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Synthesis and antigastric ulcer activity of novel 5-isoproyl-3,8-dimethylazulene derivatives

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ABSTRACT

5-Isoproyl-3,8-dimethylazulene derivatives were synthesized and evaluated for antigastric ulcer activity in vivo. Some of them possess the best activity against gastric ulcer with ulcer index values lower than the drug reference (omeprazole). The structure–activity relationship (SAR) shows that the lipophilic flat structure contributes to quite potent antigastric ulcer activity.

Gastric ulcer is a chronic inflammation of the stomach, and more serious one can even lead to gastric cancer, which is the second most common tumor in human beings.[1] Although there are many effective treatments for gastric ulcer, the number of new gastric ulcer patient continues to rise. Therefore, the quest for more efficacious and more selective drugs which bind to gastric ulcer is vital in chemotherapy.

Guaiazulene (GA) (Fig. 1) is the main active ingredient of the plant 'Matricaria chamomilla L.', and exhibits attractive pharmacological properties, including antipepsin, antiinflammatory, antianaphylaxis and promoting mucosa's metabolism.[2–4]

Many derivatives of guaiazulene have some certain activities.[5,6] Sodium guaiazulene sulfonate (sodium 5-isopropyl-3,8-dimethylazulene-1-sulfonate, GAS-Na) (Fig. 1), a hydrophilic derivative of guaiazulene, with its excellent antiinflammatory effect, is the chief ingredient of Compound Glutamine Granules which has treatment for gastric ulcer. Conjugation of two bioactive fragments is now accepted as an effective approach for designing inhibitors, ligands, and other drugs.[7] Meanwhile, the sulfonamides which have been clinically used for many years, have been found to possess a large number of biological activities,[9] such as antioxidant,[8] antitumor,[9] antiinflammatory,[10,11] and antibacterial.[12,13] Additionally, many investigations show that the most of schiff bases also display a broad range of biological activities, including antibacterial,[14] antimalarial,[15] antiviral,[16] and antifungal.[17] Moreover, sulfonyl hydrazone has variety of bactriostatic and antineoplastic activity,[18] too. In order to explore biologically more antigastric ulcer drugs, three series of guaiazulene derivatives were designed and synthesized by combining with different biological groups.

Sodium guaiazulene sulfonate is an important intermediate, prepared by the way as shown in Scheme 1. It was carried out by introducing sulfonic group into the C-1 position of the guaiazulene through electrophilic substitution, subsequently stirred for 3 h at

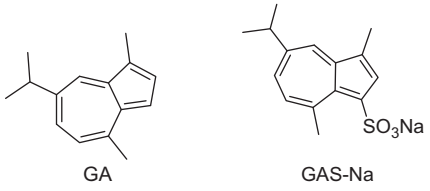
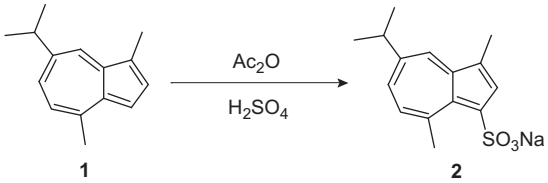


Figure 1. Guaiazulene and sodium guaiazulene sulfonate.



Scheme 1. Synthesis of sodium guaiazulene sulfonate. Reagents and conditions: $(CH_3CO)_2O$, H_2SO_4, rt, 3 h. NaOH solution basified, **2**, 86% (Mp 106–107 °C).

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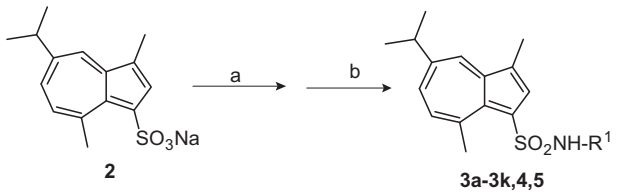


Scheme 2. Synthesis of N-substituted-5-isopropyl-3,8-dimethylazulene-1-sulfonamide. Reagents and conditions: (a) $(COCl)_2$, cat. DMF, CH_2Cl_2, Py, ice-bath, 10 min; (b) amine, Et_3N, Py.

