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Synthesis of Zinc (II)N-Benzylmethyl Dithiocarbamate as an Antibacterial against *Salmonella typhi*

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Abstract

Dithiocarbamate complex compounds are widely used as anticancer, antibacterial, and antifungal. The compound Zinc (II) N-Benylmethyl Dithiocarbamate was successfully synthesized to find a picture of the structure and antibacterial activity against Salmonella typhi bacteria. This compound was synthesized by in situ method, namely by the addition of N-benzyl methylamine, carbon disulfide, and zinc chloride, identification using FTIR, ^{1}H NMR, and ^{13}C NMR. Testing of antibacterial activity by disc method. The results of research from synthesized compounds using FTIR obtained groups (C-N) 1203.58, (C-H) 2918.30, (C-S) 640.37, (Zn-S) 352.97. The measurement results of ^{1}H NMR obtained 0-3.3650 (δ CH_3), 5.1256 (δ CH_2), 7.3259-7.4105 (δ C_6H_5). The results of ^{13}C NMR measurements were obtained 0-41.7650 (δ CH_3), 60.4114 (δ CH_2), 127.9929-134.7094 (δ C_6H_5), and 205.0874 (δ C-S_2). Zinc (II)N-Benylmethyl Dithiocarbamate compound is effective as an antibacterial with a concentration of 100 ppm with an inhibitory power of 12.65 mm. Conclusion The compound was successfully synthesized and has antibacterial activity with a strong category.

Keywords: Antibacterial, Synthesis, Tifoid, Zink (II)N-Benzylmethyl Dithiocarbamate.

1. Introduction

Infection is an infectious disease and can be caused by microorganisms. Microorganisms that cause disease in the body are referred to as pathogenic microorganisms, such as fungi, bacteria, viruses, and parasites. Typhoid fever is an acute systemic infectious disease that attacks the gallbladder, lymph glands, and reticuloendothelial system transmitted through the fecal-oral route caused by the bacterium Salmonella typhi (1). Salmonella serovar typhi (S.typhi) and Salmonella serovar enteritidis (S.entritidis) are anaerobic gram-negative bacteria in the form of bacilli that have distinctive endotoxin characteristics and have Vi antigens that are believed to increase virulence activity (2) Typhoid symptoms are fever of one week or more accompanied by disorders of the digestive tract and with or without impaired consciousness (3). According to the World Health Organization (WHO), typhoid fever cases in the world reach 11-20 million cases and 128.000-161.000 deaths each year (4). The prevalence of typhoid fever in Indonesia is 1.60%, the highest occurs in the age group of 5-14 years because at that age children do not pay attention to personal hygiene and careless snacking habits that can cause transmission of typhoid fever (5).

Dithiocarbamate is a very potent ingredient in agriculture, industry, and medicine. The dithiocarbamate compound used depends on the chelating properties of the dithiocarbamate ligand on the metal ion (6). It is not only used as an insecticide but can also be used as an antibacterial. This was shown in several studies before testing phenyltin(IV) dithiocarbamate as an antibacterial. From this study it was produced that this compound has antibacterial activity and also does not cause cytotoxic in liver cells (7).

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Based on previous Research (6) has synthesized Dibutyl Tin (iv) Bis-Methyl Dithiocarbamate compounds as antibacterial and showed antibacterial activity on Salmonella typhi *bacteria* with an inhibitory power of 27,33 mm (very strong) at a concentration of 90 ppm. On research (8) sodium phenyl dithiocarbamate has antibacterial properties against Salmonella typhi with an inhibitory zone of 19 mm at a concentration of 100mg/mL and sodium cyclohexyl dithiocarbamate compounds have antibacterial properties against Salmonella typhi with an inhibitory zone of 16,3 mm at a concentration of 100mg/ mL.

