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Synthesis and Characterization of Cannabimimetic Aminoalkylindole Based 5-(4-Alkyl-1-naphthoylamino)-1,3,4-Thiadiazole-2-Sulfonamides

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ABSTRACT: *A novel series of cannabimimetic aminoalkylindole-based sulfonamide derivatives was synthesized. These new compounds were synthesized by reacting acyl chlorides of naphthoic acids with deacetylated acetazolamide in the presence of N-ethyl-morpholine to give structures incorporating 1-naphthoyl groups of cannabimimetic aminoalkylindoles and a five-membered heteroring typical of antiglaucoma sulfa drugs. The synthesized compounds were characterized using standard techniques. Photoluminescence of these derivatives was also studied, where more electron-donating groups on the aromatic ring at the para-position caused an increase in the intensity of the main peaks and shifts to higher emission wavelengths.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 22:707–714, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20738

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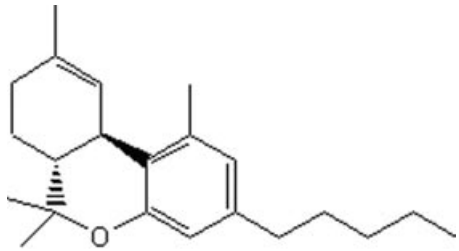
INTRODUCTION

Cannabis sativa L. has long been used for medicinal and recreational purposes. Δ^9-Tetrahydrocannabinol (Δ^9-THC, Fig. 1) is the major psychoactive component of marijuana and was first identified by Gaoni and Mechoulam in 1964 [1]. Since the characterization of THC many cannabinoids, that is, compounds related to THC, and their metabolites have been synthesized. The discovery of the cannabinoid receptors CB_1 [2], and CB_2 receptors [3–5], has advanced the understanding of the manner in which cannabinoids interact with biological systems.

Cannabinoids exhibit a wide range of biological properties, including analgesic, antiinflammatory, antiemetic, anticonvulsive, and anticancer properties. Studies into the action of cannabinoids have strongly implicated the presence of a cannabinoid receptor located mainly in the central nervous system (CNS) and several peripheral tissues, and is known as the CB_1 cannabinoid receptor [2]. This receptor is the major target for psychoactivity; however, the newly discovered ocular CB_1 cannabinoid receptor prompted research and development of novel



Δ^9-THC

FIGURE 1 Structure of Δ^9-THC.

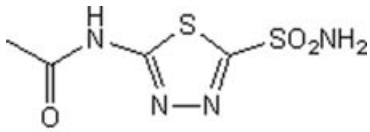


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FIGURE 2 Structure of acetazolamide (**1**).

ophthalmic cannabinoid drugs to act specifically via the cannabinoid receptors of the eye [6–8]. The second cannabinoid receptor, the CB_2 receptor, discovered in 1993, is found to be associated with the immune system, and is primarily located in the spleen, tonsils, and immune cells [3–5].

Cannabinoid research extends out into modifying the structure of cannabinoids, as well as in developing compounds structurally diverse from the classical dibenzopyran structure. Recently, there has been a burst of interest in the development of ophthalmic cannabinoid research with the discovery of the ocular cannabinoid receptor in particular for the treatment and management of glaucoma. Glaucoma is an ophthalmic disorder characterized by an increase in intraocular pressure (IOP), resulting in damage to the optic disk. It causes visual disturbances and is one of the leading causes of irreversible blindness. Although the use of sulfonamides as antiglaucoma agents has already been initiated [9–11], Kaur and coworkers have presented a review of acetazolamides, members of the sulfonamide drug types, as topical glaucoma therapeutics and offer promising areas for future investigation [12]. Kaur in earlier studies investigated various ophthalmic preparations of acetazolamide [13]; the structure of acetazolamide (**1**) is shown in Fig. 2. Recently, several workers studied acetazolamide and its analogues as chitinase inhibitors and presented an interesting report on their SAR [14]. Other workers developed numerous aroyl acetazolamide and sufonamide derivatives as carbonic anhydrase inhibitors, where such were applied as potential gastric drugs [15], tumor suppressants [16–18], and for the treatment of glaucoma [19]. Ohta and coworkers studied sulfonamide derivatives as new CB_2 cannabinoid agonists [20], and later imine derivatives based on five-membered heterocycles as cannabinoids with analgesic action [21].

