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Short Communication

A Comparative Study on the Antibacterial Effects of Some Newly Synthesized Thiazole, Imidazolidine and Tetrahydropyrimidine Derivatives Against *Bacillus cereus* and *Salmonella typhimurium*

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ABSTRACT

Background: Bacillus cereus and Salmonella typhimurium are important human pathogenic bacteria. The spread of strains of drug-resistant these pathogens has encouraged researchers to identify and use novel antibacterial compounds. In this research project, we studied antibacterial effects of some newly synthesized thiazole, imidazolidine and tetrahydropyrimidine derivatives against B. cereus and S. typhimurium.

Methods: 2-(E)-Cyano(thiazolidin-2-ylidene)thiazoles 1-4 and (imidazolidin or tetrahydropyrimidin-2-ylidene)malononitriles 5-11 were synthesized. Then, the disk diffusion and broth microdilution methods were applied to evaluate antibacterial effects. Results were recorded as the minimum inhibitory concentrations (MICs) and the growth inhibition zone diameters.

Results: The in vitro assessment of antibacterial effects showed that only thiazole derivative 4 had considerable inhibitory effects against B. cereus and S. Typhimurium, whereas the others didn't have so. The inhibitory effects of thiazole derivative 4 against B. cereus and S. typhimurium were proven according to the MICs 125 and 500 µg/mL and the growth inhibition zone diameters 19.2±0.1 and 8.4±0.2 mm, respectively.

Conclusion: The antibacterial effects of thiazole, imidazolidine and tetrahydropyrimidine derivatives were different, these effects were observed only in thiazole derivative 4. It could be due to the presence of 4-thiazolone ring in derivative 4, witch could reinforce these effects. After confirming that compound 4 is bactericidal against B. cereus and S. typhimurium, further studies can be accomplished on the determination of the cytotoxic and therapeutic effects of this compound in laboratory animals.

Introduction

Bacillus cereus and *Salmonella typhimurium* are zoonotic and foodborne pathogens that infect a wide variety of animal species and human. These pathogens can cause food poisoning and diarrhea; The elderly individuals, pregnant women and immunocompromised patients are at greater risk. The use of antibiotics is the most common method to harness bacteria but thier overuse has resulted in the advent of antibiotic-resistant strains which has retarded the disease treatment. In recent years, researchers have identified the some novel antibacterial compounds to inhibit the drug-resistant strains such as *B. cereus* and *S. typhimurium*.[1,2]

Thiazoles have a crucial role in active biological compounds. For instance, the thiazole ring exists in vitamin B_1 which is the important coenzyme of the carboxylase enzyme. Some of the thiazole derivatives are applicable as drug in treatment of cancer, blood cholesterol, blood pressure and HIV virus infection.[3] Also, antioxidant and anti-inflammatory activities and inhibitory effects aginst parasites such as *Anopheles mosquito* or *Trypanosoma* and fungi such as *Candida albicans* have been observed with these compounds.[4-8] Scientists have substantiated the *in vitro* potency of thiazole derivatives to inhibit the bacterial pathogens like *Staphylococcus aureus*, *Escherichia coli*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Pseudomonas fluorescens* and *Streptococcus faecalis*.[9] Many researchers have implied to the inhibitory potency of thiazole derivatives against bacteria by measuring the growth inhibition zone diameter or MIC or both and we can briefly mention some of the following works; Cheng and colleagues in 2013 showed the *in vitro* potency of thiazole derivatives to inhibit *E. coli*, *S. aureus* and *B. subtilis* bacteria by measuring MIC.[10] Shah and colleagues in 2012 asserted

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the *in vitro* power of thiazole compounds to inhibit *Pseudomonas aeruginosa*, *S. aureus* and *B. subtilis* by the growth inhibition zone diameter.[11] Bondoc and colleagues in 2007 reported the *in vitro* activity of thiazole derivatives against *E. coli* and *B. megaterium* organisms by measuring MICs.[12] Juspin and colleagues in 2010 proved the *in vitro* activity of thiazole derivatives by means of MIC and the growth inhibition zone diameter against *Pseudomonas aeruginosa*, *S. aureus* and *Enterococcus hirae*.[13] Sarojini and colleagues in 2010 reported the *in vitro* power of thiazole compounds to inhibit *E. coli*, *Klebsiella pneumoniae* and *S. Aureus*.[14]

