Acta Pharm. Sci. Vol 57 No: 1. 2019
DOI: 10.23893/1307-2080.APS.05707

Antimicrobial Evaluation of Trisubstituted 2-piperazinyl Thiazoles

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ABSTRACT

Thiazole and basic nitrogen containing rings are important chemical moieties of antimicrobial drugs. In recent, third generation cephalosporins include thiazole ring system. In this study, we synthesized 33 piperazine thiazole derivatives which were thought to show antimicrobial activity. Synthesize were realized with good yield using the method which reports the anticholinesterase properties of these compounds. Similar compounds with the same scaffold (2, 4, 5 trisubstituted thiazoles) are investigated for antimicrobial activity. Compounds **23-27** exhibited MIC: 256 μM against *S. aureus* ATCC 25923. Besides, 27-33 group showed MIC: 256 μM against *K. pneumoniae* UC57 and *B. cereus*. It is remarkable that the compound **27** showed antimicrobial activity against 4 different microorganisms and **26** showed antimicrobial activity against *L. monocytogenes by* MIC: 32 μM which is same as the standart chloramphenicol.

Keywords: thiazole, piperazine, antimicrobial, trisubstituted thiazole, N-benzoylthioamide.

INTRODUCTION

Bacterial resistance to the treatment of infectious diseases is the main problem. Many classes of antibiotics are facing resistance and have initiated new efforts to develop new derivatives and discover new chemical classes.[1] Gram positive and gram-negative bacteria such as *Escherichia coli, Staphylococcus aureus, Micrococcus luteus, Bacillus subtilis, Bacillus cereus, Pseudomonas aeruginosa* etc. are responsible for many diverse infections which even can cause of death.[2]

Thiazole and basic nitrogen containing rings are important chemical moieties of antimicrobial drugs. Recently, third generation cefepime, ceftriaxone, cefix-

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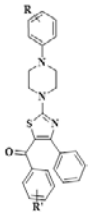
(Received 03 December 2018, accepted 23 December 2018)

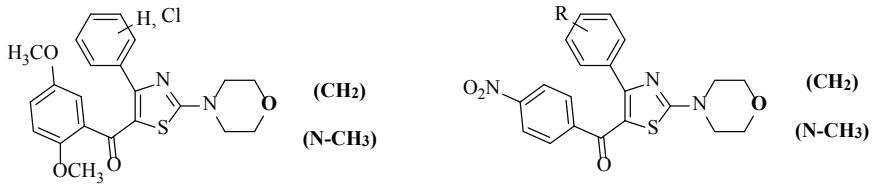
ime, ceftazimide drugs are wide spectrum cephalosporins containing thiazole ring system. Also, new studies on compounds with thiazole moiety are investigated.[3-5] List of the synthesized compounds, which were first evaluated for their acetylcholinesterase inhibitor activity by our group[6] is given in Table 1.

Table 1. Synthesized compounds

	C. no	R	R'	C. no	R	R'	C. no	R	R'
	**1**	2-Cl	H	**12**	3-Cl	H	**23**	4-Cl	H
	2	2-Cl	3-CH_3	**13**	3-Cl	3-CH_3	**24**	4-Cl	3-CH_3
	3	2-Cl	4-CH_3	**14**	3-Cl	4-CH_3	**25**	4-Cl	4-CH_3
	4	2-Cl	3-OCH_3	**15**	3-Cl	3-OCH_3	**26**	4-Cl	3-OCH_3
	5	2-Cl	4-OCH_3	**16**	3-Cl	4-OCH_3	**27**	4-Cl	4-OCH_3
	6	2-Cl	3-F	**17**	3-Cl	3-F	**28**	4-Cl	3-F
	7	2-Cl	4-F	**18**	3-Cl	4-F	**29**	4-Cl	4-F
	8	2-Cl	3-Cl	**19**	3-Cl	3-Cl	**30**	4-Cl	3-Cl
	9	2-Cl	4-Cl	**20**	3-Cl	4-Cl	**31**	4-Cl	4-Cl
	10	2-Cl	3-NO_2	**21**	3-Cl	3-NO_2	**32**	4-Cl	3-NO_2
	11	2-Cl	3-NO_2	**22**	3-Cl	3-NO_2	**33**	4-Cl	3-NO_2