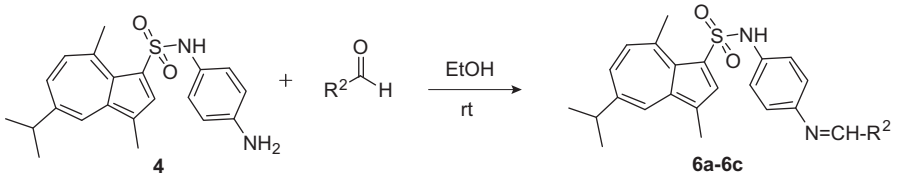
room temperature, finally basified by sodium hydroxide solution, gave sodium guaiazulene sulfonate.

The synthesis of N-substituted-5-isopropyl-3,8-dimethylazulene-1-sulfonamide is depicted in Scheme 2. Azulene sulfonyl chloride was given by sodium guaiazulene sulfonate reacting with oxalyl chloride. Then the corresponding amine was added in it to afford **3a–3k, 4, 5**. But the yields of these compounds are very low, the reasons may be summarized as follows. (1) High temperature makes the intermediate azulene sulfonyl chloride be easily decomposed. (2) The different structures of amines have great influence on the nucleophilic acylation. (3) There are some side reactions along with the sulfonylation.

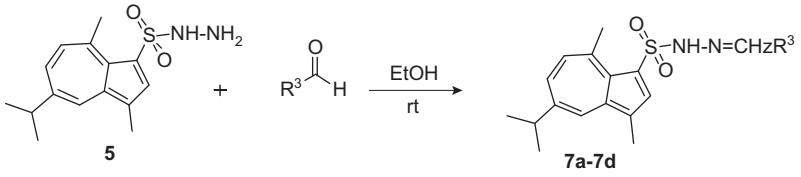
Compound **5** was unstable intermediate, which gradually decomposed even in the solid state at room temperature. Therefore, **5** was added the next reaction immediately as soon as we got crude product.

The synthesis of schiff base and sulfonyl hydrazone derivatives are shown in Scheme 3 and Scheme 4, respectively. A mixture of **4** and benzaldehyde in anhydrous ethanol was stirred at room temperature for 1 h, then concentrated, purified, gave **6a**. Compounds **6b–6c**, **7a–7d** were achieved in the similar conditions. However, schiff base derivatives decomposed as soon as came across silica gel, **6a-6c** were purified by neutral alumina column chromatography.

On the basis of the guaiazulene, three series of guaiazulene derivatives (Table 1) were designed and synthesized, and all of them were not reported in literatures. All of the synthesized compounds were structurally confirmed by means of analytical and spectral data.[19] We performed analysis of the structure by comparing the ^1H NMR of these compounds. The C-2 hydrogen is a singlet with a chemical shift around ~8.05 ppm which moves to the lower field because of electron-withdrawing of sulfonic groups.[20] Meanwhile, the C-4 hydrogen is a singlet or doublet with a chemical shift around ~8.28 ppm for the weak coupling with C-6 hydrogen. The chemical shifts of N=CH appear with a singlet in lower filed, around ~8.50 (schiff base).



Scheme 3. Schiff bases were synthesised via **4** condensation with arylaldehydes.



Scheme 4. Sulfonyl hydrazone were synthesised via **5** condensation with arylaldehydes.