2. Methods

The tools used in the research are beakers (Pyrex), measuring pipettes (Pyrex), analytical balances (Ohaus®), funnels, measuring cups (Iwaki), Erlenmeyer (Pyrex®), stirrers (IKA® C-MAG), hotplates, desiccants, sample vials, filter paper, micro pipettes® (Eppendorf Research Plus®), Petri dishes, ose needles, L rods, bunsen, incubators (Memmerte®), test tubes, test tube racks, panels, empty discs (OXOID), chloramphenicol discs (OXOID), ketoconazole discs, calipers, autoclaves (Hirayama®), FTIR (Fourier Transform Infrared) spectrophotometers (Shimadzu) and NMR *(*Nuclear Magnetic Resonance) 500 MHz (^{1}H) and 125 MHz (^{13}C) (Agilent). The materials used in this study were primary amines -N- Benzylmethylamine, carbon disulfide, chloroform, zinc chloride (Sigma Aldrich®), Methanol Pro Analis (Pa), NA media (Nutrient Agar), MHA media (*Muller Hinton Agar*), PDA media *(Potato Dextrose Agar)*, Salmonella typhi *bacteria*, Aspergillus *niger* fungus, DMSO (Dimethyl Sulfoxide), aqua dest, physiologically sterile NaCl 0.9%, BaCl2 1%, H2SO4 1%.

1. Compound Sitesis

N-Benzylmethyl amin ($C_8H_{11}N$) 2.58 mL of the pipette was put into Erlenmeyer 1 and 15 mL of methanol was added. Dissolve carbon disulfide (CS_2) 1.2 mL of the pipette is put into Erlenmeyer 2 and 15mL of methanol is added. Zinc weighed 2.725 grams and then put into Erlenmeyer 3 and added 15 mL of methanol. After dissolving each solution, mix the solution in Erlenmeyer 1 slowly, then mix the *stirrer* for ± 2 hours at a speed of 120rpm. After the precipitate is formed, it is filtered and put into a vial bottle and then stored in a desiccator. The sample formed (flour form) will be tested for FTIR, NMR, and antibacterial and antifungal activity tests.

2. FTIR Spectrophotometer Testing

Take ± 1 mg powder then grind with KBr using a mortar until homogeneous. Place the homogenized mixture in the FTIR instrument, and measure its absorption at wavenumber 20-4000 cm^{-1} (9).

3. NMR Spectrophotometer Testing

20 mg of the compound is dissolved in chloroform. The ready solution is then injected into the injection tube and then analyzed on spectra 500MHz for ^{1}H-NMR and 125MHz for ^{13}C-NMR(9)

4. Antibacterial Activity Test

a. Bacterial Rejuvenation
A pure isolate of Salmonella typhi bacteria was taken as much as 1 ose, then inoculated on inclined media NA (Nutrient Agar*)* carried out by scraping zigzagging from bottom to top and then incubating at a temperature of 37^{o}C for 24 hours (10).

b. Manufacture of Bacterial Suspension
Rejuvenated Salmonella typhi bacteria were taken using an ose needle, then suspended by insertion in a tube that contained 5 ml of 0,9% physiologically sterile NaCl. Then in the vortex until homogeneous equalized to the Mc Farland standard 0,5 (11). The suspension transmittance is then measured with a UV-Vis spectrophotometer at 580nm band to obtain a 25% transmittance. If the turbidity of bacteria with a transmittance of <25% NaCl is added and if a transmittance of >25% is added test bacteria (Hamz *et al*., 2021).

c. Antibacterial Activity Test
Test antibacterial activity using the scattering technique with disc method. Take a bacterial suspension of 0.1 ml then pour it into a petri dish containing MHA (*Muller Hinton Agar*) media that has solidified and flatten it using *a sterile* Cotton Swab rod (13). Prepare disc paper, the first disc uses as a positive control, namely

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chloramphenicol, the second disc as a negative control is DMSO, then the next disc is used for a solution of the test compound, namely Zinc(II) N-Benylmethyl dithiocarbamate at every concentration of 80 *ppm*, 90 ppm, *100* ppm *soak for 5 minutes*. Place each disc using sterile tweezers into a petri dish that has contained media that has been poured into bacterial suspension. Cover and incubate Petri dishes for 24 hours at 37^{o}C. Observe the inhibitory zone by using a caliper (14).

