

SYNTHESIS AND ANTIMICROBIAL ACTIVITY
OF SOME 4-ALKYL AND ARYL SUBSTITUTED
[(2-OXOBENZOTHAZOLIN-3-YL) ACETYL]-3-SEMICARBAZIDES
AND THIOSEMICARBAZIDES

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Key Word Index

(2-Oxobenzothiazolin-3-yl)acetohydrazide, alkyl isocyanate, aryl isocyanate, alkyl isothiocyanate, aryl isothiocyanate, antifungal activity, antibacterial activity.

ABSTRACT

(2-Oxobenzothiazolin-3-yl)acetohydrazide as a starting material has been prepared by stirring of (2-oxobenzothiazolin-3-yl)acetate with hydrazine hydrate in alcohol for 6 days at room temperature. Then fifteen alkyl and aryl substituted [(2-oxobenzothiazolin-3-yl)acetyl]-3-semicarbazide and thiosemicarbazide derivatives have been synthesized by refluxing (2-oxobenzothiazolin-3-yl)acetohydrazide with alkyl and aryl substituted isocyanates and isothiocyanates in absolute ethanol for 3 hours. All the compounds in this study are reported for the first time.

Antimicrobial activities of the synthesized compound have been tested against yeast-like fungi such as *Candida albicans*, *Candida stellatoidea* and Gram(+) microorganisms such as *Staphylococcus aureus*, *Streptococcus faecalis*, *Mycobacterium tuberculosis* and Gram(-) microorganisms such as *Escherichia coli*, *Pseudomonas aeruginosa*.

INTRODUCTION

2-Oxobenzothiazolin derivatives bearing substituents at position 3 have wide spectrum of biological activity such as antifungal^{1,2} antibacterial², antiallergic³, anti-inflammatory³, antihistamin⁴, anticonvulsant^{5,6}, antinociceptive activity^{7,9}.

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Moreover it is well known that 1-acyl-4substituted thiosemicarbazide derivatives show diverse biological activities like antibacterial^{10,11} antifungal¹², antimycobacteri-
al^{13,14}, antiviral¹⁵, anticonvulsant^{16,17}, cytostatic¹⁸, cardiovascular¹⁹ and hypoglycemic²⁰ activity.

It was also pointed out that some thiosemicarbazides of 1,3,4-thiadiazole deriva-
tives²¹ had antimicrobial activity. In addition there have been several reports on the
antibacterial and antifungal activity of 4(3H)-quinazolinone thiosemicarbazides and
their cyclized products²²⁻²⁴.

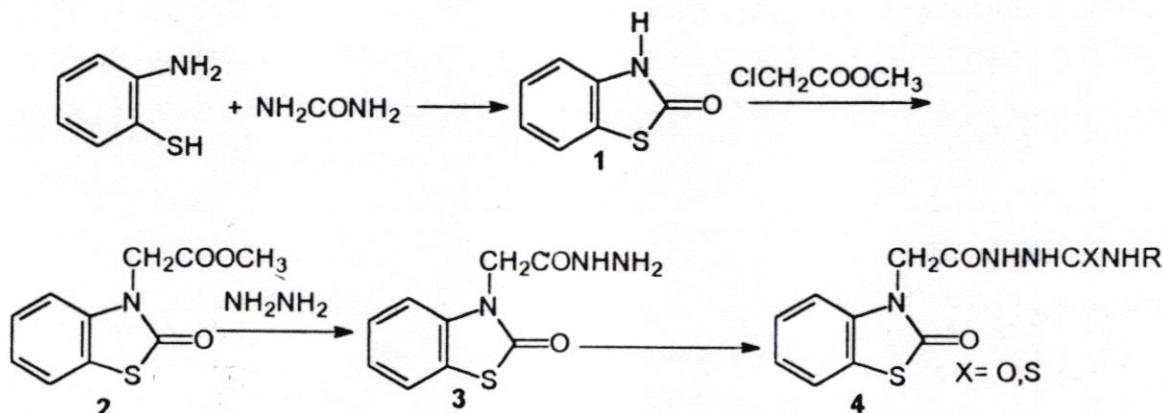
In 1998 Hassan et al. synthesized several derivatives of N¹-(4-benzyl-1-pipera-
zinyl aceto)N⁴-substituted thiosemicarbazides and evaluated their *in vitro* antimicro-
bial activity²⁵. N¹-(4-benzyl-1-piperaziny aceto)N⁴-benzoylthiosemicarbazide deri-
vative was the most active compound. This compound was also found to posses a
significant cytotoxicity against several tumor cell lines.

