Pergamon

Bioorganic & Medicinal Chemistry 10 (2002) 2893–2898

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis of New 2,5-Disubstituted-1,3,4-thiadiazoles and Preliminary Evaluation of Anticonvulsant and Antimicrobial Activities

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Received 8 March 2002; accepted 3 May 2002

Abstract—Two new series of 2,5-disubstituted-1,3,4-thiadiazoles were synthesized for their possible anticonvulsant, antibacterial and antifungal activities. The degree of protection afforded by these compounds at a dose of 100 mg/kg ip against pentylenetetrazole-induced convulsions in mice ranged from 0 to 90%. Among these compounds, **2a** (90%) and **2g** (70%) showed maximum protection. Antimicrobial tests showed that the MIC value of **3j** against *Pseudomanas aeruginosa* was equal to that of penicillin.

Introduction

Many compounds bearing five-membered heterocyclic ring in their structure have an extensive spectra of pharmacological activities. Therefore, new derivatives of triazoles, oxadiazoles and thiadiazoles have been synthesized in our laboratory for a long time and their potential anticonvulsant and antimicrobial activities have been investigated. Previous studies from this laboratory have revealed the anticonvulsant activity of 1,3,4-oxadiazolines.[1] After intraperitoneal injection in mice, one of these compounds showed maximum protection (60%) against pentylenetetrazole-induced convulsions. We intended to change the oxygen atom of 1,3,4-oxadiazoline ring with a more lipophilic sulphur atom with the aim to potentiate the anticonvulsant activity.[2]

The increasing clinical importance of drug-resistant bacterial pathogens has lent additional urgency to microbiological and antibacterial research. Derivatives of 1,3,4-thiadiazoles are known to exhibit antibacterial[3–7] and antifungal[5,7–11] activities. In a previous paper,[7] we showed antibacterial and antifungal activities of 1,4-dihydro-3-(3-hydroxy/acetyloxy-2-naphthyl)-4-substituted-5*H*-1,2,4-triazoline-5-thiones and 5-(3-hydroxy-2-naphthyl)-2-substituted amino-1,3,4-thiadiazoles which were synthesized by us. We observed that, the acetylated triazoles were more potent against *Staphylococcus aureus* than nonacetylated ones and similarly we intended to acetylate 1,3,4-thiadiazoles synthesized in this study, in the hope of increasing their antibacterial activity against *S. aureus*.

As a result of these ideas, eighteen new compounds, which contain 1,3,4-thiadiazole moiety were synthesized and their anticonvulsant, antibacterial and antifungal activities were tested. Thus the degree of protection was increased up to 90%. But unfortunately the MIC values of most of the compounds against tested microorganisms[12] were 500 μg/mL or higher, except **2e** (62.5 μg/mL), which was marginally active against *S. aureus*. These results were compared with those of penicillin and ketoconazole as references. The MIC value of **3j** (500 μg/mL) against *Pseudomanas aeruginosa* was equivalent to penicillin.

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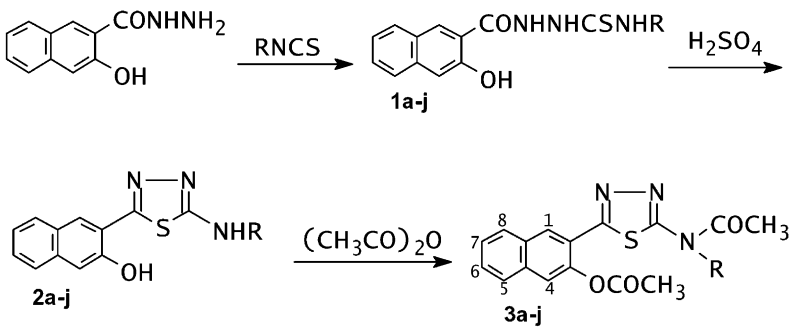
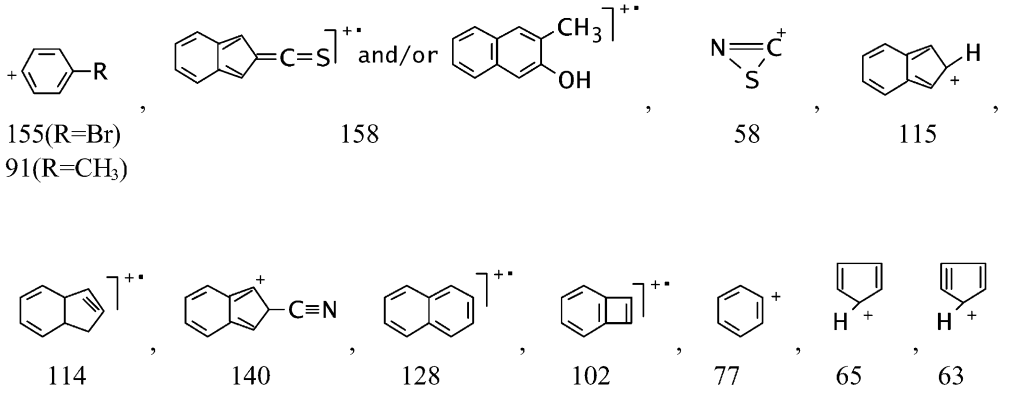
0968-0896/02/$ - see front matter
PII: S0968-0896(02)00143-8



