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Crystallization of [Zn(Pyrazinamide)$_2$(Cl)$_2$] Complex and *In Vitro* Antibacterial Activity of the Complex Against *E. coli* and *S. aureus*

Naila Azmi Adiba [1], Danar Purwonugroho [1], Arie Srihardyastutie [1], Yuniar Ponco Prananto [1,*]

[1] Department of Chemistry, Faculty of Sciences and Mathematics, Brawijaya University, Malang, Indonesia

* Corresponding author: prananto@ub.ac.id

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Abstract

A complex of [Zn(pza)$_2$(Cl)$_2$], pza = pyrazinamide, was successfully crystallized from methanol or ethanol solvents with different morphology. The complex was synthesized using the solution method in $ZnCl_2$: pza mol ratios of 1:2 and 1:4 in both ethanol and methanol solvents. FTIR and single crystal XRD analyses were done to confirm the complex. The complex was then used for *in vitro* antibacterial test against *E. coli* and *S. aureus*. Experimental data shows that the type of solvent and metal-to-ligand mol ratio yields the same compound, resulting in colorless crystals that melt at 234-236°C. Large block crystals were obtained from the methanolic solution, while a higher yield was obtained from the use of a higher mol ratio of 1:4. Infrared spectra analysis confirms the presence of characteristic carbonyl and amide groups of the pza ligand. Meanwhile, single crystal XRD screening indicates that unit cell parameters of the crystals from both solvents are identical to a known zinc(II)-pza complex. *In vitro* antibacterial tests against *E. coli* and *S. aureus* show that the complex had much better activity than the $ZnCl_2$ and the free pza. In addition, the complex performs better antibacterial activity toward gram-positive *S. aureus* than the gram-negative *E. coli*.

1. Introduction

There has been a lot of research on multidentate ligands, which are used to make metal complexes because of their interesting properties and because they have more than one donor atom, such as nitrogen and oxygen. These ligands are widely researched because of their potential applications in catalysis, medicine, and materials science [1]. One ligand containing nitrogen and oxygen donor atoms is pyrazinamide or pyrazin-2-carboxamide. Particularly, a metal complex featuring C=N bonds exhibits greater antimicrobial activity compared to those with C=C bonds [2, 3, 4].

Efforts to develop effective antimicrobials against multi-resistant bacteria involve synthesizing drugs with novel activation targets whose activity is well-understood. One approach is to modify existing antibacterial agents by combining them with transition metal ions to create complex compounds [3, 5]. One promising antibacterial agent is the transition metal complex, which either has an unknown mechanism of action against pathogenic bacteria or functions differently from other antibacterial agents [6]. Based on previous research, the interactions that occur between metal ions and organic ligands show better antimicrobial activity compared to free (uncoordinated) ligands [3].

The M(II)-pyrazinamide complex is a type of coordination polymer that has been developed for various applications depending on the type of metal (M) chosen, especially in medical applications, namely as an antibacterial agent [7]. There have been many reports on the preparation of transition metal complexes containing pyrazinamide ligands and its evaluation for their antibacterial efficacy against *Staphylococcus aureus* (gram-positive), *Escherichia coli* (gram-negative), and *Mycobacterium smegmatis* (gram-positive) such as, [Zn(pyrazinamide)$_2$(H_2O)](NO_3)$_2$, [Mn(pyrazinamide)$_2$(H_2O)$_2$](NO_3), [Ag(pyrazinamide)$_2$](NO_3), and [Ag(pyrazinamide)$_2$(NO_3)]. The results showed that there was an increase in antibacterial properties against bacteria compared to free ligands [8].

One of the transition metal ions that has benefits in clinical medicine is zinc. Zinc ions in medicine are linked with antimicrobial, antioxidant, antifungal, and anti-inflammatory properties [9]. Depending on the bacterial strain, zinc ions have optimal levels found in microbial cells ranging from 10^{-7} to 10^{-5} M. It has been observed that zinc ions with concentrations above 10^{-4} M can disrupt homeostasis and increase permeability through cell membranes and thus have a cytotoxic effect on prokaryotic cells. The antibacterial properties can be influenced by not only the zinc concentration but also the structure of the complex. The latter are also affected by the synthetic condition, one of which is the type of solvent and metal-to-ligand (M:L) mol ratio [10].

Therefore, a complex involving zinc ion and pyrazinamide ligand was synthesized under various conditions, using ethanol or methanol as solvents and different M: L molar ratios (1:2 and 1:4). The antibacterial activity of the complexes was evaluated against *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) using the Kirby-Bauer test.

