonitrile (**5a**), whose structure was characterized by ^{1}H NMR, ^{13}C NMR, IR spectra and elemental analysis. The IR spectrum of **5a** showed the characteristic absorptions of a primary amine group (NH_2) at 3365 and 3325 cm^{-1}, and a cyanide group (CN) at 2196 cm^{-1}. The ^{1}H NMR spectrum of **5a** showed signals at δ 1.51, 2.81, 2.29, and 2.97 ppm for methyl groups, and exhibited characteristic signal for C4-H at 4.73 ppm. The aromatic protons signals at δ 7.17 (d, J =

10.8 Hz, 1H), 7.30 (d, *J* = 10.8 Hz, 1H), 7.40-7.50 (m, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.63-7.69 (m, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.87 (s, 1H), 8.34 (s, 1H) for azulene and benzene nucleus protons and a singlet at δ = 7.32 corresponding to the amine group (NH_2).



Scheme 2. Synthesis of 2-amino-4-(guaiazulen-1-yl)-4*H*-chromene-3-carbonitrile (**5a)**

To give variety of 2-amino-4-(guaiazulen-1-yl)-4*H*-chromene-3-carbonitrile derivatives, the reaction was carried out by equimolar amounts of 1-hydroxy-2-(3-guaiazulenylmethylium)benzene **3a** with malononitrile **4a** in the presence of several bases (Table 1). One equiv. of triethylamine (TEA), triethyl−enediamine (DABCO), or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as organic bases, and using NaOAc, K_2CO_3, or KOH as an inorganic base in several solvents resulted in the desired product **5a**.

Table 1. Optimizing the reaction condititions for the synthesis of **5a***

Entry	Catalyst / (equiv.)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	none	CH_2Cl_2	25	24	26
2	none	MeCN	25	11	42
3	TEA (1.0 eq)	MeCN	25	5	76
4	DABCO (1.0 eq)	MeCN	25	6	85
5	DBU (1.2 eq)	MeCN	25	5	83
6	DBU (0.8 eq)	MeCN	25	8	62
7	NaOAc (1.0 eq)	MeCN	25	8	75
8	K_2CO_3 (1.0 eq)	MeCN	25	5	80
9	KOH (1.0 eq)	MeCN	25	4	58
10	DABCO (1.0 eq)	MeCN	50	4	78
11	DABCO (1.0 eq)	EtOH	25	7	65
12	DABCO (1.0 eq)	EtOAc	25	8	78
13	DABCO (1.0 eq)	DMF	25	5	65

* Reaction conditions: 1-hydroxy-2-(3-guaiazulenylmethylium)benzene (**3a**, 1.0 mmol), malononitrile (**4a,** 1.0 mmol), and solvent (20 mL), and required amount of the catalysts.

Among the different catalysts, DABCO showed the best activity (entry 4, Table 1). In order to find the best reaction medium, we utilized various solvents such as MeCN, EtOH, EtOAc, and DMF in the presence of DABCO. MeCN proved to be the solvent of choice due to its safe nature and because it provided higher yields. The amount of catalyst required was optimized in MeCN; the use of 1.0 equiv. of DABCO appeared to be optimal