Similar compounds with the same scaffold (2, 4, 5 trisubstituted thiazoles) are investigated for antimicrobial activity. These compounds also have the same substituents on the thiazole ring such as piperazine (morpholine) at 2nd position, phenyl at 4th position and benzoyl at 5 th position.

As a pioneer of this study, 2, 4, 5-trisubstituted thiazole derivatives (I) were screened for antimicrobial activity against *E. coli, S. aureus, M. luteus, B. subtilis, B. cereus, P. aeruginosa* bacterial strains by paper disc diffusion method. In this study, all 7 compounds showed moderate to good activity. According to zone diameters, activity was found approximately %40-45 of ciprofloxacin.[7]



Darji et al. 2012a **I**

Darji et al. 2012b **II**

Figure 1. Trisubstituted thiazole compounds with antimicrobial activity

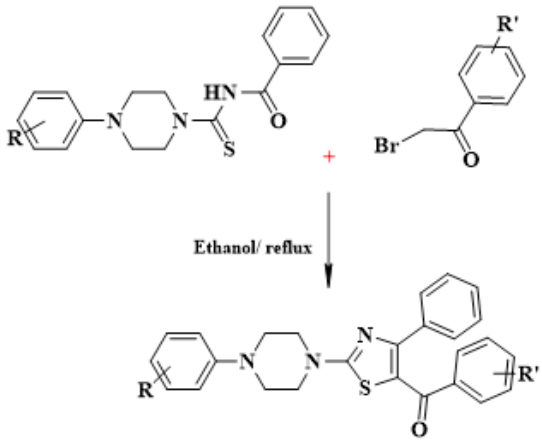
In another study of the same group, similar compounds (II) were evaluated for antimicrobial activity against same strains. 7 of 8 compounds exhibited good activity, which was very close to standard ciprofloxacin. [8]

In this study, we synthesized 33 compounds, which are thought to show antimicrobial activity. Synthesize were realized with good yield using the method which reports the anticholinesterase activity of these compounds.[6]

METHODOLOGY

Chemistry

Synthesis of 33 compounds were carried out by the method used in a recent study.[6] Following the method, N'-benzoyl piperazine thioureas (10 mmol) and bromoacetophenones (10 mmol) reacted to give the compounds. The equivalent mole of materials was boiled in ethyl alcohol until the reaction was being completed. After cooling, it was poured into the water and neutralized with $NaHCO_3$ solution. The products were crystallized from ethanol. [6,9]



Scheme 1. Synthesis of compounds

Antimicrobial Activity Test

Antimicrobial activity test was determined on both gram positive and gram-negative bacteria strains including, *Escherichia coli* ATCC 25922, *Klebsiella pneumonia* UC57, *Enterococcus faecalis* ATCC 29212, *Listeria monocytogenes* ATCC 7644, *Salmonella typhi* ATCC 19430, Pseudomonas aeriginosa ATCC 27853, *Staphylococcus aureus* ATCC 25923, *Bacillus cereus* ATCC 7064, *Listeria monocytogenes* ATCC 7644. Clinically isolated *Acinetobacter baumannii* and *Shigella dysenteria* were provided by Hospital of İstanbul Medipol University. All these compounds were dissolved in DMSO to prepare stock solution at 10 mg/mL. Broth microdilution method was carried out in accordance with the relevant 2012 CLSI standard. [10,11] The bacterial strains were inoculated and grown to mid-log phase in Muller Hinton Broth (MHB) at 37 degrees. Bacterial inoculum suspensions were prepared at a final concentration of approximately 1 x105 cfu/ml. Materials were 2-fold serially diluted to make different concentration, from 0.5 to 256 micromolar. Equal volumes of inoculum suspensions were than added to each well of sterile 96 well-plate with different concentration of materials, and the plate was incubated 18 h at 37 °C. Positive or negative control were set to wells with and without bacteria, respectively. Besides, chloramphenicol is used as positive control. MIC was defined as the lowest concentration of materials that prevented visible turbitidy by visual inspection. Experiments were performed duplicate.

