Original Article

Comparative Antibacterial Activity of Synthetic *N,S-Heterocyclic* Derivatives, MgO Nanoparticles, and Glycine on Zoonotic *Vibrio fluvialis*

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Abstract

Background: *Vibrio fluvialis* is an emerging zoonotic pathogen that its antibiotic-resistant strains are rapidly expanding. Discovering new antibacterial agents is one way to control it. **Aims and Objectives:** In this research, inhibitory potentials of glycine, magnesium oxide nanoparticles (NPs), and some synthesized thiazole, imidazolidine-2-thione, and tetrahydropyrimidine-2-thione derivatives were studied against *V. fluvialis* in an *in vitro* manner. **Materials and Methods:** Thiazoles were prepared through Hantzsch reaction. Cyclic thioureas were synthesized from the reaction of diaminoalkanes and carbon disulfde. MgO NPs were created in 23.7–25.7 nm by sol–gel processing. Antibacterial properties of all compounds as inhibition zone diameter, the minimum inhibitory concentration, and the minimum bactericidal concentration values were assessed through both disk diffusion and broth microdilution methods. **Results:** No inhibitory activity on *V. fluvialis* was observed with MgO NPs and glycine. Among thiazole derivatives, only compound 7e could effciently block the growth of this pathogen. All thioureas except derivative 6c showed antibacterial properties. The best results belonged to imidazolidine-2-thione 7a. **Conclusion:** Significant inhibitory potentials were observed with some synthetic thiazoles and cyclic thioureas. If antibacterial activates of these heterocycles are proved on resistant strains and their toxic effects are desirable, an important step will be taken in the introduction of these new antibacterial agents.

Keywords: Antibacterial effect, glycine, heterocyclic compound, MgO nanoparticle, Vibrio fluvialis

Introduction

Vibrio fluvialis is a Gram-negative, oxidase-positive, and nitrate-positive bacterium that has been found in both human and animal feces.[1] Its strains have been isolated from patients with diarrhea, bacteremia, and food poisoning. This pathogen, like *Vibrio cholera*, causes bacterial gastroenteritis. In addition, symptoms such as severe diarrhea, vomiting, palpitations, fever, dehydration, hypovolemic shock, skin lesions, and tissue necrosis have been found with the diseases caused by this bacterium.[2] Fish farming centers and untreated drinking water and wastewater are the most important contaminating agents.[3] Several cases of child mortality have been reported in countries including Bahrain, Bangladesh, America, Mexico, and Brazil.[4] *V. fluvialis* strains were resistant to many common antibiotics such as ampicillin, chloramphenicol, streptomycin, gentamicin, and furazolidone due to gene mutation or drugs transport. The drug-resistant strains of this bacterium threaten public health, which increases the cost of treatment. For these reasons, new antibacterial agents must be identified and designed to inhibit *V. fluvialis* strains.

Thiazoles as an important class of heterocyclic compounds are present in various enzymes, vitamins, and pharmaceutics.[5] They were used in the treatment of cancer, blood fat, blood pressure, as well as infectious diseases caused by HIV, *Candida albicans*, anopheles, and trypanosomes.[6] Thiazole derivatives could efficiently block the growth of Gram-positive *Staphylococcus aureus*, *Streptococcus faecalis*, and *Bacillus subtilis* and Gram-negative *Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterobacter clavata*.[7] Some thiazoles are effective on resistant bacterial strains.[8]

Imidazolidines are present in the chemical structure of drugs such as midazolam, phenytoin, and ketoconazole. They were applied as pain relief, anti-inflammatory, anticancer, antidiabetic, antiparasitic, and antifungal agents.[9-14] Good to excellent

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inhibitory activities were observed with some derivatives of imidazolidines against *S. aureus*, *P. aeruginosa*, and *E. coli*.[15,16]

Inhibitory activities were observed with tetrahydropyrimidine derivatives against enzymes, cancer and tuberculosis cells, *Aspergillus niger*, *C. albicans*, and *Plasmodium malariae*.[17-20] Pathogenic bacteria such as *P. aeruginosa* and *Klebsiella pneumoniae* were also controlled with them.[21]