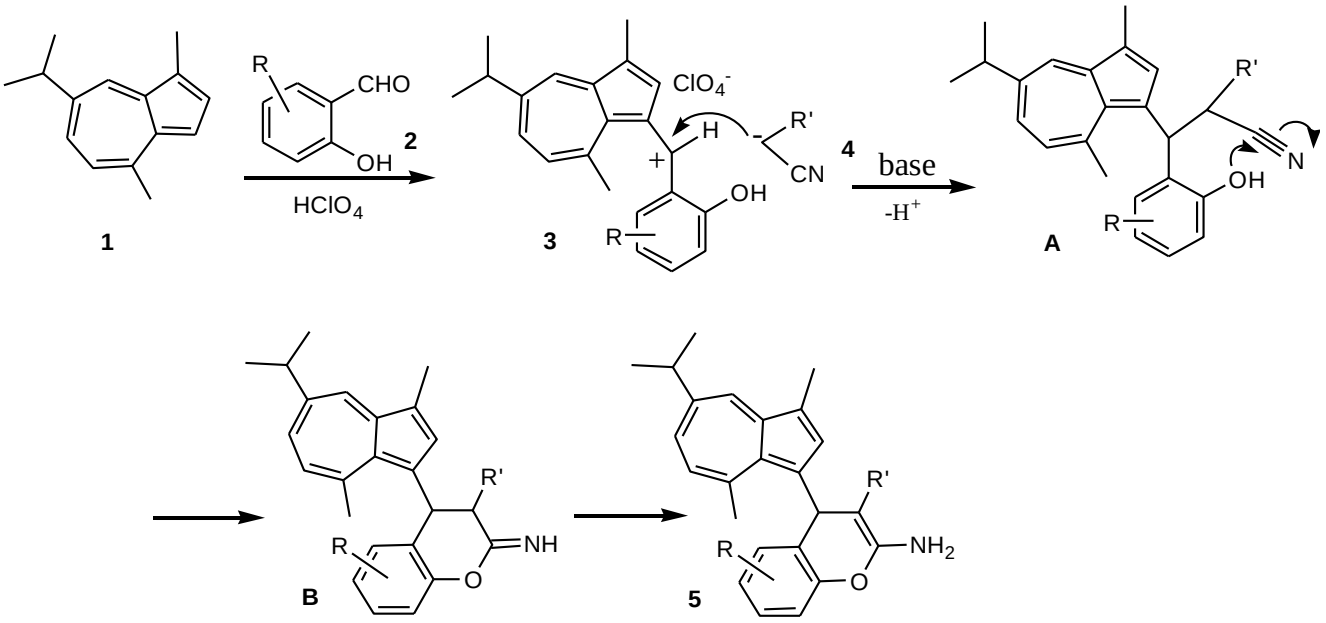
With the optimized reaction conditions in hand, we next surveyed the substrate scope of 1-hydroxy-2-(3-guaiazulenylmethylium)benzenes (**3a-3g**), and malononitrile (**4a**)/ethyl cyanoacetate (**4b**) for the synthesis of guaiazulene substituted 2-amino-4*H*-chromenes (see Scheme 1), and the results are summarized in Table 2. The results demonstrated that the substrates, regardless of electron-donating or electron-withdrawing groups on the benzene ring, could undergo the reaction smoothly to afford the expected products in good yields. It is also noteworthy that ethyl cyanoacetate (**4b**) required a little longer reaction time compared to malononitrile (**4a**) (entries 8 and 9). This may be attributed to the capability of the cyanide group in stabilizing the reaction intermediates compared to the ester group.

Table 2. Synthesis of guaiazulene substituted 2-amino-4*H*-chromene derivatives **5**

Entry	R^1	R^2	R^3	Time (h)	Product	Yield (%)[a]
1	H	H	CN	3	**5a**	85
2	Me	H	CN	3	**5b**	82
3	OMe	H	CN	3	**5c**	86
4	OH	H	CN	3	**5d**	78
5	Cl	H	CN	4	**5e**	80
6	Br	H	CN	4	**5f**	82
7	-HC=CH-	-CH=CH-	CN	4	**5g**	84
8	H	H	CO_2Et	5	**5h**	78
9	Cl	H	CO_2Et	5	**5i**	82

[a] The yields refer to the isolated product.

On the basis of these results, a plausible mechanism for the construction of 2-amino-4-(guaiazulen-1-yl)-4*H*-chromenes is proposed (Scheme 3). In the initial step, it is believed that nucleophilic attack of guaiazulene **1** to the activated 2-hydrobenzaldehyde **2** (by perchloric acid), followed by H_2O elimination provides intermediate 1-hydroxy-2-(3-guaiazulenylmethylium)benzenes **3**. Next, the nucleophilic attack of malononitrile/ethyl cyanoacetate **4** to intermediate **A** in the presence of base. Subsequently, the intramolecular nucleophilic addition of hydroxy group to nitrile group affords the cyclization intermediate **B**, followed by tautomerization to furnish the final annulation product **5**.



Scheme 3. Proposed mechanism for the synthesis of 2-amino-4-(guaiazulen-1-yl)-4*H*-chromenes **5**

In summary, we have successfully developed the cycloaddition of the 1-hydroxy-2-(3-guaiazulenyl-methylium)benzenes with malononitrile/ethyl cyanoacetate using DABCO as catalyst, providing a facile access to 2-amino-4-(guaiazulen-1-yl)-4*H*-chromenes with good yields. This approach offers an effective route for the construction of new heteroarylazulene frameworks in a two-step process from commercially available starting materials. Further studies on the extension of this strategy to synthesize other novel guaiazulen compounds are ongoing in our laboratory.

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. All other chemicals used in this study were commercially available.