5. Data Analysis

Data from the measurement of the inhibitory zone of Zinc(II) N-Benylmethyl dithiocarbamate compounds were processed by manual calculations and analyzed descriptively in the form of tables and averaged calculations.

3. Results

Table 1: Synthesis of Zinc (II) Dimethyl Dithiocarbamate Compounds

Compound Weight	Organoleptic properties		
	Construction	Shape	Color
7,2 gram	Odorless	Powder	White

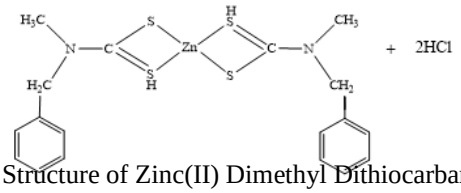

Figure 1 : Structure of Zinc(II) Dimethyl Dithiocarbamate

Figure 2: Zinc (II) Compound Dimethyl Dithiocarbamate

Table 2 : FTIR Spectrophotometer Analysis

Wavelength absorption region (cm^{-1}) (15)	Analysis Results of Zinc (II) N-Benylmethyl Dithiocarbamate Compounds	
	Wavenumber (cm^{-1})	Functional Groups
1300-1266 cm^{-1}	1203,58	C-N
3800-2700 cm^{-1}	2918,30	C-H
700-600 cm^{-1}	640,37	C-S

Wavelength absorption region (cm^{-1}) (16)	Analysis Results of Zinc (II) N-Benylmethyl Dithiocarbamate Compound	
	Wavenumber (cm^{-1})	Functional Groups
20-400 cm^{-1}	352,97	Zn-S

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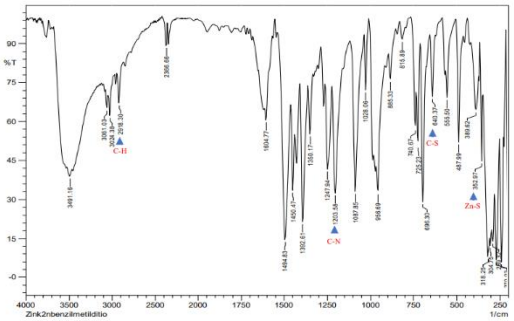

Figure 3: FTIR Analysis

Table 3 ^{1}H Spectrum NMR Spectrophotometer Analysis

Proton Shift Region (ppm)(7)	Analysis Results of Zinc (II) N-Benylmethyl Dithiocarbamate Compound
δ 0-3 ppm (CH_3)	0-3,3650 (CH_3)
δ 3-6 ppm (β-Monosubstitued aliphatic)	5,1256 (CH_2)
δ 6-9 ppm (Aromatik)	7,3259-7,4105 (C_6H_5)

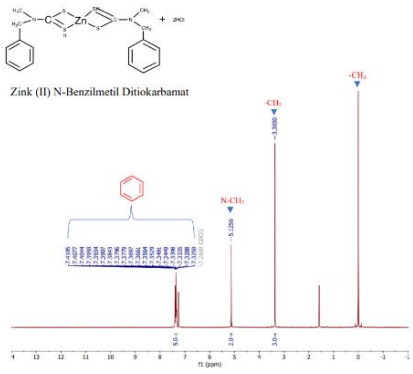

Figure 4: ^{1}H Spectrum NMR Spectrophotometer Analysis

Table 4: ^{13}C Spectrum NMR Spectrophotometer Analysis

Carbon Shift Areas (ppm) (9)	Analysis Results of Zinc (II) N-Benylmethyl Dithiocarbamate Compound (δ C)
δ 0-50 ppm (CH_3)	0-41,7650 (CH_3)
δ 40-75 ppm (CH_2)	60,4114 (CH_2)
δ 100-150 ppm (C Aromatik)	127,9929-134,7094 (C_6H_5)
δ 180-220 ppm (C-S_2)	205,0874 (C-S_2)