Metallic nanoparticles (NPs) are attractive chemicals due to their therapeutic effects on parasitic, viral, bacterial, and neurological diseases and blood disorders. Magnesium is the fourth most important element of the body and the second most important element in the cell, which plays a vital role in the activity of the nervous system, muscles and enzymes, energy production, bone and teeth formation. Mg NPs were utilized as broad-spectrum antibacterial agents due to their low toxicity as well as easy and inexpensive preparation.[22]

Protective effects of glycine, the simplest of the amino acids, have been confirmed in alcohol-induced oxidative stress. It could inhibit the growth of *Helicobacter pylori* under *in vitro* culture conditions.[23]

In this research, the *in vitro* inhibitory potential of glycine, magnesium oxide NPs, and some synthesized thiazole, imidazolidine-2-thione, and tetrahydropyrimidine-2-thione derivatives was studied against *V. fluvialis*.

Materials and Methods

General procedure for the synthesis of thiazole derivatives 3a-f

The reaction of thioamide (1) (1 mmol, 0.23 g), sodium bicarbonate (1 mmol, 0.08 g), and 1-bromocarbonyl compounds 2a-f in 1 ml of *N*, *N*-dimethylformamide as the solvent at room temperature for 24-46 h afforded thiazoles 3a-f [Figure 1].[24]

3-Methyl-4-(4-methylthiazol-2-yl)-1-phenyl-1H-pyrazol-5-amine (3a)

m.p. 170°C–172°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.37 (3H, s), 2.40 (3H, s), 6.71 (1H, d, J = 9.5 Hz), 7.04 (1H, s), 7.39 (1H, m), 7.54–7.56 (3H, m), 7.62 (2H, d, J = 7.8 Hz) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 161.9, 151.1, 146.5, 146.3, 138.7, 129.8, 127.2, 123.2, 109.1, 98.1, 17.3, 14.4 ppm; IR (KBr) v: 3314, 3262, 1620, 1556, 1401, 1200, 641 cm^{-1}. Anal. Calcd. for $C_{14}H_{14}N_4S$: C 62.20, H 5.22, N 20.72, S 11.86; found: C 62.23, H 5.23, N 20.70, S 11.84.

1-(2-(5-Amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4-methylthiazol-5-yl) ethan-1-one (3b)

m.p. 118°C–120°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.38 (3H, s), 2.54 (3H, s), 2.69 (3H, s), 6.97 (1H, s),

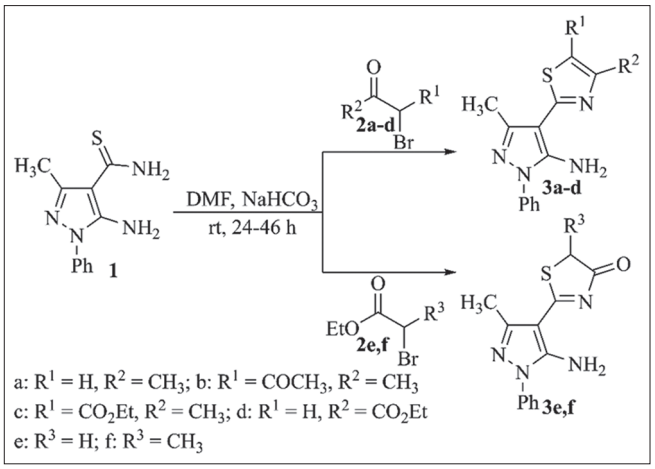

Figure 1: Steps of the synthesis of thiazole derivatives

7.42 (1H, t, J = 7.1 Hz), 7.54–7.61 (5H, m) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 164.5, 161.9, 159.5, 147.7, 147.0, 138.3, 129.8, 127.5, 123.6, 115.3, 97.7, 17.5, 14.7, 14.7 ppm; IR (KBr) v: 3442, 3296, 1653, 1617, 1548, 1397, 1237, 656 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_4OS$: C 61.52, H 5.16, N 17.94, S 10.26; found: C 61.49, H 5.18, N 17.93, S 10.29.