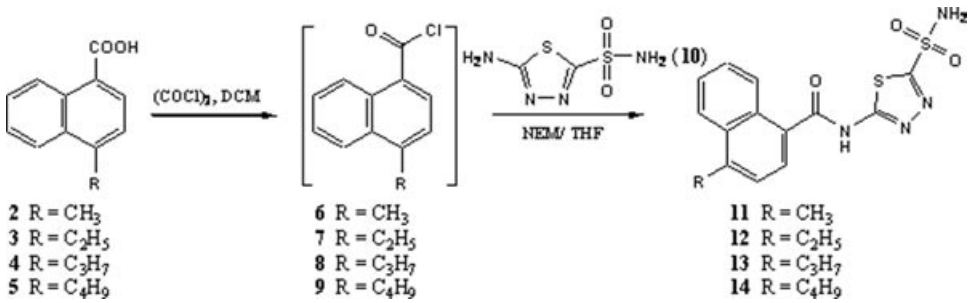
The Winthrop group detailed the structural requirements of cannabimimetic aminoalkylindoles (AAIs) as structure–activity relationships (SAR) [22]. They revealed that a 1-naphthoyl substituent provided potent CB_1 cannabinoid activity. Now, as a result of work on cannabimimetic indoles lacking carbonyl groups, the naphthyl group with its lipophilic and bulky character has been shown to interact with the CB_1 receptor primarily by aromatic stacking [23,24]. Furthermore, a 1-naphthyl group of sulfonamide cannabinoids showed an increased affinity for the CB_2 receptor [20]. In addition, the heteroring indole of AAIs has been replaced by the optimal five-membered thiadiazole ring for potent CB_2 affinity [21]. Also, receptor docking and mutation studies identified a pharmacophore crucial for receptor-ligand interaction by hydrogen bonding between the carbonyl group of the cannabinoid ligand and a lysine on transmembrane helix (TMH) 3 of the CB_1 receptor [25,26].

As a consequence, the naphthyl group, thiadiazole function, and carbonyl group form structural features in the design of the cannabinoids presented herein. Whereas sulfonamides are known to have antibacterial properties playing an important role in chemotherapy [27,28], these new compounds presented in this study may also have potential as antimicrobials. These new cannabimimetic AAI-based 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides were characterized and evaluated for antimicrobial properties. The results of these investigations may offer further insight into the treatment of glaucoma and reveal promising impetus for antibiotic developments.

RESULTS AND DISCUSSION

Chemistry

In previous work, some 1-alkyl-3-(1-naphthoyl) indoles were synthesized for cannabinoid activity at the cannabinoid CB_1 and CB_2 receptors, where 1-naphthoyl groups were incorporated into these structures [29]. Studies herein on the synthesis of novel cannabimimetic AAI-based 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides are presented. 4-Methyl-1-naphthoic acid (**2**) is commercially available, whereas 4-ethyl-, 4-propyl-,



SCHEME 1 Synthesis of 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides.

and 4-butyl- analogues of 4-alkyl-1-naphthoic acid (**3-5**) were synthesized following the procedure described in a previous paper [29]. Scheme 1 illustrates the synthesis of cannabimimetic AAI-based 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides. Acetazolamide (**1**) was deacetylated with concentrated hydrochloric acid to give 5-amino-1,3,4-thiadiazole-2-sulfonamide (**10**) [30]. 1-Naphthoic acids were converted to the acyl chloride by refluxing with oxalyl chloride and subsequent coupling with deacetylated acetazolamide in the presence of *N*-ethyl-morpholine (NEM) gave 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides **11–14**.

