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Synthesis and antimicrobial activity of some 1,3,4-oxadiazole derivatives

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Abstract

Six new 5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-thione, 2-amino-5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole, 5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-one derivatives have been synthesized from 1-and/or 2-naphthol. The structures of the compounds were confirmed by IR and ^{1}H NMR spectral data and microanalysis. The antimicrobial properties of the compounds were investigated against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*, *Candida albicans*, *C. krusei* and *C. parapsilosis* using microbroth dilution method. 2-Amino-5-(2-naphthyloxymethyl)-1,3,4-oxadiazole and 5-(2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-one show significantly (32 μg/ml), compounds 5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-thione, 2-amino-5-(1-naphthyloxymethyl)-1,3,4-oxadiazole and 5-(1-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-one moderately (64 μg/ml) active against *C. krusei*. All the compounds were active against *S. aureus*, *E. coli*, *P. aeruginosa*, *C. albicans*, and *C. parapsilosis* at 64–256 μg/ml concentration.

Keywords: 1,3,4-Oxadiazole-2(3*H*)-thione; 1,3,4-Oxadiazole-2(3*H*)-one; 2-Amino-1,3,4-oxadiazole; Synthesis; Antimicrobial activity

1. Introduction

1,3,4-Oxadiazole ring is associated with many types of biological properties such as anti-inflammatory [1–3], hypoglycemic [4], antifungal and antibacterial [5–9] activities. On the other hand, some 5-[isoxazolo[5,4-*d*]pyrimidinyloxymethyl] - 2 - substitutedphenylamino-1,3,4-oxadiazole and -1,3,4-oxadiazole-2(3*H*)-thione derivatives [9] have been reported as significantly active antimicrobials against *Staphylococcus aureus* and *Candida albicans*. Keeping the above facts in view, we considered it of interest to synthesize some new 5-(1-/2-naphthyloxymethyl) - 1,3,4 - oxadiazole - 2(3*H*) - thione (**2a**–**b**), 2-amino-5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole(**3a**–**b**),5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-one (**4a**–**b**) derivatives and investigate their antimicrobial properties against *S. aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*, *C. albicans*, *C. krusei* and *C. parapsilosis* using microbroth dilution method.

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2. Experimental procedures

2.1. Chemistry

All chemicals were supplied from Aldrich, Merck and Fluka Co. Melting points were taken in a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded in Perkin Elmer 1720x FT-IR Spectrophotometer (KBr disc). ^{1}H NMR spectra were run on a Bruker AC 400 MHz FT NMR Spectrometer (DMSO-d_6, $CDCl_3$, TMS).

2.1.1. 1-/2-Naphthyloxyacetylhydrazine (*1a*–*b*)

1-Naphthyloxyacetylhydrazine and 2-naphthyloxyacetylhydrazine were synthesized by using the method reported earlier [1,4].

2.1.2. 5-(1-/2-Naphthyloxymethyl)-1,3,4-oxadiazole-2(3H)thione (*2a*–*b*)

To a 0 °C solution of hydrazide (0.65 g, 3 mmol) and carbon disulfide (0.46 g, 6 mmol) in absolute ethanol (20 ml), potassium hydroxide (0.2 g) was added in one portion. The resulting mixture was stirred and refluxed

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for 6 h. The solvent was removed in vacuo and the residue was acidified with 2 M hydrochloric acid and extracted with ethyl acetate (2 ×). Organic layers were washed with water and dried with anhydrous sodium sulfate. Filtration and concentration in vacuo gave a solid which was recrystallized from suitable solvents.

*2.1.3. 2-Amino-5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole (**3a–b**)*

0.25 g (3 mmol) Sodium bicarbonate was dissolved in 15 ml of water and added to a solution of hydrazide (**1a** or **1b**) (0.65 g, 3 mmol) in 15 ml dioxane. Cyanogen bromide (0.35 g, 3.3 mmol) was added to the resulting mixture and stirred for 4 h at room temperature, concentrated, diluted with water and filtered. The residue was recrystallized from suitable solvents.

*2.1.4. 5-(1-/2-Naphthyloxymethyl)-1,3,4-oxadiazole-2(3H)one (**4a–b**)*

1,1′-Carbonyldiimidazole (CDI) (0.55 g, 3.4 mmol) was added to a solution of hydrazide (0.65 g, 3mmol) and triethylamine (TEA) (0.3 g, 3 mmol) in tetrahydrofuran (10 ml) at 0 °C. The mixture was stirred for 20 h at room temperature and concentrated in vacuo. The residue was dissolved in diethyl ether, washed with 2 M hydrochloric acid and saturated aqueous sodium bicarbonate and dried over sodium sulfate. Filtration and concentration in vacuo gave a solid which was recrystallized from suitable solvents.