2. Experimental

2.1. Materials and Instrument

Laboratory-grade chemicals without further purification were used as received from the supplier: zinc(II) chloride dihydrate (Merck), pyrazinamide (Merck), methanol (Merck), ethanol (Merck), Mueller Hinton Broth (MHB) - from Himedia M391-500G, and Mueller Hinton Agar (MHA) - from Himedia GRM026-500G. The bacteria used in this study were *S. aureus* bacteria (ATCC 33591D-5) and *E. coli* bacteria (ATCC 25922). Instrumentation analyses used in this research were the Fourier Transform Infrared Spectrophotometer (FTIR IRSpirit – T Shimadzu), single crystal XRD (Bruker D8 Quest Eco), and melting point apparatus (InnoTech DMP800).

2.2. Synthesis of The Complex

The synthesis was carried out using a slow evaporation technique. Ligand and metal salt solutions were prepared in accordance with Table 1. Both solutions were mixed and stirred for 30 minutes (700 rpm). Crystals were formed after leaving the solution in a closed vial at room temperature for several days; the crystals were isolated, then washed with a similar type of solvent, and dried in an oven at 105°C for 2 hours.

Table 1. Reaction detail used in this work

Reaction code	Solvent	Mol ratio	$ZnCl_2$ (mmol)	Pyrazinamide (mmol)
A	Ethanol	1: 2	0.4875	0.975
B	Ethanol	1: 4		1.950
C	Methanol	1: 2		0.975
D	Methanol	1: 4		1.950

2.3. Characterization Techniques

Functional group analysis was performed using FTIR with ATR in the range 4000-400 cm^{-1}. The four sample spectra were compared with the free ligand spectra to determine the coordination bond of the metal with the ligand. Meanwhile, crystal structure of the complex was determined using Bruker D8 Quest Eco single crystal XRD. The crystal sample was placed at the end of the sample holder, and then the crystal position was adjusted on the tool. An x-ray beam from a Mo K/α radiation source at a wavelength of 0.71076 Å was shot at the crystal at 298 K for unit cell determination. The unit cell parameters were compared with CCDC. The files obtained are in the form of hkl res file, which was then processed using the Olex2 ver1.5 [11]. Data collection was done using APEX5 software to determine the initial model of the crystal structure, and the data was refined by Olex2 software to improve the R- factor of the crystal structure. Olex2 was also used for visualization.

2.4. Antibacterial Tests

Antibacterial tests were conducted at the Central Laboratory of Life Sciences (LSIH), Brawijaya University, Indonesia, on *S. aureus* (Gram-positive) and *E. coli* (Gram-negative). The antibiotic effectiveness was assessed by determining the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). Microbial activity was further evaluated by measuring the zone of inhibition (ZoI), with results compared to those of the free ligand and initial $ZnCl_2$. The concentration series used ranged from 1000 to 6000 ppm. Water served as the negative control (K-), while bacterial solutions (*E. coli* or *S. aureus*) were used as positive controls (K+), with bacterial suspensions diluted to 5×10^5 CFU/mL and dissolved in MHB.

The MIC and MBC results were used to assess the inhibition zones of the complexes against *E. coli* and *S. aureus*. Discs containing the antibacterial agents were applied to MHA plates within 20 minutes of bacterial inoculation. Each petri dish contained four discs: $ZnCl_2$, pyrazinamide, the complex, and the solvent (water). The plates were inverted and incubated at 37°C for 24 hours, after which the inhibition zones were measured in millimeters.

3. Results and Discussion

3.1. Synthesis of Zinc(II)-Pyrazinamide

Four complexes were synthesized by directly reacting $ZnCl_2$ and pyrazinamide solutions and producing needle colorless crystals from the ethanol (A and B) (Figure 1(a, b)) and block colorless crystals from the methanol (C and D) (Figure 1(c, d)). Complexes with a mol ratio 1:4 produced higher yields than those from the 1:2 ratio in both ethanol and methanol (Table 2). This is because a higher mol ratio of the reactant can affect the reaction equilibrium. If the number of moles of the ligand increases, the probability of the ligand reacting and binding with the metal ion gets higher, thus resulting in a higher yield. The higher moles of the ligand also shift the equilibrium to the right (formation of product); therefore, more complex precipitated out as crystals.