Scheme 1. Synthesis of the compounds: *R*: ethyl (**a**), phenethyl (**b**), phenyl (**c**), *p*-bromophenyl (**d**), *p*-chlorophenyl (**e**), *p*-fluorophenyl (**f**), *m*-fluorophenyl (**g**), *p*-methoxyphenyl (**h**), *p*-methylphenyl (**i**), *m*-trifluoromethylphenyl (**j**).



Scheme 2. Significant mass fragmentations and *m*/*z* values of **3c** and **3f**.

Results and Discussion

Chemistry

The compounds were synthesized according to the sequence shown in Scheme 1. First, 1,3,4-thiadiazoles **2a**–**j** were formed by the dehydrative cyclization in acidic medium of the thiosemicarbazides **1a**–**j**,[13] which were obtained by the condensation of 3-hydroxy-2-naphthoic acid hydrazide with alkyl/aryl isothiocyanates. Then, these cyclization products **2a**–**j** were acetylated with acetic anhydride to obtain acetylated thiadiazole derivatives **3a**–**j**. The purities of the synthesized compounds were checked using thin layer chromatography in three mobile phase systems.[14] Each of the synthesized compounds gave isolated spot at different distance from its starting compound.

According to the UV spectroscopic data, π–π* transitions of the thiadiazole structures were observed at 239.8–252.0 nm for **2a**–**j** and this band shifted bathochromically to 271.6–274.2 nm due to the additional two carbonyl chromophore for **3a**–**j**. E_1 band of naphthalene ring together with benzene ring was observed 210.0–222.8 and 215.4–220.4 nm for **2** and **3** series, respectively. Strong bands which observed at 327.6–352.6 nm for **2** series and 309.6–311.4 nm for **3** series, characterized to B band of naphthalene. This band had much more absorption intensity than expected band for unsubstituted naphthalene. Because of the additional auxochrome and chromophore groups, these compounds showed bathochromic shift and hyperchromic effect.

In the IR spectra, broad absorption bands in the O–H and N–H stretching regions (3444–3181 cm^{-1}) characterized hydrogen bonding for **2a**–**j**. As expected, as a consequence of the acetylation, these bands were not observed for **3a**–**j** and only C–H stretching bands were observed in this region. The absorption bands of C=O stretching characteristic of an ester and an amide were observed in the range of 1772–1757 and 1694–1668 cm^{-1}, respectively. β-Substituted naphthalene moiety showed two absorption bands (917–864 and 774–737 cm^{-1}) due to out-of-plane C–H bending, these correspond to two isolated hydrogen atom (C_1H and C_4H) and four adjacent hydrogen atoms on the other ring.[15] The other bands of the compounds were as expected.[16]

The ^1H NMR spectra of **2a**–**j** displayed the OH and NH resonance at 10.94–11.39 and 8.36–10.76 ppm, respectively. In the acetylated thiadiazoles **3a**–**j**, the signal of these protons were not observed because of removal of these protons by acetylation and the methyl protons of the acetyl groups (*O*-acetyl and *N*-acetyl) showed two singlets at 2.40–1.96 and 2.53–2.33 ppm, respectively. The other protons of the compounds were as expected.

The mass spectrum of **3d** and **3i** did not reveal the molecular ion peak. The important common fragments were shown in Scheme 2.

