Synthesis and Antibacterial Evaluations of New Pyridazino-[4,3-e][1,3,4]oxadiazines

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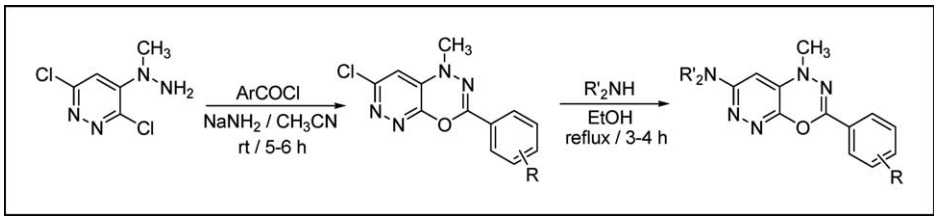

Several derivatives of the new pyridazino[4,3-e][1,3,4]oxadiazine ring system were prepared, and their antibacterial evaluations were performed on four different Gram-negative and Gram-positive bacteria.

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INTRODUCTION

Oxadiazines are a group of heterocyclic compounds which their syntheses have been a challenge for organic chemists. They have a diverse biological properties [1] such as inhibitors of bacterial growth [2], antimicrobial agents [2,3], and also useful intermediates in the synthesis of tenidap prodrugs or β-lactam antibiotics, especially, in the synthesis of carbapenems and penems [4,5], cardiovascular antibacterial, miticidal, nematocidal, acricidal, insecticidal, and anticonvulsive activities [6,7].

The published methods for the synthesis of oxadiazines especially fused [1,3,4]oxadiazines are limited. These compounds have been prepared by treatment of (–)-2-methyl-2-(α-methyl-β-hydroxyphenyl)benzoic acid hydrazid with sulfuric acid [8] or treatment of N′-chloroacetyl salicyl hydrazide with NaOH in DMF [9] which leads to [1,3,4]oxadiazines derivatives. Elliot and Gibson in 1972 [10] and Shawali and Hassaneen in 1977 [11,12] reported the synthesis of 1,3,4-benzoxadiazines from hydrazidoyl bromides. The reaction of *o*-mercaptobenzohydrazide with chloroacetylchloride gave [1,3,4] oxadiazines derivatives [13]. Mattinen and his coworkers synthesized some tetrahydro[1,2-d][1,3,4]oxadiazine derivatives and studied the conformational preference by NMR spectroscopy and X-ray analysis [14]. More recently 1,3,4-oxadiazine-5,10-dione derivatives were obtained by the reaction of *p*-chloranil with acetic acid azide of hydrazine and phenylhydrazine in ethylene glycol and sodium bicarbonate [3]. Furtheremore, thiazolo[4,3-b][1,3,4]oxadiazine-6(4H)-thiones were obtained from the reaction of 3-aminorhodanine with 1,1,2,2-ethenetetracarbonitrile as by-product in low yields [15].

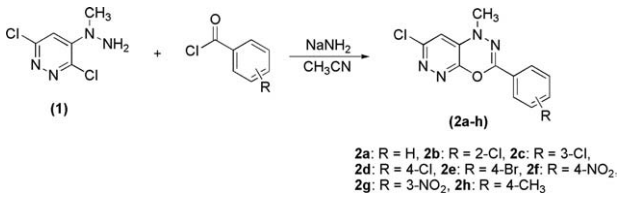
A perusal of the literature revealed that there is no report on the synthesis of pyridazino[4,3-e][1,3,4]oxadiazine ring system. Since fused oxadiazines are biologically active compounds and due to our interest in the synthesis of heterocyclic compounds of biological interest [16], in this article we wish to report on the synthesis of some new pyridazino[4,3-e][1,3,4]oxadiazines and the outcome of our investigation on their antibacterial properties.