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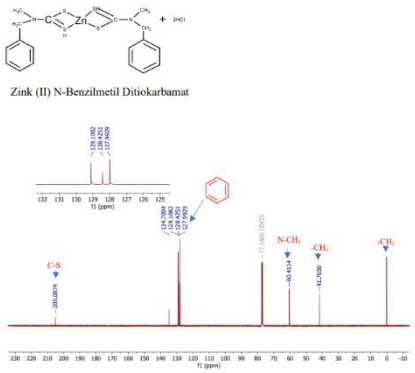
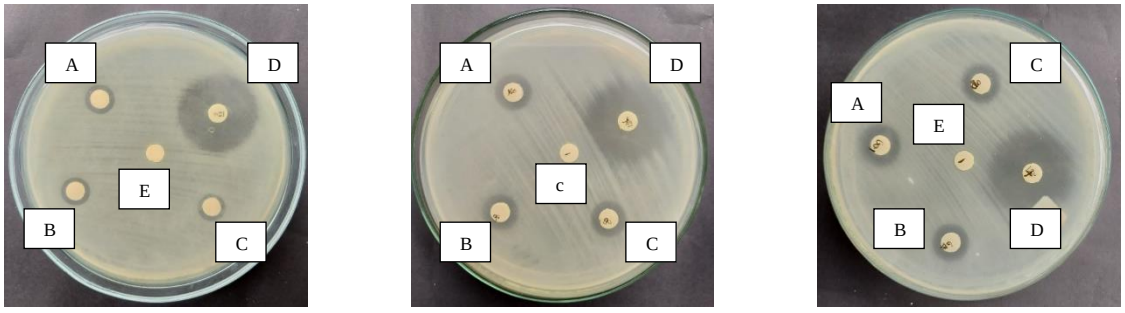


Figure 5: ^{13}C Spectrum NMR Spectrophotometer Analysis

Table 5: Antibacterial Activity Test Against *Salmonella typhi Bacteria*

Concentration	Repetition (mm)			Average (mm)	Category Inhibitory Power (Luntungan *et al*., 2021)
	1	2	3		
K -	0	0	0	0	Tidak Ada
K +	26,40	26,00	27,40	26,60	Sangat Kuat
80 ppm	10,85	12,50	12,60	11,98	Kuat
90 ppm	11,20	12,75	12,80	12,25	Kuat
100 ppm	11,50	13,00	13,45	12,65	Kuat



Repetition 1 **Repetition 2** **Repetition 3**

Figure 6: Antibacterial Activity Test *of Salmonella typhi*

Information : A : Concentration 100 ppm D : Positive Control / K+
B : Concentration 90 ppm E : Control Negative / K-
C : Concentration 80 ppm

4. Discussion

Infrared (IR) spectroscopy is a technique based on the atomic vibrations of molecules. The use of this tool is to determine the functional groups found in organic compounds. In general, the IR spectrum is obtained by IR radiation passing through a sample and determining the fraction of radiation absorbed at a given energy. The energy at which each peak in the absorption spectrum appears corresponds to the vibrational frequency of the sample part of the molecule (7). The results of FTIR analysis show that according to the type of functional group contained in the complex compound Zinc (II) N-Benylmethyl Dithiocarbamate. This can be seen in the absorption area 1300-1266 cm^{-1} is an absorption region in the C-N group with a spectral value of 1203.58 cm^{-1}, absorption area 3800-2700 cm^{-1} is an absorption region in the C-H group with a spectral value of 2918.30 cm^{-1},