Determination of Antimicrobial Activity

The agar diffusion method using sterile filter paper disks was used for the screening of antibacterial and antifungal activities of synthesized 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides [31]. Inhibition zones formed on Mueller Hinton Agar (MHA) and Sabourand Dextrose Agar (SDA) (measured in mm) were evaluated. Experiments were performed in triplicate, and the developing inhibition zones were compared with those of the reference parent compound, 5-amino-1,3,4-thiadiazole-2-sulfonamide. The following collection of microbes was used: three Gram-positive (*Bacillus cereus* EU, *Bacillus megaterium* DSM 32, *Enterococcus faecalis* A10), one Gram-negative (*Escherichia coli* DM), and one yeast (*Saccharomyces cerevisiae*). All microorganisms were provided by the Microbiology Laboratory Culture Collection, the Department of Biology, Kahramanmaras Sutcu Imam University, Turkey.

All the bacteria mentioned above were incubated at 37 ± 0.1°C for 24 h by inoculation into Nutrient Broth (Difco), and the yeast studied were incubated at 25°C in Sabouraud Dextrose Broth (SDB) (Difco) for 24 h. MHA (Oxoid) and SDA sterilized in a flask and cooled to 40–45°C were distributed over sterilized petri dishes having a diameter of 9 cm, (15 mL) after injecting cultures (0.1 mL) of bacteria and yeast (10^5/mL for bacteria and 10^4/mL for yeast), ensuring homogeneous distribution of the food medium over the petri dishes. Sterile filter paper disks (6 mm) injected with 10 μL solutions in dichloromethane (80 μg/disk) at a concentration of 8.0 mg/mL were placed on the surface of the solid agar medium and were slightly pressed. Petri dishes prepared as described above were kept at 4°C for 2 h to enable prediffusion of the samples into the agar, and subsequently samples inoculated with bacteria were incubated at 37 ± 0.1°C for 24 h and those with yeast were incubated at 25°C for 24 h. The inhibition zones formed on the medium were measured and recorded in mm. These studies were performed in triplicate. Streptomycin was used as the standard antibiotic for the evaluation of antimicrobial activity.

Antimicrobial Studies

The test solutions were prepared in dichloromethane. The inhibition zones on the medium were measured and recorded in mm. The results of the antimicrobial activities are summarized in Table 1.

The synthesized compounds were found to have interesting antimicrobial activity inhibition zones ranging in size from 12 to 32 mm. The antimicrobial activity observed for all synthesized compounds and the standard streptomycin were in general greater than the reference compound 5-amino-1,3,4-thiadiazole-2-sulfonamide (**10**). Synthesized compounds exhibited in general higher activity against the Gram-positive bacteria than the Gram-negative bacteria. Derivatives **13** and **14** both showed much greater activity than the reference compound **10** and the standard streptomycin. The reference precursor compound**10** revealed minimal antimicrobial activity against all bacteria. Streptomycin had greater

TABLE 1 Antimicrobial Activity Data and Selected Physicochemical Properties for 5-Amino-1,3,4-Thiadiazole-2-Sulfonamide and 5-(4-Alkyl-1-naphthoylamino)-1,3,4-Thiadiazole-2-Sulfonamides

	Microorganism[c]				*Physicochemical Properties*			
Entity[a,b]	*B. cereus*	*B. megaterium*	*E. fecalis*	*E. coli*	*MW*	*MV (Å^3)*	*MR (Å^3)*	*logP*
Streptomycin[d]	14	17	15	9	NA	NA	NA	NA
10	10	10	8	12	222.24	571.79	47.78	0.44
11	–	–	–	–	348.39	880.20	94.57	1.82
12	12	14	–	–	362.42	890.36	99.18	2.22
13	30	20	16	14	376.45	989.30	103.78	2.62
14	32	24	28	20	390.47	996.75	108.38	3.01

[a]Entity refers to compounds.
[b]Concentration: 80 μg/ per disk.
[c]Microorganism inhibition zone, mm; – denotes no activity; *S. cereviciae* (not shown here) was also used; however, all entities showed no antifungal activity against *S. Cerevisiae*.
[d]Standard compound.

activity than derivatives **11** and **12**. Only derivative **11** showed no activity against all bacteria whereas derivative **12** only showed activity against *Bacillus cereus* and *Bacillus megaterium*. In addition, no activity was observed against the yeast (*Saccharomyces cerevisiae*).