In this study, for the development of new biological active 2-oxobenzothiazolin
compounds, a series of novel alkyl and aryl substituted [(2-oxobenzothiazolin-3-
yl)acetyl]-3-semicarbazide and thiosemicarbazide derivatives were synthesized. All
these compounds have been tested on antimicrobial activity.

RESULTS AND DISCUSSION

In our previous study, (2-oxobenzothiazolin-3-yl)acetohydrazide 3 and its hydra-
zone derivatives were synthesized and anticonvulsant activity of these compounds
were investigated^{5,6}. Some of them were exhibited promising activity. In this paper,
as a continuation of previous study fifteen [(2-oxobenzothiazolin-3-yl)acetyl]-3-se-
micarbazide and thiosemicarbazide 4a-o derivatives have been synthesized and an-
timicrobial activity of the compounds were evaluated.

Synthesized compounds have been shown Table 1. Synthesis pathway of the
compound 4 derivatives has been given Scheme 1. Chemical structure of compound
4a-o have been elucidated by the data of elemental analysis, IR, ¹H-NMR spectral
data (Table 1 and 2).



Scheme 1. Synthesis of compound 4

The (2-oxobenzothiazolin-3-yl)acetohydrazide **3** which are the starting material have been synthesized according to literature methods^{6,27} using (2-oxobenzothiazolin-3-yl)acetate and hydrazine hydrate in alcohol. The title compounds **4a-o** have been obtained by refluxing compound **3** and corresponding isocyanates and isothiocyanates in alcohol.

Antifungal activities of compounds **4a-o** have been evaluated against two yeast-like fungi using fluconazole as standard. Antibacterial activity of the compounds have been tested three Gram(+) and two Gram(-) microorganisms using ampicillin trihydrate, ciprofloxacin, streptomycin and prothionamide as a standard. The compounds exhibited modest antimicrobial activity. The results of antimicrobial activity test have been shown in Table 3.

Table 1. Physical constant of derivatives alkyl and aryl substituted [(2-oxobenzothiazolin-3-yl)acetyl]-3-semicarbazide and thiosemicarbazide **4** (See structure formula compound **4**).

Comp	R	X	Mp (°C)	Yield	Formula	Elemental Analysis (Calculated/Found)
4a	Phenyl	O	219	61	C ₁₆ H ₁₄ N ₄ O ₃ S	C: 56.13/55.85, H: 4.12/4.07, N: 16.36/16.80
4b	Allyl	O	201	72	C ₁₃ H ₁₄ N ₄ O ₃ S	C: 50.97/51.26, H: 4.61/4.53, N: 18.29/18.10
4c	Cyclohexyl	S	221	68	C ₁₆ H ₂₀ N ₄ O ₂ S ₂	C: 52.73/53.24, H: 5.53/5.84, N: 15.37/15.41
4d	Methyl	S	219	71	C ₁₁ H ₁₂ N ₄ O ₂ S ₂	C: 44.58/44.89, H: 4.08/4.31, N: 18.90/18.84
4e	Allyl	S	217	78	C ₁₃ H ₁₄ N ₄ O ₂ S ₂	C: 48.43/48.63, H: 4.38/4.60, N: 17.38/17.20
4f	Phenyl	S	255	86	C ₁₆ H ₁₄ N ₄ O ₂ S ₂	C: 53.62/54.03, H: 3.94/4.19, N: 15.63/15.79
4g	p-Methoxyphenyl	O	243	31	C ₁₇ H ₁₆ N ₄ O ₄ S	C: 54.83/54.18, H: 4.33/4.36, N: 15.08/14.56
4h	p-Chlorophenyl	S	207	92	C ₁₆ H ₁₃ ClN ₄ O ₂ S ₂	C: 48.92/49.60, H: 3.34/2.98, N: 14.26/14.27
4i	p-Methylphenyl	O	234	42	C ₁₇ H ₁₆ N ₄ O ₃ S	C: 57.29/58.18, H: 4.52/4.55, N: 15.72/15.69
4j	p-Nitrophenyl	S	248	99.5	C ₁₆ H ₁₃ N ₅ O ₄ S ₂	C: 47.64/47.72, H: 3.25/3.48, N: 17.36/17.22
4k	Benzyl	O	230	54	C ₁₇ H ₁₆ N ₄ O ₃ S	C: 57.29/57.71, H: 4.52/4.39, N: 15.72/15.29
4l	Benzyl	S	245	82	C ₁₇ H ₁₆ N ₄ O ₂ S ₂	C: 54.82/54.57, H: 4.32/3.90, N: 15.04/14.79
4m	p-Methoxyphenyl	S	198	79	C ₁₇ H ₁₆ N ₄ O ₃ S ₂	C: 52.56/52.19, H: 4.15/4.28, N: 14.42/14.03
4n	p-Chlorophenyl	O	252	50	C ₁₆ H ₁₃ ClN ₄ O ₃ S	C: 50.99/50.43, H: 3.47/2.91, N: 14.86/14.33
4o	p-Methylphenyl	S	261	76	C ₁₇ H ₁₆ N ₄ O ₂ S ₂	C: 54.82/54.38, H: 4.32/4.22, N: 15.04/14.67