Ethyl2-(5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-4-methylthiazole-5-carboxylate (3c)

m.p. 144°C–146°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.31 (3H, t, J = 7.1 Hz), 2.38 (3H, s), 2.67 (3H, s), 4.28 (2H, q, J = 7.1 Hz), 6.93 (1H, d, J = 7.3 Hz), 7.42 (1H, t, J = 7.1 Hz), 7.54–7.61 (5H, m) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 192.2, 183.8, 171.4, 150.1, 149.7, 137.5, 130.0, 128.2, 124.1, 123.2, 99.4, 64.5, 18.8, 15.1, 14.3 ppm; IR (KBr) v: 3378, 3287, 1670, 1619, 1545, 1396, 1263, 649 cm^{-1}. Anal. Calcd. for $C_{17}H_{18}N_4O_2S$: C 59.63, H 5.30, N 16.36, S 9.36; found: C 59.65, H 5.28, N 16.38, S 9.37.

Ethyl2-(5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl) thiazole-4-carboxylate (3d)

m.p. 165°C–167°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.33 (3H, t, J = 7.1 Hz), 2.40 (3H, s), 4.33 (2H, q, J = 7.1 Hz), 6.85 (1H, d, J = 8.1 Hz,), 7.41 (1H, t, J = 7.2 Hz), 7.55 (3H, t, J = 7.4 Hz), 7.62 (2H, d, J = 7.8 Hz), 8.32 (1H, s) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 162.9, 161.1, 146.9, 146.5, 145.2, 138.5, 129.8, 127.4, 123.4, 123.9, 97.6, 61.2, 14.6 ppm; IR (KBr) v: 3434, 3314, 1729, 1602, 1563, 1394, 1221, 639 cm^{-1}. Anal. Calcd. for $C_{16}H_{16}N_4O_2S$: C 58.52, H 4.91, N 17.06, S 9.76; found: C 58.54, H 4.88, N 17.09, S 9.75.

2-(5-Amino-3-methyl-1-phenyl-1H-pyrazol-4-yl) thiazol-4 (5H)-one (3e)

m.p. 238°C–240°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.42 (3H, s), 4.01 (2H, s), 7.46 (1H, m), 7.55 (1H, m), 7.56–760 (5H, m) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 189.8, 165.6,

149.9, 149.7, 137.4, 130.0, 128.3, 124.2, 99.4, 36.3, 15.1 ppm; IR (KBr) *v*: 3342, 3272, 1732, 1627, 1540, 1402, 1203, 639 cm^{-1}. Anal. Calcd. for $C_{13}H_{12}N_4OS$: C 57.34, H 4.44, N 20.57, S 11.77; found: C 57.31, H 4.47, N 20.53, S 11.79.

2-(5-Amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-methylthiazol-4(5H)-one (3f)

m.p. 137°C–139°C; ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.55 (3H, d, J = 7.2 Hz), 2.41 (3H, s), 3.85 (1H, m), 7.46 (1H, m), 7.55–760 (5H, m), 7.63 (1H, m) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 190.1, 164.5, 147.7, 147.1, 138.5, 129.8, 127.5, 123.6, 97.8, 65.1, 30.5, 14.7 ppm; IR (KBr) *v*: 3329, 3265, 1736, 1629, 1534, 1396, 1194, 659 cm^{-1}. Anal. Calcd. for $C_{14}H_{14}N_4OS$: C 58.72, H 4.93, N 19.57, S 11.20; found: C 58.73, H 4.96, N 19.55, S 11.17.

Synthesis of imidazolidines 6a-c and tetrahydropyrimidines 6d-f

A mixture of diaminoalkanes 4a-e (10 mmol) and carbon disulfide (5) (10 mmol, 0.76 g) in the presence of MgO NPs (2.5 mmol, 0.1 g) and 96% ethanol (20 ml) were stirred at room temperature for 2.5–5 h to give cyclic thioamides 6a-f [Figure 2].[25]

Imidazolidine-2-thione (6a)

m.p. 196°C–197°C; ^1H NMR (DMSO-d_6, 400 MHz) δ: 3.54 (4H, s), 7.91 (2H, s) ppm; IR (KBr) *v*: 3312, 1480, 1075, 760 cm^{-1}.