Table 2. Physical properties of the complex

Reaction code	Solvent	Mol ratio (M: L)	Yield (%)	Crystal	Melting point (°C)
A	Ethanol	1: 2	28.61	Needle colorless	234-236
B		1: 4	55.02	Needle colorless	234-236
C	Methanol	1: 2	38.43	Block colorless	234-236
D		1: 4	87.34	Block colorless	234-236
Pyrazinamide	-	-	-	-	180

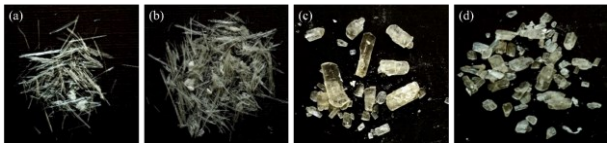

Figure 1. Crystal images of the complexes were obtained under the following conditions: (a) 1:2 ratio in ethanol; (b) 1:4 ratio in ethanol; (c) 1:2 ratio in methanol; (d) 1:4 ratio in methanol

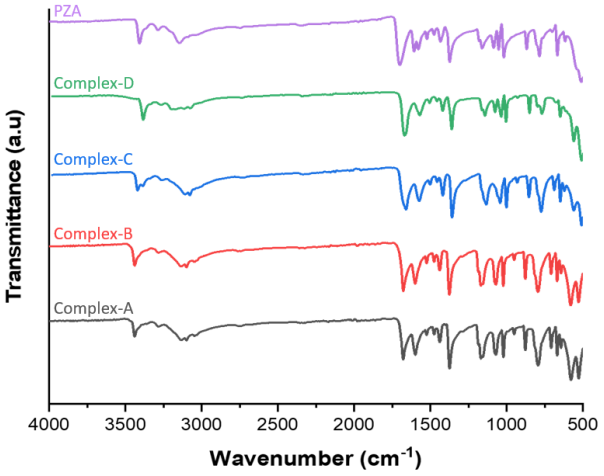

Figure 2. Infrared spectra of the complexes for each reaction code (A-D) and the free pyrazinamide (pza)

Differences in the polarity of the alcohol solvent also affected the yield, and a higher yield was obtained when methanol was used. However, in general, the nature of the solvent may alter the complex structure, including the yield [12, 13]. It is commonly observed that a polar complex is easily dissolved in a polar solvent. Methanol is more polar than ethanol. Thus, the synthesized complex is more likely to have polarity properties closer to the ethanol than the methanol.

The crystal size and morphology are influenced by the solvent, with methanol producing larger crystals. Complexes crystallized from methanol exhibited a block shape, while those from ethanol formed needle-like crystals. During crystallization, the solid surface interacts directly with the solvent, meaning the solvent remains involved in the equilibrium between solvation and crystallization of the complex. If the lattice energy of the crystal is lower than the solvation energy of the solvent, the crystal will likely dissolve or form only small crystals with minimal surface area. Conversely, larger crystals will form if the lattice energy is much higher than the solvation energy, although other factors may also play a role [14]. Since methanol produces larger crystals and higher yields than ethanol, it is predicted that the synthesized complex's lattice energy is higher than methanol's solvation energy but slightly lower than ethanol's. Therefore, methanol is preferred over ethanol for crystallizing the complex to achieve larger crystals and higher yields.

3.2. Characterization of the Complex

Based on the melting point test results (Table 2), all four complexes are air-stable and exhibit high melting points above 200°C. The similar melting points across the complexes suggest they are the same compound despite crystallizing in different morphologies.

Infrared spectra of all complexes (Figure 2) show an identical pattern, which indicates that the synthesized products are the same compound. Moreover, the characteristic absorption bands of pyrazinamide ligands were observed [15], namely the vibrations of N-H asymmetric stretch (~3400 cm^{-1}) and N-H symmetric stretch (~3200 cm^{-1}), C=O stretch (~1600 cm^{-1}), and CC=N deformation mode (~500 cm^{-1}).

Based on the spectra data in Table 3, there is a shift in the adsorption of the carbonyl group (~35 cm^{-1}) and amide group (~40 cm^{-1}), which suggests that hydrogen bonds occurred between those groups. Additionally, compared to the free pyrazinamide, splitting was observed in the absorption bands at around 520 and 570 cm^{-1} [16], which suggests the coordination bond occurred on one of the nitrogen atoms in the pyrazine rings. This was also confirmed in the single crystal XRD analysis.

Determination of crystal structure was carried out using single crystal XRD on crystals from both the ethanol and the methanol reactions. Crystallographic data of the complex are shown in Table 4. The screening phase of the synthesized compound showed that the cell parameters were identical to those reported by Shirvan and Haydari Dezfuli [17], the structure of the synthesized complex was identical to the known compound of $[Zn(pza)_2(Cl)_2]$. This also means that the use of different solvents results in the same crystal structure, although, in some cases, the use of different solvents may lead to different structures, as reported by Prananto *et al.* [12] and Yuan *et al.* [13]. This is understandable since some solvents may involve as coordinated ligands, stay as lattice molecules, or react with the ligand to form other species [18, 19].