Synthesis of 1-hydroxy-2-(3-guaiazulenylmethylium)benzene perchlorate (3). To a solution of guaiazulene (**1**) (200 mg, 1.0 mmol) in MeOH (20 mL) was added a solution of 2-hydroxybenzaldehyde (**2**) (1.0 mmol) in MeOH (5 mL) containing perchloric acid (60% aqueous solution, 200 mg). The mixture was stirred at 25 °C for 3 h, giving a precipitation of a dark-red solid. The crude product **3** thus obtained was carefully washed with MeOH, and was recrystallized from MeCN to provide pure **3** as stable crystals.

1-Hydroxy-2-(3-guaiazulenylmethylium)benzene perchlorate (3a). Red-brown crystals; yield:

93%; mp 225–227 °C (lit:[17] 220-225 °C); IR (KBr): *v* 3312, 1578, 1093, 630 cm^{-1}; ^1H NMR (400 MHz, CF_3CO_2D): δ 1.57 (d, *J* = 6.6 Hz, 6H), 2.59 (s, 3H), 3.28 (s, 3H), 3.68-3.70 (m, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 7.6 Hz,1H), 8.05 (s, 1H), 8.41 (d, *J* = 10.6 Hz, 1H), 8.54 (d, *J* = 10.6 Hz, 1H), 8.68 (s, 1H), 9.23 (s, 1H). *Anal*. Calcd for $C_{22}H_{23}ClO_5$: C 65.59, H 5.75. Found: C 65.61, H 5.77.

1-Hydroxy-4-methyl-2-(3-guaiazulenylmethylium)benzene perchlorate (3b). Red-brown crystals; yield: 95%; mp 179–181 °C; IR (KBr): *v* 3352, 1567, 1083, 632 cm^{-1}; ^1H NMR (400 MHz, CF_3CO_2D): δ 1.53 (d, *J* = 6.8 Hz, 6H), 2.38 (s, 3H), 2.55 (s, 3H), 3.37 (s, 3H), 3.55-3.59 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.49 (s, 1H), 8.01 (s, 1H), 8.35 (d, *J* = 11.0 Hz, 1H), 8.49 (d, *J* = 11.0 Hz, 1H), 8.63 (s, 1H), 9.15 (s, 1H). *Anal*. Calcd for $C_{23}H_{25}ClO_5$: C 66.26, H 6.04. Found: C 66.28, H 6.08.

1-Hydroxy-4-methoypenyl-2-(3-guaiazulenylmethylium)benzene perchlorate (3c). Red-brown crystals; yield: 90%; mp 215–217 °C; IR (KBr): *v* 3382, 1583, 1071, 634 cm^{-1}; ^1H NMR (400 MHz, CF_3CO_2D): δ 1.53 (d, *J* = 6.8 Hz, 6H), 2.55 (s, 3H), 3.24 (s, 3H), 3.45-3.52 (m, 1H), 4.02 (s, 3H), 7.10 (d, *J* = 6.4 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.37 (s, 1H), 8.00 (s, 1H), 8.38 (d, *J* = 11.2 Hz, 1H), 8.53 (d, *J* = 11.2 Hz, 1H), 8.64 (s, 1H), 9.07 (s, 1H). *Anal*. Calcd for $C_{23}H_{25}ClO_6$: C 63.81, H 5.82. Found: C 63.86, H 5.84.

1,4-Dihydroxy-2-(3-guaiazulenylmethylium)benzene perchlorate (3d). Red-brown crystals; yield: 87%; mp 213–215 °C; IR (KBr): *v* 3380, 1584, 1086, 628 cm^{-1}; ^1H NMR (400 MHz, CF_3CO_2D): δ 1.55 (d, *J* = 6.6 Hz, 6H), 2.60 (s, 3H), 3.23 (s, 3H), 3.51-3.58 (m, 1H), 7.78 (s, 1H), 8.09 (s, 1H), 8.32 (d, *J* = 11.2 Hz, 1H), 8.43 (d, *J* = 11.2 Hz, 1H), 8.66 (s, 1H), 9.27 (s, 1H). *Anal*. Calcd for $C_{22}H_{23}ClO_6$: C 63.08, H 5.53. Found: C 60.11, H 5.54.