4,4-Dimethylimidazolidine-2-thione (6b)

m.p. 105°C–107°C; ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.17 (6H, q, J = 5.7 Hz), 3.09 (2H, t, J = 5.7 Hz), 7.83 (2H, s) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 175.5, 39.7, 39.6, 19.1 ppm; IR (KBr) *v*: 3316, 1491, 1075, 763 cm^{-1}; Anal. Calcd. for $C_5H_{10}N_2S$: C 46.12, H 7.74, N 21.51, S 24.63; found: C 46.07, H 7.77, N 21.49, S 24.67.

Octahydro-2H-benzo[d]imidazole-2-thione (6c)

m.p. 153°C–155°C; ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.30 (2H, m), 1.47 (2H, m), 1.81 (2H, m), 2.04 (2H, m), 3.29 (2H, m), 7.47 (2H, br) ppm; IR (KBr) *v*: 3312, 1480, 1075, 760 cm^{-1}.

Tetrahydropyrimidine-2(1H)-thione (6d)

m.p. 210°C–212°C; ^1H NMR (DMSO-d_6, 400 MHz) δ: 1.90 (2H, m), 3.27 (2H, t, J = 6.1 Hz) 3.33 (2H, d, J = 2.7 Hz), 7.59 (2H, br) ppm; IR (KBr) *v*: 3307, 1510, 1022, 786 cm^{-1}.

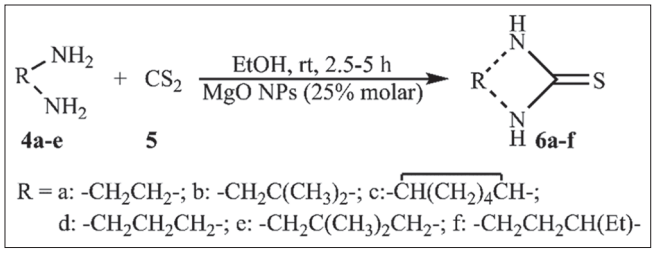

Figure 2: Steps of the synthesis of imidazolidines and tetrahydropyrimidines derivatives

5,5-Dimethyltetrahydropyrimidine-2(1H)-thione (6e)

m.p. 228°C–230°C; ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.91 (6H, s), 3.31 (4H, s), 7.88 (2H, br) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 175.1, 51.2, 25.6, 23.7 ppm; IR (KBr) *v*: 3316, 1491, 1075, 763 cm^{-1}; Anal. Calcd. for $C_6H_{12}N_2S$: C 49.96, H 8.39, N 19.42, S 22.23; found: C 49.93, H 8.44, N 19.46, S 22.17.

4-Ethyltetrahydropyrimidine-2(1H)-thione (6f)

m.p. 139°C–140°C; ^1H NMR (DMSO-d_6, 400 MHz) δ: 0.84 (3H, t, J = 7.4 Hz), 1.39–1.48 (2H, m), 1.77–1.84 (2H, m), 3.07–3.17 (3H, m), 7.82 (1H, br), 7.89 (1H, br) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 175.3, 51.5, 38.3, 27.3, 23.7, 9.4 ppm; IR (KBr) *v*: 3316, 1491, 1075, 763 cm^{-1}; Anal. Calcd. for $C_4H_8N_2OS$: C 36.35, H 6.10, N 21.19, S 24.25; found: C 36.41, H 6.15, N 21.16, S 24.23.

Synthesis of MgO nanoparticles

MgO NPs were synthesized in size 23.7–25.7 nm through sol–gel method.[25] 25 ml of 0.008 M NaOH was gradually added to a stirring mixture of $MgNO_3$ (12.83 g) and starch (0.1 g). Mixture was stored for 24 h at room temperature. Precipitates were collected and heated at 300°C for 4 h to produce MgO NPs. NPs were characterized using X-ray diffractometer and scanning electron microscopy (SEM) techniques [Figures 3 and 4].