Table 3. Infrared data of the synthesized Zn(II)-pyrazinamide complexes and free pyrazinamide

PZA (cm^{-1})	A (cm^{-1})	B (cm^{-1})	C (cm^{-1})	D (cm^{-1})	Interpretation	Functional group vibrations
3407	3440	3440	3445	3446	N-H asymmetric	Amide group
3285	3284	3284	3294	3295	N-H symmetric	
1701	1678	1677	1680	1681	C=O carbonyl	carboxamide group
1373	1374	1374	1381	1382	C-NH_2	
1578	1524	1524	1533	1533	C-C aromatic	Pyrazine ring
510	527	527	520	520	CC=N aromatic (deformation mode)	
	577	580	575	574		

Table 4. Crystallographic data of the complexes

Parameter	Synthesized compound		Literature [17]
	In ethanol	In methanol	
Temperature	298 K	298 K	298 K
Empirical formula	$[ZnCl_2(C_5H_5N_3O)_2]$	$[ZnCl_2(C_5H_5N_3O)_2]$	$[ZnCl_2(C_5H_5N_3O)_2]$
Empirical mass	382.531	382.531	382.53
System	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_{1/m}$	$P2_{1/m}$	$P2_{1/m}$
a (Å)	5.4172 (4)	5.4162 (4)	5.4296 (5)
b (Å)	19.7372 (10)	19.7363 (10)	19.7629 (14)
c (Å)	6.8375 (5)	6.8355 (6)	6.8396 (5)
α (°)	90°	90°	90°
β (°)	104.981 (2)	104.972 (3)	105.131 (7)
γ (°)	90	90	90°
V (Å³)	706.22 (8)	706.25 (7)	708.48 (10)
Z	2	2	2
R_{int}	0.0254	0.0253	0.085
Final R_1 values (obs. data)	0.0254	0.0258	0.045
Final $wR(F^2)$ values (obs. data)	0.0628	0.0621	0.093
Final R_1 values (all data)	0.0273	0.0222	0.045
Final $wR(F^2)$ values (all data)	0.0656	0.0655	0.093
Goodness of fit on F^2	1.1016	1.1019	0.970

The complex structure, shown in Figure 3, shows that each molecule contains one Zn(II) center, two pyrazinamide molecules, and two chlorides. The Zn(II) metal center is four-coordinated by two pyrazinamide ligands via the nitrogen of the pyrazine ring and two terminal Cl atoms forming a distorted tetrahedral geometry (regular tetrahedral has angles of 109°). This is also confirmed by the angles around the metal center (Table 5), in which the Cl–Zn–Cl angle (128.10°) is larger than the N_{pza}–Zn–N_{pza} angle (99.16°). This distorted structure also commonly observed in identical tetrahedral $[ZnCl_2L_2]$ complex [17].

As shown in Table 5, the Zn–Cl bond is longer than the Zn–N_{pza} bond. This is expected, as the Cl ligand has higher electronegativity and requires more space to stabilize its surroundings. Consequently, Cl binds to the Zn(II) metal center at a longer distance, creating a larger Cl–Zn–Cl angle. This leads to a smaller N_{pza}–Zn–N_{pza} angle, with the Zn–N_{pza} bond being shorter than the Zn–Cl bond. Although the complex forms a discrete structure (Figure 3), crystal packing reveals hydrogen bonding between the carbonyl oxygen atom and the amide group, forming an intermolecular hydrogen bond with a dimer motif (N—H···O=C), as indicated by shifted peaks in the infrared spectra. The structure further extends into wave-like 1D hydrogen-bonded chains (Figure 4). These hydrogen bonds contribute to the compound's high melting point.

Table 5. Selected bond lengths (Å) and angles (°) of complex

Selected bond length	(Å)	Selected angles	(°)
Zn1-N1	2.077 (3)	Cl1-Zn1-Cl2	128.10 (5)
Zn1-N1a	2.077 (3)	N1#a-Zn1-Cl2	107.47(8)
Zn1-Cl1	2.1946 (13)	N1-Zn1-Cl2	107.47 (8)
Zn1-Cl2	2.1927 (14)	N1#a-Zn1-Cl1	105.49 (8)
		N1-Zn1-Cl1	105.49 (8)
		N1#a-Zn-N1	99.16 (15)

#a = +x, ½-y, +z

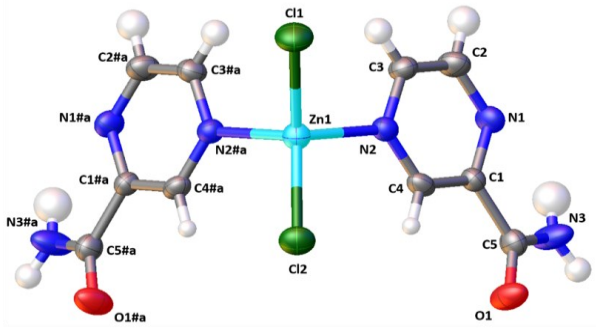

Figure 3. Crystal structure of the complex (symmetry #a = *+x, ½-y, +z*) ellipsoids is shown at 50% probability; the structure obtained in this work is similar to a known compound reported by Shirvan and Haydari Dezfuli [17]