In recent years, the imidazolidine derivatives have attracted researchers to inhibit tumor cells, *Leishmania parasite*, *Aspergillus* and *Fusarium* fungi.[15-17] Studies have shown the antibacterial effects of imidazolidine derivatives against pathogenic agents such as *Enterococcus faecalis*, *Escherichia coli* and *Staphylococcus aureus*.[18]

Recent surveys have represented the function of tetrahydropyrimidine derivatives to inhibit *Mycobacterium tuberculosis* bacterium and *Aspergillus niger* and *Candida albicans* fungi.[19] Several derivatives of this substrate were developed in order to treat Alzheimer's and infectious diseases.[20,21] Antibacterial effects of tetrahydropyrimidine derivatives have been substantiated *in vitro* against pathogens like *Klebsiella pneumonia* and *Pseudomonas aeruginosa*.[22]

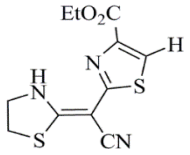
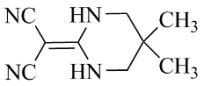
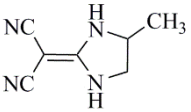
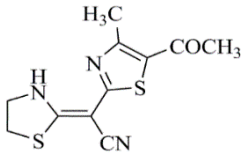
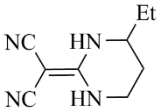
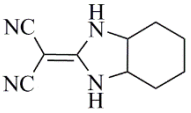
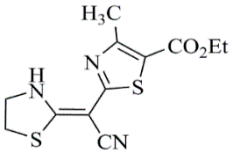
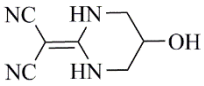
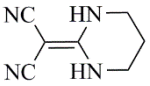
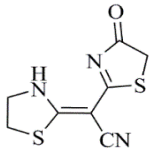
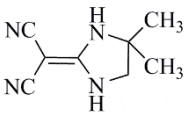
The broad spectrum of biological activities of thiazole, imidazolidine and tetrahydropyrimidine derivatives has encouraged researchers to develope new synthetic methods. Antibacterial evaluation was one of the first examinations performed after synthesizing these compounds. In this study, we have evaluated the antibacterial effects of novel thiazole, imidazolidine and tetrahydropyrimidine deravetives, which have recently been synthesized in Iran, against *B. cereus* and *S. typhimurium*.

Material and Methods

Synthesis of compounds

Thiazole derivatives 1-4, imidazolidine and tetrahydropyrimidine derivatives 5-11 were prepared according to the literature procedures [3] and [23].[3,23] The chemical structure of compounds was confirmed by elemental analysis, ^{1}HNMR, ^{13}CNMR and IR spectrometry, which have been presented in the Table1.

Table 1. The structure of compounds 1-11.

Compound	Structure	Compound	Structure	Compound	Structure
1		**5**		**9**	
2		**6**		**10**	
3		**7**		**11**	
4		**8**			

Ethyl 2-[(*E*)-cyano(thiazolidin-2-ylidene)methyl]thiazole-4-carboxylate (1)
(*E*)-2-(5-Acetyl-4-methylthiazol-2-yl)-2-(thiazolidin-2-ylidene)acetonitrile (2)
Ethyl 2-((*E*)-cyano(thiazolidin-2-ylidene)methyl)-4-methylthiazole-5 carboxylate (3)
(2*E*)-2-(4,5-Dihydro-4-oxothiazol-2-yl)-2-(thiazolidin-2-ylidene)acetonitrile (4)
2-(5,5-Dimethyltetrahydropyrimidin-2(1*H*)-ylidene)malononitrile (5)
2-(4-Ethyltetrahydropyrimidin-2(1*H*)-ylidene)malononitrile (6)
2-(5-Hydroxytetrahydropyrimidin-2(1*H*)-ylidene)malononitrile (7)
2-(4,4-Dimethylimidazolidin-2-ylidene)malononitrile (8)
2-(4-Methylimidazolidin-2-ylidene)malononitrile (9)
2-(Octahydro-2*H*-benzo[*d*]imidazol-2-ylidene)malononitrile (10)
2-(Tetrahydropyrimidin-2(1*H*)-ylidene)malononitrile (11)