1-Hydroxy-4-chloro-2-(3-guaiazulenylmethylium)benzene perchlorate (3e). Red-brown crystals; yield: 96%; mp 143–145 °C; IR (KBr): *v* 3381, 1573, 1072, 627 cm^{-1}; ^1H NMR (400 MHz, CF_3CO_2D): δ 1.52 (d, *J* = 6.8 Hz, 6H), 2.54 (s, 3H), 3.31 (s, 3H), 3.48-3.57 (m, 1H), 7.02 (s, 1H), 7.40 (d, *J* = 8.7 Hz, 1H), 7.59 (s, 1H), 7.95 (s, 1H), 8.37 (d, *J* = 11.0 Hz, 1H), 8.52 (d, *J* = 11.2 Hz, 1H), 8.63 (s, 1H), 9.01 (s, 1H). *Anal*. Calcd for $C_{22}H_{22}Cl_2O_5$: C 60.42, H 5.07. Found: C 60.46, H 5.09.

1-Hydroxy-4-bromo-2-(3-guaiazulenylmethylium)benzene perchlorate (3f). Red-brown crystals; yield: 88%; mp 138–140 °C; IR (KBr): *v* 3367, 1579, 1080, 627 cm^{-1}; ^1H NMR (400 MHz, CF_3CO_2D): δ 1.73 (d, *J* = 6.5 Hz, 6H), 2.75 (s, 3H), 3.46 (s, 3H), 3.74-3.80 (m, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.95 (s, 1H), 8.15 (s, 1H), 8.59 (d, *J* = 11.2 Hz, 1H), 8.73 (d, *J* = 10.8 Hz, 1H), 8.85 (s, 1H), 9.22 (s, 1H). *Anal*. Calcd for $C_{22}H_{22}BrClO_5$: C 54.85, H4.60. Found: C 54.89, H 4.63.

1-Hydroxy-2-(3-guaiazulenylmethylium)naphthalene perchlorate (3g). Red-brown crystals; yield: 90%; mp 165–167 °C; IR (KBr): *v* 3351, 1590, 1084, 632 cm^{-1}; ^1H NMR (400 MHz, CF_3CO_2D): δ 2.15 (d, *J* = 6.5 Hz, 6H), 3.03 (s, 3H), 3.95 (s, 3H), 4.28 (s, 3H), 4.39-4.35 (m, 1H), 7.89 (d, *J* = 10.2 Hz, 1H),

8.06-8.13 (m, 3H), 8.46-8.58 (m, 3H), 9.00 (d, *J* = 11.2 Hz, 1H), 9.16 (d, *J* = 11.2 Hz, 2H), 9.20 (s, 1H), 9.71 (s, 1H). *Anal*. Calcd for $C_{26}H_{25}ClO_5$: C 68.95, H 5.56. Found: C 68.98, H 5.57.

General procedure for the preparation of 2-amino-4-(guaiazulen-1-yl)-4*H*-chromenes (5). To a solution of 1-((2-hydroxylaryl)methylene)guaiazulenim perchlorate **3** (1.0 mmol), malononitrile (or ethyl cyanoacetate) **4** (1.0 mmol), and DABCO (1.0 mmol) was dissolved in CH_2Cl_2 (20 mL). And the mixture was stirred at 25 °C. After completion monitored by TLC, and then water (30mL) was added to the mixture. EtOAc (30 mL) was added to the mixture. The organic layer was washed with brine (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the residue. The residue was recrystallized from MeCN to afford the corresponding products **5a-h**.

2-Amino-4-(guaiazulen-1-yl)-4*H*-chromene-3-carbonitrile (5a): Blue scaly crystals. mp 222–224 °C ; IR (KBr): *v* 3268, 2195 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.51 (d, *J* = 6.8 Hz, 6H), 2.81 (s, 3H), 2.97 (s, 3H), 3.25-3.27 (m, 1H), 4.73 (s, 1H), 7.17 (d, *J* = 10.8 Hz, 1H), 7.30 (d, *J* = 10.8 Hz, 1H), 7.32 (s, 2H), 7.40-7.50 (m, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.63-7.69 (m, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.87 (s, 1H), 8.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 145.61, 144.30, 139.88, 137.16, 136.17, 136.04, 134.86, 134.06, 133.32, 128.88, 127.57, 127.37, 125.17, 125.04, 124.86, 124.49, 116.11, 112.70, 38.26, 37.56, 24.80, 24.57, 24.09, 12.90. *Anal*. Calcd for $C_{25}H_{24}N_2O$: C 81.49, H 6.57, N 7.60. Found: C 81.50, H 6.59, N 7.64.