Table 2. Spectral data of compounds synthesized (See structure formula compound 4).

Comp.	IR(cm^{-1})		NMR(δ ppm) (DMSO- d_6)
	C=O (lactam)	N-H (semicarbazide)	
4a	1675	3315	10.35(s, 1H, NH), 9.46(s, 1H, NH), 8.72(s, 1H, NH), 7.70-6.85(m, 9H, Ar-H), 4.66(s, 2H, CH_2CO)
4b	1715	3371	7.93(s, 1H, NH), 7.67(d, 1H, H^a), 7.35(t, 1H, H^b), 7.22(m, 1H, H^c), 7.14(d, 1H, H^d), 6.65(s, 1H, NHCH), 5.85(m, 1H, $\text{CH}_2\text{-CH=CH}_2$), 5.10(m, 2H, $\text{CH}_2\text{-CH=CH}_2$), 4.72(d, 2H, N- $\text{CH}_2\text{-CO}$), 3.68(m, 2H, $\text{CH}_2\text{-CH=CH}_2$)
4c	1668	3271	10.25(s, 1H, NH), 9.60(s, 1H, NH), 9.15(s, 1H, NH), 7.70-7.25(m, 4H, ArH), 4.60(s, 2H, CH_2O), 1.91.1(m, 1H, cyclohexyl.)
4d	1677	3274	10.30(s, 1H, NH), 9.25(s, 1H, NH), 9.15(s, 1H, NH), 7.60(d, 1H, H^a), 7.45(t, 2H, H^b, H^c), 7.30(d, 1H, H^d), 4.75 (s, 2H, CH_2CO), 3.35(s, 3H, NH- CH_3)
4e	1679	3221	10.25(s, 1H, NH), 9.35(s, 1H, NH), 8.40(s, 1H, NH), 7.68(d, 1H, H^a), 7.35(t, 1H, H^b), 7.18(t, 3H, $\text{H}^c, \text{H}^d, \text{H}^e$), 5.80(m, 1H, $\text{CH}_2\text{-CH=CH}_2$), 5.13(m, 2H, $\text{CH}_2\text{-CH=CH}_2$), 4.30(s, 2H, $\text{CH}_2\text{-CH=CH}_2$)
4f	1687	3236	10.50(s, 1H, NH), 9.85 (s, 1H, NH), 9.65(s, 1H, NH), 7.58-7.20(m, 9H, Ar-H), 4.75 (s, 2H, CH_2CO)
4g	1685	3330	10.23(s, 1H, NH), 8.60(s, 1H, NH), 8.15(s, 1H, NH), 7.70-6.80(m, 8H, Ar-H), 4.65 (s, 2H, CH_2CO), 2.45 (s, 3H, OCH_3)
4h	1670	3251	10.55(s, 1H, NH), 9.90(s, 1H, NH), 9.75(s, 1H, NH), 7.70-7.25(m, 8H, Ar-H), 4.70 (s, 2H, CH_2CO)
4i	1684	3316	10.22(s, 1H, NH), 9.46(s, 1H, NH), 8.58(s, 1H, NH), 7.42-7.08(m, 8H, Ar-H), 4.65 (s, 2H, CH_2CO), 2.23 (s, 3H, CH_3)
4j	1712	3310	10.65(s, 1H, NH), 10.25(s, 1H, NH), 9.90(s, 1H, NH), 8.33-7.15(m, 8H, Ar-H), 4.36 (s, 2H, CH_2CO)
4k	1628	3313	10.20(s, 1H, NH), 8.15(s, 1H, NH), 7.65(s, 1H, NH), 7.43-7.12(m, 9H, Ar-H), 4.68 (s, 2H, CH_2CO), 4.23 (d, 2H, NH, $\text{CH}_2\text{-Ar}$)
4l	1709	3303	10.38(s, 1H, NH), 9.47(s, 1H, NH), 8.65(s, 1H, NH), 7.70-7.20(m, 9H, Ar-H), 4.65 (s, 2H, CH_2CO)
4m	1638	3266	10.20(s, 1H, NH), 8.9(s, 1H, NH), 7.95(s, 1H, NH), 7.75-6.95(m, 8H, Ar-H), 5.45 (s, 2H, CH_2CO), 3.75 (s, 3H, CH_3)
4n	1670	3324	10.25(s, 1H, NH), 8.8(s, 1H, NH), 8.36(s, 1H, NH), 7.70-7.05(m, 8H, Ar-H), 4.75 (s, 2H, CH_2CO)
4o	1677	3254	10.45(s, 1H, NH), 9.23(s, 1H, NH), 9.12(s, 1H, NH), 7.7(d, 1H, H^a), 7.40-7.15 (m, 7H, Ar-H), 4.75(s, 2H, CH_2CO), 2.25(s, 3H, CH_3)