Table 1
Structure, yield and melting point of derivatives **3a–3k**, **4**, **6a–6c**, **7a–7d**

Compounds	R^1 or R^2 or R^3	Yield (%)	Mp (°C)
3a	3-BrC_6H_4	25	172–174
3b	2,4-$OCH_3C_6H_3$	27	114–116
3c	Iso-C_3H_7	34	128–130
3d	1-Naphthyl	35	140–142
3e	Iso-C_4H_9	20	117–118
3f	*n*-C_3H_7	31	60–62
3g	4-$CH_3C_6H_4$	33	146–148
3h	C_2H_5	35	96–98
3i	Cyclohexyl	42	108–109
3j	$CH_2C_6H_5$	48	124–126
3k	4-ClC_6H_4	22	134–135
4	4-$NH_2C_6H_4$	29	88–90
6a	C_6H_5	80	147–148
6b	2-OHC_6H_4	83	88–90
6c	2-Thienyl	77	56–58
7a	4-$OCH_3C_6H_4$	89	174–176
7b	4-$CF_3C_6H_4$	85	134–136
7c	2-OHC_6H_4	87	148–150
7d	2-Thienyl	82	113–114

Table 2
Antigastric ulcer activity of the test compounds (**3a**–**3i**)

Compounds	Dose (mg/kg)	Mice	Ulcer index($\bar{X}$ ± SD)	Inhibitory ratio (%)
Base control	—	8	13.00 ± 1.77	—
Omeprazole	13.4	8	6.86 ± 3.77*	47.23
GAS-Na	3.0	8	7.14 ± 4.73*	45.08
3a	4.3	8	6.33 ± 4.50*	51.31
3b	4.1	8	6.14 ± 2.85*	52.77
3c	3.2	8	10.57 ± 5.35	18.69
3d	4.0	8	6.43 ± 2.99*	50.54
3e	3.3	8	8.60 ± 4.72	33.85
3f	3.2	8	8.71 ± 2.81	33.00
3g	3.7	8	10.00 ± 5.55	23.07
3h	3.1	8	9.86 ± 6.28	24.15
3i	3.6	8	6.38 ± 3.85*	50.92

* P <0.05 compared with the base control group.

Table 3
Antigastric ulcer activity of the test compounds (**3j**–**3k**, **4**, **6a**–**6c**, **7a**–**7d**)

Compounds	Dose (mg/kg)	Mice	Ulcer index($\bar{X}$ ± SD)	Inhibitory ratio (%)
Base control	—	8	20.33 ± 12.23	—
Omeprazole	13.4	8	12.86 ± 11.89*	36.74
GAS-Na	3.0	8	13.71 ± 10.75*	32.56
3j	3.7	8	19.83 ± 6.49	2.46
3k	3.9	8	15.29 ± 5.77	24.79
4	3.7	8	11.14 ± 6.41*	45.20
6a	4.6	8	16.86 ± 10.48	17.07
6b	4.7	8	14.50 ± 10.34	28.68
6c	4.6	8	10.13 ± 9.48*	50.17
7a	4.1	8	19.50 ± 8.61	4.08
7b	4.5	8	15.29 ± 12.88	24.79
7c	4.0	8	17.86 ± 6.87	12.15
7d	3.9	8	14.09 ± 9.87*	30.69

* P <0.05 compared with the base control group.

The antigastric ulcer activity of compounds were tested through an ethanol-induced gastric ulcer mouse model method. Kunming mice, consisting of both males and females, each weighing 18–22 g, were divided into groups of 8 at random. The tested compounds, omeprazole and sodium guaiazulene sulfonate which were made into suspensions using 5% CMC-Na were administered orally (0.4 mL/20 g) to the dose group, the drug reference group and the GAS-Na group, respectively. While the base control group was treated with only 5% CMC-Na. Vehicle or test compounds were administered by the oral route once a day for five consecutive days. After 0.5 h of the last dose, the mice were given orally 0.5 mL of anhydrous ethanol. Half an hour after anhydrous ethanol administration, the animals were sacrificed. The stomachs were removed and scored by an investigator in terms of each degree category.

The results of these screenings are summarized in Table 2 and Table 3. The structure–activity relationship (SAR), as revealed by the antigastric ulcer activity from animal experiments associated with the test compounds, may be analyzed as follows.

(1) The pharmacological test shows that compounds **3a, 3b, 3d, 3i, 4, 6c** and **7d** display promising antigastric ulcer activities superior to sodium guaiazulene sulfonate.