A comparison of the antibacterial activity of the 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides **11–14** revealed that the longer the chain length of the 4-alkyl group, the greater the activity; thus, activity decreased with decreasing chain length. As the chain length decreases, activity is lost, primarily for *Enterococcus faecalis* and *Escherichia coli* bacteria and lost completely for the smallest molecule having a 4-methyl group. The chain length plays a significant role in the antimicrobial activities of these 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides.

Structure–Activity Relationships

Lipophilicity of compounds has an important effect on their biological activity [32,33]. It is expressed as logP, the octanol/water partition coefficient, and high values indicate good permeation of compounds through lipid layers of cell membranes. The prediction of lipophilicity and other physicochemical properties such as molecular weight (MW), molecular volume (MV), and molecular refractivity (MR) for **11–14** and the parent compound **10** was calculated using HyperChem software in an attempt to correlate physicochemical properties of the compounds with their antimicrobial activity [34]. The physicochemical properties MW, MV, MR, and logP of the compounds are presented in Table 1.

Lipophilicity increased from 5-(4-methyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamide to 5-(4-butyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamide. The antimicrobial activity for these synthesized compounds showed a similar trend, where antimicrobial activity was the lowest for 5-(4-methyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamide and the highest for 5-(4-butyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamide. The results showed there was a dependency between biological activity and lipophilicity, where antimicrobial activity increased with increasing lipophilicity. In addition, antimicrobial activity increased with increasing MV, indicating that both the 4-alkyl group and naphthoyl group appear to play a dominating role on antimicrobial activity. MR, as with lipophilicity, is also a molecular descriptor used to relate chemical structure to observe behavior. It can be seen from Table 1 that MR increased with increasing lipophilicity, and, thus, antimicrobial activity increased with increasing MR.

The increasing chain length of the 4-alkyl group of the synthesized compounds together with the naphthoyl groups make these compounds highly lipophilic, and therefore can greatly influence their antimicrobial activity. In addition, all the synthesized compounds possess carbonyl groups; thus, possible hydrogen bonding with the active cell components may be influential for the antimicrobial activity, resulting in the interference and disruption of normal cell processes.

Fluorescence Measurements

Absorption and photoluminescence spectra were studied for 5-amino-1,3,4-thiadiazole-2-sulfonamide (**10**) and 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamide (**11–14**) solutions,

excited at 261 nm. The most striking feature was that these compounds gave an intense emission upon irradiation by UV light. The photoluminescence spectra of these compounds in $CHCl_3$ are shown in Fig. 3. Maximum luminescent intensity was observed at 378 nm and the full width at half maximum was 102 nm for compound **10**. Compound **10** exhibited a photoluminescence quantum yield of 30% and a long excited-state lifetime of 2.84 ns. The photoluminescence intensity of peaks and the quantum yields of the synthesized compounds 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides (**11–14**) increased compared to that of compound **10** due to the formation of larger cyclic molecular structures. Also, the addition of more electron-donating groups via the 4-alkyl group onto ring at para-position of derivatives caused an increase in intensity of main peaks and shifted to the higher emission wavelengths. High quantum yield is due to the extensive π-electron delocalization in the large molecular structure. Thus, it is evident that the fluorescence emission intensity of the compound increases with more π bonds in larger compounds or with the formation of an electron-rich cyclic molecule. This electron-rich cyclic molecule increases electron delocalization and/or energy transfer from the excited state of the 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides, thus increasing the nonradiated transition of the 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides excited state, and increasing the fluorescence emission.

The photoluminescence data for 5-amino-1,3,4-thiadiazole-2-sulfonamide (**10**) and 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides **11–14** are summarized in Table 2. The photoluminescent properties of these compounds may indicate great potential for numerous optical applications and for medicinal biomarkers.