Preparation of glycine solution

Glycine purchased from Sigma-Aldrich was sterilized by filter 0.22 µm.[23]

Preparation of bacterial suspension

V. fluvialis (IBRC-M 10800) was purchased as lyophilized form from the Iranian Biological Resource Center, Tehran, Iran. Bacterium was cultured in Mueller–Hinton broth at 30°C for 24 h. The 0.5 McFarland turbidity (1.5 × 10^8 CFU/ml) of bacterium was spectrophotometrically prepared, which was considered as stored source.[26]

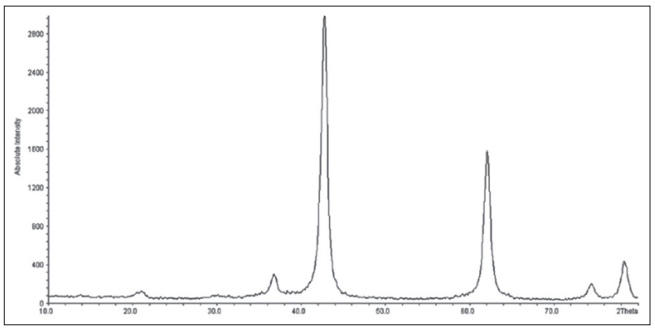

Figure 3: X-ray diffractometer spectrum of MgO nanoparticles

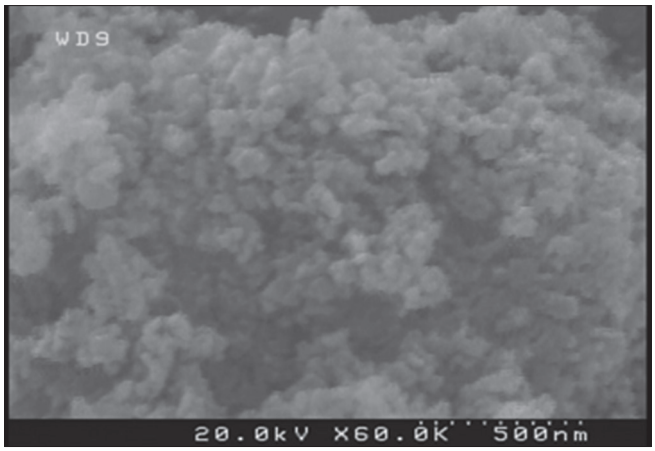

Figure 4: Scanning electron microscopy image of MgO nanoparticles

Determination of the minimum inhibitory concentration

All antimicrobial susceptibility tests were done through broth microdilution and disk diffusion methods according to the CLSI guidelines and repeated three times.[26] The results were reported as the mean of these experiments. The antibiotic ciprofloxacin was applied as positive control. In minimum inhibitory concentration (MIC) experiment, initial bacterial suspension was diluted 150 times to achieve a concentration of 1×10^6 CFU/ml. 10 µl of diluted bacterial suspension and 170 µl of Mueller–Hinton broth were added to each well in a 96 well microplate. 20 µl of different concentrations of derivatives was added to wells to achieve the final concentrations in the range of 8192-4 µg/ml. Microplates were placed in a shaking incubator at 30°C for 24 h. MIC values were determined as the lowest concentration in which the turbidity of bacterial growth was not observed.

Determination of the minimum bactericidal concentration

A sample of all wells without turbidity in MIC test was cultured in Mueller-Hinton agar and incubated at 30°C for another 24 h.[27] The lowest concentration inhibited the visible growth of bacterial colonies was reported as minimum bactericidal concentration (MBC) values.

Measurement of the inhibition zone diameter

100 µl of initial bacterial suspension was spread on Mueller-Hinton agar. Sterile blank discs were placed on the agar media. 10 µl of compounds at a concentration of 10240 µg/ml were poured onto them. Plates were incubated under similar conditions. Visible inhibition zone diameters (IZDs) were measured by caliper.

Results

No inhibitory activity was observed with MgO NPs and glycine [Table 1]. In thiazoles 3a-f, only derivative 3e could block the growth of pathogen with IZD = 7.1 mm, MIC = 2048 µg/ml, and MBC = 4096 µg/ml. Imidazolidine derivatives 6a and b and tetrahydropyrimidine derivatives 6d-f showed antibacterial properties against *V. fluvialis* with IZDs = 6.7-19.1 mm, MICs = 256-2048 µg/ml, and MBCs = 1024-4096 µg/ml. The best inhibitory activity was recorded with imidazolidine-2-thione (6a).