Table 1. The effect of compounds on seizure latency and protection against pentylenetetrazole-induced generalized convulsions

Groups	Seizure latency (min)	Protection (%)	Groups	Seizure latency (min)	Protection (%)
Control	2.00±0.14				
S. valproate	7.20±1.30***	80			
2a	5.92±1.01***	90	**3a**	7.65±0.64***	60
2b	3.87±0.28***	20	**3b**	5.20±0.62***	30
2c	5.43±0.47***	40	**3c**	5.25±0.57***	60
2d	3.28±0.36**	50	**3d**	4.70±0.48***	00
2e	6.27±0.52***	60	**3e**	5.55±0.73***	30
2f	6.20±1.06***	20	**3f**	3.57±0.20***	50
2g	4.41±0.59***	70	**3g**	2.85±0.33*	20
2h	4.42±0.59***	60	**3h**	3.93±0.33***	50
2i	3.90±0.37***	60	**3i**	3.00±0.28**	50
2j	5.10±0.50***	40			

*$p<0.05$; **$p<0.01$; ***$p\leq0.001$ ($n=10$).

Pharmacology

Balb/C mice of either sex weighing 20–25 g were housed in groups of 10 and acclimatized to their environment for at least two days before the experiments. The animals were allowed free access to tap water before being tested and to standard commercial mice pellets.

The anticonvulsant activities of the compounds were determined against pentylenetetrazole-induced seizures. The test compounds were suspended in a 5% aqueous suspension of gum acacia as a vehicle and were administered at a dose of 100 mg/kg intraperitoneally.[1,17] Control animals were injected with vehicle only. Four h after the administration of either vehicle or test compounds, mice were injected with pentylenetetrazole 55 mg/kg intraperitoneally. This dose was determined on the basis of a pilot experiments in which it produced tonic-clonic convulsions without being fatal.

Seizure latency was defined as the time elapsed from the injection of pentylenetetrazole to the first two myoclonic jerks of the forelimbs. This has been concluded to be the first sign of the beginning of the seizure activity.[18] Animals devoid of generalized convulsions were considered to be protected and results were represented as protection (%). These results were compared with that of sodium valproate (150 mg/kg, ip) as a standard pharmacological drug for pentylenetetrazole-induced seizures. Seizure latency results were assessed by the Student's *t*-test and expressed as means±SEM. Table 1 shows the anticonvulsant activities for the compounds. **3d** was effective in delaying the onset of the first myoclonic twitches, but was not protective against pentylenetetrazole-induced generalized convulsions. **2a** and **2g** showed maximum protection (90 and 70%, respectively) as well as sodium valproate (80%), and substitution of ethyl (**2b**) reduced protection. **2a** and **2g** may be considered promising for the development of new anticonvulsant agents. The acetylation of thiadiazoles retained anticonvulsant effectiveness to a lesser degree. The ED_{50} values of the most effective compounds, **2a** and **2g** were 33 and 66 mg/kg, respectively. Twenty animals were tested for ED_{50} determination. We also tested lower or higher doses of the most effective compounds, **2a** and **2g**. The lower dose (50 mg/kg) was ineffective (**2a**: 50% and **2g**: 40%) and the higher dose (150 mg/kg) did not increase the efficiency (**2a**: 90% and **2g**: 70%). Therefore the dose of 100 mg/kg was selected as the best one.

Calculations were performed using the Instat and Prism statistical analysis packages (GraphPad Software, San Diego, CA, USA) with $p<0.05$ considered statistically significant.

Microbiology

The assessment of the antimicrobial action of the synthesized compounds was performed using the minimal inhibitory concentration test in Muller–Hinton Broth and Sabouraud Dextrose Broth was used for the determination of antibacterial and antifungal activity. The suspensions of microorganisms containing 1.5×10^5 colony forming units (cfu) in 1 mL were incubated overnight and then diluted to 10^{-3}.

The compounds were dissolved in DMSO at 1000 μg/mL and 0.5 mL of this solution were added into the first and second tubes. Starting from the second tube, two fold dilutions were performed and 0.5 mL of microorganism suspensions were added into the all tubes and the control tube which did not contain any compound. The tubes were incubated at 37 °C for 24 h. The minimal inhibitory concentrations (MIC) were determined at the end of the incubation period.[19]

The results from these experiments were compared with those of penicillin and ketoconazole as references for antibacterial and antifungal agents, respectively. Under the experimental conditions, the minimum inhibitory concentrations (MICs) of penicillin for *S. aureus*, *Escherichia coli*, *P. aeruginosa* and *Bacillus subtilis* were $\leq$0.45, 31.25, 500 and $\leq$0.45 μg/mL, respectively, and the MIC of ketoconazole for *Candida albicans*, was 62.5 μg/mL. For the microorganisms indicated above, these data with DMSO as a solvent were 0.9, 0.45, 1.9, 1.9 and 1.9 μg/mL with respectively. Among tested compounds, the MIC value of **3j** (500 μg/mL) was the same as that of penicillin against *P. aeruginosa* and the MIC value of **2e** was the lowest (62.5 μg/mL) against *S. aureus*. Therefore, these two compounds, **2e** and **3j** may be considered promising for the development of new antibacterial agents.