3.3. Antibacterial Activity

Based on the MIC and MBC test results, the complex showed an MIC of 2000 ppm and an MBC of 6000 ppm for both bacteria. Consequently, the concentrations used for the ZoI test were 2000 ppm and 6000 ppm. The inhibition zone test results, presented in Table 6, indicate that the complex exhibits stronger antibacterial activity compared to the metal salt and free ligand. The complex at 6000 ppm demonstrated higher antibacterial effectiveness than at 2000 ppm, likely due to the greater availability of active substances to interact with the target microorganisms at higher concentrations. According to Patel [20], the compound $[Zn(C_5H_5N_3O)_2(Cl)_2]$ at 6000 ppm achieves an inhibition zone diameter indicative of good or susceptible effectiveness, exceeding 19 mm.

The zone of inhibition diameter of the $[Zn(pza)_2(Cl)_2]$ is larger than that of other complexes that use niacinamide ligands by Shelar *et al.* [21]. This is probably due to pyrazinamide having a more functional group than niacinamide; thus, the complex is able to penetrate the bacteria's lipid membrane. Moreover, initial antimicrobial screening against *S. aureus* and *E. coli* bacteria showed that the $[ZnCl_2(C_5H_5N_3O)_2]$ complex was quite active in inhibiting the bacteria.

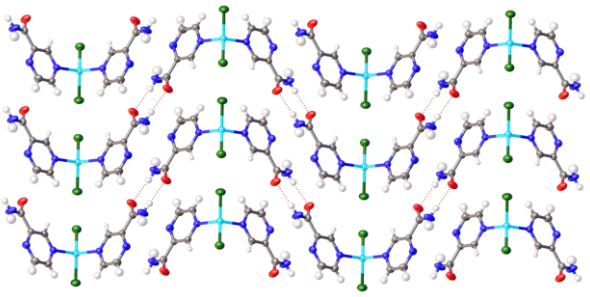

Figure 4. Part of the crystal packing of $[Zn(C_5H_5N_3O)_2(Cl)_2]$ viewed along the *a* axis (hydrogen bonds shown as red dashed lines)

Based on its structure, the pyrazinamide complex is more lipophilic due to the pyrazine heterocyclic ring, which consists of six members with two nitrogen atoms at positions 1 and 4. The electron distribution within the pyrazine ring makes it more nonpolar than the pyridine ring. The absence of strong polar functional groups in the pyrazine ring contributes to its hydrophobicity and increased lipophilicity. In contrast, the niacinamide complex exhibits lower lipophilicity because the pyridine heterocyclic ring, which also consists of six members, contains one nitrogen atom at position 1. The presence of this nitrogen atom imparts more polar characteristics to the pyridine ring, resulting in a greater electron-attracting ability and an uneven charge distribution.

Consequently, the pyridine ring's polarity enhances its interaction with polar solvents, thereby increasing the overall molecule's lipophilic nature [22]. In other words, the larger zone of inhibition for the pyrazinamide complex is primarily attributed to its higher lipophilicity, which enhances membrane penetration and intracellular targeting, leading to more effective bacterial growth inhibition. In contrast, the niacinamide complex, being more polar, exhibits reduced membrane penetration and antibacterial efficacy, resulting in a smaller zone of inhibition.

Table 6. Diameter of the inhibition zone of the complexes, free pza, metal salts, and distilled water (solvent)

Compound	Concentration (ppm)	Zone of inhibition (mm)	
		S. aureus	*E. coli*
$[Zn(C_6H_6N_2O)_x]Cl_2$ [21]	5000	not detected	not detected
$[Zn(H_2(C_5H_5N_3O))OHCl].H_2O$ [23]	No information	14	14
$[Zn(C_5H_5N_3O)_2(Cl)_2]$	2000	16 ± 0.58	15 ± 0.53
	6000	24 ± 0.58	20 ± 1.1
Pyrazinamide	2000	12 ± 0.50	11 ± 0.23
	6000	13 ± 0.87	12 ± 0.29
$ZnCl_2$	2000	10 ± 0.75	8 ± 0.55
	6000	11 ± 0.42	10 ± 0.89
Water (solvent)	-	0	0

This result suggests that the reaction between metal ions and ligands significantly enhances antibacterial activity. In this study, the Zn(II)-pyrazinamide complex exhibited greater antibacterial effectiveness than the corresponding metal salt and free ligand. This increased activity is attributed to the strong interaction between the chloride ion and the zinc central atom, which enhances the lipophilic character of the metal complex [24]. Electrons in the metal complex can delocalize due to metal-ligand interactions, which may reduce the polarity of the metal ion by sharing some of its positive charge with the ligand donor atom. This delocalization can enhance the lipophilic and hydrophobic properties of the metal complex, facilitating its passage through the lipid layer of the bacterial membrane [25, 26].