(2) Comparison of **3a, 3b** and **3c, 3e, 3f, 3h** in Table 2 show that arylamino substituted compounds are more effective than alkylamino substituted compounds.

Other aromatic rings were also investigated, for example, the 1-naphthyl amine derivative (**3d**) shows quite potent antigastric ulcer activity which is comparable to that of GAS-Na (see Table 2). This result indicates that the flat structure would be essential for potent antigastric ulcer activity in this area.[21] (3) Alternatively, we also prepared the m- and p-halogen substituted phenylamine derivatives (**3a** and **3k**, respectively), only the m-Br derivative **3a** is shown to have potent antigastric ulcer activity. Accordingly, p-substituted derivatives (**3g** and **3k**) show less potent activity. (4) The cyclohexylamine derivative **3i** shows very much more potent activity may because of its lipophilic property. (5) **6c, 7d** in Table 3 demonstrate that 2-thienyl derivatives more potent activity than benzene ring substituted compounds.

In general, three series of 5-isopropyl-3,8-dimethylazulene-1-sulfonamide, some schiff base and sulfonyl hydrazones derivatives of guaiazulene were prepared, characterized, and evaluated for antigastric ulcer activity. Most of the assayed compounds show attractive activity against gastric ulcer. The modifications on the position C-1 of the guaiazulene (as just revealed by the introduction of sulfanilamido) brought good inhibitory activity toward gastric ulcer and, in particular, the lipophilic flat structure afford quite potent antigastric ulcer activity, such as compounds **3a, 3b**, **3d**, **3i** and **4**, so they may be considered as leading compounds for further development in this field.

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19. The chemicals, solvents for synthesis and spectral grade solvents were purchased from commercial suppliers (China) and used without further purification. Melting points (uncorrected) were recorded on a XT-4 microscope melting point apparatus. ^{1}H NMR spectra were measured with a BRUKER AV II-400 MHz spectrometer, using TMS as an internal reference. Chemical shifts are expressed as δ units (parts per million) relative to the solvent peak. Coupling constants J are valued in Hertz (Hz). Infrared (IR) spectra were obtained on a Perkin-Elmer 16PC-FT infrared spectrometer, using KBr pellets. HRMS spectra were determined on Bruker Daltonics ESI-Bio TOF-Q mass spectroscopy.
General procedure for the preparation of 5-isopropyl-3,8-dimethylazulene-1-sulfonamide **3a**–**3k**, **4**. To a solution of sodium guaiazulene sulfonate (0.3 g, 1 mmol) in CH_2Cl_2 (10 mL) under ice bath were added 3–5 drops of DMF, Py (0.5 mL) and followed by oxalyl chloride (0.32 g, 2.5 mmol) in CH_2Cl_2 (5 mL), and the resulting solution was stirred for 10 min. Then the corresponding amine (1.5 mmol) and the mixture of Et_3N (2 mL) in Py (1 mL) were added slowly. After the mixture was stirred at room temperature for 1 h, water (15 mL) was added. The resulting mixture was acidified to pH = 5–6 by the addition of diluent HCl, extracted with CH_2Cl_2, and dried over anhydrous Na_2SO_4, then evaporation of the solvent under reduced pressure obtained product as a solid. The crude product was purified by chromatograph on silica gel with appropriate solvent to afford **3a**–**3k**, **4**.
N-(3-Bromophenyl)-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**3a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, J = 7.2 Hz, 6H), 2.54 (s, 3H), 3.12 (q, J = 7.2 Hz, 1H), 3.38 (s, 3H), 6.99 (d, J = 8.0 Hz, 1H, PhH), 7.06 (t, J = 8.0 Hz, 1H, PhH), 7.13 (d, J = 8.0 Hz, 1H, PhH), 7.21 (s, 1H, PhH), 7.42 (d, J = 10.4 Hz, 1H), 7.61 (d,

