



ANTIBACTERIAL EVALUATIONS OF NOVEL CARBONYL THIOUREA DERIVATIVES

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ABSTRACT

Seven new synthetic carbonyl thiourea derivatives were successfully synthesized by heating carbonyl isothiocyanate with amines and characterized by using FT-IR, in order to search for new anti-bacterial compounds to overcome the problem of existence of many antibiotic resistant-bacteria. The anti-bacteria activity of these seven derivatives were investigated on pathogenic Methicillin-resistant *Staphylococcus aureus* (MRSA) by using disc diffusion (Kirby Bauer) method. These compounds were prepared at different concentrations in dimethyl sulfoxide (DMSO). Minimum inhibition concentration (MIC) values of the compounds toward the bacteria were determined. Results obtained in this study indicated that MRSA was slightly sensitive only towards two compounds; *N*-(3-nitrobenzoyl)-*N'*-(2-bromo-4,6-dinitrophenyl)thiourea and *N*-(pentanoyl)-*N'*-(2-chloro-4,6-dinitrophenyl)thiourea. Their MIC values obtained were 0.512mg/mL and 0.256mg/mL, respectively. The preliminary findings to relate the molecular structure with their anti-bacterial activity indicated that the presence of nitro, chloro and bromo group as the substituent on the carbonyl compounds may enhance the activity of the derivatives against this bacteria.

ABSTRAK

Tujuh terbitan karbonil tiourea sintetik telah berjaya disintesis melalui tindakbalas karbonil isotiosianat dengan sebatian amina, dan dicirikan menggunakan FT-IR bagi menghasilkan kompaun baru yang mempunyai aktiviti antibakteria. Aktiviti antibakteria tujuh terbitan tiourea diuji ke atas Methicillin-resistant *Staphylococcus aureus* (MRSA) dengan menggunakan teknik resapan disk (Kirby Bauer). Kompaun ini disediakan mengikut kepekatan berbeza dalam pelarut dimetil sulfoksida (DMSO). Nilai kepekatan rencatan minimum (MIC) ke atas bakteria tersebut dikaji. Hasil ujian menunjukkan MRSA sensitif terhadap dua kompaun; *N*-(3-nitrobenzoi)-*N'*-(2-bromo-4,6-dinitrofenil)tiourea dan *N*-(pentanoil)-*N'*-(2-kloro-4,6-dinitrofenil)tiourea. Nilai MIC yang diperolehi masing-masing adalah 0.512mg/mL dan 0.256mg/mL. Kesimpulan berdasarkan eksperimen menunjukkan kehadiran kumpulan nitro, kloro dan bromo sebagai terbitan pada kompaun karbonil ini boleh meningkatkan aktiviti antibakteria kompaun ke atas bakteria ini.

Keywords: Thiourea, Antibacterial activity, Methicillin-resistant *Staphylococcus aureus*

INTRODUCTION

Thiourea, CSN_2H_4 is basically occurs in two tautomeric forms and has three functional groups which are very important for the structural modifications to synthesize new derivatives. Thiourea and its derivatives display a broad spectrum of applications in industries, chemistry, medicine and others. In these present years, a lot of thiourea derivatives have been synthesized and their antimicrobial properties were widely explored [1-5]. It is well known that a number of heterocyclic compounds containing nitrogen and sulfur exhibited a wide variety of biological activity [3]. Previous researches revealed the potentials of thiourea derivatives as antioxidant [6], anti-HIV and anti-tuberculosis agent [7]. Therefore in this study, seven new carbonyl thiourea derivatives were synthesized and characterized by Fourier transform infrared (FT-IR). This synthesis work was carried out by Dr Mohd Sukeri Mohd Yusof's research group from the Department of Chemical Sciences, Universiti Malaysia Terengganu.

This study focused on antimicrobial activity of new carbonyl thiourea derivatives. These compounds were examined for their antibacterial activity on Methicillin-resistant *Staphylococcus aureus* (MRSA) which is a pathogenic strain of *Staphylococcus aureus* bacteria. MRSA is one of the most prominent bacteria which are resistant and adaptable to most antibiotics such as penicillin, methicillin, tetracycline and erythromycin. MRSA is now quite common in hospitals

and becomes a public health problem. For that reason, MRSA was used as the target pathogen to study the effect of these new compounds.

EXPERIMENTAL

Evaluations of antibacterial activity in vitro

The newly synthesized compounds were screened for their antibacterial activities against Methicillin-resistant *Staphylococcus aureus* (MRSA) which was obtained from Universiti Sains Malaysia, Penang. The disc diffusion (Kirby Bauer) method was used to determine the minimum inhibition concentration (MIC) of these newly synthesized carbonyl thiourea derivatives. The MIC was defined as the lowest concentration of the test compound, which inhibits the visible growth after 18 h incubation at 37°C [3].

The compounds were diluted by using dimethyl sulfoxide (DMSO) as the solvent for the dilutions. Two-fold dilutions were carried out for each compound in two replicates to give final concentrations of 512, 256, 128, 64, 32, and 16µg/mL to each tube of compound samples from 1mg/mL stock. The Mueller-Hinton (MH) was used as the media and pour plate technique was chosen for the test. The bacteria culture in broth used was standardized and compared to 0.5 McFarland to give approximately 1.5×10^8 CFU/mL. Then, 30µL of the diluted samples were impregnated into 6mm Whatman No. 1 disc and placed on the MH agar plate containing MRSA culture. Chloramphenicol was used as the positive control, while for the negative control, plain DMSO without compound samples was used.