Experimental

Melting points were determined in glass capillary tubes on a Büchi 530 apparatus and uncorrected. Elemental analyses were performed with Leco-932 (C, H, N, S-Elemental analyser) and Carlo Erba 1106 (C, H, N-Elemental analyser). UV spectra were obtained on a Shimadzu UV 2100S spectrophotometer (1 mg/100 mL in ethanol). IR spectra were recorded using a Perkin Elmer 1600 FTIR spectrophotometer (KBr, ν cm^{-1}). ^1H NMR spectra were recorded on a Bruker AVANC DPX 400 and Bruker AC 200L Krotas MS-9/50 spectrometers

in DMSO-d_6 with tetramethylsilane as the internal standard, the following abbreviations were used: s: singlet, d: doublet, t: triplet, m: multiplet. Mass spectra were obtained with a Fisons Instruments VG Platform II LS–MS spectrometer. Thin layer chromatograpy (TLC) was carried out on DC-Alufolien plates (Kieselgel 60 F_{254} −0.2 mm, Fluka) and spots were visualized with UV light.

General procedure for preparation of 2-(alkyl/arylamino)-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazoles (2a–j)

A solution of 3-hydroxy-2-naphthoic acid hydrazide in ethanol was treated with equimolecular amounts of the appropriate isothiocyanate and refluxed for 3 h. The precipitated thiosemicarbazide **1a**–**j**[13] was recrystallized from ethanol. A solution of appropriate thiosemicarbazide (**1a**–**j**) (0.003 mol) in 3 mL concentrated sulfuric acid was stirred at room temperature for 30 min and then poured into ice cold distilled water. The precipitated product was filtered, washed with distilled water and recrystallized from ethanol.

2-Ethylamino-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole (2a). IR: 3406–2981, 1621, 1457, 917, 750, 708 cm^{-1}. The other data for structural analysis were present in the literature.[7]

2-Phenethylamino-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole (2b). White powder (92.6%); mp 183–186 °C; IR: 3181–2916, 1637, 1521, 1496, 1455, 864, 745, 700, 622 cm^{-1}. ^{1}H NMR, δ ppm: 10.94 (1H, s, OH), 8.36 (1H, s, C_1H), 7.92 (1H, t, NH), 7.82 (1H, d, C_8H, J = 8.11 Hz), 7.64 (1H, d, C_5H, J = 8.11 Hz), 7.36 (1H, t, C_6H, J = 7.54 Hz), 7.26–7.20 (6H, m, C_4H, C_7H, *o*- and *m*-protons of phenyl), 7.14 (1H, t, *p*-proton of phenyl), 3.51 (2H, q, $\underline{CH_2}$–NH), 2.87 (2H, t, $\underline{CH_2}$–C_6H_5). Anal. calcd. for $C_{20}H_{17}N_3OS$: C, 69.14; H, 4.93; N, 12.09; S, 9.23. Found: C, 68.23; H, 4.67; N, 11.70; S, 9.24.

2-Phenylamino-5-(3-hydroxy-2-naphthyl)-1,3,4-thia diazole (2c). Yellow powder (98.6%); mp 260 °C; IR: 3187–2938, 1638, 1600, 1499, 1454, 1430, 868, 743, 756, 693 cm^{-1}. ^{1}H NMR, δ ppm: 11.15 (1H, s, OH), 10.41 (1H, s, NH), 8.63 (1H, s, C_1H), 7.94 (1H, d, C_8H, J = 8.02 Hz), 7.77–7.30 (8H, m, C_5H, C_6H, C_4H, C_7H, *o*- and *m*-protons of phenyl), 7.02 (1H, t, *p*-proton of phenyl, J = 7.29 Hz). Anal. calcd. for $C_{18}H_{13}N_3OS$: C, 67.69; H, 4.10; N, 13.16; S, 10.04. Found: C, 67.67; H, 4.10; N, 12.93; S, 10.45.