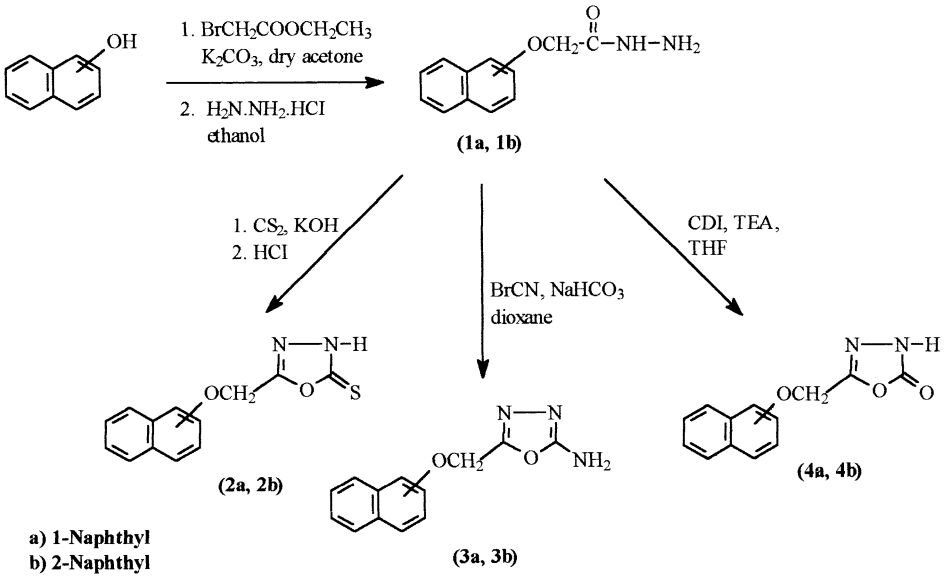
2.2. Microbiology [10]

The compounds were tested against some Gram-positive and Gram-negative bacteria such as *S. aureus* (ATCC 25923), *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853) by using microbroth dilution method. The antifungal activities of compounds were evaluated in vitro against some yeast like fungi such as *Candida albicans* (ATCC 90028), *C. krusei* (ATCC 6258) and *C. parapsilosis* (ATCC 22018). Ceftazidime and fluconazole were used as reference compounds in antibacterial and antifungal activity studies, respectively. The stock solutions of the compounds were prepared in dimethylsulfoxide. The solutions in the test medium furnished the required concentration ranging from 512 to 0.5 μg/ml. The microtiter plates were incubated at 35 °C and read visually after 24 h, but for *Candida* species at 48 h. The MIC values were recorded as the lowest concentrations of the substances that had no visible turbidity.

3. Results and discussion

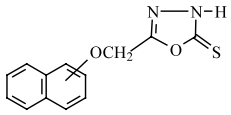
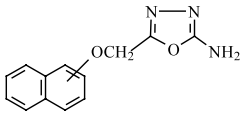
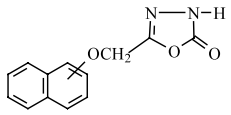
1-/2-Naphthyloxyacetic acid hydrazide was prepared by esterification of 1-/2-naphthol with ethylbromoacetate and anhydrous potassium carbonate in dry acetone, followed by refluxing with hydrazine hydrate in absolute ethanol [1,4]. The 1,3,4-oxadiazole-2(3*H*)-thiones **2a–b** were synthesized by the reaction of acid hydrazides with carbon disulfide [2,3]. Treatment of hydrazide with cyanogen bromide under alkaline conditions gave 2-amino-1,3,4-oxadiazole derivatives **3a–b**. 1,3,4-Oxadiazol-2(3*H*)-one derivatives **4a–b** were prepared by treating hydrazides with CDI in the presence of TEA (Scheme 1).

The structures of the compounds were elucidated by IR, ^{1}H-NMR and microanalyses. Formula, melting points, yields%, spectral data and microanalyses of the compounds are given in Table 1. All spectral data were



Scheme 1. Synthesis of the compounds.