To conclude, a series of 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides was obtained where these structures combined the 1-naphthoyl groups of AAI with a five-membered thiadiazole moiety typical of heterocyclic sulfonamide antiglaucoma agents. These new derivatives prepared were tested for antimicrobial activity. It was noted that the chain length and the naphthoyl group of these 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides appears to play a dominating role on their antimicrobial activity. Furthermore, these compounds possess carbonyl functional groups, allowing for possible hydrogen bonding with the active cell components, being influential for antimicrobial activity, and resulting in the interference and disruption of normal cell processes. The fluorescence emission intensity of the synthesized compounds increased with the increasing π bonds as for larger compounds or with the formation of an electron-rich cyclic molecule.

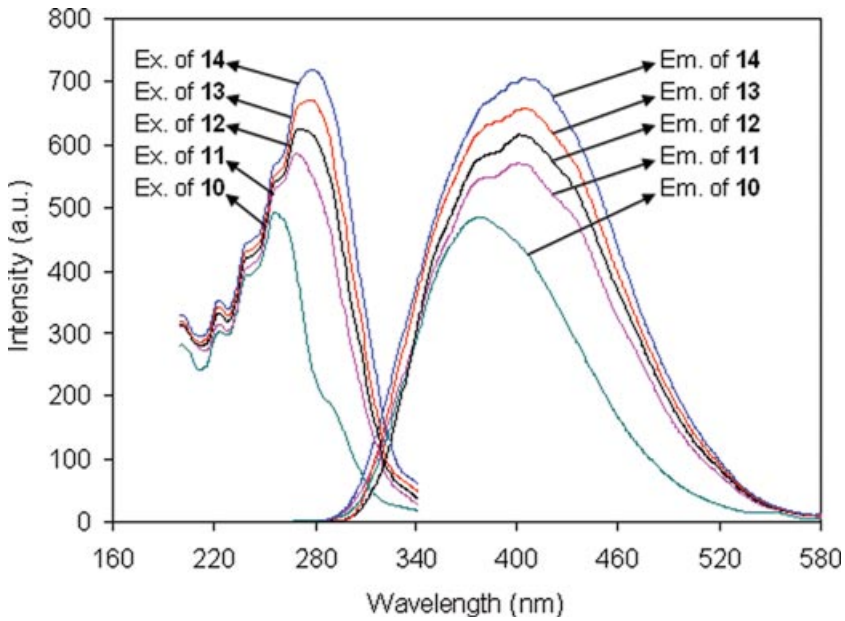


FIGURE 3 Photoluminescence spectra of 5-amino-1,3,4-thiadiazole-2-sulfonamide (**10**) and 5-(4-alkyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamides **11-14** in $CHCl_3$; samples were excited at 261 nm.

TABLE 2 Photoluminescence Data for 5-(4-Alkyl-1-naphthoylamino)-1,3,4-Thiadiazole-2-Sulfonamides

Entity	$\lambda_{max} E_x$ *(nm)*	*In* E_x	$\lambda_{max} E_m$ *(nm)*	*In* E_m	ϕ_f *(%)*	τ_f *(ns)*
10	258 (221; 235; 291)	489	378 (352; 405)	484	30	2.84
11	271 (220; 236; 254)	578	403 (353; 381; 436)	572	35	3.26
12	275 (220; 236; 255)	621	406 (354; 381; 435)	614	37	3.45
13	279 (222; 237; 255)	664	408 (354; 385; 436)	656	39	3.64
14	281 (225; 241; 259)	713	411 (354; 384; 442)	704	41	3.84

λ_{max} E_x: maximum excitation wavelength; In E_x: maximum excitation intensity.
λ_{max} E_m: maximum emission wavelength; In E_m: maximum emission intensity.
ϕ_f: quantum yield; τ_f: excited-state lifetime.

EXPERIMENTAL

General

Commercially available and/or reagent grade solvents and reagents purchased from Sigma-Aldrich, Germany, or Merck, Germany were used without purification unless otherwise stated. Column chromatography was carried out using silica gel (Merck, Kiesegel 60, 230-240 mesh). Analytical thin-layer chromatography (tlc) was performed using aluminum-coated Merck, Kieselgel 60 F254 plates.