2-(*p*-Bromophenylamino)-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole (2d). Yellow powder (92.0%); mp 299 °C; IR: 3200–2912, 1618, 1593, 1516, 1490, 1438, 864, 737, 820, 667 cm^{-1}. ^{1}H NMR, δ ppm: 11.25 (1H, s, OH), 10.68 (1H, s, NH), 8.78 (1H, s, C_1H), 8.07 (1H, d, C_8H, J = 8.10 Hz), 7.87 (1H, d, C_5H, J = 8.29 Hz), 7.81–7.77 (2H, m, *o*-protons to Br), 7.68–7.62 (2H, m, *m*-protons to Br), 7.59 (1H, t, C_6H, J = 7.47 Hz), 7.51–7.45 (2H, m, C_4H and C_7H). Anal. calcd for $C_{18}H_{12}BrN_3OS$: C, 54.28; H, 3.04; N, 10.55; S, 8.05. Found: C, 54.27; H, 2.77; N, 10.11; S, 8.01.

2-(*p*-Chlorophenylamino)-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole (2e). Yellow powder (81.1%); mp 260–263 °C; IR: 3265–2900, 1618, 1598, 1537, 1493, 1441, 867, 774, 828, 708 cm^{-1}. ^{1}H NMR, δ ppm: 11.08 (1H, s, OH), 10.51 (1H, s, NH), 8.73–8.64 (2H, m, C_1H, C_8H), 7.94 (1H, d, C_5H, J = 8.05 Hz), 7.77–7.70 (3H, m, C_6H and *o*-protons to Cl), 7.55–7.31 (4H, m, C_4H, C_7H and *m*-protons to Cl). Anal. calcd for $C_{18}H_{12}ClN_3OS{\cdot}2/3H_2SO_4{\cdot}1/3C_2H_5OH$: C, 51.59; H, 3.56; N, 9.67; S, 12.29. Found: C, 51.58; H, 2.74; N, 9.72; S, 11.61.

2-(*p*-Fluorophenylamino)-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole (2f). Yellow powder (97.5%); IR: 3220–3065, 1621, 1578, 1543, 1508, 1457, 1415, 911, 771, 827, 622 cm^{-1}. The other data for structural analysis were present in the literature.[7]

2-(*m*-Fluorophenylamino)-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole (2g). Yellow powder (97.2%); mp 267 °C; IR: 3197–2932, 1618, 1514, 1488, 1463, 867, 737, 820, 777, 652 cm^{-1}. ^{1}H NMR, δ ppm: 11.39 (1H, s, OH), 10.76 (1H, s, NH), 8.80 (1H, s, C_1H), 8.07 (1H, d, C_8H, J = 8.14 Hz), 7.88–7.84 (2H, m, C_5H and *m*-proton to F), 7.59 (1H, t, C_6H, J = 7.26 Hz), 7.55–7.45 (4H, m, C_4H, C_7H and *o*-protons to NH), 6.95 (1H, t, *p*-proton to NH, J = 8.40 Hz). Anal. calcd for $C_{18}H_{12}FN_3OS{\cdot}1/2$ C_2H_5OH: C, 63.32; H, 4.20; N, 11.66. Found: C, 62.84; H, 3.59; N, 11.61.

2-(*p*-Methoxyphenylamino)-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole (2h). Yellow powder (74.3%); mp 265 °C; IR: 3233–2834, 1627, 1586, 1509, 1455, 1422, 873, 748, 828, 708 cm^{-1}. ^{1}H NMR, δ ppm: 11.29 (1H, s, OH), 10.34 (1H, s, NH), 8.72 (1H, s, C_1H), 8.06 (1H, d, C_8H, J = 8.19 Hz), 7.86 (1H, d, C_5H, J = 7.86 Hz), 7.69 (2H, d, *m*-protons to OCH_3, J = 9.49 Hz), 7.59 (1H, t, C_6H, J = 7.37 Hz), 7.48–7.44 (2H, m, C_4H and C_7H), 7.09 (2H, d, *o*-protons to OCH_3, J = 7.04 Hz), 3.88 (3H, s, OCH_3). Anal. calcd for $C_{19}H_{15}N_3O_2S{\cdot}2/3H_2SO_4{\cdot}1/2$ C_2H_5OH: C, 54.87; H, 4.45; N, 9.60; S, 12.20. Found: C, 55.69; H, 3.78; N, 9.74; S, 11.32.