2-Amino-4-(guaiazulen-1-yl)-6-methyl-4*H*-chromene-3-carbonitrile (5b): Blue scaly crystals. mp 212–214 °C; IR (KBr): *v* 3283, 2194 cm^{-1} (CN); ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.41 (d, *J* = 6.8 Hz, 6H), 2.19 (s, 3H), 3.18 (s, 3H), 3.28-3.31 (m, 1H), 5.90 (s, 1H), 6.99-7.01 (m, 2H), 7.03(s, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.26 (s, 1H), 7.37 (d, *J* = 10.8 Hz, 1H), 7.51 (d, *J* =10.8 Hz, 1H), 8.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.65, 146.58,144.37, 140.43, 139.30, 138.88, 134.54, 134.25, 133.89, 132.67, 130.33, 129.84, 128.75, 127.35, 125.69, 125.35, 121.46, 116.20, 58.88, 37.23, 28.50, 24.79, 20.59, 19.00, 13.20. *Anal*. Calcd for $C_{26}H_{26}N_2O$: C 81.64, H 6.85, N 7.32. Found: C 81.68, H 6.87, N 7.35.

2-Amino-4-(guaiazulen-1-yl)-6-methoxy-4*H*-chromene-3-carbonitrile (5c): Blue scaly crystals. mp 218–220 °C; IR (KBr): *v* 3272, 2197 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.26 (d, *J* = 6.8 Hz,6H), 2.43 (s, 3H), 3.01 (s, 3H), 3.08-3.13 (m, 1H), 3.52 (s, 3H), 5.70 (s, 1H), 6.32 (s, 1H), 6.74-6.78 (m, 3H), 6.98 (d, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 7.13 (s, 1H), 7.34 (d, *J* =10.8 Hz, 1H), 8.02 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 144.42, 142.73, 140.42, 139.27, 138.72, 134.59, 134.25, 132.28, 129.98, 127.41, 126.69, 125.67, 121.49, 117.30, 114.75, 113.57, 58.45, 55.74, 37.23, 34.25, 28.43, 24.79, 13.20. *Anal.* Calcd for $C_{26}H_{26}N_2O_2$: C 78.36, H 6.58, N 7.03. Found: C 78.40, H 6.59, N 7.05.

2-Amino-4-(guaiazulen-1-yl)-6-hydroxy-4*H*-chromene-3-carbonitrile (5d): Blue scaly crystals.

mp 139–142 °C; IR (KBr): *v* 3328, 3268, 2195 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.26 (d, *J* = 6.8 Hz, 6H), 2.04 (s, 3H), 3.00-3.05 (m, 4H), 5.60 (s, 1H), 6.37-6.40 (m, 2H), 6.58 (d, *J* = 8.6Hz, 1H), 6.72 (s, 2H), 6.90 (d, *J* = 10.4 Hz, 1H), 7.14 (s, 1H), 7.32 (d, *J* = 10.4 Hz, 1H), 8.00 (s, 1H), 9.61 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.56, 157.11, 148.93, 144.24, 140.30,138.97, 134.40, 134.09, 133.05, 130.97, 129.90, 127.18, 125.58, 121.45, 118.53, 118.36, 112.68, 102.49, 59.07, 37.23, 33.23, 28.45, 24.80, 13.20. *Anal.* Calcd for $C_{25}H_{24}N_2O_2$: C 78.01, H 6.29, N 7.29. Found: C 78.03, H 6.31, N 7.31.

2-Amino-6-chloro-4-(guaiazulen-1-yl)-4*H*-chromene-3-carbonitrile (5e): Blue scaly crystals. mp 238–241 °C; IR (KBr): *v* 3265, 2196 cm-1; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.41 (d, *J* = 6.8 Hz,6H), 2.19 (s, 3H), 3.18 (s, 3H), 3.28-3.30 (m, 1H), 5.90 (s, 1H), 6.99-7.03 (m, 3H), 7.13 (d, *J* =10.8 Hz, 1H), 7.23 (d, *J* = 10.8 Hz, 1H), 7.25 (s, 1H), 7.37 (d, *J* = 9.8 Hz, 1H), 7.51 (d, *J* = 9.8 Hz, 1H), 8.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 147.41, 144.63, 140.65, 139.17, 138.61, 134.78, 134.47, 131.62, 130.16, 129.72, 128.36, 128.16, 127.89, 127.64, 125.85, 121.04, 118.46, 56.45, 37.24, 28.37, 24.77, 18.98, 13.16. *Anal*. Calcd for $C_{25}H_{23}ClN_2O$: C 74.52, H 5.75, N 6.95. Found: C 74.57, H 5.78, N 6.97.

