

Synthesis and evaluation of antibacterial activity of new derivatives of pyrimido[4,5-*e*][1,3,4]oxadiazine

Mehdi Bakavoli^{1,*}, Mohammad Rahimizadeh¹,
Ali Shiri¹, Hossein Eshghi¹, Simin Vaziri-Mehr²,
Parvaneh Pordeli³ and Mohsen Nikpour⁴

¹Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, 91775-1436 Mashhad, Iran

²Department of Chemistry, School of Sciences, Islamic Azad University, Mashhad Branch, Mashhad, Iran

³Department of Biology, School of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran

⁴Department of Chemistry, School of Sciences, Islamic Azad University, Ahvaz Branch, Ahvaz, Iran

*Corresponding author
e-mail: mbakavoli@yahoo.com

Abstract

New derivatives of pyrimido[4,5-*e*][1,3,4]oxadiazine were prepared and their antibacterial evaluations were performed on four different Gram-negative and Gram-positive bacteria.

Keywords: antibacterial evaluation; heterocyclization; pyrimidooxadiazine.

Introduction

The synthesis of fused oxadiazines has been a challenging subject. These compounds with diverse biological activities are reported to act as inhibitors of bacterial growth (Barbaric et al., 2003), antimicrobial agents (Berkowitz et al., 1977; Shindy et al., 2006), useful intermediates in the synthesis of tenidap prodrugs or β -lactam antibiotics, especially in the synthesis of carbapenems and penems (Gravestock, 1987; Robinson and Donahue, 1994), cardiovascular antibacterial and plant growth regulating agents with mitocidal, nematocidal, acaricidal, insecticidal and anticonvulsive activities (Kornet, 1996; Khan et al., 2002). The methods for the synthesis of oxadiazines, especially [1,3,4]oxadiazine systems, are limited (Elliot and Gibson, 1980; Kim and Kurasawa, 1998). The treatment of (-)-2-methyl-2-(α -methyl- β -hydroxyphenyl)benzoic acid hydrazide with sulfuric acid (Trepanier et al., 1965) or *N*'-chloroacetyl salicyl hydrazide with NaOH in DMF (Gaozza and Lamdan, 1970) leads to the formation of [1,3,4]oxadiazine derivatives. Elliot and Gibson (1972) and Shawali and Hassaneen (1977) reported the synthesis of 1,3,4-benzoxadiazines from hydrazidoyl bromides. The reaction of *ortho*-mercaptobenzohydrazide with chloroacetyl chloride gave a [1,3,4]oxadiazine derivative (Freeman et al., 1975). Rosling et al.

(1999) synthesized some tetrahydro[1,2-*d*][1,3,4]oxadiazine derivatives and studied the conformational preference by NMR spectroscopy and X-ray analysis. More recently, 1,3,4-oxadiazine-5,10-dione derivatives were also obtained (Shindy et al., 2006). In addition, thiazolo[4,3-*b*][1,3,4]oxadiazine-6(4*H*)-thiones were synthesized by the reaction of 3-aminorhodanine with 1,1,2,2-ethenetetracarbonitrile (Mourad et al., 2007). In pursuing our research on the synthesis of fused heterocyclic compounds with potential biological activities (Bakavoli et al., 2007, 2008a,b, 2009, 2010) and taking into account the literature reports on biological activities of fused oxadiazines, in this paper we describe the synthesis of new pyrimido[4,5-*e*][1,3,4]oxadiazines and their antibacterial evaluations.

Results and discussion

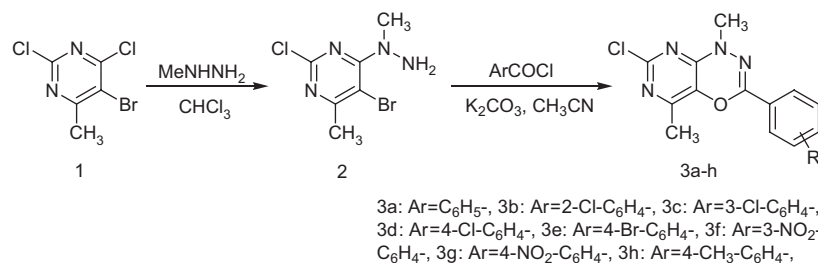
Chemistry

5-Bromo-2-chloro-6-methyl-4-(1-methylhydrazino)pyrimidine (**2**) was prepared by the reaction of 5-bromo-2,4-dichloro-6-methyl pyrimidine (**1**) with methylhydrazine according to our previously published method (Bakavoli et al., 2006). Treatment of **2** with aroyl halides in the presence of K_2CO_3 in boiling acetonitrile afforded the new derivatives of the pyrimido[4,5-*e*][1,3,4]oxadiazine **3a–h** (Scheme 1).