All reactions were carried out under an atmosphere of nitrogen gas. Reaction temperatures were measured either externally, or by a thermometer inserted into the reaction mixture. Melting points were recorded using an Electrothermal 9200 apparatus and were determined using sealed capillaries and are reported uncorrected. NMR spectra were recorded on a Varian Mercury Plus 300 MHz, using $CDCl_3$ as the solvent. The NMR chemical shifts are presented in parts per million (ppm), relative to the tetramethylsilane (TMS) ($\delta = 0$), the internal standard.

The products obtained were investigated by GC–MS (Agilent Technologies 6890N Network GC System coupled with Agilent Technologies 5975C VL MSD MS). Elemental analyses for carbon, hydrogen, and nitrogen sulfur were performed using a Thermo Scientific FLASH 2000 CHNS Organic Elemental Analyzer.

FT-IR spectra were obtained using a PerkinElmer Spectrum 100 FT-IR Spectrometer equipped with a Universal ATR Sampling Accessory. The UV–vis spectra were recorded from from 190 to 1100 nm on a PG Instruments Ltd T80 + UV–vis Spectrometer. The single-photon fluorescence spectra were collected on a PerkinElmer LS55 luminescence spectrometer. All the samples were prepared in spectrophotometric grade $CHCl_3$ and analyzed in a 1 cm optical path quartz cuvette. The solution concentration of the compounds in $CHCl_3$ was 1.0×10^{-5} mol L^{-1} and the samples were excited at 261 nm wavelength. The photoluminescence quantum efficiencies of the 4-alkyl-1-naphthoylacetazolamide derivatives were calculated using 9,10-diphenylanthracene as the standard [35].

5-(4-Methyl-1-naphthoylamino)-1,3,4-Thiadiazole-2-Sulfonamide (**11**). 5-(4-Methyl-1-naphthoylamino)-1,3,4-thiadiazole-2-sulfonamide (**11**) was prepared using the following typical procedure: To a solution of 0.20 g (1.07 mmol) of 4-methyl-1-naphthoic acid (**2**) in 5.0 mL of dichloromethane at 0°C, 0.45 mL (5.37 mmol) of oxalyl chloride was added dropwise over 5 min. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was then heated at reflux for 1 h. After cooling to room temperature, the solvent and excess oxalyl chloride were removed by evaporation *in vacuo* to leave a residue. The residue was dissolved in 6.0 mL of THF. The resulting mixture was placed in an ice bath and after chilling for several minutes a preprepared mixture of 0.21 g (1.18 mmol) of 5-amino-1,3,4-thiadiazole-2-sulfonamide (**9**) and 0.20 mL of NEM (1.61 mmol) in 6.0 mL of THF was added dropwise. The resulting reaction mixture was allowed to stir overnight at 0°C. After warming to room temperature, the white precipitate of NEM.HCl salt was filtered out. THF was removed by evaporation *in vacuo* to leave a residue. The residue was dissolved in ethyl acetate. The organic extract was washed with 3 M hydrochloric acid and then saturated sodium bicarbonate solution and finally with brine. The extract was dried ($MgSO_4$) and concentrated by evaporation *in vacuo* to give a residue. The crude product was purified by column chromatography (hexane/diethyl ether 9/1 v/v) to afford the product as a yellow solid, yield: 70%; mp 41–42°C; UV–vis (CH_2Cl_2) λ_{max}: 207, 219, 240, 314 nm; IR (KBr): 3390, 3262, 2968, 2934, 1703, 1682, 1163, 1067, 849, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.80 (s, 3H), 5.00 (s, 1H), 6.98 (s, 2H), 7.40 (d, $J = 7.3$ Hz, 1H), 7.53–7.61 (m, 2H), 8.20 (d, $J = 8.3$ Hz, 1H), 8.38 (d, $J = 8.2$ Hz, 1H), 9.20 (d,

$J = 8.1$ Hz, 1H); Anal. Calcd. for $C_{14}H_{12}N_4O_3S_2$: C, 48.26; H, 3.47; N, 16.08; S, 18.41. Found: C, 48.38; H, 3.51; N, 16.40; S, 18.55.