Preparation of bacterial suspension and chemical solutions

B. cereus (PTCC 1015) and *S. typhimurium* (PTCC 1596) were obtained from Iranian Research Organization for Science and Technology (IROST). The bacteria were cultured in the Mueller-Hinton agar (MHA) medium (Merck®, Germany) in 37 ºC for 24 h. Henceforth, under sterile conditions for MHA medium and in logarithmic growth phase, the concentration of 10^6 CFU/mL was obtained using spectrophotometer. Each bacterium was assigned as a stock solution.[24] All of the synthesized derivatives were resolved in DMSO by the concentration of 8000 µg/mL.

Determination of the minimum inhibitory concentration (MIC)

The MIC test was performed using broth microdilution method in a sterile 96-well plate according to the CLSI guideline. Average results of three performed tests were calculated. First, 100 µL of Mueller-Hinton broth (MHB) medium (Merck®, Germany) was added to each well. Then, 100 µL of thiazole, imidazolidine and tetrahydropyrimidine derivatives (in control groups, 100 µL of penicillin or gentamicin antibiotics by the concentration of 512 µg/mL) (Sigma®) were added to the first well and then, 100 µL of this mixture was embedded into the second well. Similarly, dilution procedure was done in other wells. 10 µL of bacterial suspension was also added to each well. For negative control, 100 µL of MHB, 100 µL of DMSO and 10 µL of bacterial suspension were added to the last well in each row. The result was recorded after 24 h incubation in 37 ºC. The turbidity and lucidity in each well indicated growth or lack of growth for bacteria, respectively. The last well witch didn't show any turbidity, was reported as MIC.[24]

Determination of the growth inhibition zone diameter

First, the superficial bacterial culture was accomplished in MHA medium with a swab impregnated to bacterial suspension. Then, 15 µL of obtained MIC for derivatives and antibiotics (15 µL of DMSO for negative control) was shed on blank sterile disks and incubated for 24 h at 37 ºC. Finally, the growth inhibition zone diameter was measured with coulisse.[24]

Data analysis

All experiments were repeated independently three times. The results of the growth inhibition zone diameter have been rendered as average ± standard deviation. Data were analyzed statistically by ANOVA and Tukey's tests at a significance level of P-Vaule<0.05 using the SPSS statistical software (version 22).[24]

Results and Discussion

The results indicated that imidazolidine and tetrahydropyrimidine compounds 5-11 and thiazole derivatives 1-3 didn't have inhibitory effects against *B. cereus and S. typhimurium* bacteria, only the inhibitory effects of thiazole derivative 4 were recorded against these bacteria with the growth inhibition zone diameters = 19.2±0.1, 8.4±0.2 mm and MICs = 125, 500 µg/mL, respectively. In the antibiogram test, the most susceptibility was measured for gentamicin with MIC = 1 µg/mL against *S. typhimurium*. The results confirmed that DMSO as solvent didn't show inhibitory effects against *B. cereus and S. typhimurium* (Tables 2 and 3).

Table 2. The growth inhibition zone diameter sizes (mm) of synthesized derivatives and antibiotics against *B. cereus* and *S. typhimurium*.