2-(*p*-Methylphenylamino)-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole (2i). Yellow powder (75.9%); mp 262–265 °C; IR: 3185–2912, 1637, 1614, 1516, 1441, 864, 742, 822, 669 cm^{-1}. ^{1}H NMR, δ ppm: 11.21 (1H, s, OH), 10.44 (1H, s, NH), 8.74 (1H, s, C_1H), 8.06 (1H, d, C_8H, J = 8.18 Hz), 7.87 (1H, d, C_5H, J = 8.25 Hz), 7.67 (2H, d, *o*-protons to CH_3, J = 8.38 Hz), 7.58 (1H, t, C_6H, J = 7.41 Hz), 7.47–7.44 (2H, t, C_4H and C_7H), 7.35 (2H, d, *m*-protons to CH_3, J = 8.36 Hz), 2.40 (3H, s, CH_3). Anal. calcd. for $C_{19}H_{15}N_3OS$: C, 68.45; H, 4.53; N, 12.60; S, 9.62. Found: C, 67.91; H, 4.26; N, 12.11; S, 8.66.

2-(*m*-Trifluoromethylphenylamino)-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole (2j). Yellow powder (76.9%); mp 209–212 °C; IR: 3444–2718, 1632, 1491, 1458, 1401, 890, 753, 851, 804, 701 cm^{-1}. ^{1}H NMR, δ ppm: 13.34 (1H, s, OH), 10.67 (1H, s, NH), 8.69 (1H, s, C_1H), 8.58 (1H, d, C_8H, J = 8.79 Hz), 8.21 (2H, m, *o*-protons to CF_3), 7.86 (1H, d, C_5H, J = 8.06 Hz), 7.74 (1H, d, *p*-proton to CF_3, J = 9.21 Hz), 7.52 (1H, t, C_6H, J = 7.98 Hz), 7.45 (1H, t,

C_7H, $J = 7.51$ Hz), 7.31–7.25 (2H, m, C_4H and *m*-proton to CF_3). Anal. calcd for $C_{19}H_{12}F_3N_3OS \cdot H_2SO_4$: C, 47.01; H, 2.90; N, 8.66; S, 13.21. Found: C, 47.52; H, 3.26; N, 8.53; S, 11.95.

General procedure for preparation of 2-(*N*-alkyl/aryl-*N*-acetylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazoles (3a–i)

A mixture of appropriate thiadiazole (0.001 mol) **2a–i** in 5 mL acetic anhydride was heated under reflux 90 min. Distilled water was added to the reaction mixture and allowed to cool. The resulting precipitate was filtered and washed with distilled water. The residue was purified by recrystallization from ethanol.

2-(*N*-Acetyl-*N*-ethylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazole (3a). Creamy crystal (50.1%); mp 169 °C; IR: 3033–2982, 1768, 1668, 1628, 1599, 1508, 1438, 897, 744, 622 cm^{-1}. ^1H NMR, δ ppm: 8.72 (1H, s, C_1H), 8.14 (1H, d, C_8H, $J = 7.94$ Hz), 7.97 (1H, d, C_5H, $J = 7.91$ Hz), 7.89 (1H, s, C_4H), 7.68–7.56 (2H, m, C_6H and C_7H), 4.31 (2H, q, CH_2), 2.48 (3H, s, $NCOCH_3$, with DMSO), 2.40 (3H, s, $OCOCH_3$), 1.38 (3H, t, CH_3). Anal. calcd for $C_{18}H_{17}N_3O_3S$: C, 60.83; H, 4.82; N, 11.82. Found: C, 60.18; H, 4.23; N, 12.47.

2-(*N*-Acetyl-*N*-phenethylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazole (3b). Creamy crystal (55.5%); mp 129 °C; IR: 3052, 1768, 1681, 1626, 1597, 1468, 1442, 901, 741, 705, 620 cm^{-1}. ^1H NMR, δ ppm: 8.70 (1H, s, C_1H), 8.07 (1H, d, C_8H, $J = 7.83$ Hz), 7.90 (1H, d, C_5H, $J = 7.86$ Hz), 7.83 (1H, s, C_4H), 7.59–7.51 (2H, m, C_6H, C_7H), 7.28–7.17 (5H, m, C_6H_5), 4.38 (2H, t, $\underline{CH_2}$–$NCOCH_3$), 3.05 (2H, t, $\underline{CH_2}$–C_6H_5), 2.33 (3H, s, $NCOCH_3$), 2.20 (3H, s, $OCOCH_3$). Anal. calcd for $C_{24}H_{21}N_3O_3S$: C, 66.80; H, 4.91; N, 9.74; S, 7.43. Found: C, 67.43; H, 4.78; N, 9.72; S, 7.01.