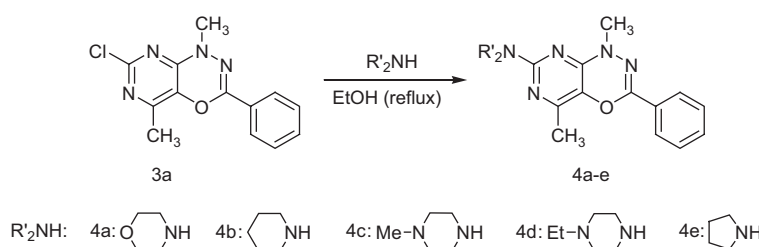
The structures of new compounds were elucidated by their spectral and microanalytical data. For example, the ¹H NMR spectrum of compound **3d** does not exhibit the signal at δ 4.21 belonging to the NH₂ moiety of the precursor **2** but shows two singlets at δ 2.22 and 3.21 for the methyl signals of the pyrimidine and oxadiazine rings, respectively. The spectrum also shows two doublets at δ 7.33 and 7.74 (*J*=8 Hz) for the aromatic ring protons. The IR spectrum is devoid of the stretching vibration bands at 3360 and 3280 cm⁻¹ for the NH₂ moiety that is observed in the spectrum of the precursor **2**. The band at 1660 cm⁻¹ for the carbonyl group of **2** is also absent in the spectrum of **3d**. In the mass spectrum of **3d** the molecular ion peaks are observed at *m/z* 319 and 321, which is consistent with the presence of a chlorine atom in the molecule. These results together with the microanalytical data fully support the molecular formula C₁₃H₁₀Cl₂N₄O. Further treatment of compound **3a**, as an example, with selected secondary amines in boiling ethanol led to the displacement of the chlorine atom and gave the substituted products **4a–e** (Scheme 2).

Biological activities

The newly synthesized compounds **3a–h** and **4a–e** were screened for the antibacterial activity against



Scheme 1 Synthesis of compounds 3a–h.



Scheme 2 Synthesis of compounds 4a–e.

several pathogenic representative Gram-positive bacteria (*Staphylococcus aureus* PTCC 1074 and *Bacillus subtilis* PTCC 1365) and Gram-negative bacteria (*Escherichia coli* BA 7601C and *Pseudomonas aeruginosa* PTCC 1431) using the disc diffusion sensitivity test (Cruickshank et al., 1975; Collins, 1976). Mueller-Hinton agar media were sterilized for 15 min at 120°C and poured into the plates to a uniform depth of 5 mm and allowed to solidify. The microbial suspension (1.2×10^8 CFU/ml) (0.5 McFarland Nephelometry Standards) was streaked over the surface of media using a sterile cotton swab (15 min at 180°C) to ensure confluent growth of the organisms. The tested compounds were dissolved in *N,N*-dimethylformamide (DMF) and diluted with ethanol to obtain a solution of 100–500 µg/ml concentration. The discs measuring 6.25 mm in diameter (Whatman no. 1 filter paper) were impregnated with the prepared solution of compounds 3a–h and 4a–e, and placed on Muller-Hinton agar media previously inoculated with bacterial suspension. The inhibition zones as a criterion for antimicrobial activity were measured at the end of an incubation period of 24 h at 37°C. The results of these evaluations are given in Table 1. Streptomycin was chosen as a standard drug at a concentration of 10 µg/ml. Streptomycin is an antibiotic that inhibits both Gram-positive and Gram-negative bacteria and is, therefore, a useful broad spectrum antibiotic (Table 1).

It can be concluded from the data in Table 1 that compounds 3d and 3g show the highest sensitivity against *E. coli* and are moderately sensitive against other organisms. Compound 3e exhibits the highest activity against *B. subtilis*, whereas compound 4a shows activity against *S. aureus*. All the other compounds were found to exhibit slight to moderate sensitivity against the mentioned organisms.

Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus and were not corrected. The ¹H NMR spectra were recorded in CDCl₃ at 100 MHz on a Bruker AC 100 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constants *J* are given in Hertz. The IR spectra were recorded in KBr pellets. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

General procedure for the synthesis of 3-aryl-7-chloro-1,5-dimethyl-1H-pyrimido[4,5-e][1,3,4]oxadiazines 3a–h

To a magnetically stirred solution of 5-bromo-2-chloro-6-methyl-4-(1-methylhydrazino)pyrimidine (2, 1 mmol, 0.25 g) and an appropriate acyl halide (1 mmol) in dry acetonitrile (20 ml), K₂CO₃ (2 mmol, 0.28 g) was added and the mixture was stirred at room temperature for 1 h. Then, the mixture was refluxed for 6–7 h and the progress of the reaction was monitored by TLC using petroleum ether/ethyl acetate (7:3). After the completion of the reaction the mixture was cooled and the solvent was removed under reduced pressure. Water (5 ml) was added to the residue and the mixture was neutralized with 0.1 M HCl solution. The crude solid was filtered and crystallized from aqueous ethanol.

7-Chloro-1,5-dimethyl-3-phenyl-1H-pyrimido[4,5-e][1,3,4]oxadiazine (3a) This compound was obtained as yellow needles; yield 70%; m.p. 156–157°C; ¹H NMR: δ 2.22 (s, 3H, CH₃-pyrimidine), 3.21 (s, 3H, CH₃-N), 7.1–7.8 (m, 5H, phenyl); IR: ν 3010, 2950, 1154 cm⁻¹ (C–O); MS: (*m/z*) 274 (M⁺), 276 (M⁺+2). Anal. calcd. for C₁₃H₁₁ClN₄O: C, 56.84; H, 4.04; N, 20.39. Found: C, 55.48; H, 3.20; N, 21.97.

Table 1 Antibacterial activity data for compounds **3a–h** and **4a–e**.

Compound	Gram-positive bacteria		Gram-negative bacteria	
	<i>Staphylococcus aureus</i> PTCC 1074	<i>Bacillus subtilis</i> PTCC 1365	<i>Escherichia coli</i> HB101 BA 7601C	<i>Pseudomonas aeruginosa</i> PTCC 1431
3a	14 (+)	11 (-)	10 (-)	11 (-)
3b	10 (-)	11 (-)	12 (+)	10.5 (-)
3c	11 (-)	11 (-)	12 (+)	12 (+)
3d	13 (+)	12 (+)	15 (++)	12 (+)
3e	11 (-)	15 (++)	12 (+)	10 (-)
3f	10 (-)	11 (-)	11 (-)	11 (-)
3g	12 (+)	10.5 (-)	16 (++)	10.5 (-)
3h	12 (+)	12 (+)	12 (+)	12 (+)
4a	15 (++)	12 (+)	12 (+)	13 (+)
4b	9 (-)	11 (-)	11 (-)	11 (-)
4c	9 (-)	9 (-)	12 (+)	8 (-)
4d	10 (-)	13 (+)	12 (+)	8 (-)
4e	10 (-)	11 (-)	11 (-)	9 (-)
Streptomycin (standard)	13	10	13	15

Zones of inhibition are given in millimeters (mm). (++) Highly sensitive, (+) moderately sensitive, (-) slightly sensitive.

7-Chloro-3-(2-chlorophenyl)-1,5-dimethyl-1H-pyrimido[4,5-*e*][1,3,4]oxadiazine (3b) This compound was obtained as yellow needles; yield 60%; m.p. 165–166°C; ¹H NMR: δ 2.21 (s, 3H, CH₃-pyrimidine), 3.20 (s, 3H, CH₃-N), 7.3–7.7 (4H, m, phenyl); IR: ν 3020, 2980, 1207 cm⁻¹ (C-O); MS: (*m/z*) 308 (M⁺), 310 (M⁺+2), 312 (M⁺+4). Anal. calcd. for C₁₃H₁₀Cl₂N₄O: C, 50.51; H, 3.26; N, 18.12. Found: C, 50.42; H, 3.19; N, 18.03.

7-Chloro-3-(3-chlorophenyl)-1,5-dimethyl-1H-pyrimido[4,5-*e*][1,3,4]oxadiazine (3c) This compound was obtained as yellow needles; yield 65%; m.p. 172–173°C; ¹H NMR (CDCl₃, ppm) δ 2.21 (s, 3H, CH₃-pyrimidine), 3.20 (s, 3H, CH₃-N), 7.2–7.6 (4H, m, phenyl); IR: ν 3020, 2940, 1202 cm⁻¹ (C-O); MS: (*m/z*) 308 (M⁺), 310 (M⁺+2), 312 (M⁺+4). Anal. calcd. for C₁₃H₁₀Cl₂N₄O: C, 50.51; H, 3.26; N, 18.12. Found: C, 50.40; H, 3.20; N, 18.07.