J = 11.2 Hz, 1H), 8.06 (s, 1H), 8.28 (d, *J* = 2.0 Hz, 1H). *N*-(2,4-Dimethoxyphenyl)-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**3b**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, *J* = 6.8 Hz, 6H), 2.50 (s, 3H), 3.10 (q, *J* = 6.4 Hz, 1H), 3.42 (s, 3H), 3.72 (s, 6H, 2 × OCH_3), 6.31–6.37 (m, 2H, PhH), 7.00 (s, 1H, PhH), 7.37 (d, *J* = 10.8 Hz, 1H), 7.56 (d, *J* = 11.2 Hz, 1H), 8.02 (s, 1H), 8.22 (d, *J* = 2.0 Hz, 1H). *N*,5-Diisopropyl-3,8-dimethylazulene-1-sulfonamide (**3c**). ^{1}H NMR(400 MHz, $CDCl_3$) δ 1.15 (d, *J* = 7 Hz, 6H, 2 × CH_3), 1.38 (d, *J* = 7.2 Hz, 6H), 2.58 (s, 3H), 3.12 (q, *J* = 6.8 Hz, 1H), 3.37 (s, 3H), 3.53 (m, 1H, CH), 4.28 (br, 1H, NH), 7.37 (d, *J* = 11.2 Hz, 1H), 7.57 (d, *J* = 11.2 Hz, 1H), 8.16 (s, 1H), 8.26 (d, *J* = 2.0 Hz, 1H). *N*-(Naphthalen-1-yl)-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**3d**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, *J* = 7.6 Hz, 6H), 2.49 (s, 3H), 3.12 (q, *J* = 7.2 Hz, 1H), 3.45 (s, 3H), 7.17–7.60 (m, 5H, PhH), 7.39 (d, *J* = 11.2 Hz, 1H), 7.58 (d, *J* = 10.8 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 8.08 (s, 1H), 8.26 (d, *J* = 2.0 Hz, 1H). *N*-Isobutyl-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**3e**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.8 Hz, 6H, 2 × CH_3), 1.38 (d, *J* = 6.8 Hz, 6H), 1.79 (m, 1H, CH), 2.58 (s, 3H), 2.89 (t, *J* = 6.4 Hz, 2H, CH_2), 3.12 (q, *J* = 7.2 Hz, 1H), 3.37 (s, 3H), 4.53 (br, 1H, NH), 7.37 (d, *J* = 10.4 Hz, 1H), 7.57 (d, *J* = 11.2 Hz, 1H), 8.07 (s, 1H), 8.27 (s, 1H). *N*-Propyl-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**3f**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.2 Hz, 3H, CH_3), 1.38 (d, *J* = 6.8 Hz, 6H), 1.56 (m, 2H, CH_2), 2.57 (s, 3H), 3.06 (m, 2H, CH_2), 3.12 (q, *J* = 7.2 Hz, 1H), 3.36 (s, 3H), 4.48 (br, 1H, NH), 7.37 (d, *J* = 11.2 Hz, 1H), 7.57 (d, *J* = 11.2 Hz, 1H), 8.08 (s, 1H), 8.27 (s, 1H). *N*-(*P*-toly)-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**3g**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, *J* = 6.8 Hz, 6H), 2.23 (s, 