RESULTS AND DISCUSSION

Chemistry. 4-Bromo-3,6-dichloro pyridazine which was prepared according to ref. 17 was treated with methylhydrazine in $CHCl_3$ at 0–5°C giving 3,6-dichloro-4-(1-methylhydrazino) pyridazine (**1**) [18]. The heterocyclization of compound (**1**) as precursor with various aroyl halides in the presence of $NaNH_2$ at room temperature yielded the new corresponding pyridazino[4,3-e][1,3,4]oxadiazine derivatives (Scheme 1).

The structures of the synthesized compounds were elucidated by their spectral and microanalytical data. For example, the ^{1}H NMR spectrum of compound (**2h**)

Scheme 1



did not exhibit the signal at δ 4.2 ppm belonging to NH_2 moiety of the precursor but showed an AB quartet peak at the aromatic region indicating the occurrence of the heterocyclization step. The IR spectrum was devoid of the stretching vibration bands belonging to the precursor at 3360 and 3280 cm^{-1} resembling the NH_2 moiety, and at 1660 cm^{-1} for carbonyl group, but instead exhibited the C—O stretching vibration band at 1110 cm^{-1}. The molecular ion peak of compound **(2h)** which was observed at *m*/*z* 274 (M^+) and 276 ($M^+ + 2$) together with the result of microanalytical data are fully supportive of the molecular formula $C_{13}H_{11}ClN_4O$.

Further treatment of the pyridazino[4,3-e][1,3,4]oxadiazines with few secondary amines, as examples, led to the replacement of the chlorine atom and gave the substituted products **(3a–f)** (Scheme 2).

Biological activities. The *in vitro* antibacterial activity of the newly synthesized compounds **(2a–h)** and **(3a–f)** were screened for the antibacterial activity against several pathogenic representative Gram-positive bacteria (*Staphylococcus aureus* PTCC 1074 and *Bacillus subtilis* PTCC 1365); Gram-negative bacteria (*Escherichia coli* HB101 BA 7601C and *Pseudomonas aeruginosa* PTCC 1431) using disc diffusion sensitivity test [19,20]. Mueller-Hinton agar media were sterilized (15 min at 121°C) and poured into the plates to a uniform depth of 5 mm and allow it to solidify. The microbial suspension (1.2 × 108 CFU/mL) (0.5 McFarland Nephelometery 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 DMF and diluted with ethanol to get a solution of 100–600 μg mL^{-1} concentration. The discs measuring 6.25 mm in diameter (Whatman no. 1 filter paper) were impregnated with prepared solution of compounds **(2a–h)** and **(3a–f)** by 1 mL of the chemical solution which was added to each bottle contained 12 discs and placed on Muller-Hinton agar media previously inoculated with bacterial suspension. The inhibition zones as a criterion for antimicrobial activity were measured in millimeter at the end of an incubation period of 24 h at 37°C. The results of these evaluations are given in Table 1. Streptomycin (binds to the 16SrRNA of the bacterial ribosome, interfering with the binding of formyl-methionyl-tRNA to the 30S subunit therefore prevents initiation of protein synthesis and leads to death of microbial cell) was chosen as a standard drug at a concentration of 10 μg mL^{-1}. Streptomycin is an antibiotic that inhibits both gram positive and gram negative bacteria, and is therefore a useful broad spectrum antibiotic (Table 1).

As it can be concluded from the data in Table 1, compound **(2d)** and **(2g)** has shown the highest sensitivity against *E. coli*, and moderately sensitive against the other organisms. Compound **(2e)** exhibited the best activity against *B. subtilis* while compound **(3a)** showed activity against *S. aureus*. All the other compounds were found to exhibit slight to moderate sensitivity against the mentioned organisms.

In summary, we have developed a simple, one-pot synthesis of new pyridazino[4,3-e][1,3,4]oxadiazines through intermediates formed by reaction of 3,6-dichloro-4-(1-methylhydrazino) pyridazine with various aroyl halides and tested for their antibacterial activities.

EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus and are not corrected. The IR spectra were obtained on a 4300 Shimadzu spectrometer. The ^1H NMR (100 MHz) spectra were recorded on a Bruker AC l00 spectrometer. The mass spectra were obtained on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was performed on a ThermoFinnigan Flash EA 1112 micro analyzer.

General procedure for the preparation of pyridazino[4,3-e][1,3,4]oxadiazine (2a–h). All of these reactions were carried out under an atmosphere of nitrogen. To a magnetically stirred solution of 3,6-dichloro-4-(1-methylhydrazino) pyridazine **(1)** (0.38 g, 2 mmol) and various aroyl halides (2 mmol) in dry acetonitrile (20 mL), $NaNH_2$ (0.2 g, 5 mmol) was added and the mixture stirred for 5–6 h at room temperature (monitored by TLC using chloroform-methanol 9:1 as the eluent). After the reaction was completed, the solvent was removed under reduced pressure. Water (20 mL) was added, and the resultant was neutralized with 5% HCl solution. The precipitate was filtered off, washed with water, and recrystallized from ethanol-water.

7-Chloro-1-methyl-3-phenyl-1H-pyridazino[4,3-e][1,3,4]oxadiazine (2a). This compound was obtained as yellow plate, yield: 65%; mp 185–186°C; ^1H NMR: (DMSO-d_6, ppm), δ 3.09 (s, 3H, CH_3), 6.66 (s, 1H, pyridazine), 7.51–7.70 (m, 5H, Phenyl protones). ir (KBr disc) ν 3010, 2950, 1150 cm^{-1}. ms: (*m*/*z*) 260 (M^+), 262 ($M^+ + 2$). Anal. Calcd. for $C_{12}H_9ClN_4O$:

Scheme 2

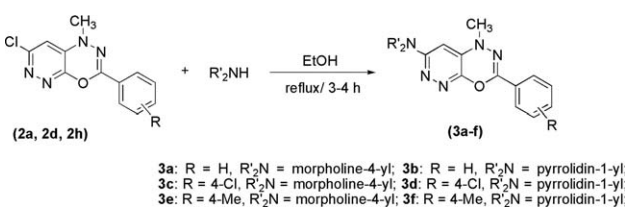


Table 1

Antibacterial data of the synthesized compounds **2(a–h)** and **3(a–f)**.[a]

Compound	Gram-negative bacteria		Gram-positive bacteria	
	Escherichia coli HB101 BA 7601C	*Pseudomonas aeruginosa* PTCC 1431	*Staphylococcus aureus* PTCC 1074	*Bacillus subtilis* PTCC 1365
2a	14(+)	11(−)	14(+)	11(−)
2b	12(+)	10.5(−)	10(−)	11(−)
2c	12(+)	12(+)	11(−)	11(−)
2d	15(++)	12(+)	13(+)	12(+)
2e	12(+)	10(−)	11(−)	15(++)
2f	11(−)	11(−)	10(−)	11(−)
2g	16(++)	10.5(−)	12(+)	10.5(−)
2h	12(+)	12(+)	12(+)	12(+)
3a	12(+)	13(+)	15(++)	12(+)
3b	11(−)	11(−)	9(−)	11(−)
3c	12(+)	8(−)	9(−)	9(−)
3d	12(+)	8(−)	10(−)	13(++)
3e	11(−)	9(−)	10(−)	11(−)
3f	12(+)	9(−)	10(−)	11(−)
Streptomycin (standard)	13	15	13	10

++, Highly Sensitive; +, Moderately Sensitive; −, Slightly Sensitive.
[a] Zones of inhibition in millimeter.

C, 55.29; H, 4.48; N, 21.49. Found: C, 55.16; H, 4.41; N, 21.45.