7-Chloro-3-(4-chlorophenyl)-1,5-dimethyl-1H-pyrimido[4,5-*e*][1,3,4]oxadiazine (3d) This compound was obtained as yellow needles; yield 50%; m.p. 175–176°C; ¹H NMR: δ 2.22 (s, 3H, CH₃-pyrimidine), 3.21 (s, 3H, CH₃-N), 7.33 (d, *J*=8 Hz, 2H, phenyl), 7.74 (d, *J*=8 Hz, 2H, phenyl); IR: ν 3060, 2950, 1153 cm⁻¹ (C-O); MS: (*m/z*) 308 (M⁺), 310 (M⁺+2), 312 (M⁺+4). Anal. calcd. for C₁₃H₁₀Cl₂N₄O: C, 50.51; H, 3.26; N, 18.12. Found: C, 50.60; H, 3.23; N, 18.15.

3-(4-Bromophenyl)-7-chloro-1,5-dimethyl-1H-pyrimido[4,5-*e*][1,3,4]oxadiazine (3e) This compound was obtained as yellow needles; yield 75%; m.p. 178–180°C; ¹H NMR: δ 2.19 (s, 3H, CH₃-pyrimidine), 3.19 (s, 3H, CH₃-N), 7.51–7.72 (AB quartet, 4H, phenyl); IR: ν 3030, 2930, 1154 cm⁻¹ (C-O); MS: (*m/z*) 352 (M⁺), 354 (M⁺+2), 356 (M⁺+4). Anal. calcd. for C₁₃H₁₀BrClN₄O: C, 44.16; H, 2.85; N, 15.84. Found: C, 44.01; H, 2.81; N, 15.79.

7-Chloro-1,5-dimethyl-3-(3-nitrophenyl)-1H-pyrimido[4,5-*e*][1,3,4]oxadiazine (3f) This compound was obtained as yellow needles; yield 50%; m.p. 180–181°C; ¹H NMR: δ 2.24 (s, 3H, CH₃-pyrimidine), 3.23 (s, 3H, CH₃-N), 7.2–8.5 (m, 4H, phenyl); IR: ν

3015, 2965, 1101 cm⁻¹ (C-O); MS: (*m/z*) 319 (M⁺), 321 (M⁺+2). Anal. calcd. for C₁₃H₁₀ClN₅O₃: C, 48.84; H, 3.15; N, 21.91. Found: C, 48.89; H, 3.18; N, 21.98.

7-Chloro-1,5-dimethyl-3-(4-nitrophenyl)-1H-pyrimido[4,5-*e*][1,3,4]oxadiazine (3g) This compound was obtained as yellow needles; yield 70%; m.p. 208–210°C; ¹H NMR: δ 2.23 (s, 3H, CH₃-pyrimidine), 3.22 (s, 3H, CH₃-N), 7.91 (d, *J*=9 Hz, 2H, phenyl) 8.23 (d, *J*=9 Hz, 2H, phenyl); IR: ν 3045, 2925, 1107 cm⁻¹ (C-O); MS: (*m/z*) 319 (M⁺), 321 (M⁺+2). Anal. calcd. for C₁₃H₁₀ClN₅O₃: C, 48.84; H, 3.15; N, 21.91. Found: C, 48.94; H, 3.17; N, 22.02.

7-Chloro-1,5-dimethyl-3-(4-methylphenyl)-1H-pyrimido[4,5-*e*][1,3,4]oxadiazine (3h) This compound was obtained as yellow needles; yield 60%; m.p. 150–151°C; ¹H NMR: δ 2.23 (s, 3H, CH₃-pyrimidine), 2.40 (s, 3H, CH₃-phenyl), 3.21 (s, 3H, CH₃-N), 7.33 (d, *J*=7 Hz, 2H, phenyl), 7.82 (d, *J*=7 Hz, 2H, phenyl); IR: ν 3015, 2930, 1152 cm⁻¹ (C-O); MS: (*m/z*) 288 (M⁺), 290 (M⁺+2). Anal. calcd. for C₁₄H₁₃ClN₄O: C, 58.24; H, 4.54; N, 19.40. Found: C, 58.32; H, 4.60; N, 19.61.