3H, $PhCH_3$), 2.51 (s, 3H), 3.12 (q, *J* = 7.2 Hz, 1H), 3.41 (s, 3H), 6.94 (d, *J* = 8.4 Hz, 2H, PhH), 7.00 (d, *J* = 8.4 Hz, 2H, PhH), 7.38 (d, *J* = 11.2 Hz, 1H), 7.57 (d, *J* = 11.2 Hz, 1H), 8.06 (s, 1H), 8.25 (d, *J* = 2.0 Hz, 1H). *N*-Ethyl-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**3h**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.2 Hz, 3H, CH_3), 1.37 (d, *J* = 6.8 Hz, 6H), 2.58 (s, 3H), 3.09 (m, 2H, CH_2), 3.16 (q, *J* = 7.2 Hz, 1H), 3.37 (s, 3H), 4.42 (br, 1H, NH), 7.37 (d, *J* = 10.8 Hz, 1H), 7.58 (d, *J* = 11.2 Hz, 1H), 8.09 (s, 1H), 8.27 (d, *J* = 2.0 Hz, 1H). *N*-Cyclohexyl-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**3i**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, *J* = 7.2 Hz, 6H), 1.91–1.50 (m, 10H), 2.58 (s, 3H), 3.12 (q, *J* = 7.2 Hz, 1H), 3.27 (m, 1H, CH), 3.37 (s, 3H), 4.37 (br, 1H, NH), 7.36 (d, *J* = 10.4 Hz, 1H), 7.57 (d, *J* = 10.4 Hz, 1H), 8.15 (s, 1H), 8.26 (d, *J* = 2.0 Hz, 1H). *N*-Benzyl-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**3j**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (d, *J* = 6.8 Hz, 6H), 2.58 (s, 3H), 3.14 (q, *J* = 7.2 Hz, 1H), 3.37 (s, 3H), 4.23 (d, *J* = 6.0 Hz, 2H, CH_2), 4.74 (br, 1H, NH), 7.22–7.24 (m, 5H, PhH), 7.38 (d, *J* = 10.8 Hz, 1H), 7.57 (d, *J* = 10.8 Hz, 1H), 8.13 (s, 1H), 8.28 (d, *J* = 2.0 Hz, 1H). *N*-(4-Chlorophenyl)-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**3k**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, *J* = 6.8 Hz, 6H), 2.51 (s, 3H), 3.13 (q, *J* = 7.2 Hz, 1H), 3.39 (s, 3H), 6.99 (d, *J* = 8 Hz, 2H, PhH), 7.15 (d, *J* = 8 Hz, 2H, PhH), 7.40 (d, *J* = 11.2 Hz, 1H), 7.61 (d, *J* = 10.8 Hz, 1H), 8.02 (s, 1H), 8.27 (d, *J* = 2.0 Hz, 1H). *N*-(4-Aminophenyl)-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**4**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (d, *J* = 6.4 Hz, 6H), 2.49 (s, 3H), 3.17 (q, *J* = 6.8 Hz, 1H), 3.30 (s, 3H), 4.84 (s, 2H, NH_2), 6.37 (d, *J* = 8.0 Hz, 2H, PhH), 6.78 (d, *J* = 8.0 Hz, 2H, PhH), 7.44 (d, *J* = 10.8 Hz, 1H), 7.73 (d, *J* = 10.4 Hz, 1H), 7.92 (s, 1H), 8.30 (s, 1H).