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in the absorption area of 700-600 cm^{-1} is the absorption region of the C-S group with a spectral value 640,37 cm^{-1} and in absorption areas of 20-400 cm^{-1} is an absorption region in the Zn-S group with a spectral value of 352.97 cm^{-1} (15). Therefore, the complex compound Zinc (II) N-Benzylmethyl dithiocarbamate can be characterized by FTIR, thus proving that the bonds in the compound have been formed. NMR is an easy-to-use analytical method in modern chemistry. NMR can be used in determining the structure of new natural and synthetic components as well as the purity of the components and the direction of chemical reactions as well as the relationships of components in solutions that can undergo chemical reactions. The advantage of NMR measurement is that the sample is not damaged and there is less sample preparation (6). Based on NMR testing of complex compounds tested on spectra ^{1}H NMR obtained proton value on CH_3 in the area of 0-3.3650 ppm shift, proton value CH_2 in the area of shift 5.1256 ppm, and aromatic value at shift 7.3259-7.4105 ppm (7). The value of carbon shift in CH_3 is 0-41.7650 ppm, the carbon shift value in CH_2 of 60.4114 ppm, the value of carbon C Aromatic shift is 127.9929-134.7094 ppm, then the carbon shift value on C-S_2 amounted to 205.0874 ppm so that the carbon shift value obtained from testing compounds tested with spectra ^{13}C NMR according to the expected formula as well as according to the range of carbon shift areas specified by the literature (9). Based on the results of spectral data, it was found that the complex compound formed had the molecular formula $C_{18}H_{22}N_2S_4Zn$ with a molecular weight (BM) of 460.01 g / mol.

The results of testing antibacterial activity using the disc agar diffusion method in *Salmonella typhi bacteria* using the compound Zinc (II) N-Benzyl methyl Dithiocarbamate at a concentration of 80 ppm gave an inhibitory zone of antibacterial activity of 11.98 mm, for a concentration of 90 ppm with an inhibitory zone of 12.25 mm and a concentration of 100 ppm gave an inhibitory zone of antibacterial activity of 12.65 mm. Chloramphenicol disc 30µg/disk used as a positive control provides antibacterial activity of 26.6 mm while the negative control used is DMSO, DMSO does not provide inhibitory power, this proves DMSO does not affect the growth of these bacteria. According to (17) The category of antibacterial inhibitory strength is the diameter of the inhibitory zone less than 5 mm categorized as weak, 5-10 mm categorized as medium, 10-20 mm categorized as strong, and large than 20 mm categorized as strong. Based on this inhibitory power category, the antibacterial inhibitory power of the compound Zinc (II) N-Benzyl methyl Dithiocarbamate against Salmonella typhi bacteria at concentrations of 80 ppm (11.98 mm), 90 ppm (12.25 mm), and 100ppm (12.65 mm) is included in the strong antibacterial category. Tests conducted show that the greater the concentration of complex compounds, the greater the antibacterial activity that arises. This is also by previous research on research (6) which tested dithiocarbamate compounds, namely Dibutyl Tin (IV) Bis-Methyl Dithiocarbamate compounds against *Escherichia coli bacteria* at a dose of 90 ppm providing antibacterial activity with an inhibitory power of 26.48 mm in the very strong category and *Salmonella typhi* bacteria with a dose of 90 ppm provides activity with an inhibitory power of 27.33 mm with a strong sting category as well. The antibacterial activity of this dithiocarbamate compound affects inhibiting bacterial growth, this causes the occurrence of antimicrobial active mechanisms with disruptions in cell wall synthesis, and metabolic disorders with various cellular enzymes by weakening cells so that protein denaturation occurs (6).

5. Conclusion

The complex compound Zinc(II) N-Benylmethyl Dithiocarbamate can be synthesized and proven by FTIR and NMR. Zinc (II) N-Benylmethyl Dithiocarbamate compound has antibacterial activity on *Salmonella typhi bacteria* with an inhibitory power of 12.65 mm (strong) at a concentration of 100 ppm.

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