The carbonyl thiourea derivative compounds being used for the test is shown in Table 1. The letters in the bracket (C1-C7) were used to indicate the code for the compounds to facilitate the results.

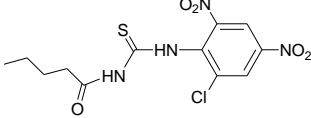
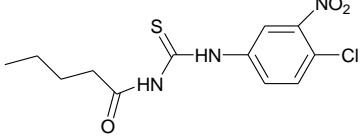
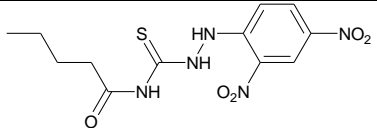
RESULTS AND DISCUSSIONS

Antibacterial activity of new derivative compounds in vitro

This study was aimed to investigate the presence of antibacterial activities of new carbonyl thiourea derivative compounds against methicillin-resistant *Staphylococcus aureus* (MRSA).

Seven derivative compounds (C1-C7) were tested against this bacteria by using disc diffusion method. MIC values were determined by measuring the diameter of inhibition zone after 18 hours of exposure to test compounds. The results obtained shows only two out of seven compounds namely; *N*-(3-nitrobenzoyl)-*N'*-(2-bromo-4,6-dinitrophenyl)thiourea and *N*-pentanoyl-*N'*-(2-chloro-4,6-dinitrophenyl)thiourea showed antibacterial activity on MRSA with MIC values 0.512mg/mL and 0.256mg/mL respectively. The result of the experiment was shown in Table 3. The rest of these compounds did not demonstrate any antibacterial activity against the bacteria.

Table 1 Seven carbonyl thiourea derivatives (C1-C7)

<p><i>N</i>-(<i>m</i>-methylbenzoyl)-<i>N'</i>-(4-chloro-3-nitrophenyl)thiourea (C1)</p>	<p><i>N</i>-hexanoyl-<i>N'</i>-(4-chloro-3-nitrophenyl)thiourea(C2)</p>
<p><i>N</i>-(3-nitrobenzoyl)-<i>N'</i>-(2-bromo-4,6-dinitrophenyl)thiourea (C3)</p>	 <p><i>N</i>-pentanoyl -<i>N'</i>-(2-chloro-4,6-dinitrophenyl)thiourea(C4)</p>
 <p><i>N</i>-pentanoyl-<i>N'</i>-(4-chloro-3-nitrophenyl)thiourea (C5)</p>	<p><i>N</i>-pentanoyl-<i>N'</i>-(3,4-dichlorophenyl)thiourea (C6)</p>
 <p><i>N</i>-pentanoyl-<i>N'</i>-(2,4-dinitrophenylhydrazine)thiourea (C7)</p>	

For the compound *N*-(3-nitrobenzoyl)-*N'*-(2-bromo-4,6-dinitrophenyl)thiourea, it gave inhibition zone 8.0mm at 0.512mg/mL, while for the *N*-pentanoyl-*N'*-(2-chloro-4,6-dinitrophenyl)thiourea it gave 8.0mm inhibition zone at two times lower concentration. The result from the experiment

indicated that these two potential compounds had slight effect on MRSA as compared to the positive control.

Table 3 Measurement of the inhibition zone diameter on Methicillin-resistant *Staphylococcus aureus* (MRSA) cultures after the treatment with various concentrations of carbonyl thiourea derivatives compounds (C1- C7). Zone of inhibition were measured in millimeters

Concentration of Compounds (mg/mL)	Mean diameter of inhibition zone (mm)						
	C1	C2	C3*	C4**	C5	C6	C7
0.512	-	-	8.0	9.0	-	-	-
0.256	-	-	-	8.0	-	-	-
0.128	-	-	-	-	-	-	-
0.064	-	-	-	-	-	-	-
0.032	-	-	-	-	-	-	-
0.016	-	-	-	-	-	-	-
DMSO				-			
Chloramphenicol				19.7			

* C3 *N*-(3-nitrobenzoyl)-*N'*-(2-bromo-4,6-dinitrophenyl)thiourea

** C4 *N*-pentanoyl-*N'*-(2-chloro-4,6-dinitrophenyl)thiourea

CONCLUSION

We have synthesized a series of carbonyl thiourea derivatives which comprised of seven compounds for the antibacterial properties investigation. The antibacterial activity data from the prepared compounds indicated that the presence of substituent group such as nitro, chloro and bromo on the carbonyl thiourea might enhance the activity of the compounds toward methicillin-resistant *Staphylococcus aureus* (MRSA). The study showed that these two compounds; *N*-(3-nitrobenzoyl)-*N'*-(2-bromo-4,6-dinitrophenyl)thiourea and *N*-pentanoyl-*N'*-(2-chloro-4,6-dinitrophenyl)thiourea had slight effect on MRSA. Future research should envision studies on modification of the carbonyl compounds to increase their antibacterial activity.

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