General Procedure for schiff base and sulfonyl hydrazone of guaiazulene: A mixture of an arylaldehyde (1 mmol) and **4** (1 mmol) or **5** (1 mmol) in anhydrous ethanol (10 mL) was stirred at room temperature for 1 h. After checking for product formation via TLC in petroleum ether-ethyl acetate (4:1), the mixture was concentrated with reduced pressure. The products were collected by neutral alumina column chromatography and silica gel column chromatography to give compounds **6a**–**6c** and compounds **7a**–**7d**, respectively.

N-[4-(Benzylideneamino)phenyl]-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**6a**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (d, *J* = 7.2 Hz, 6H), 2.52 (s, 3H), 3.16 (q, *J* = 7.2 Hz, 1H), 3.33 (s, 3H), 7.14–7.19 (m, 4H, PhH), 7.46–7.48 (m, 3H, PhH), 7.49 (d, *J* = 10.4 Hz, 1H), 7.75 (d, *J* = 11.2 Hz, 1H), 7.86 (m, 2H, PhH), 8.02 (s, 1H), 8.33 (d, *J* = 2.0 Hz, 1H), 8.54 (s, 1H,N=CH). *N*-[4-(2-Hydroxybenzylideneamino)phenyl]-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**6b**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, *J* = 6.8 Hz, 6H), 2.51 (s, 3H), 3.11 (q, *J* = 6.8 Hz, 1H), 3.43 (s, 3H), 4.12 (br, 1H, NH), 6.85–7.34 (m, 8H, PhH), 7.40 (d, *J* = 11.2 Hz, 1H), 7.60 (d, *J* = 11.2 Hz, 1H), 8.08 (s, 1H), 8.26 (d, *J* = 2.0 Hz, 1H), 8.51 (s, 1H, N=CH). *N*-[4-(2-Thienylmethyleneamino)phenyl]-5-isopropyl-3,8-dimethylazulene-1-sulfonamide (**6c**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (d, *J* = 7.2 Hz, 6H), 2.51 (s, 3H), 3.16 (q, *J* = 7.2 Hz, 1H), 3.32 (s, 3H), 7.12–7.20 (m, 5H, ArH), 7.49 (d, *J* = 11.2 Hz, 1H), 7.59 (d, *J* = 11.2 Hz, 1H), 7.76 (d, *J* = 7.2 Hz, 2H, PhH), 8.00 (s, 1H), 8.32 (d, *J* = 2.0 Hz, 1H), 8.69 (s, 1H,N = CH). *N*′-(4-Methoxy-benzylidene)-5-isopropyl-3,8-dimethylazulene-1-sulfonohydrazide (**7a**). ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.37 (d, *J* = 7.2 Hz, 6H), 2.57 (s, 3H), 3.12 (q, *J* = 6.8 Hz, 1H), 3.40 (s, 3H), 3.80 (s, 3H, $PhOCH_3$), 6.83 (d, *J* = 8.0 Hz, 2H, PhH), 7.41 (d, *J* = 11.2 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 2H, PhH), 7.59 (d, *J* = 10.8 Hz, 1H), 7.88 (s, 1H), 8.16 (s, 1H, N=CH), 8.28 (d, *J* = 2.0 Hz, 1H). *N*′-(4-Trifluoromethylbenzylidene)-5-isopropyl-3,8-dimethylazulene-1-sulfonohydrazide (**7b**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (d, *J* = 7.2 Hz, 6H), 2.54 (s, 3H), 3.18 (q, *J* = 7.2 Hz, 1H), 3.33 (s, 3H), 7.72–7.79 (m, 4H, PhH), 7.50 (d, *J* = 11.2 Hz, 1H), 7.78 (d, *J* = 10.8 Hz, 1H), 7.95 (s, 1H), 8.12 (s, 1H, N=CH), 8.36 (s, 1H). *N*′-(2-Hydroxybenzylidene)-5-isopropyl-3,8-dimethylazulene-1-sulfonohydrazide (**7c**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (d, *J* = 6.8 Hz, 6H), 2.51 (s, 3H), 3.18 (q, *J* = 7.2 Hz, 1H), 3.29 (s, 3H), 6.79–6.84 (m, 2H, PhH), 7.20 (t, *J* = 7.6 Hz, 1H, PhH), 7.41 (d, *J* = 8.4 Hz, 1H, PhH), 7.51 (d, *J* = 11.2 Hz, 1H), 7.77(d, *J* = 10.4 Hz, 1H), 7.93 (s, 1H), 8.29 (s, 1H, N=CH), 8.36 (s, 1H), 10.25(br, 1H, OH). *N*′-(2-Thienylmethylene)-5-isopropyl-3,8-dimethylazulene-1-sulfonohydrazide (**7d**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (d, *J* = 6.4 Hz, 6H), 2.54 (s, 3H), 3.17 (q, *J* = 7.2 Hz, 1H), 3.30 (s, 3H), 7.06–7.55 (m, 3H, ArH), 7.50 (d, *J* = 11.2 Hz, 1H), 7.77 (d, *J* = 11.2 Hz, 1H), 7.90 (s, 1H), 8.22 (s, 1H, N=CH), 8.35 (s, 1H).

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