7-Chloro-3-(2-chlorophenyl)-1-methyl-1H-pyridazino[4,3-e][1,3,4]oxadiazine (2b). This compound was obtained as yellow plate, yield: 70%; mp 210°C; ^{1}H NMR: (DMSO-d_6, ppm), δ 3.07 (s, 3H, CH_3), 6.71 (s, 1H, pyridazine), 7.31–7.81 (m, 4H, Phenyl protones). ir (KBr disc) ν 3020, 2980, 1160 cm^{-1}. ms: (*m*/*z*) 295 (M^+), 297 ($M^+ + 2$), 299 ($M^+ + 4$). Anal. Calcd. for $C_{12}H_8Cl_2N_4O$: C, 48.84; H, 2.73; N, 18.96. Found: C, 48.95; H, 3.58; N, 19.44.

7-Chloro-3-(3-chlorophenyl)-1-methyl-1H-pyridazino[4,3-e][1,3,4]oxadiazine (2c). This compound was obtained as yellow plate, yield: 63%; mp 221–222°C; ^{1}H NMR: (DMSO-d_6, ppm), δ 3.09 (s, 3H, CH_3), 6.68 (s, 1H, pyridazine), 7.45–7.64 (m, 4H, Phenyl protones). ir (KBr disc) ν 3020, 2940, 1140 cm^{-1}. ms: (*m*/*z*) 295 (M^+), 297 ($M^+ + 2$), 299 ($M^+ + 4$). Anal. Calcd. for $C_{12}H_8Cl_2N_4O$: C, 48.84; H, 2.73; N, 18.96. Found: C, 48.75; H, 2.59; N, 18.45.

7-Chloro-3-(4-chlorophenyl)-1-methyl-1H-pyridazino[4,3-e][1,3,4]oxadiazine (2d). This compound was obtained as yellow plate, yield: 75%; mp 195–197°C; ^{1}H NMR: (DMSO-d_6, ppm) δ 3.08 (s, 3H, CH_3), 6.66 (s, 1H, pyridazine), 7.57 (AB quartet, 4H, Phenyl protones). ir (KBr disc) ν 3060, 2950, 1150 cm^{-1}. ms: (*m*/*z*) 295 (M^+), 297 ($M^+ + 2$), 299 ($M^+ + 4$). Anal. Calcd. for $C_{12}H_8Cl_2N_4O$: C, 48.84; H, 2.73; N, 18.96. Found: C, 48.58; H, 2.86; N, 19.60.s

3-(4-Bromophenyl)-7-chloro-1-methyl-1H-pyridazino[4,3-e][1,3,4]oxadiazine (2e). This compound was obtained as yellow plate, yield: 71%; mp 255–256°C; ^{1}H NMR: (DMSO-d_6, ppm), δ 3.08 (s, 3H, CH_3), 6.71 (s, 1H, pyridazine), 7.87 (AB quartet, 4H, Phenyl protones). ir (KBr disc) ν 3030, 2930, 1120 cm^{-1}. ms: (*m*/*z*) 338 (M^+), 340 ($M^+ + 2$), 342 ($M^+ + 4$). Anal. Calcd. for $C_{12}H_8BrClN_4O$: C, 42.44; H, 2.37; N, 16.50. Found: C, 42.50; H, 2.30; N, 16.30.

7-Chloro-1-methyl-3-(4-nitrophenyl)-1H-pyridazino[4,3-e][1,3,4]oxadiazine (2f). This compound was obtained as yellow plate, yield: 68%; mp 247°C; ^{1}H NMR: (DMSO-d_6, ppm), δ 3.14 (s, 3H, CH_3), 6.72 (s, 1H, pyridazine), 7.9 (2H, d, J = 8 Hz, Phenyl protones), 8.3 (2H, d, J = 8 Hz, Phenyl protones). ir (KBr disc) ν 3015, 2965, 1150 cm^{-1}. ms: (*m*/*z*) 305 (M^+), 307 ($M^+ + 2$). Anal. Calcd. for $C_{12}H_8ClN_5O_3$: C, 47.15; H, 2.64; N, 22.91. Found: C, 46.85; H, 2.63; N, 23.27.