5-(4-Ethyl-1-naphthoylamino)-1,3,4-Thiadiazole-2-Sulfonamide (**12**). 4-Ethyl-1-naphthoic acid (**3**) was used as the starting compound and the reaction was carried out as described above. Yellow solid, yield: 65%; mp 46-47°C; UV–vis (CH_2Cl_2) λ_{max}: 207, 219, 242, 316 nm; IR (KBr): 3360, 3200, 2958, 2924, 1723, 1683, 1122, 1067, 849, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.35–1.42, (t, $J = 7.3$, 3H), 3.20 (q, $J = 7.4$ Hz, 2H), 5.00 (s, 1H), 7.00 (s, 2H), 7.41 (d, $J = 7.2$ Hz, 1H), 7.60–7.71 (m, 2H), 8.25 (d, $J = 8.2$ Hz, 1H), 8.39 (d, $J = 8.1$ Hz, 1H), 9.22 (d, $J = 8.1$ Hz, 1H); Anal. Calcd. for $C_{15}H_{14}N_4O_3S_2$: C, 49.71; H, 3.89; N, 15.46; S, 17.70. Found: C, 48.84; H, 3.92; N, 15.60; S, 17.81.

5-(4-Propyl-1-naphthoylamino)-1,3,4-Thiadiazole-2-Sulfonamide (**13**). 4-Propyl-1-naphthoic acid (**4**) was used as the starting compound and the reaction was carried out as described above. Yellow solid, yield: 65%; mp 80–81°C; UV–vis (CH_2Cl_2) λ_{max}: 209, 219, 246, 320 nm; IR (KBr): 3360 (NH_2), 3200, 2958, 2928, 1729, 1670, 1137, 1041, 849, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, $J = 7.2$ Hz, 3H), 1.35–1.42 (m, 2H), 3.15 (t, $J = 7.4$ Hz, 2H), 5.02 (s, 1H), 7.00 (s, 2H), 7.40 (d, $J = 7.1$ Hz, 1H), 7.52–7.64 (m, 2H), 8.15 (d, $J = 8.1$ Hz, 1H), 8.30 (d, $J = 8.2$ Hz, 1H), 9.10 (d, $J = 8.2$ Hz, 1H); Anal. Calcd. for $C_{16}H_{16}N_4O_3S_2$: C, 51.05; H, 4.28; N, 14.88; S, 17.04. Found: C, 51.15; H, 4.32; N, 14.95; S, 17.15.

5-(4-Butyl-1-naphthoylamino)-1,3,4-Thiadiazole-2-Sulfonamide (**14**). 4-Butyl-1-naphthoic acid (**5**) was used as the starting compound and the reaction was carried out as described above. Yellow solid, yield: 67%; mp 84-86 °C; UV–vis (CH_2Cl_2) λ_{max}: 207, 220, 246, 322 nm; IR (KBr): 3360, 3200, 2956, 2927, 1723, 1672, 1120, 1071, 848, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, $J = 7.3$ Hz, 3H), 1.22–1.32 (m, 2H), 1.40–1.50 (m, 2H), 3.22 (t, $J = 7.4$ Hz, 2H), 5.00 (s, 1H), 7.00 (s, 2H), 7.40 (d, $J = 7.2$ Hz, 1H), 7.56-7.65 (m, 2H), 8.13 (d, $J = 8.2$ Hz, 1H), 8.32 (d, $J = 8.2$ Hz, 1H), 9.15 (d, $J = 8.3$ Hz, 1H); Anal. Calcd. for $C_{17}H_{18}N_4O_3S_2$: C, 52.29; H, 4.65; N, 14.35; S, 16.42. Found: C, 52.44; H, 4.76; N, 14.38; S, 16.53.

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