General procedure for the synthesis of 7-substituted-1,5-dimethyl-3-phenyl-1H-pyrimido[4,5-*e*][1,3,4]oxadiazines 4a–e A mixture of 7-chloro-1,5-dimethyl-3-phenyl-1H-pyrimido[4,5-*e*][1,3,4]oxadiazine (**3a**, 1 mmol, 0.27 g) and appropriate secondary amine (**4a–e**, 2.2 mmol) in ethanol (5 ml) was heated under reflux for approximately 2–3 h. After cooling to room temperature, water was added to the solution. The resulting solid was collected by filtration, washed with water and dried.

1,5-Dimethyl-7-morpholino-3-phenyl-1H-pyrimido[4,5-*e*][1,3,4]oxadiazine (4a) This compound was obtained as yellow plates; yield 70%; m.p. 189°C; ¹H NMR: δ 2.18 (s, 3H, CH₃-pyrimidine), 3.21 (s, 3H, CH₃-oxadiazine), 3.70 (m, 8H, CH₂), 7.3–7.8 (m, 5H, phenyl); IR: ν 3945, 2930, 1154 cm⁻¹ (C-O); MS: (*m/z*) 325 (M⁺). Anal. calcd. for C₁₇H₁₉N₅O₂: C, 62.75; H, 5.89; N, 21.52. Found: C, 62.43; H, 5.50; N, 21.11.

1,5-Dimethyl-7-piperidino-3-phenyl-1H-pyrimido[4,5-*e*][1,3,4]oxadiazine (4b) This compound was obtained as yellow plates; yield 75%; m.p. 180°C; ¹H NMR: δ 1.60 (m, 6H, CH₂), 2.19 (s, 3H, CH₃-pyrimidine), 3.23 (s, 3H, CH₃-oxadiazine), 3.66 (m, 4H, CH₂), 7.3–7.9 (m, 5H, phenyl); IR: ν 3055, 2940, 1155 cm⁻¹ (C-O); MS: (*m/z*) 323 (M⁺). Anal. calcd. for C₁₈H₂₁N₃O: C, 66.85; H, 6.55; N, 21.66. Found: C, 66.75; H, 6.50; N, 21.32.

1,5-Dimethyl-7-(4-methylpiperazino)-3-phenyl-1H-pyrimido[4,5-*e*][1,3,4]oxadiazine (4c) This compound was obtained as yellow plates; yield 70%; m.p. 177°C; ¹H NMR: δ 2.18 (s, 3H, CH₃-pyrimidine), 2.34 (s, 3H, CH₃-piperazine), 2.43 (t, 4H, CH₂), 3.22 (s, 3H, CH₃-oxadiazine), 3.72 (t, 4H, CH₂), 7.4–7.9 (m, 5H, phenyl); IR: ν 3035, 2930, 1150 cm⁻¹ (C-O); MS: (*m/z*) 338 (M⁺). Anal. calcd. for C₁₈H₂₂N₆O: C, 63.89; H, 6.55; N, 24.83. Found: C, 63.82; H, 6.44; N, 24.66.

7-(4-Ethylpiperazino)-1,5-dimethyl-3-phenyl-1H-pyrimido[4,5-*e*][1,3,4]oxadiazine (4d) This compound was obtained as yellow plates; yield 70%; m.p. 190°C; ¹H NMR: δ 1.11 (t, *J*=5 Hz, 3H, CH₃ of ethyl), 2.17 (s, 3H, CH₃-pyrimidine), 2.41 (t, 6H, CH₂), 3.21 (s, 3H, CH₃-oxadiazine), 3.74 (t, 4H, CH₂), 7.4–7.9 (m, 5H, phenyl); IR (KBr disc) ν 3055, 2950, 1140 cm⁻¹ (C-O); ms (*m/z*) 352 (M⁺). Anal. calcd. for C₁₉H₂₄N₆O: C, 64.75; H, 6.86; N, 23.85. Found: C, 64.69; H, 6.80; N, 23.71.

1,5-Dimethyl-3-phenyl-7-pyrrolidino-1H-pyrimido[4,5-*e*][1,3,4]oxadiazine (4e) This compound was obtained as yellow plates; yield 79%; m.p. 168°C; ¹H NMR: δ 1.93 (t, *J*=4 Hz, 4H, CH₂), 2.21 (s, 3H, CH₃-pyrimidine), 3.24 (s, 3H, CH₃-oxadiazine), 3.51 (t, 4H, CH₂), 7.4–7.8 (m, 5H, phenyl); IR: ν 3065, 2940, 1155 cm⁻¹ (C-O); MS: (*m/z*) 309 (M⁺). Anal. calcd. for C₁₇H₁₉N₅O: C, 66.00; H, 6.19; N, 22.64. Found: C, 65.79; H, 6.12; N, 22.50.

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