As it is seen Table 3, compound 4 derivatives have been more active on Gram(+)bacteria than on Gram(-) bacteria in comparison. Effects of derivatives 4a-o on *Pseudomonas aeruginosa* have been found equal when they were compared with ampicillin trihydrate. Therefore, it can be said that synthesized compounds have promising antibacterial activity on Gram(-) bacteria.

Compounds 4a-o were exhibited too week antitubercular and antifungal activity than streptomycin, prothionamide and fluconazole as using standarts respectively in comparison.

Table 3 . Antimicrobial activity (MIC as molar) of the synthesized compounds.

Comp.	A	B	C	D	E	F	G
4a	9.12×10^{-2}	3.65×10^{-1}	4.48×10^{-2}	3.65×10^{-1}	3.65×10^{-1}	3.65×10^{-1}	3.65×10^{-1}
4b	1.02×10^{-1}	4.08×10^{-1}	5.09×10^{-2}	4.08×10^{-1}	4.08×10^{-1}	4.08×10^{-1}	4.08×10^{-1}
4c	8.57×10^{-2}	3.43×10^{-1}	8.56×10^{-2}	3.43×10^{-1}	3.43×10^{-1}	3.43×10^{-1}	3.43×10^{-1}
4d	1.05×10^{-1}	4.22×10^{-1}	1.05×10^{-2}	4.22×10^{-1}	4.22×10^{-1}	4.22×10^{-1}	4.22×10^{-1}
4e	9.69×10^{-2}	3.87×10^{-1}	4.83×10^{-2}	3.87×10^{-1}	3.87×10^{-1}	3.87×10^{-1}	3.87×10^{-1}
4f	8.70×10^{-2}	3.48×10^{-1}	8.70×10^{-2}	3.48×10^{-1}	3.48×10^{-1}	3.48×10^{-1}	3.48×10^{-1}
4g	7.09×10^{-2}	3.09×10^{-1}	7.71×10^{-2}	3.09×10^{-1}	3.09×10^{-1}	3.09×10^{-1}	3.09×10^{-1}
4h	7.95×10^{-2}	3.18×10^{-1}	7.94×10^{-2}	3.18×10^{-1}	3.18×10^{-1}	3.18×10^{-1}	3.18×10^{-1}
4i	8.76×10^{-2}	3.50×10^{-1}	8.75×10^{-2}	3.50×10^{-1}	3.50×10^{-1}	3.50×10^{-1}	3.50×10^{-1}
4j	7.74×10^{-2}	3.09×10^{-1}	3.86×10^{-2}	3.09×10^{-1}	3.09×10^{-1}	3.09×10^{-1}	3.09×10^{-1}
4k	8.76×10^{-2}	3.50×10^{-1}	8.75×10^{-2}	3.50×10^{-1}	3.50×10^{-1}	3.50×10^{-1}	3.50×10^{-1}
4l	8.39×10^{-2}	3.35×10^{-1}	8.37×10^{-2}	3.35×10^{-1}	3.35×10^{-1}	3.35×10^{-1}	3.35×10^{-1}
4m	8.04×10^{-2}	3.21×10^{-1}	1.61×10^{-1}	3.21×10^{-1}	3.21×10^{-1}	3.21×10^{-1}	3.21×10^{-1}
4n	8.04×10^{-2}	3.21×10^{-1}	8.03×10^{-2}	3.21×10^{-1}	3.21×10^{-1}	3.21×10^{-1}	3.21×10^{-1}
4o	8.39×10^{-2}	3.35×10^{-1}	1.61×10^{-1}	3.35×10^{-1}	3.35×10^{-1}	3.35×10^{-1}	3.35×10^{-1}
Amp.Trihydrate	1.18×10^{-4}	1.93×10^{-3}	-	7.74×10^{-2}	3.09×10^{-1}	-	-
Ciprofloxacin	1.17×10^{-2}	2.32×10^{-2}	-	3.62×10^{-4}	2.89×10^{-2}	-	-
Fluconazole	-	-	-	-	-	2.54×10^{-2}	2.54×10^{-2}
Streptomycin	-	-	3.35×10^{-3}	-	-	-	-
Prothionamide	-	-	1.08×10^{-2}	-	-	-	-