2-(*N*-Acetyl-*N*-phenylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazole (3c). Yellow crystal (70.7%); mp 185 °C; IR: 3057, 1757, 1686, 1629, 1592, 1489, 1433, 897, 754, 703, 620 cm^{-1}. ^1H NMR, δ ppm: 8.82 (1H, s, C_1H), 8.26 (1H, d, C_8H, $J = 7.92$ Hz), 8.10 (1H, d, C_5H, $J = 7.98$ Hz), 8.03 (1H, s, C_4H), 7.77–7.71 (7H, m, C_6H, C_7H and C_6H_5), 2.53 (3H, s, $NCOCH_3$), 2.17 (3H, s, $OCOCH_3$). Anal. calcd for $C_{22}H_{17}N_3O_3S$: C, 65.49; H, 4.25; N, 10.41; S, 7.95. Found: C, 65.67; H, 3.65; N, 10.06; S, 7.33.

2-(*N*-Acetyl-*N*-*p*-bromophenylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazole (3d). Creamy crystal (59.5%); mp 227 °C; IR: 3066, 1757, 1686, 1628, 1600, 1487, 1433, 896, 754, 847, 620 cm^{-1}. ^1H NMR, δ ppm: 8.69 (1H, s, C_1H), 8.14 (1H, d, C_8H, $J = 7.88$ Hz), 7.97 (1H, d, C_5H, $J = 8.05$ Hz), 7.90 (1H, s, C_4H), 7.82 (2H, d, *o*-protons to Br, $J = 8.67$ Hz), 7.71–7.54 (4H, m, C_6H, C_7H and *m*-protons to Br), 2.40 (3H, s, $NCOCH_3$), 2.07 (3H, s, $OCOCH_3$). Mass (EI) *m*/*z* (relative intensity): 187 (20), 169 (25), 158 (79), 155 (12), 141 (39), 140 (52), 128 (23), 126 (22), 115 (93), 114 (81), 102 (24), 89 (21), 77 (23), 76 (44), 65 (20), 63 (100), 58 (35). Anal. calcd for $C_{22}H_{16}BrN_3O_3S$: C, 54.78; H, 3.34; N, 8.71; S, 6.65. Found: C, 54.60; H, 3.48; N, 8.47; S, 6.90.

2-(*N*-Acetyl-*N*-*p*-chlorophenylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazole (3e). Creamy crystal (55.5%); mp 222–226 °C; IR: 3056, 1761, 1690, 1628, 1599, 1487, 1436, 897, 748, 843, 621 cm^{-1}. ^1H NMR, δ ppm: 8.69 (1H, s, C_1H), 8.14 (1H, d, C_8H, $J = 8.12$ Hz), 7.97 (1H, d, C_5H, $J = 7.25$ Hz), 7.90 (1H, s, C_4H), 7.67–7.56 (6H, m, C_6H, C_7H and C_6H_4), 2.40 (3H, s, $NCOCH_3$), 2.07 (3H, s, $OCOCH_3$). Anal. calcd for $C_{22}H_{16}ClN_3O_3S$: C, 60.34; H, 3.68; N, 9.60; S, 7.32. Found: C, 59.75; H, 3.74; N, 9.14; S, 7.36.

2-(*N*-Acetyl-*N*-*p*-fluorophenylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazole (3f). Yellow crystal (36.6%); mp 223 °C; IR: 3066, 1763, 1686, 1628, 1598, 1507, 1435, 897, 747, 842, 622 cm^{-1}. ^1H NMR, δ ppm: 8.69 (1H, s, C_1H), 8.13 (1H, d, C_8H, $J = 8.55$ Hz), 7.97 (1H, d, C_5H, $J = 7.25$ Hz), 7.90 (1H, s, C_4H), 7.71–7.56 (4H, m, C_6H, C_7H and *m*-protons to F), 7.44 (2H, t, *o*-protons to F, $J = 8.75$ Hz), 2.40 (3H, s, $NCOCH_3$), 2.06 (3H, s, $OCOCH_3$). Anal. calcd for $C_{22}H_{16}FN_3O_3S$: C, 62.70; H, 3.83; N, 9.97. Found: C, 62.56; H, 3.77; N, 9.42.