In the context of antibacterial activity, the high lipophilicity of the metal complex causes it to be easily dissolved in the bacterial lipid membranes. This allows metal complexes to penetrate bacterial cell walls and disrupt vital functions, such as affecting cell membrane integrity, inhibiting essential enzymes, or producing reactive species that damage microorganisms more easily. Meanwhile, organic ligands that do not form metal complexes usually have lower lipophilic properties [6, 27].

According to Rehman *et al.* [25], it is estimated that the antibacterial effect of coordination compounds is caused by the release of metal ions and degradation of organic ligands, in addition to their synergistic effect. The environment surrounding the bacterial cells can be altered by the released metal ions, allowing the bacteria to disturb the ion balance, damage ion channels, and compromise membrane integrity. The bacteria finally perish due to the rupture of the cell membrane and the discharge of cytoplasm. In addition, organic ligands with antibacterial action on complex compounds can also exert antibacterial effects through sustained release [28]. Therefore, it can be concluded that transition metal complexes have a better antibacterial effect compared to their free ligands because they work synergistically to create a stronger antibacterial effect than if both occurred separately.

Based on the results of the antibacterial test, the $[Zn(pza)_2Cl_2]$ complex has better antibacterial activity on *S. aureus* (gram-positive) than on *E. coli* (gram-negative). Gram-positive bacteria such as *S. aureus* have thick cell walls containing peptidoglycan, making it easier for the complex to penetrate the cell. Gram-negative bacteria, such as *E. coli*, are less penetrable because they have an outer membrane that contains a lot of lipid layers [29, 30, 31].

4. Conclusion

The $[Zn(pza)_2Cl_2]$ complex has been successfully crystallized from alcoholic solvent, in which the highest yield (87.34%) was obtained from reaction in methanol solvent using a mol ratio of 1:4. The mol ratio and solvent affects the crystal yield. Infrared spectra analysis of the complex shows characteristic carbonyl and amide groups of the pyrazinamide. Meanwhile, single crystal XRD screening analysis confirm that the complex adopts distorted tetrahedral geometry that has similar structure to previously known compound of $[Zn(pza)_2Cl_2]$. *In vitro* antibacterial test against *E. coli* and *S. aureus* bacteria shows that the synthesized complex has a moderate level and shows better activity compared to that of the $ZnCl_2$ and the pyrazinamide which probably due to the increased lipophilic character of the complex. In addition, the complex performs better antibacterial activity toward *S. aureus* than that of *E. coli*, due to different type of gram bacteria. For future works, development of metal complex based antibacterial agent can be done by varying the ligand and/or the metal ions.

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References

[1] Jasmin Ara Shampa, Md. Rakibul Islam, Md. Saddam Hossain, Gagi Tauhidur Rahman, C. M. Zakaria, Kudrat-E.-Zahan Md., Physiochemical and Antibacterial Activity Investigation on Noble Schiff Base Cu(II) Complex, *American Journal of Heterocyclic Chemistry*, 3, 4, (2017), 37-41 https://doi.org/10.11648/j.ajhc.20170304.11

[2] N. Raman, R. Jeyamurugan, Synthesis, characterization, and DNA interaction of mononuclear copper(II) and zinc(II) complexes having a hard–soft NS donor ligand, *Journal of Coordination Chemistry*, 62, 14, (2009), 2375-2387 https://doi.org/10.1080/00958970902825195

[3] Antonio F. Santos, Débora F. Brotto, Lis R. V. Favarin, Natália A. Cabeza, Geziel R. Andrade, Margareth Batistote, Alberto A. Cavalheiro, Ademir Neves, Daniela C. M. Rodrigues, Ademir dos Anjos, Study of the antimicrobial activity of metal complexes and their ligands through bioassays applied to plant extracts, *Revista Brasileira de Farmacognosia*, 24, 3, (2014), 309-315 https://doi.org/10.1016/j.bjp.2014.07.008

[4] Jianghua Liu, Di Wu, Niu Zhu, Yongning Wu, Guoliang Li, Antibacterial mechanisms and applications of metal-organic frameworks and their derived nanomaterials, *Trends in Food Science & Technology*, 109, (2021), 413-434 https://doi.org/10.1016/j.tifs.2021.01.012

[5] A. A. Warra, Transition metal complexes and their application in drugs and cosmetics-a Review, *Journal of Chemical and Pharmaceutical Research*, 3, 4, (2011), 951-958