RESULTS

Chemistry

Synthesis of compounds were carried out up to %80 yield. Characterizations were corresponded our previous study IR, ^{1}H-NMR and ^{13}C-NMR results were previously reported in the related paper.[6]

Antimicrobial activity

No antimicrobial activity was detected against *E. coli, S. Typhii, P. aeriginosa*, *S. dysanteria* ve *A. Baumanni* bacteria. Activity on the other bacteria is summarized in Table 2.

27-33 compound series against *K. pneumoniae* and *B. Cereus* microorganisms are effective. It is important that these compounds are effective against two different microorganisms in serials. When the whole table was examined, the compounds in the range 23-33 were found to be effective against to the microorganisms. This indicates that the 4-chlorophenyl structure attached to the piperazine ring is beneficial for antimicrobial activity. The structures in

the 23-27 group against *S. aureus* have been found effective. In this group, electron donating substituents (R') were prominent. 13, 17, 27, 31 (MIC: 256 μM), 32 (MIC: 128 μM), 33 (MIC: 64 μM) effects have been found against *E. facealis*. Chloramphenicol has no effect on this microorganism.

Table 2. MIC of te materials against bacteria.

Compounds	MIC (μM)				
	K. pneumoniae UC57	S. aureus ATCC 25923	E. faecalis ATCC 29212	B. cereus	L. monocytogenes ATCC 7644
1	-	-	-	-	-
2	-	-	-	-	-
3	-	-	-	≥ 256	-
4	-	-	-	-	-
5	-	-	-	-	-
6	-	-	-	-	-
7	-	-	-	-	-
8	-	-	-	-	-
9	-	-	-	-	-
10	-	-	-	-	-
11	-	-	-	-	-
12	-	-	-	-	-
13	-	-	≥ 256	-	-
14	-	-	-	-	-
15	-	-	-	-	-
16	-	-	-	-	-
17	-	-	≥ 256	-	-
18	-	-	-	-	-
19	-	-	-	-	-
20	-	-	-	-	-
21	-	-	-	≥ 256	-
22	-	-	-	-	≥ 256
23	-	≥ 256	-	-	-
24	-	≥ 256	-	≥ 256	-
25	-	≥ 256	-	-	-
26	-	≥ 256	-	-	≥ 32
27	≥ 256	≥ 256	≥ 256	≥ 256	-
28	≥ 256	-	-	≥ 256	-
29	≥ 256	-	-	≥ 256	-
30	≥ 256	-	-	≥ 256	-
31	≥ 256	-	≥ 256	≥ 256	-
32	≥ 256	-	≥ 128	≥ 256	-
33	≥ 256	-	≥ 64	≥ 256	-
Chloramphenicol	≥ 256	≥ 256	-	≥ 32	≥ 32

Against *L. monocytogenes*, compounds 22 (MIC: 256 μM) and 26 (MIC: 32 μM) were found active. Although it is not appropriate to make a chemical interpretation here, the activity of compound 26 is the same as the standard compound chloramphenicol.

CONCLUSION

Compound 27 has effect on 4 of 5 microorganisms with 256 MIC values. Besides, 27-33 has 256 μM MIC value against *K. pneumoniae* and *B. cereus* as series. This empowers the idea that activity is related to chemical structure. Furthermore 23-27 on *S. aureus* has antimicrobial effect as a chemical series. These results can be associated with the chemical structure and efforts can be continued in these chemical groups for investigating new antimicrobial drugs.

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