2-Amino-6-bromo-4-(guaiazulen-1-yl)-4*H*-chromene-3-carbonitrile (5f): Blue scaly crystals. mp 195–197 °C; IR (KBr): *v* 3279, 2196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.26 (d, *J* = 6.8 Hz, 6H), 2.44 (s, 3H), 3.03 (s, 3H), 3.17-3.21 (m, 1H), 5.75 (s, 1H), 6.89-6,91 (m, 3H), 6.95-7.05 (m, 2H), 7.12 (s, 1H), 7.35-7.37 (m, 2H), 8.04 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.25, 147.90, 144.65, 140.66, 139.17, 138.61, 134.81, 134.50, 132.63, 131.67, 131.04, 130.13, 128.34, 127.65, 125.88, 121.03, 118.84, 116.32, 58.65, 37.24, 33.72, 28.39, 24.79, 13.19. *Anal*. Calcd for $C_{25}H_{23}BrN_2O$: C 67.12, H 5.18, N 6.26. Found: C 67.15, H 5.20, N 6.29.

3-Amino-1-(guaiazulen-1-yl)-1*H*-benzo[*f*]chromene-2-carbonitrile (5g): Blue scaly crystals. mp 167–170 °C; IR (KBr): *v* 3293, 2195 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.25 (d, *J* = 6.8 Hz, 6H), 2.30 (s, 3H), 2.96-3.03 (m, 1H), 3.33 (s, 3H), 6.14 (s, 1H), 6.87-7.90 (m, 2H), 6.94 (s, 1H), 7.04 (d, *J* = 9.4 Hz, 1H), 7.30-7.36 (m, 4H), 7.68-7.70 (d, *J* = 10.4 Hz, 1H), 7.87-7.90 (m, 2H),7.96 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.30, 146.71, 144.59, 140.32, 139.02, 138.36, 134.89, 134.41, 132.28, 131.35, 130.98, 129.69, 129.41, 128.94, 127.68, 127.51, 125.59, 125.07, 123.82, 121.43, 117.82, 117.38, 59.67, 37.20, 32.06, 28.45, 24.78, 13.10. *Anal*. Calcd for $C_{29}H_{26}N_2O$:C 83.22, H 6.26, N 6.69. Found: C 83.25, H 6.28, N 6.73.

Ethyl 2-Amino-4-(guaiazulen-1-yl)-4*H*-chromene-3-carboxylate (5h): Blue scaly crystals. mp 196–199 °C; IR (KBr): *v* 3262, 1656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 0.91 (t, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 6.8 Hz, 6H), 2.47 (s, 3H), 2.95 (s, 3H), 2.97-3.01 (m, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 5.92 (s, 1H), 6.58-6.60 (m, 2H), 6.69 (d, *J* = 7.2 Hz, 1H), 6.76-6.78 (m, 2H), 6.91-6.93 (m, 2H), 7.24 (d, *J* = 10.4 Hz, 1H), 7.85 (s, 1H), 8.01 (d, *J* = 10.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *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. *Anal*.Calcd for $C_{27}H_{29}NO_3$: C 78.04, H 7.03, N 11.55. Found: C 78.07, H 7.06, N 11.57.

Ethyl 2-Amino-6-chloro-4-(guaiazulen-1-yl)-4*H*-chromene-3-carboxylate (5i): Blue scaly crystals. mp 238–241 °C; IR (KBr): *v* 3274, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.2Hz, 3H), 1.24 (d, *J* = 6.8 Hz, 6H), 2.39 (s, 3H), 3.22 (s, 3H), 3.38-3.42 (m, 1H), 3.89 (q, *J* = 7.2 Hz, 2H), 5.87 (s, 1H), 6.92-6.94 (m, 2H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.57-7.18 (m, 2H), 7.31 (d, *J* = 10.4 Hz, 1H), 7.62-7.64 (m, 2H), 7.94 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.83, 160.52, 147.07, 144.97, 139.88, 139.02, 138.15, 134.80, 134.57, 134.13, 130.45, 129.25, 128.55,128.14, 127.49, 127.20, 125.31, 118.49, 78.30, 59.24, 37.15, 32.93, 28.08, 24.79, 14.54, 13.19. *Anal*. Calcd for $C_{27}H_{28}ClNO_3$: C 72.07, H 6.27, N 7.88. Found: C 72.09, H 6.29, N 7.90.

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