[6] Nadia Cikita Handayani, Putri Nuzilla Shafira, Sasti Gona Fadhilah, Potensi Pengembangan Agen Antibakteri dari Senyawa Kompleks Logam Transisi di Indonesia, *The Indonesian Green Technology Journal*, 10, 1, (2021), 9-20

[7] Hossein Chiniforoshan, Zahra Sadeghian Radani, Leila Tabrizi, Hossein Tavakol, Mohammad R. Sabzalian, Gholamhossein Mohammadnezhad, Helmar Görls, Winfried Plass, Pyrazinamide drug interacting with Co(III) and Zn(II) metal ions based on 2,2′-bipyridine and 1,10-phenanthroline ligands: Synthesis, studies and crystal structure, DFT calculations and antibacterial assays, *Journal of Molecular Structure*, 1081, (2015), 237-243 https://doi.org/10.1016/j.molstruc.2014.10.027

[8] Sílvia Quaresma, Paula C. Alves, Patrícia Rijo, M. Teresa Duarte, Vânia André, Antimicrobial Activity of Pyrazinamide Coordination Frameworks Synthesized by Mechanochemistry, *Molecules*, 26, 7, (2021), 1904 https://doi.org/10.3390/molecules26071904

[9] L. Findoráková, K. Győryová, M. Melník, M. Koman, Faten A. Nour El-Dien, Preparation, thermal decomposition, and crystal structure of Zn(II) 2-chlorobenzoate complex with nicotinamide, *Journal of Coordination Chemistry*, 63, 19, (2010), 3348-3355 https://doi.org/10.1080/00958972.2010.512083

[10] Julia Pasquet, Yves Chevalier, Jocelyne Pelletier, Emmanuelle Couval, Dominique Bouvier, Marie-Alexandrine Bolzinger, The contribution of zinc ions to the antimicrobial activity of zinc oxide, *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 457, (2014), 263-274 https://doi.org/10.1016/j.colsurfa.2014.05.057

[11] Oleg V. Dolomanov, Luc J. Bourhis, Richard J. Gildea, Judith A. K. Howard, Horst Puschmann, OLEX2: a complete structure solution, refinement and analysis program, *Journal of Applied Crystallography*, 42, 2, (2009), 339-341 https://doi.org/10.1107/S0021889808042726

[12] Yuniar P. Prananto, David R. Turner, Jinzhen Lu, Stuart R. Batten, Solvent-Induced Structural Changes in Complexes of 1,2-Bis(3-(3-pyridyl)pyrazolyl)ethane, *Australian Journal of Chemistry*, 62, 2, (2009), 108-114 https://doi.org/10.1071/CH08483

[13] Hong-Bo Yuan, Shi-Yao Yang, Zhao-Xiong Xie, Rong-Bing Huang, Stuart R. Batten, Solvent-induced assembly of two supramolecular isomers of Mn^{II} thiophenedicarboxylate coordination polymers, *Inorganic Chemistry Communications*, 12, 8, (2009), 755-757 https://doi.org/10.1016/j.inoche.2009.06.007

[14] Daotan Liu, Siyuan Zhang, Zhijian Wu, Lattice Energy Estimation for Inorganic Ionic Crystals, *Inorganic Chemistry*, 42, 7, (2003), 2465-2469 https://doi.org/10.1021/ic025902a

[15] H. Marshan Robert, D. Usha, M. Amalanathan, R. Racil Jeya Geetha, M. Sony Michael Mary, Spectroscopic (IR, Raman, UV, NMR) characterization and investigation of reactive properties of pyrazine-2-carboxamide by anti-bacterial, anti-mycobacterial, Fukui function, molecular docking and DFT calculations, *Chemical Data Collections*, 30, (2020), 100583 https://doi.org/10.1016/j.cdc.2020.100583

[16] Tutik Setianingsih, Yuniar Ponco Prananto, *Spektroskopi Inframerah untuk Karakterisasi Material Anorganik*, Universitas Brawijaya Press, 2020,

[17] Sadif A. Shirvan, Sara Haydari Dezfuli, Dichloridobis (pyrazine-2-carboxamide-κN4) zinc (II), *Acta Crystallographica Section E: Structure Reports Online*, 68, 5, (2012), m546 https://doi.org/10.1107/S1600536812013888

[18] Jiang-Feng Song, Jing-Jing Luo, Ying-Ying Jia, Li-Dong Xin, Zhi-Zhu Lin, Rui-Sha Zhou, Solvent-induced construction of two zinc supramolecular isomers: synthesis, framework flexibility, sensing properties, and adsorption of dye molecules, *RSC Advances*, 7, 58, (2017), 36575-36584 https://doi.org/10.1039/C7RA05049F