Table 1: Antibacterial effects of compounds against *Vibrio fluvialis*

Compounds	IZD[a]	MIC[b]	MBC[c]
3a	-	-	-
3b	-	-	-
3c	-	-	-
3d	-	-	-
3e	7.1	2048	4096
3f	-	-	-
6a	19.1	256	1024
6b	7.8	2048	4096
6c	-	-	-
6d	7.5	2048	4096
6e	6.7	2048	4096
6f	7.4	2048	4096
Glycine	-	-	-
MgO NPs	-	-	-
Ciprofloxacin	23.6	4	8

[a]mm; [b]µg/ml, [c]µg/ml. IZD: Inhibition zone diameter, MIC: Minimum inhibitory concentration, MBC: Minimum bactericidal concentration

Discussion

The excessive consumption of antibiotics has led to the spread of resistant bacterial strains. *V. fluvialis* is an emerging pathogen that its standard and drug-resistant strains are rapidly expanding. In this research project, antimicrobial potentials of glycine, MgO NPs, and synthetic heterocyclic compounds including thiazoles 3a-f, imidazolidines 6a-c, and tetrahydropyrimidines 6d-f were assessed on standard strain of *V. fluvialis*.

Glycine did not show inhibitory activity against *V. fluvialis*. It was suggested that this amino acid could block the growth of bacteria, especially Gram-positive strains by inhibiting peptidoglycan synthesis.[28] It was found that chloro and bromoglycine derivatives could more efficiently inhibit the activity of *B. subtilis*, although they were ineffective on *Salmonella enterica*.[29] In addition, no antimicrobial activity has been observed with glycine betaine.[30]

No antimicrobial activity was recorded with MgO NPs. These NPs are effective on bacteria through generation of oxygen-free radicals, alkalization of environment, and destruction of cell wall.[31] Factors such as size, pH, form, and concentration affect antibacterial properties. They were more effective on Gram-positive bacteria than Gram-negative strains.[32] They are ineffective against bacteria of the family *Vibrionaceae* such as *Vibrio harveyi* and *Vibrio parahaemolyticus*.[33]

Derivative 3e was the only effective thiazole on *V. fluvialis*. It contains a thiazolone ring, unlike derivatives 3a-d, it

contains a thiazolone ring. Molecular structure of heterocycle 3f is similar to 3e, except that it contains methyl substituent on the 5-position of the thiazolone ring instead of hydrogen. Inhibition of DNA gyraseB enzyme or HFq protein was recommended for their action mechanism.[8,34] A variety of antibacterial activities were observed with compounds containing thiazole ring; substituents including phenyl, nitro, chloro, fluoro, bromo, and fused or attached heterocycles have improved their inhibitory effects.[8] Antimicrobial potential of thirty thiazole derivatives were evaluated by Bharti *et al.* against *V. cholera*; only two compounds containing bromophenyl and diphenyl substituents were effective on this pathogen.[35] Similar inhibitory activities were observed with some chlorothiazole derivatives on *Vibrio parahaemolyticus*.[36]

Antibacterial activity was recorded with imidazolidines 6a and b. It seems that antibacterial effects of imidazidines 6a-c had decreased with increasing the molecular volume. Imidazolidine derivatives could inhibit dihydrofolate reductase, which reduces dihydrofolic acid to tetrahydrofolic acid and lipid synthesis.[37] A variety of biological activities such as antitumor, antiviral, and antifungal were observed with *N*-aryl imidazolidineiminothiones;[38] they were quite successful in inhibiting *E. coli*, *P. aeruginosa*, and *B. subtilis*.

All tetrahydropyrimidines 6d-f were effective on *V. fluvialis.* Molecular volume has been ineffective on antibacterial activity. Inhibitory activity of tetrahydropyrimidine derivatives was evaluated on pathogenic bacteria such as *E. coli*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, and *B. subtilis*.[39-41]

Conclusion

To conclude, some synthetic heterocycles, especially imidazolidine-2-thion (6a) showed inhibitory activity against *V. fluvialis*, while their effects were not significant in comparison with ciprofloxacin. Introduction of new substituents on these heterocyclic compounds or their utilization as ligand in complexes can improve antibacterial effects; it must be considered in future researches.

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Conflicts of interest

There are no conflicts of interest.

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