7-Chloro-1-methyl-3-(3-nitrophenyl)-1H-pyridazino[4,3-e][1,3,4]oxadiazine (2g). This compound was obtained as yellow plate, yield: 73%; mp 220–221°C; ^{1}H NMR: (DMSO-d_6, ppm), δ 3.13 (s, 3H, CH_3), 6.72 (s, 1H, pyridazine), .7.71–8.41 (m, 4H, Phenyl protones). ir (KBr disc) ν 3045, 2925, 1130 cm^{-1}. ms: (*m*/*z*) 305 (M^+), 307 ($M^+ + 2$). Anal. Calcd. for $C_{12}H_8ClN_5O_3$: C, 47.15; H, 2.64; N, 22.91. Found: C, 47.03; H, 2.75; N, 23.08.

7-Chloro-1-methyl-3-(4-methylphenyl)-1H-pyridazino[4,3-e][1,3,4]oxadiazine (2h). This compound was obtained as yellow plate, yield: 78%; mp 212–214°C; ^{1}H NMR: (DMSO-d_6, ppm), δ 2.34 (s, 3H, CH_3), 3.07 (s, 3H, CH_3), 6.64 (s, 1H, pyridazine), 7.3 (2H, d, J = 8 Hz, Phenyl protones), 7.6 (2H, d, J = 8 Hz, Phenyl protones). ir (KBr disc) ν 3015, 2930, 1110 cm^{-1}. ms: (*m*/*z*) 274 (M^+), 276 ($M^+ + 2$). Anal. Calcd. for $C_{13}H_{11}ClN_4O$: C, 56.84; H, 4.04; N, 20.40. Found: C, 55.37; H, 4.00; N, 20.38.

General procedure for the preparation of compounds (3a–f). To a mixture of compounds **(2a)**, **(2d)**, or **(2h)** (1 mmol) in ethanol (15 mL), morpholine or pyrrolidine (2 mmol) was added, and the solution was refluxed for 3–4 h. After the solution was cooled, water was added and the resulting precipitant was filtered, washed with water and recrystallized from ethanol.

1-Methyl-7-(morpholin-4-yl)-3-phenyl-1H-pyridazino[4,3-e][1,3,4]oxadiazine (3a). This compound was obtained as creamy plate, yield: 65%; mp 253–254°C; ^{1}H NMR: (DMSO-d_6, ppm), δ 3.19 (s, 3H, CH_3), 3.45 (t, 4H, N—CH_2), 3.88 (t, 4H, O—CH_2), 6.27 (s, 1H, pyridazine), 7.4–7.7 (m, 5H, Phenyl protones). ir (KBr disc) ν 3045, 2930, 1160 cm^{-1}. ms: (*m*/*z*)

311 (M^+). Anal. Calcd. for $C_{16}H_{17}N_5O_2$: C, 61.72; H, 5.50; N, 22.49. Found: C, 61.59; H, 5.33; N, 22.22.

1-Methyl-3-phenyl-7-(pyrrolidin-1-yl)-1H-pyridazino[4,3-e][1,3,4]oxadiazine (3b). This compound was obtained as creamy plate, yield: 60%; mp 267–268°C; ^{1}H NMR: (DMSO-d_6, ppm), δ 1.91 (m, 4H, CH_2—CH_2), 3.19 (s, 3H, CH_3), 3.31 (t, 4H, CH_2—N), 5.88 (s, 1H, pyridazine), 7.4—7.8 (m, 5H, Phenyl protones). ir (KBr disc) ν 3055, 2940, 1150 cm^{-1}. ms: (*m*/*z*) 295 (M^+). Anal. Calcd. for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71. Found: C, 64.89; H, 5.33; N, 23.52.