[19] Run-Qing Miao, Qi-Qi Zhou, Shi-Qiang Wang, Xiao-Yue Cheng, Dan-Feng Wang, Rong-Bin Huang, Solvent-induced Zn(II) coordination polymers with 1, 3, 5-benzenetricarboxylic acid, *Journal of Molecular Structure*, 1184, (2019), 219-224 https://doi.org/10.1016/j.molstruc.2019.02.015

[20] Jean B. Patel, *Performance standards for antimicrobial susceptibility testing*, Clinical and laboratory standards institute, 2017,

[21] P. Shelar, C. Nazareth, R. Khorjuwenkar, O. Pinto, G. Kamat, B. Naik, A Novel UV Spectrophotometric Method For Simultaneous Estimation of Metoprolol Tartrate and Atorvastatin Calcium Based on Absorbance Correction Principle, *Rasayan Journal of Chemistry*, 15, 4, (2022), 2822-2827 https://doi.org/10.31788/rjc.2022.1547065

[22] Giovanni Piccaro, Giovanna Poce, Mariangela Biava, Federico Giannoni, Lanfranco Fattorini, Activity of lipophilic and hydrophilic drugs against dormant and replicating *Mycobacterium tuberculosis*, *The Journal of Antibiotics*, 68, 11, (2015), 711-714 https://doi.org/10.1038/ja.2015.52

[23] Alaa E. Ali, Gehan S. Elasala, Essam A. Mohamed, Sherif A. Kolkaila, Spectral, thermal studies and biological activity of pyrazinamide complexes, *Heliyon*, 5, 11, (2019), e02912 https://doi.org/10.1016/j.heliyon.2019.e02912

[24] I Wayan Dasna, Dewi Mariyam, Husni Wahyu Wijaya, Ubed Sonai Fahruddin Arrozi, Sugiarto Sugiarto, Synthesis, Structural Determination and Antibacterial Properties of Zinc(II) Complexes Containing 4-Aminopyridine Ligands, *Indonesian Journal of Chemistry*, 23, 4, (2023), 1108-1119 https://doi.org/10.22146/ijc.82801

[25] Sadia Rehman, Muhammad Ikram, Fazle Subhan, Mutasem Sinnokrot, Waliullah Khan, Antibacterial Activities of Transition Metal complexes of Mesocyclic Amidine 1,4-diazacycloheptane (DACH), *Open Chemistry*, 17, 1, (2019), 936-942 https://doi.org/10.1515/chem-2019-0108

[26] Amah Colette Benedicta Yuoh, Moise Ondoh Agwara, Divine Mbom Yufanyi, Mariam Aseng Conde, Rajamony Jagan, Kenneth Oben Eyong, Synthesis, Crystal Structure, and Antimicrobial Properties of a Novel 1-D Cobalt Coordination Polymer with Dicyanamide and 2-Aminopyridine, *International Journal of Inorganic Chemistry*, 2015, 1, (2015), 106838 https://doi.org/10.1155/2015/106838

[27] Ramesh S. Yamgar, Y. Nivid, Satish Nalawade, Mustapha Mandewale, R. G. Atram, Sudhir S. Sawant, Novel Zinc(II) Complexes of Heterocyclic Ligands as Antimicrobial Agents: Synthesis, Characterisation, and Antimicrobial Studies, *Bioinorganic Chemistry and Applications*, 2014, 1, (2014), 276598 https://doi.org/10.1155/2014/276598

[28] Bernardo Ribeiro da Cunha, Luís P. Fonseca, Cecília R. C. Calado, Antibiotic Discovery: Where Have We Come from, Where Do We Go?, *Antibiotics*, 8, 2, (2019), 45 https://doi.org/10.3390/antibiotics8020045

[29] Mofei Shen, Fereidoun Forghani, Xueqian Kong, Donghong Liu, Xingqian Ye, Shiguo Chen, Tian Ding, Antibacterial applications of metal–organic frameworks and their composites, *Comprehensive Reviews in Food Science and Food Safety*, 19, 4, (2020), 1397-1419 https://doi.org/10.1111/1541-4337.12515

[30] J. Jang, H. - G. Hur, M. J. Sadowsky, M. N. Byappanahalli, T. Yan, S. Ishii, Environmental *Escherichia coli*: ecology and public health implications — a review, *Journal of Applied Microbiology*, 123, 3, (2017), 570-581 https://doi.org/10.1111/jam.13468

[31] Gnanamani Arumugam, Hariharan Periasamy, Satyaseela Maneesh Paul, Staphylococcus aureus: Overview of Bacteriology, Clinical Diseases, Epidemiology, Antibiotic Resistance and Therapeutic Approach, in: E. Shymaa, E.C.A. Laura (Eds.) *Frontiers in Staphylococcus aureus*, IntechOpen, Rijeka, 2017, https://doi.org/10.5772/67338