Table 1
Formula, melting points, yields%, IR and ^{1}H NMR spectral data of the compounds

Comp	Formula	m.p. (°C)	Yield %	IR υ (cm^{-1})	^{1}H-NMR (δ ppm)	Analysis
						
2a	1-Naphthyl	111	32	3315 (N-H) 1626,1591 (C=N, C=C) 1244 (C=S) 1068 (Ar-O-C)	5.30 (2H; s; Ar-O-C<u>H</u>$_2$-), 6.80-8.30 (7H; m; aromatic prot.) 9.05-9.50 (1H; bs; N<u>H</u>)	C, H, N
2b	2-Naphthyl	161	62.3	3312 (N-H) 1661,1591 (C=N, C=C) 1255 (C=S) 1061 (Ar-O-C)	4.55 (2H; s; Ar-O-C<u>H</u>$_2$-), 6.95-8.45 (7H; m; aromatic prot.), 8.95-9.45 (1H; bs; N<u>H</u>)	C, H, N
						
3a	1-Naphthyl	178-9	78.8	3280, 3102 (N-H) 1660, 1598 (C=N, C=C) 1058 (Ar-O-C)	5.30 (2H; s; Ar-O-C<u>H</u>$_2$-), 6.85-8.25 (7H; m; aromatic prot.)	C, H, N
3b	2-Naphthyl	172-3	92.8	3317, 3131 (N-H) 1660, 1600 (C=N, C=C) 1013 (Ar-O-C)	5.20 (2H; s; Ar-O-C<u>H</u>$_2$-), 6.80-8.30 (7H; m; aromatic prot.)	C, H, N
						
4a	1-Naphthyl	148-50	32.2	3314 (N-H) 1768 (C=O) 1634, 1599 (C=N, C=C) 1075 (Ar-O-C)	5.35 (2H; s; Ar-O-C<u>H</u>$_2$-), 7.05-8.40 (7H; m; aromatic prot.) 12.60 (1H; s; N<u>H</u>)	C, H, N
4b	2-Naphthyl	147-8	25.5	3358 (N-H) 1776 (C=O) 1626, 1599 (C=N, C=C) 1035 (Ar-O-C)	5.10 (2H; s; Ar-O-C<u>H</u>$_2$-), 7.10-8.15 (7H; m; aromatic prot.), 12.30 (1H; s; N<u>H</u>)	C, H, N

s: singlet, bs: broad singlet, m: multiplet

in accordance with the assumed structures. In IR spectra, the disappearance of C=O stretching bands of the acylthiosemicarbazides and detection of strong C=N stretching band at 1660–1626 cm^{-1} are evidence for ring closure of 1,3,4-oxadiazol ring. The 1,3,4-oxadiazol-2(3*H*)-thiones **2a**–**b** and 1,3,4-oxadiazol-2(3*H*)-ones **4a**–**b** showed one N–H stretching band at 3358–3312 cm^{-1} and 2-amino-1,3,4-oxadiazole derivatives **3a**–**b** showed two N–H stretching bands at 3317–3102 cm^{-1}, respectively. The IR spectra of 1,3,4-oxadiazole-2(3*H*)-thiones **2a**–**b** showed N–H bands in the region of 3106–3030 cm^{-1} and C=S absorption bands at 1255 and 1244 cm^{-1} instead of S–H bands at around 2600–2550 cm^{-1}. In the ^{1}H NMR spectra, all protons were seen according to the expected chemical shift and integral values. Methylenic and aromatic protons of 1-/2-naphthyloxymethyl groups were seen at 4.55–5.35 and 6.80-8.45 ppm. The N–*H* protons of 1,3,4-oxadiazole ring (**2a**–**b**, **4a**–**b**) were seen at about 8.95–12.60 ppm, respectively. The amino protons of 2-amino-1,3,4-oxadiazole derivatives **3a**–**b** were not seen in spectra because of deuterium exchange (Table 1). The results of microanalyses were within ± 0.4% theoretical values. The compounds were tested against some Gram (+) and Gram (−) bacteria such as *S. aureus* (ATCC 25923), *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853) by using microbroth dilution method. The antifungal activities of compounds were evaluated in vitro against some yeast like fungi such as *C. albicans* (ATCC 90028), *C. krusei* (ATCC 6258) and *C. parapsilosis* (ATCC 22018). Compounds **3b**, **4b** showed significantly (32 μg/ml) and compounds **2a**, **2b**, **3a**, **4a**

Table 2
Antibacterial and antifungal activities of the compounds

Comp. (10 mg/kg)	*S. aureus* (ATCC 25923)	*E. coli* (ATCC 25922)	*P. aeruginosa* (ATCC 27853)	*C. albicans* (ATCC 90028)	*C. krusei* (ATCC 6258)	*C. parapsilosis* (ATCC 22018)
2a	64	128	256	64	64	64
2b	64	256	128	64	64	64
3a	256	128	128	64	64	64
3b	256	256	128	64	32	64
4a	128	256	128	64	64	64
4b	64	128	128	32	32	32
Ceftazidime	2	1–0.5	2			
Fluconazole				0.25	32	0.5

moderately (64 μg/ml) MIC values against *C. krusei*. All the compounds were active against *S. aureus*, *E. coli*, *P. aeruginosa*, *C. albicans*, and *C. parapsilosis* at 64–256 μg/ml MIC values (Table 2).

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