A: *Staphylococcus aureus* ATCC 25923

B: *Streptococcus faecalis* ATCC 19433

C: *Mycobacterium tuberculosis* H37 Rv

D: *Escherichia coli* ATCC 35218

E: *Pseudomonas aeruginosa* ATCC 10145

F: *Candida albicans* ATCC 10231

G: *Candida tropicalis* ATCC 13803.

EXPERIMENTAL

Chemical Studies

Material

Chemicals and all the solvents used in this study were purchased from Merck A. G., Aldrich Chemical.

Instrumental Analysis

Melting points were determined with Electrothermal-9200 Digital Melting Point Apparatus and are uncorrected values.

The IR spectra of the compounds were recorded on a Perkin Elmer 1330 IR spectrophotometer. The ^1H -NMR spectra were recorded on a Bruker 200 FT-NMR

Spectrometer and Jeol 500 Mho NMR spectrometer using tetramethylsilane as internal standard and DMSO- d_6 as solvent. All chemical shifts were recorded as (ppm). Microanalyses for C, H, N were performed by TUBITAK Analytical Laboratory and were within the range of + 0.4 % of theoretical value.

Methods

The synthesis of 2(3H)-benzothiazolone **1** was carried out by the reaction of o-aminothiophenol with urea²⁶. The physical and spectral properties of benzothiazolone were in accordance with the data in the literature²⁶⁻²⁷; therefore, we carried out the next step of the reaction without any further analysis of **1**. Compound **1** was reacted with methyl chloroacetate to obtain methyl 2(3H)-benzothiazolinon-3-ylacetate **2**. [2(3H)-benzothiazolinon-3-yl]acetohydrazide **3** was obtained by the reaction of **2** with hydrazine hydrate. The hydrazide thus obtained was reacted with isocyanate and isothiocyanate derivatives to obtain the title compounds **4**.

Synthesis of methyl (2-Oxobenzothiazolin-3-yl)acetate²⁷ 2

2-Oxobenzothiazoline (0.02 mol) was dissolved in 30 ml acetone, and 0.021 mol of potassium carbonate was added. Methyl chloroacetate (0.022 mole) was added to final mixture and refluxed for 4 h, cooled to 0 °C, poured into 100 ml ice-water mixture and stirred for 1 h at 0-10 °C. The precipitate formed, in the meantime, was filtered and washed with water until at neutral pH. The filtrate was dried at 25-30 °C. Yield : 72%, mp : 92-94 °C.