3-(4-Chlorophenyl)-1-methyl-7-(morpholin-4-yl)-1H-pyridazino[4,3-e][1,3,4]oxadiazine (3c). This compound was obtained as creamy plate, yield: 67%; mp 215–216°C; ^{1}H NMR: (DMSO-d_6, ppm), δ 3.20 (s, 3H, CH_3), 3.42 (T, 4H, N—CH_2), 3.69 (t, 4H, O—CH_2), 6.21 (s, 1H, pyridazine), 7.6 (2H, d, J = 8 Hz, Phenyl protones), 7.8 (2H, d, J = 8 Hz, Phenyl protones). ir (KBr disc) ν 3035, 2940, 1135 cm^{-1}. ms: (*m*/*z*) 345 (M^+), 347 (M^+ + 2). Anal. Calcd. for $C_{16}H_{16}ClN_5O_2$: C, 55.58; H, 4.66; N, 20.25. Found: C, 55.71; H, 4.09; N, 20.16.

3-(4-Chlorophenyl)-1-methyl-7-(pyrrolidin-1-yl)-1H-pyridazino[4,3-e][1,3,4]oxadiazine (3d). This compound was obtained as creamy plate, yield: 73%; mp 243–245°C; ^{1}H NMR: (DMSO-d_6, ppm), δ 1.91 (m, 4H, CH_2—CH_2), 3.18 (s, 3H, CH_3), 3.38 (t, 4H, N—CH_2), 5.82 (s, 1H, pyridazine), 7.6 (2H, d, J = 8 Hz, Phenyl protones), 7.8 (2H, d, J = 8 Hz, Phenyl protones). ir (KBr disc) ν 3045, 2930, 1145 cm^{-1}. ms: (*m*/*z*) 329 (M^+), 331 (M^+ + 2). Anal. Calcd. for $C_{16}H_{16}ClN_5O$: C, 58.27; H, 4.89; N, 21.24. Found: C, 58.01; H, 4.79; N, 21.19.

1-Methyl-3-(4-methylphenyl)-7-(morpholin-4-yl)-1H-pyridazino[4,3-e][1,3,4]oxadiazine (3e). This compound was obtained as creamy plate, yield: 75%; mp 247–249°C; ^{1}H NMR: (DMSO-d_6, ppm), δ 2.35 (s, 3H, CH_3), 3.14 (s, 3H, CH_3), 3.45 (m, 4H, N—CH_2), 3.65 (m, 4H, O—CH_2), 6.20 (s, 1H, pyridazine), 7.3 (2H, d, J = 8 Hz, Phenyl protones), 7.7 (2H, d, J = 8 Hz, Phenyl protones). ir (KBr disc) ν 3065, 2940, 1160 cm^{-1}. ms: (*m*/*z*) 325 (M^+). Anal. Calcd. for $C_{17}H_{19}N_5O_2$: C, 62.75; H, 5.89; N, 21.52. Found: C, 62.66; H, 5.57; N, 21.46.

1-Methyl-3-(4-methylphenyl)-7-(pyrrolidin-1-yl)-1H-pyridazino[4,3-e][1,3,4]oxadiazine (3f). This compound was obtained as creamy plate, yield: 70%; mp 243–246°C; ^{1}H NMR: (DMSO-d_6, ppm), δ 1.95 (m, 4H, CH_2—CH_2), 2.33 (s, 3H, CH_3), 3.14 (s, 3H, CH_3), 3.33 (m, 4H, N—CH_2), 5.85 (s, 1H, pyridazine), 7.3 (2H, d, J = 8 Hz, Phenyl protones), 7.7 (2H, d, J = 8 Hz, Phenyl protones). ir (KBr disc) ν 3055, 2940, 1155 cm^{-1}. ms: (*m*/*z*) 309 (M^+). Anal. Calcd. for $C_{17}H_{19}N_5O$: C, 66.00; H, 6.19; N, 22.64. Found: C, 66.06; H, 6.07; N, 22.59.

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