2-(*N*-Acetyl-*N*-*m*-fluorophenylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazole (3g). Creamy crystal (86.7%); mp 169 °C; IR: 3058, 1766, 1689, 1597, 1486, 1438, 903, 753, 823, 618 cm^{-1}. ^1H NMR, δ ppm: 8.82 (1H, s, C_1H), 8.26 (1H, d, C_8H, $J = 7.96$ Hz), 8.10 (1H, d, C_5H, $J = 8.06$ Hz), 8.03 (1H, s, C_4H), 7.80–7.70 (4H, m, C_6H, *o*- and *m*-protons of phenyl to $NCOCH_3$), 7.62–7.54 (2H, m, C_7H and *p*-proton of phenyl to $NCOCH_3$), 2.53 (3H, s, $NCOCH_3$), 2.20 (3H, s, $OCOCH_3$). Anal. calcd for $C_{22}H_{16}FN_3O_3S \cdot H_2O$: C, 60.13; H, 4.13; N, 9.56; S, 7.30. Found: C, 59.95; H, 3.51; N, 9.30; S, 6.80.

2-(*N*-Acetyl-*N*-*p*-methoxyphenylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazole (3h). Yellow crystal (88.5%); mp 215 °C; IR: 3054, 2933, 2839, 1762, 1686, 1628, 1600, 1508, 1433, 896, 748, 840, 624 cm^{-1}. ^1H NMR, δ ppm: 8.81 (1H, s, C_1H), 8.26 (1H, d, C_8H, $J = 7.88$ Hz), 8.10 (1H, d, C_5H, $J = 7.97$ Hz), 8.02 (1H, s, C_4H), 7.79–7.70 (2H, m, C_6H and C_7H), 7.62 (2H, d, *m*-protons to OCH_3, $J = 8.76$ Hz), 7.26 (2H, d, *o*-protons to OCH_3, $J = 8.80$ Hz), 3.98 (3H, s, CH_3), 2.52 (3H, s, $NCOCH_3$), 2.18 (3H, s, $OCOCH_3$). Anal. calcd for $C_{23}H_{19}N_3O_4S$: C, 63.73; H, 4.42; N, 9.69; S, 7.40. Found: C, 63.09; H, 3.91; N, 9.32; S, 6.94.

2-(*N*-Acetyl-*N*-*p*-methylphenylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazole (3i). Creamy crystal (94.0%); mp 208 °C; IR: 3055, 2920, 1764, 1686, 1628, 1598, 1509, 1435, 892, 745, 840, 622 cm^{-1}. ^1H NMR, δ ppm: 8.81 (1H, s, C_1H), 8.26 (1H, d, C_8H, $J = 7.94$ Hz), 8.10 (1H, d, C_5H, $J = 8.00$ Hz), 8.02 (1H, s, C_4H), 7.79–7.70 (2H, m, C_6H and C_7H), 7.58 (2H, d, *m*-protons to CH_3, $J = 8.24$ Hz), 7.53 (2H, d, *o*-protons to CH_3, $J = 8.20$ Hz), 2.55 (3H, s, CH_3), 2.52 (3H, s, $NCOCH_3$), 2.17 (3H, s, $OCOCH_3$). Mass (EI) *m*/*z* (relative intensity): 187 (37), 169 (13), 158 (59), 141 (21), 140 (27), 128 (53), 126 (15), 115 (96), 114 (57), 102 (89), 91 (82), 89 (45), 77 (93), 76 (15), 65 (55), 63 (42), 58 (100). Anal. calcd for $C_{23}H_{19}N_3O_3S$: C, 66.17; H, 4.59; N, 10.06; S, 7.68. Found: C, 66.08; H, 4.32; N, 9.69; S, 7.07.

2-(*N*-Acetyl-*N*-*m*-trifluoromethylphenylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazole (3j). Yellow powder (26.1%); mp 237 °C; IR: 3068, 2821, 1772, 1694, 1620, 1599, 1559, 1495, 915, 753, 846, 628 cm^{-1}. ^1H NMR, δ ppm: 8.64–7.26 (9H, m, C_1H, C_8H, C_5H, C_4H, C_6H, C_7H and *o*-, *m*-, *p*-protons to CF_3), 6.18 (1H, s, *o*-proton to CF_3 and $NCOCH_3$), 2.42 (3H, s, $NCOCH_3$ with DMSO), 1.96 (3H, s, $OCOCH_3$). Anal. calcd for $C_{23}H_{16}F_3N_3O_3S$: H, 3.42; N, 8.91. Found: H, 3.03; N, 8.41.

Acknowledgement

Chemical section of this work was supported by The Research Fund of Marmara University (Project number SA 1998/64).

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