Synthesis of (2-oxobenzothiazolin-3-yl)acetohydrazide²⁷ 3

Methyl(2-oxobenzothiazolin-3-yl)acetate (0.005 mol) and 0.1 mol of 98% hydrazine hydrate were dissolved in 10 ml of alcohol. The final mixture was stirred for 6 days at room temperature. At the end of this period, the reaction mixture was poured into 50 ml of water with stirring. The precipitate formed was filtered, washed with water. The solid material was dried at room temperature. Yield: 76% m.p. 211 °C.

Synthesis of alkyl and aryl substituted [(2-Oxobenzothiazolin-3-yl)acetyl]-3-semicarbazide 4

(2-Oxobenzothiazolin-3-yl)asetohidrazide (0.0025 mol) were refluxed in 60 ml ethanol for 1 hour. Then 0.0025 mole corresponding isocyanate or isothicyanate de-

rivative was added to the above mixture at once. The eventual mixture was refluxed, and the reaction was followed by TLC. After refluxing for 2 hours the mixture was precipitated, and the reaction was completed after 3 hours. The reaction mixture was stand overnight at the room temperature, then was filtered. The residue was washed with ethanol and the solid material was dried at the room temperature.

Microbiology

Antibacterial and Antifungal Activity Test

Material

The following Gram(+) and Gram(-) bacteria were used for antibacterial study: *Staphylococcus aureus* ATCC 25923, *Streptococcus faecalis* ATCC 19433, *Mycobacterium tuberculosis* H37 Rv, *Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 10145. The following yeast like fungi were used for antifungal activity: *Candida albicans* ATCC 10231, *Candida tropicalis* ATCC 13803.

Inoculation suspensions

The microorganism suspensions used for inoculation were prepared at 10^6 CfU/ml concentration by diluting of the fresh cultures at Mc. Farland 0.5 density (10^8 CfU/ml). It was known that there were 5×10^4 CfU/ml microorganism in each well after inoculation.

Medium

Mueller Hinton Broth (Oxoid) liquid nutrient medium was used for diluting of microorganism suspension and two fold-dilution of the compounds. Sabouraud liquid medium (Oxoid) was used for yeast like fungi for the same purpose.

Equipment

Falcon[®] microplates which have 96 wells were used for microdilution method.

Brinkmann transferpette was used for two fold-dilution of compounds in the wells.

Method

Microdilution method was employed for antibacterial and antifungal activity test²⁸. The compound synthesized and the standarts ampicillin trihydrate, ciprofloxacin and flucanazole were dissolved in DMSO at 1000 µg/ml concentration at the beginning.

The solution of each compounds at 500, 250,.....3.9 µg/ml were prepared in the wells by diluting with the mediums. Suspension of the microorganisms at 10^6 Cfu/ml concentration were inoculated to the two fold-diluted solution of the compounds, consequently the microorganism concentration in each well was approximately 5×10^4 Cfu/ml. DMSO-microorganisms mixture, the pure microorganisms, and pure media were used as control wells.

Microplates were, than, covered and incubated at 36 °C for 24-48 hours. Wet cotton-wool was placed in the incubation chamber, because it should be kept sufficiently to avoid evaporation. After this period of time, evaluation of the wells was performed. The concentration of the compounds in the wells where no growth was seen were assessed as the minimum inhibitory concentration (MIC) of the compounds. There was no inhibitory activity in the wells containing only DMSO. The microbial growth occurred, and the medium were not contaminated during the tests. The MIC values of alkyl and aryl substituted [(2-oxobenzothiazolin-3-yl)acetyl]-3-semicarbazide derivatives and the controls were given as µM/ml in table 3.

Antitubercular Activity Test^{29,30}

Mycobacterium tuberculosis H37 Rv was obtained from Refik Saydam Hifzısıhha Institute, Center for Diagnosis of Tuberculosis Ankara. « Lowenstein Jensen » medium was used. The medium was prepared as directed and divided into 5 ml portions in test tubes. The compounds were dissolved in DMSO and applied to the medium in double-dilution fashion. All the tubes at inclining position were coagulated at 85 °C for minutes. Coagulation was repeated after 24 hours period.

Blank DMSO tubes also used as references. All the tubes were sealed with parafilm and incubated at 37 °C for three weeks at the end of this period MIC (minimum inhibitory concentration) of each compound was determined.

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