Derivatives / Antibiotics	1	2	3	4	5	6	7	8	9	10	11	DMSO	Gentamicin	Penicillin
B.cereus	—	—	—	19.2±0.1	—	—	—	—	—	—	—	—	17.1±0.1	16.4±0.1
S.typhimurium	—	—	—	8.4±0.2	—	—	—	—	—	—	—	—	14.5±0.3	12.2±0.2

—: indicates no inhibitory effects at maximum concentration

Table 3. MIC values (µg/mL) of synthesized derivatives and antibiotics against *B. cereus* and *S. typhimurium* .

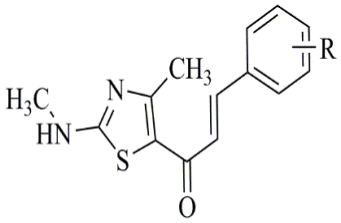
Derivatives/ Antibiotics	1	2	3	4	5	6	7	8	9	10	11	DMSO	Gentamicin	Penicillin
B.cereus	—	—	—	125	—	—	—	—	—	—	—	—	8	8
S.typhimurium	—	—	—	500	—	—	—	—	—	—	—	—	1	8

—: indicates no inhibitory effects at maximum concentration

In this study, four tetrahydropyrimidine derivatives didn't show inhibitory effects against *B. cereus and S. typhimurium* bacteria. Antibacterial evaluation of tetrahydropyrimidine derivatives against some bacterial pathogens by Vishwakarma and colleagues showed that among the tested bacteria such as *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus subtilis* and *Bacillus mycoides*, only some of them possessed inhibitory effects.[25] This research confirmed that tetrahydropyrimidine derivatives didn't have broad-spectrum activity against these different types of bacteria. Also, three derivatives of imidazolidine didn't have inhibitory effects against *B. cereus and S. typhimurium*, but previously some

imidazolidine derivatives had shown the ability to inhibit bacteria like *Staphylococcus aureus* and *Escherichia coli*, these inhibitory effects are due to substituents such as chlorine atom.[26] 1-Methyl-4-nitro-1*H*-imidazole is a heterocyclic compound known as antibacterial agent for a long time due to its broad spectrum against gram positive and gram negative bacteria and other organisms, experiments asserted the capability of this substance to inhibit or damage *Micrococcus luteus*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* by producing many different kinds of free radicals, the advantage which isn't observed in derivatives 8-10.[27]

The only inhibitory effects observed in this research were related to thiazole derivative 4 and no inhibitory effect was seen for analogues 1-3. It can be due to difference in the structure of derivatives. Thiazole derivative 4 consists of a 4-thiazolone ring which has been found to possess strong antimicrobial activities against a wide variety of bacteria.[28,29] We could prove the potent effects of this compound against *E. Coli*, *S. typhimurium*, *B. cereus* and *L. monocytogenes*.[9] Liaras and colleagues have shown the inhibitory effects of thiazole-based chalcones against *B. cereus* and *S. typhimurium* with MIC = 22.93-38.75 µg/mL. Comparison of these compounds with derivative 4 shows that thiazole nucleus and the carbonyl group are present in both systems, nevertheless, the inhibitory potency of these derivatives is more than derivative 4 that may be due to the existence of chlorine atoms as mono or dichlorophenyl substituent (Figure 1).[30]



R = H; 4-NO_2; 3-NO_2; 4-Cl; 3-Cl; 2-Cl; 4-OMe; 2-OMe; 2,6-diCl; 2,4-diCl

Figure 1: Thiazole-based chalcones as potent antimicrobial agents.

The studies on the antibacterial effects of thiazoles have suggested that these derivatives can inhibit the activities of many enzymes like DNA gyrase B (quinolone antibiotics inhibit DNA gyrase A) or genes such as *fabH* (which has a vital role in regulation of fatty acid metabolism in bacteria).[31,32]

Conclusion

It can be concluded that the derivatives containing 4-thiazolone ring could have inhibitory effects against bacteria. Synthesis of new heterocyclic compounds containing this structure, study of their antibacterial activities against various bacteria especially resistant strains and toxicity effects of synthesized deravetives on laboratory animals are suggested for next researches.

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Conflict of interest

The authors report no conflicts of interest.

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